

PPMI Status Update

Ken Marek

PPMI Investigators Meeting
May 2, 2012
New York, NY



PARKINSON'S
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PD patient vignette

- **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”**



PPMI-PD patient vignette

- **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”**



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PPMI-Control vignette

- **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 vignette

- **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 out of bed during sleep**
- **Maybe balance not quite as good on ladders**

Exam

Normal

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



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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** – 204 PD 149 HS 25 SWEDD - **378 subjects**
- **Retention** – 202 PD 146 HS 24 SWEDD - **372 subjects**
- Study governance - weekly meetings of the executive steering committee and monthly meetings of the full steering committee consisting of all study cores
- Data flow from sites to Study Cores to LONI. Outstanding success in collection of study data (98% LP at baseline and about 90% overall at 6 months and 12 months)
- Data presentation at major scientific meetings

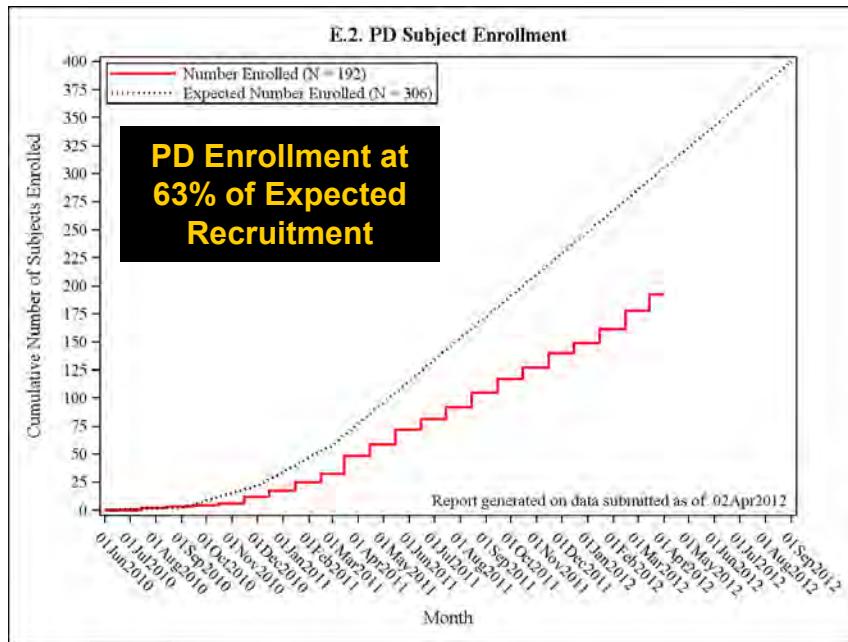


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ENROLLMENT



Recruitment – Early lessons learned

- It is do-able, but challenging to recruit at planned rate –
1 PD/month, 1 control/2months
- Multiple strategies to enhance recruitment are necessary –
Fox Trial Finder
- Control recruitment on hold
- Recruitment challenge 400 subjects by July 4.



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Recruitment – Retention - moving forward

- Ongoing recruitment will require continued efforts
- Retention strategies are crucial
 - Continued participation in all assessments
 - Need for PD medications
- PPMI Longitudinal data
 - Subject assessments
 - Subject data
- PPMI as an iterative study
 - Additional assessments/studies/cohorts
 - D/C assessments

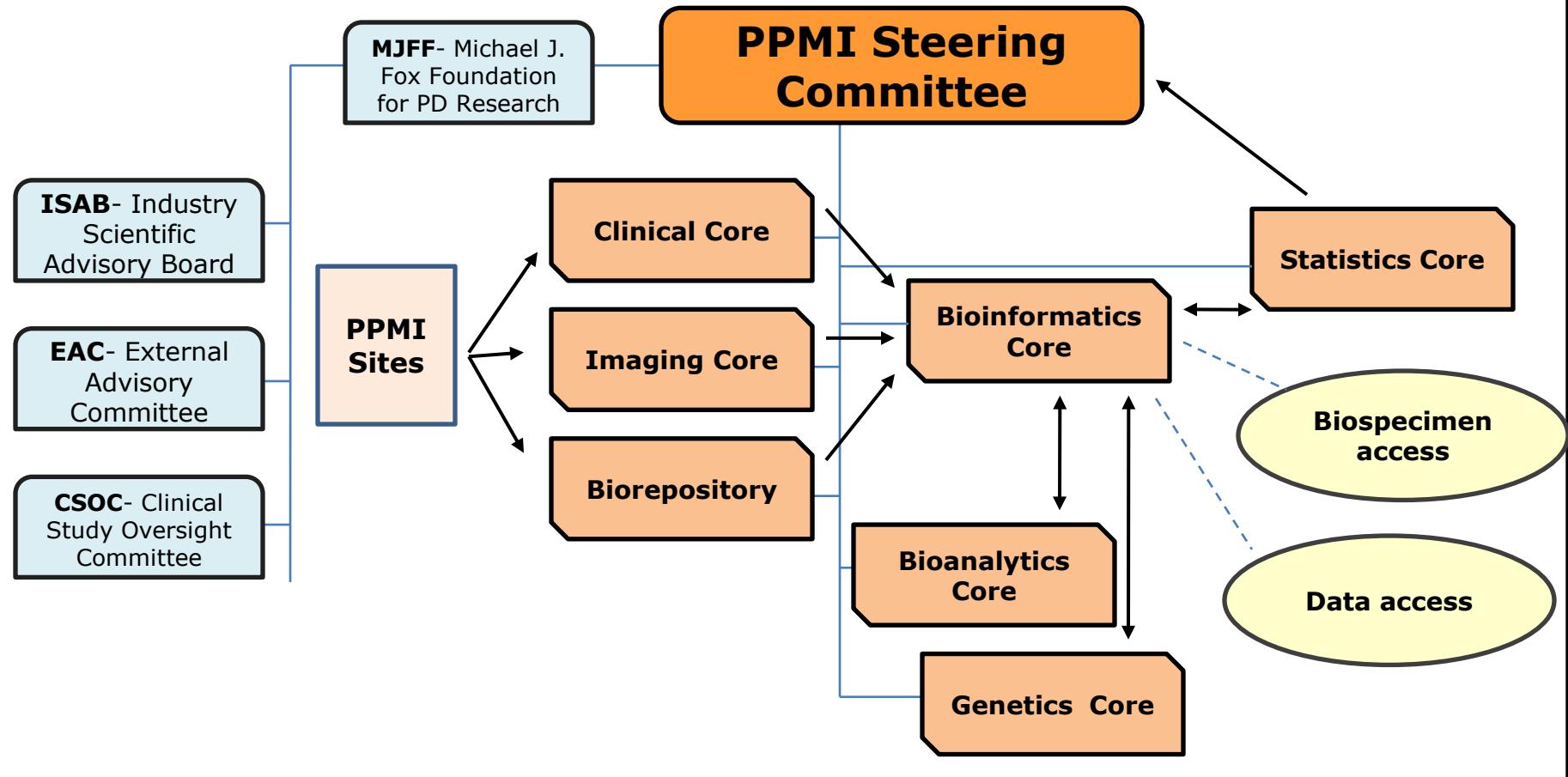


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PPMI Study



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Subject Enrollment & Sample Collection

Specimen	Collected Samples (Enrolled patients)							
	BL	V01	V02	V03	V04	V05	ST	
Plasma	370 (372)	280 (284)	178 (182)	114 (116)	79 (79)	5 (5)	37 (37)	1063 (1075)
Serum	BL	V01	V02	V03	V04	V05	ST	Total
	370 (372)	281 (284)	182 (182)	114 (116)	79 (79)	5 (5)	37 (37)	1068 (1075)
CSF	BL	V01*	V02	-	V04	-	ST	Total*
	358 (372)	6 (6)	161 (179)	-	68 (78)	-	32 (36)	625 (671)



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Parkinson's Progression Markers Initiative

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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

- **Biologic samples available via website**
- **Data available via website**
- **Ancillary study application through website**

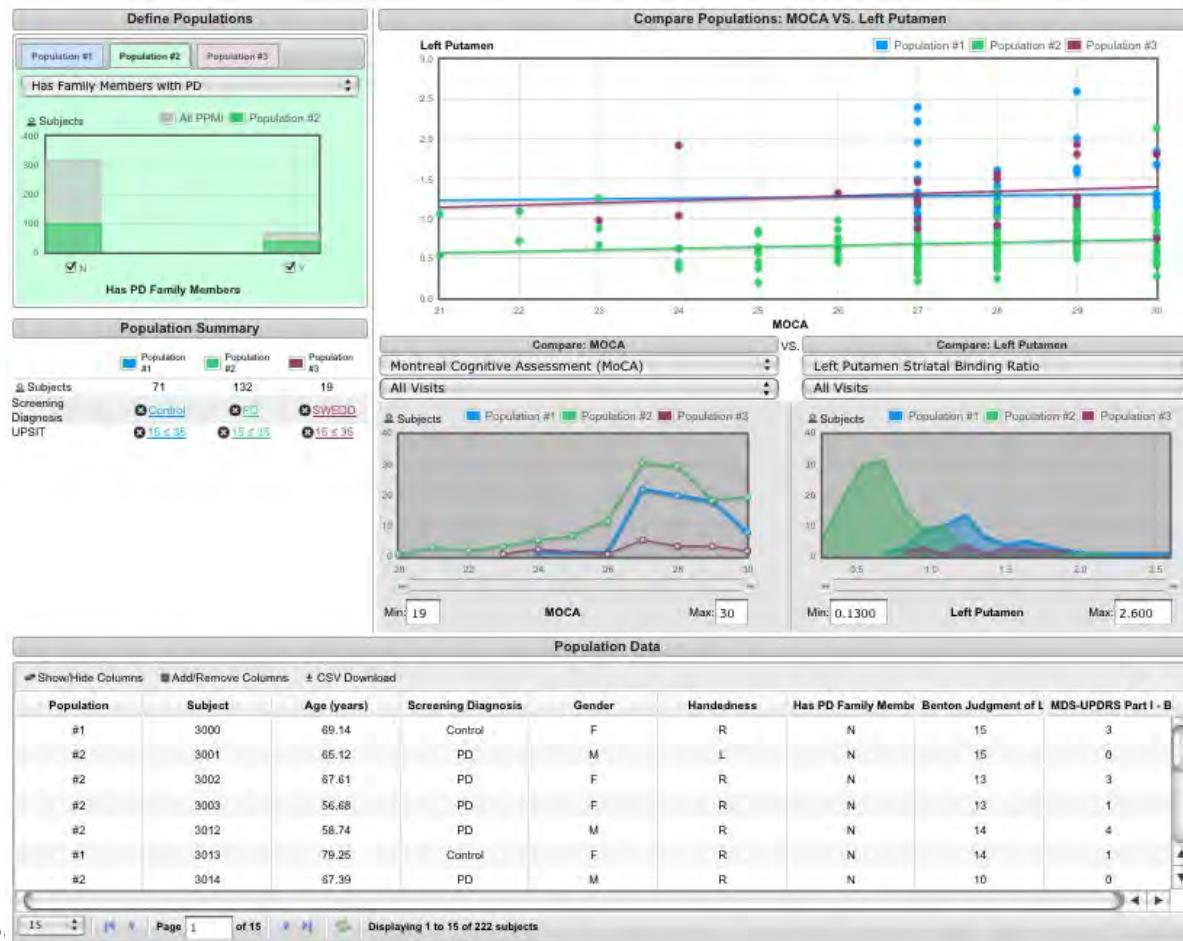


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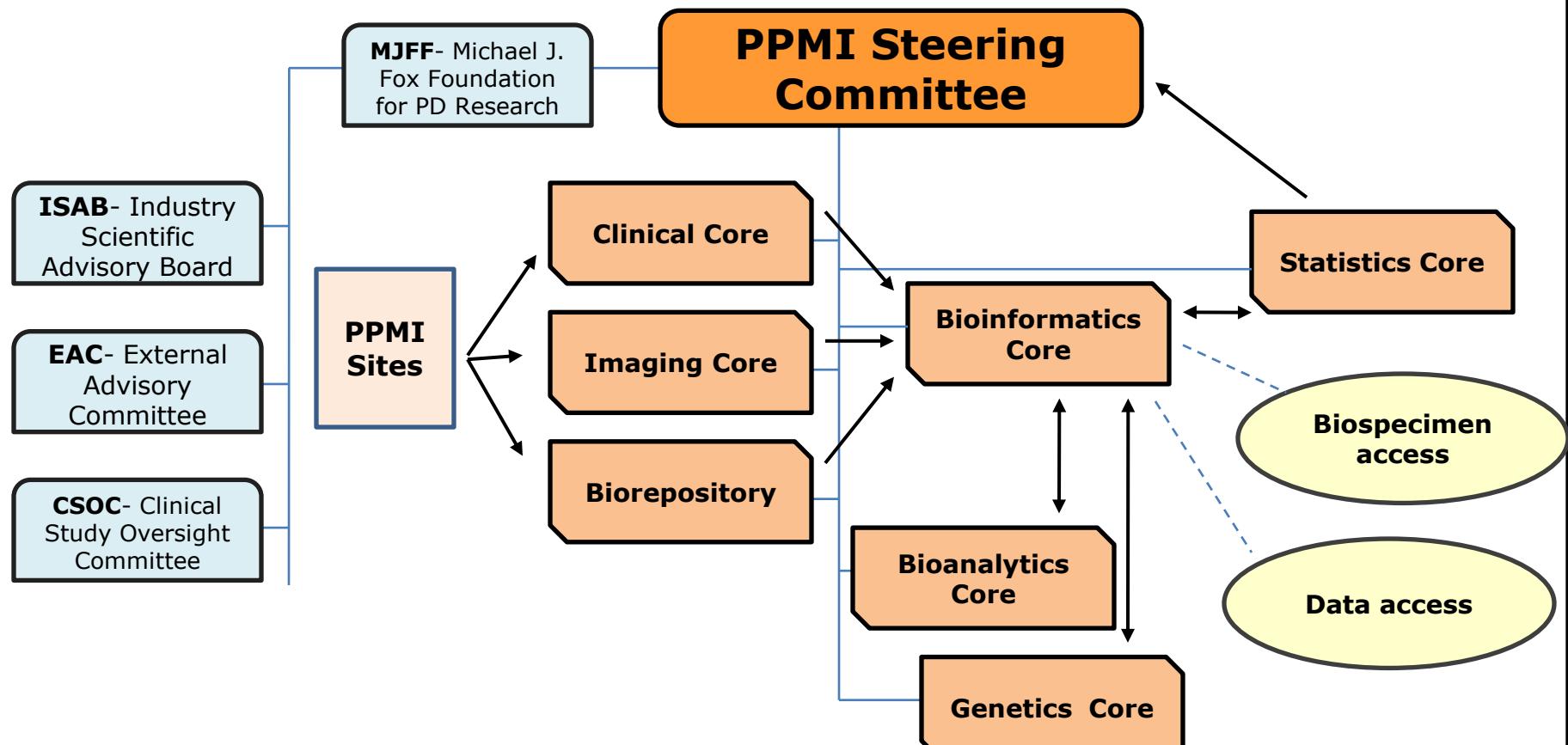


Visual Interrogation System



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PPMI Study



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PPMI SC and Study Cores

Steering Committee	PI-K Marek, A Siderowf, C Tanner, 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, Emily Flagg, Alice Rudolph, Cindy Casaceli
Imaging Core	<ul style="list-style-type: none">▪ Institute for Neurodegenerative Disorders• PI: John Seibyl, Norbert Schuff, Susan Mendick
Statistics Core	<ul style="list-style-type: none">▪ University of Iowa• PI: Chris Coffey, Qing Yang
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, Giulia Malferrari
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



PPMI Committees

- **Biologics**
 - John Trojanowski
 - Les Shaw
- **Imaging**
 - John Seibyl
- **Neuropsych /Neurobehavior**
 - Andrew Siderowf
- **Sleep**
 - Wolfgang Oertel
- **Genetics**
 - Andrew Singleton
- **Statistical**
 - Chris Coffey
- **Biospecimen review**
 - Gene Johnson
- **Data and publication**
 - David Standaert
- **Ancillary study**
 - Carlie Tanner
- **Recruitment/Retention**
 - Danna Jennings
- **Website**
 - Carlie Tanner
- **CSOC**
 - Ron Pfeiffer



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**
- **Jamie Eberling, PhD, Imaging Core and imaging SOPs**
- **Debi Brooks, Industry partnership development, Recruitment/Retention Strategies**
- **Todd Sherer, PhD, MJFF CEO**



Industry Scientific Advisory Board (ISAB) Membership



Michelle Collins
Katherine Widnell



Mark Mintun



Bernard Ravina,
Chair-elect



Peggy Taylor



Ted Yednock



GE Healthcare

Igor Grachev



Marcel van der Brug



Alastair Reith



Be well

Johan Luthman
David Michelson



Thomas Comery,
Chair



Susanne Ostrowitzki
Paulo Fontoura



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Meeting Goals

- Review study success
 - Develop and implement PPMI infrastructure, enrollment, retention.
 - Highlights – CSF, DTI, DAT, UPDRS
- Meet study challenges
 - Recruitment of PD. Retention.
 - Continue rigorous efforts to acquire high quality data.
- PPMI must continue to be innovative
 - Novel analytes, imaging tools, clinical assessments, analyses
 - P-PPMI implementation



Annual Investigators Meeting

May 2/3, 2011

AGENDA

Wednesday May 2, 2012

2:30-2:45 pm	Welcome and Introductions	Marek, Sherer
2:45-3:00 pm	PPMI Status Update <ul style="list-style-type: none"> Sites Recruitment data Enrollment Taskforces, Committees, ISAB 	Marek
3:00-3:30 pm	Clinical Data Recap <ul style="list-style-type: none"> Demographic Information Collected data (motor, non-motor, neuropsych and neurobehavioral) Data entry and future training 	Coffey, Kieburtz
3:30-4:00 pm	Imaging Recap <ul style="list-style-type: none"> Update and data on DaTSCAN, DTI and MRI Future training 	Seibyl, Schuff
4:00-4:45 pm	Biologics Recap <ul style="list-style-type: none"> Update on inventory/process Data on received samples Biospecimen request process/Biospecimen Review Committee (BRC) 	Scutti, Frasier Shaw
4:45-5:15 am	Report from Industry Scientific Advisory Board	Comery
5:15-5:30 pm	Closing Remarks – Preparation for Tomorrow	Marek
6:00 pm	Dinner (Venue TBD)	All

Thursday May 3, 2012

8:00-8:30 am	Breakfast	All
8:30-9:30 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
9:30-10:00 am	Using PPMI Data <ul style="list-style-type: none"> Access to PPMI Data Downloading Data Querying Data 	Lasch, Toga
10:00-10:15 am	Break	
10:15-11:15 am	Ancillary/Sub-Studies <ul style="list-style-type: none"> Update on on-going Ancillary Studies (SWEDD, TAP-PD, etc.) Upcoming ancillary/sub-studies 	Siderowf, Tanner
11:15-11:45 am	Strategies for PPMI analysis	Marek, Kieburtz
11:45-12:45 pm	Lunch – With Working Groups	
12:45-1:45 pm	Future PPMI Studies – Recommendations from Working Groups (WG) <ul style="list-style-type: none"> Cognitive/Neuropsych WG: Identifying dementia Biologic WG: New analytes Imaging WG: New imaging modalities 	Siderowf
1:45-2:45 pm	PPMI Data Analyses <ul style="list-style-type: none"> Description of planned analyses Input on future analyses 	Coffey, Kieburtz, Marek
2:45-3:45 pm	P-PPMI: Pre-Motor-PPMI Proposal	Marek
3:45-4:00 pm	Sharing PPMI Data and Activities <ul style="list-style-type: none"> Publications, Talks, Abstracts Upcoming meetings and activities at meetings 	Frasier, Shaw Seibyl
4:00-4:15 pm	Closing <ul style="list-style-type: none"> 2013 Annual Meeting dates 	Marek

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PPMI Status Update

Site and Study Overview



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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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Site Status

- 5 sites activated and recruiting since PPMI annual meeting 2011
 - Cleveland Clinic (Hubert and Adrienna)
 - University of California, San Diego (Doug and Deborah)
 - Imperial College London (David and Nicola)
 - PD & Movement Disorder Ctr of Boca Raton (Stuart and Bob)
 - University of Cincinnati (Alberto and Kristy)
- We will welcome Italy and Australia very soon!



Study Status

- Enrolled 50% of the PD subjects and 50 more to go for healthy controls
- Three amendments since May 2011
 - Amendments 2, 3 and 4
- Implementation of another cohort into the study – SWEDD subjects



Study Status

- Procedural changes and requests
 - Fasting/low-fat diet for blood and LP
 - Reminders for blood processing
 - Recruitment restrictions
 - Enrollment ratios
- Annual renewals
- Amendment 5 planning phase.....



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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 Clinical Data Recap

Christopher S. Coffey
The University of Iowa

Karl Kieburtz
The University of Rochester

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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 04/02/12



ENROLLMENT

Group	Consented	Enrolled	Pending	Excluded/ Declined
PD Subjects	237	192	13	32
Healthy Controls	182	147	3	32
SWEDD Subjects	36	25	1	10

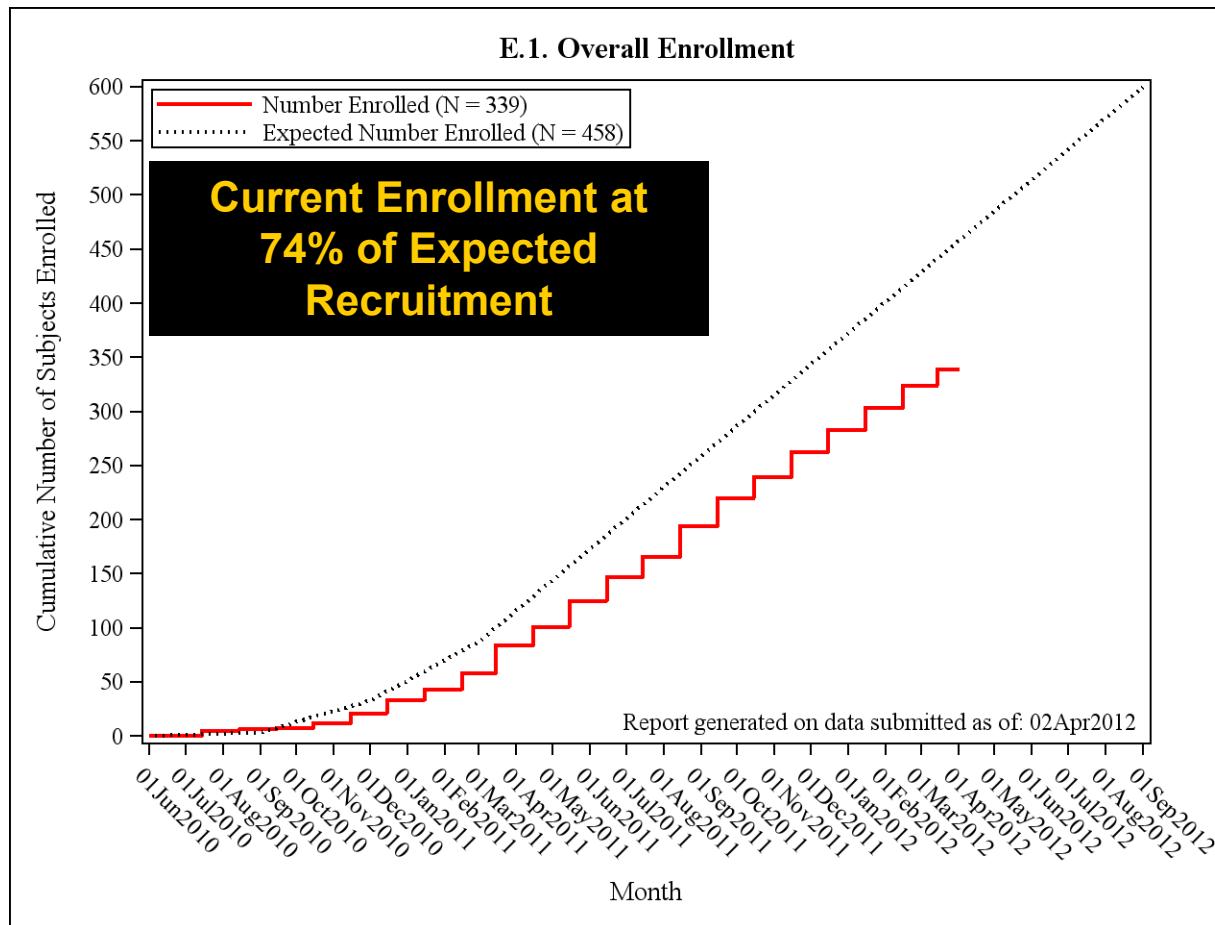
364 Total Subjects
Enrolled



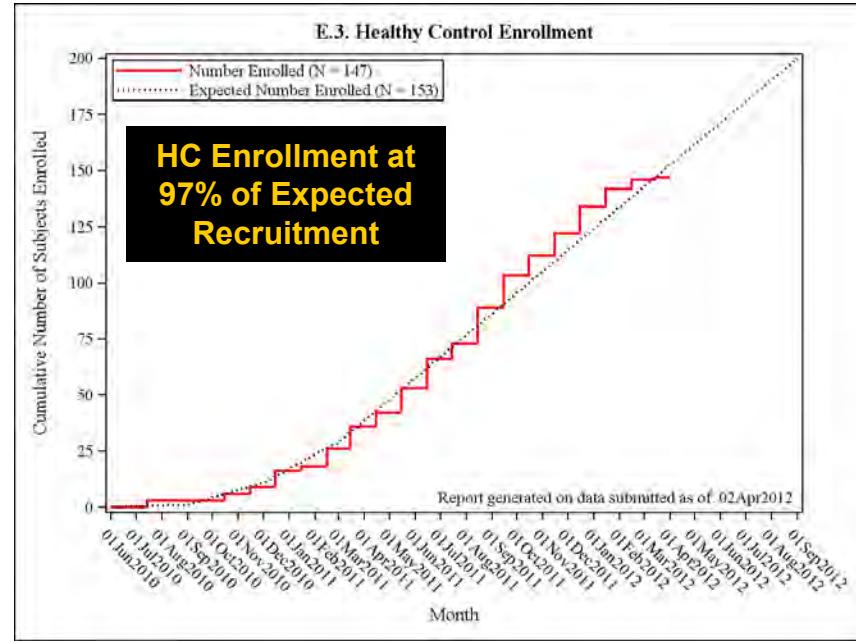
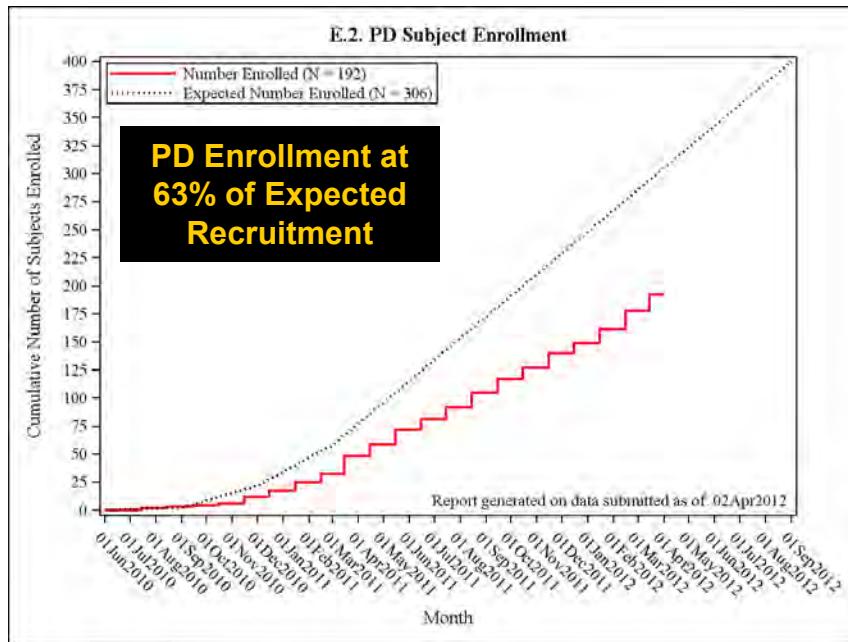
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ENROLLMENT



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

To differentiate concerns beyond control of sites, the PPMI investigators produced two versions of CSOC tables.

A modified version counted forms as complete, and did not count deviations, once the scan was completed.

The CSOC agreed that the scan could be counted as complete ***if conducted within 4 months of baseline.***



DaTSCAN AVAILABILITY ISSUES

PD Subjects:

- 46 enrolled without baseline DaTSCAN
 - 43 (94%) had DaTSCAN completed within 4 months
 - 2 (4%) had DaTSCAN completed after 4 months
 - 1 (2%) did not have DaTSCAN completed (termination)

Healthy Controls

- 49 enrolled without baseline DaTSCAN
 - 23 (47%) had DaTSCAN completed within 4 months
 - 8 (16%) had DaTSCAN completed after 4 months
 - 18 (37%) have not yet had a DaTSCAN (German sites)
 - 14 (29%) have already passed 4 month window



DaTSCAN AVAILABILITY ISSUES

SWEDD Subjects:

- 6 enrolled without baseline DaTSCAN
 - 4 (67%) had DaTSCAN completed within 4 months
 - 2 (33%) had DaTSCAN completed after 4 months



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BASELINE DATA COMPLETENESS

Including forms with DaTSCAN performed within 4 months of baseline:

- 290 (80%) have all baseline information entered into the publicly-accessible database
 - 359 (99%) have cognitive testing
 - 357 (98%) have a blood sample
 - 355 (98%) have a urine sample
 - 354 (97%) have all clinical forms entered
 - 349 (96%) have a lumbar puncture
 - 338 (93%) have an MRI
 - 326 (90%) have a DaTSCAN



GENDER/AGE DISTRIBUTION

➤ PD Subjects:

Group	Enrolled
Male / <56	30
Male / 56-65	54
Male / >65	51
Female / <56	17
Female / 56-65	21
Female / >65	19



GENDER/AGE DISTRIBUTION

➤ Healthy Controls:

Group	Enrolled	Expected Based on PD Enrollment	p-value
Male / <56	29	23.0	< 0.001
Male / 56-65	27	41.3	
Male / >65	29	39.0	
Female / <56	24	13.0	
Female / 56-65	25	16.1	
Female / >65	13	14.5	

Controls are more likely to be:

- Young / Female



GENDER/AGE DISTRIBUTION

➤ SWEDD Subjects:

Group	Enrolled	Expected Based on PD Enrollment	p-value
Male / <56	4	3.9	0.14
Male / 56-65	4	7.0	
Male / >65	5	6.6	
Female / <56	6	2.2	
Female / 56-65	3	2.7	
Female / >65	3	2.5	



DEMOGRAPHIC CHARACTERISTICS

	PD Subjects (N = 192)	Healthy Controls (N = 147)	SWEDD Subjects (N = 25)
Males	135 (70%)	85 (58%)	13 (52%)
Age (mean)	62	59	58
• <56 years	47 (24%)	53 (36%)	10 (40%)
• 56-65 years	75 (39%)	52 (35%)	7 (28%)
• >65 years	70 (36%)	42 (29%)	8 (32%)
Hispanic/Latino	3 (2%)	3 (2%)	1 (4%)
Race			
• Caucasian	180 (94%)	136 (93%)	23 (92%)
• African-American	1 (1%)	9 (6%)	0 (0%)
• Asian	3 (2%)	0 (0%)	1 (4%)
• Other	8 (4%)	1 (1%)	1 (4%)



BASELINE CHARACTERISTICS

	PD Subjects (N = 192)	Healthy Controls (N = 147)	SWEDD Subjects (N = 25)
UPDRS Part III	20.4	1.2	15.4
MOCA Total	27.2	28.3	27.7
GDS Total	2.3	1.3	3.0
SCOPA AUT	9.5	6.0	12.3



PD CHARACTERISTICS

	PD Subjects (N = 192)	SWEDD Subjects (N = 25)
Family Hx of PD	50 (26%)	4 (16%)
Mn duration of disease	8 months	10 months
Mn MDS-UPDRS score		
• Total score	33.5	29.8
• Part I	5.7	7.8
• Part II	6.1	5.8
• Part III (Motor Exam)	21.7	16.2
Mn Modified Schwab	93	95
Hoehn & Yahr		
• Stage 1	73 (38%)	12 (48%)
• Stage 2	113 (59%)	13 (52%)
• Stage 3-5	2 (1%)	0 (0%)



VISIT COMPLIANCE

Group	Month 6 # Expected (% Seen)	Month 12 #Expected (% Seen)
PD Subjects	105 (97%)	32 (100%)
Healthy Controls	89 (97%)	26 (88%)
SWEDD Subjects	6 (83%)	N/A

There are 3 sites with 100% in-window accuracy for in-person visits:

023 (5 total follow-up visits)

028 (9 total follow-up visits)

291 (26 total follow-up visits.)



LUMBAR PUNCTURE COMPLETENESS

Group	Baseline # Expected (% Complete)	Month 6 # Expected (% Complete)	Month 12 #Expected (% Complete)
PD Subjects	192 (95%)	105 (92%)	32 (91%)
Healthy Controls	147 (97%)	89 (83%)	26 (69%)
SWEDD Subjects	25 (96%)	6 (83%)	N/A



PROTOCOL DEVIATIONS

PD Subjects: 38 protocol deviations (in 34 subjects)

- 18 due to eligibility criteria
 - 1 due to baseline DaTSCAN not performed
 - 1 due to baseline DaTSCAN performed beyond 4 months
- 10 due to DaTSCAN (dosage)
- 3 due to Lumbar Puncture
- 3 due to research specimen(s)
- 2 due to clinical labs
- 1 due to 'Other' (CSF testing for hemoglobin)



PROTOCOL DEVIATIONS

Healthy Controls: 53 protocol deviations
(in 45 subjects)

- 30 due to eligibility criteria
 - 7 due to baseline DaTSCAN performed beyond 4 months
 - 18 due to missing baseline DaTSCAN
- 11 due to DaTSCAN (dosage)
- 3 due to research specimen(s)
- 2 due to lumbar puncture (CSF testing for hemoglobin)
- 2 due to clinical labs
- 1 due to MRI not done

Controls are significantly more likely to have a deviation – mostly due to German DaTSCAN issue.



PROTOCOL DEVIATIONS

SWEDD Subjects: 5 protocol deviations (in 5 subjects)

- 3 due to DaTSCAN (dosage)
- 2 due to eligibility criteria
 - Both due to baseline DaTSCAN performed beyond 4 months



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EARLY STUDY TERMINATIONS

PD Subjects: 3 early study terminations

- 2 due to adverse event (headache, exasperation of PD symptoms)
- 1 due to 'other' ("patient decided to take anti-parkinsonian medication today")

Healthy Controls: 3 early study terminations

- 2 withdrew consent
- 1 due to 'other' (unwilling to comply with lumbar puncture)



REPORTABLE EVENTS

PD Subjects: 52 reportable events (in 50 subjects)

- 45 due to starting PD meds
 - 5 within 3 months from baseline
 - 24 within 4-6 months from baseline
 - 9 within 7-9 months from baseline
 - 4 within 10-12 months from baseline
 - 3 greater than 12 months from baseline
- 3 started another study
- 2 due to early withdrawal
- 1 due to an SAE



REPORTABLE EVENTS

Healthy Controls: 4 reportable events (in 4 subjects)

- 2 due to early withdrawal
- 1 due to change of diagnosis
- 1 started another study

SWEDD Subjects: No reportable events



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ADVERSE EVENTS

PD Subjects: 79 adverse events (in 41 subjects)

- 55 LP-related AE's
 - 23 occurrences of "Headache"
 - 6 occurrences of "Injection Site Pain"
 - 6 occurrences of "Myalgia"
 - 5 occurrences of "Back Pain"
 - 2 occurrences each of "Musculoskeletal Discomfort", "Dizziness", & "Post Lumbar Puncture Syndrome"
 - 1 occurrence each of "Nausea", "Pain", "Tenderness", "Pain in Extremity", "Loss of Consciousness", "Parkinson's Disease", and "Presyncope"
- 2 DaTSCAN-related AE's



ADVERSE EVENTS

Healthy Controls: 92 adverse events (in 52 subjects)

- 76 LP-related AE's
 - 34 occurrences of "Headache"
 - 12 occurrences of "Back Pain"
 - 7 occurrences of "Injection Site Pain"
 - 4 occurrences of "Myalgia"
 - 4 occurrences of "Dizziness"
- 5 DaTSCAN-related AE's
 - 1 occurrence each of "Sensation of Pressure", "Myalgia", "Dysgeusia", "Headache", & "Pruritus"



ADVERSE EVENTS

SWEDD Subjects: 11 adverse events (in 6 subjects)

- 6 LP-related AE's
 - 3 occurrences of "Headache"
 - 1 occurrence each of "Back Pain", "Muscle Spasms", & "Myalgia"
- 2 DaTSCAN-related AE's
 - 1 occurrence each of "Dysgeusia" & "Headache"



ADVERSE EVENTS

➤ Subjects with an AE:

- PD Subjects – 41/192 (21%)
- Healthy Controls – 52/147 (35%)
- RR = 0.60, 95% CI: (0.42, 0.85)

➤ Subjects with an LP-related AE:

- PD Subjects – 34/192 (18%)
- Healthy Controls – 48/147 (33%)
- RR = 0.54, 95% CI: (0.37, 0.79)

➤ Subjects with a DaTSCAN-related AE:

- PD Subjects – 2/192 (1%)
- Healthy Controls – 4/147 (3%)
- RR = 0.37, 95% CI: (0.07, 1.99)



ADVERSE EVENTS

➤ Subjects with an AE:

- PD Subjects – 41/192 (21%)
- SWEDD Subjects – 6/25 (24%)
- RR = 0.89, 95% CI: (0.42, 1.88)

➤ Subjects with an LP-related AE:

- PD Subjects – 34/192 (18%)
- SWEDD Subjects – 4/25 (16%)
- RR = 1.11, 95% CI: (0.43, 2.87)

➤ Subjects with a DaTSCAN-related AE:

- PD Subjects – 2/192 (1%)
- SWEDD Subjects – 2/25 (8%)
- RR = 0.13, 95% CI: (0.02, 0.88)



SERIOUS ADVERSE EVENTS

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

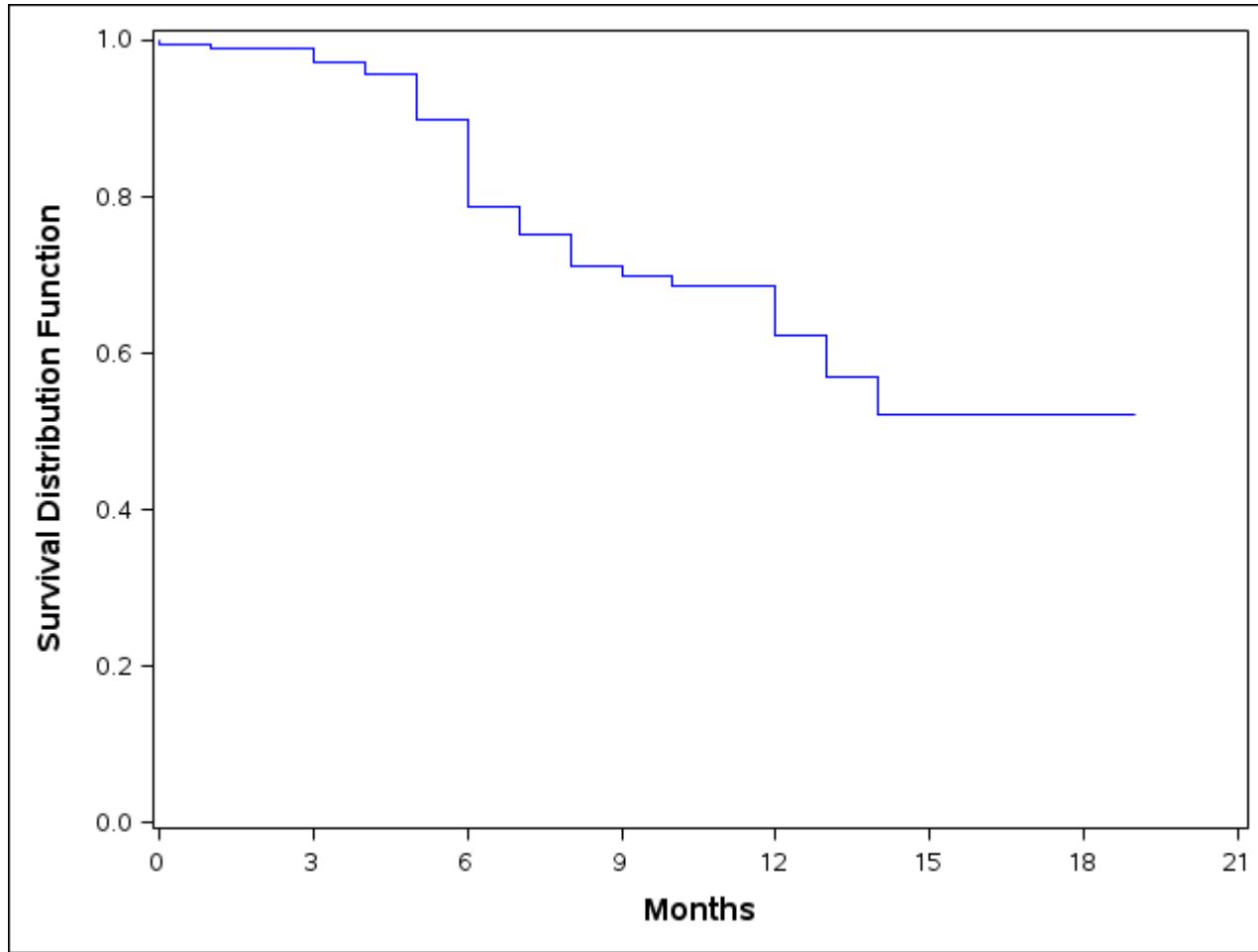
- 1 'Colitis' and 1 'Pancreatitis'
- None related to LP or DaTSCAN

Healthy Controls: No serious adverse events to date

SWEDD Subjects: No serious adverse events to date



TIME TO START PD MEDICATIONS



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PPMI Imaging Core Update

2 May 2012



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Imaging Technical Sites Visited

Northwestern

IND- New Haven

Johns Hopkins

Federico II - Naples

Parkinson's Institute- Sunnyvale

Univ Pennsylvania

Univ Rochester

APDC- Sun City, Az

Baylor

London

Univ Cincinnati

Univ Alabama-Birmingham

Boston University

Portland

Innsbruck

Marburg

Tübingen

Univ Washington

Tampa

Emory Univ

San Diego

Cleveland Clinic

Boca Raton

Sydney



PPMI DAT Imaging Studies In-house at IND Core Lab

Scans received: controls = 186 PD baseline = 217

SWEDDs = 39 (about 15%), 25 enrolled for follow-up

PD Year 1 scans = 55

DATScans uploaded to LONI = 275

Healthy volunteers with abnormal scans = 6

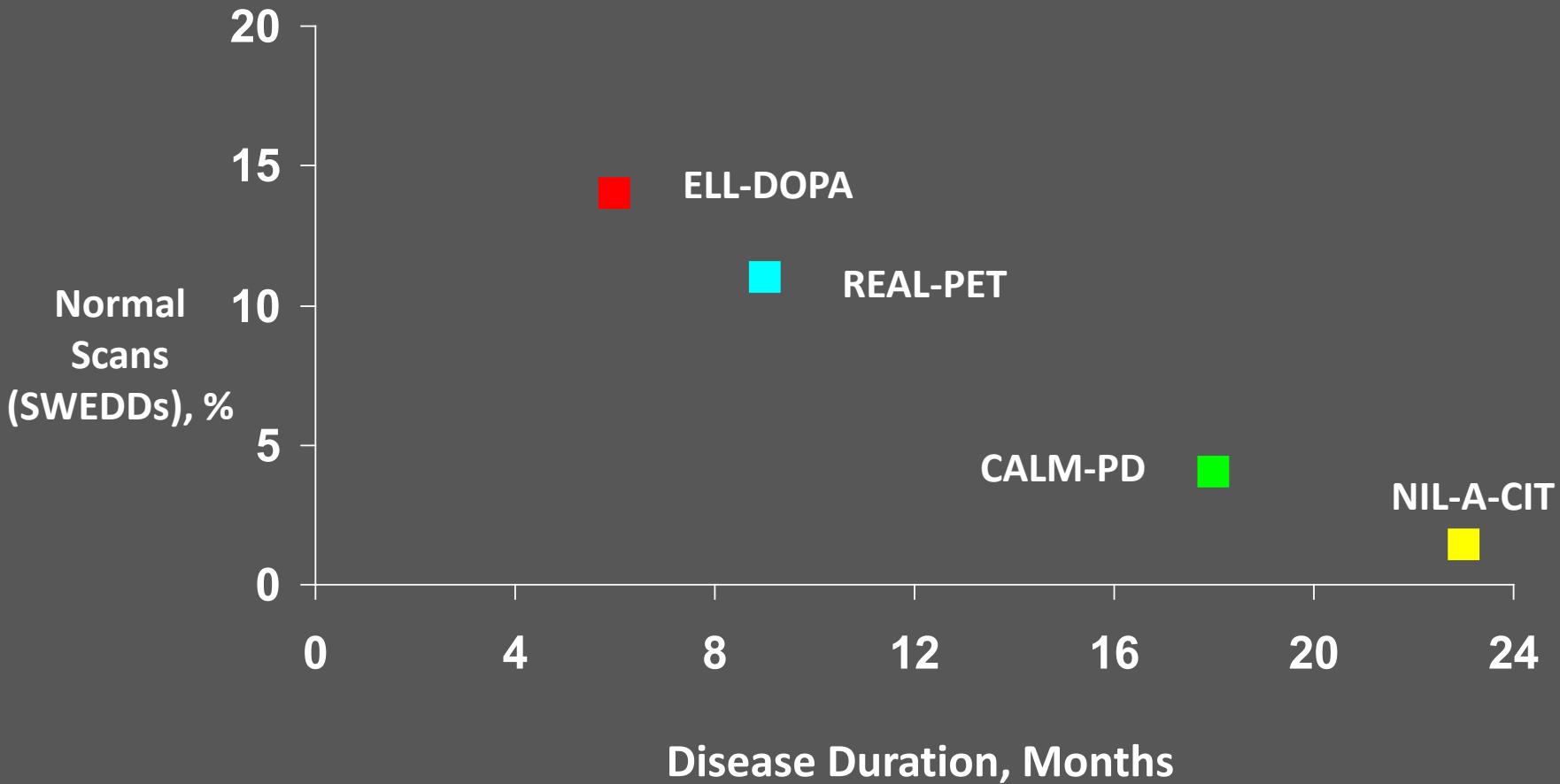


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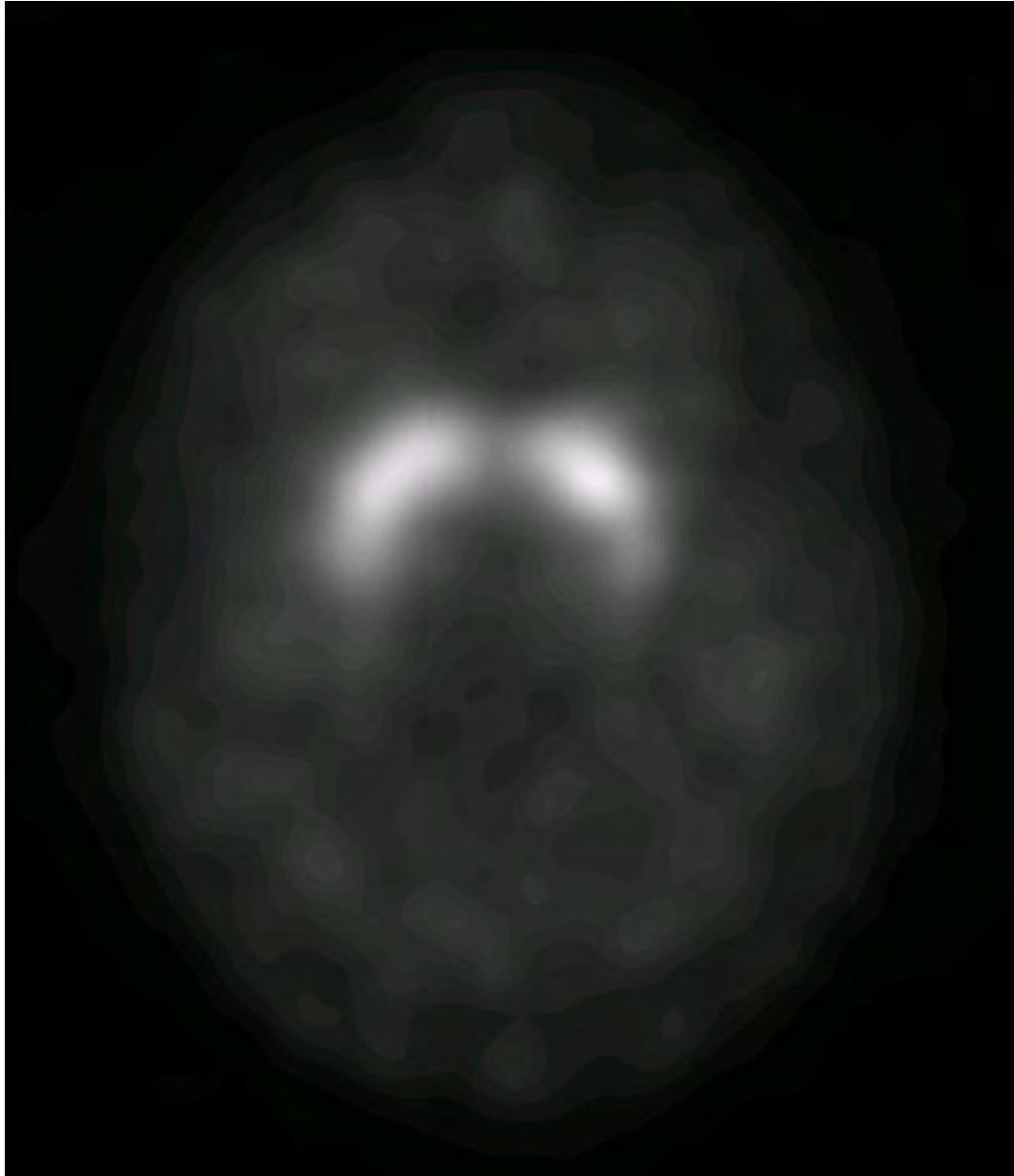
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Percent of SWEDDs Decreases With Disease Duration



Example Healthy with Abnormal Scan



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DAT SPECT Quantitative Analysis

1. Core lab reconstruction from raw projection data, including attenuation correction based on phantoms from site visit
2. Spatial normalization of image creates consistent orientation
3. Apply standard volume of interest template on caudate, putamen, occipital regions
4. Extract count densities and calculate Striatal Binding Ratios (SBR)
5. ^{57}Co Phantom correction of SBRs (?)



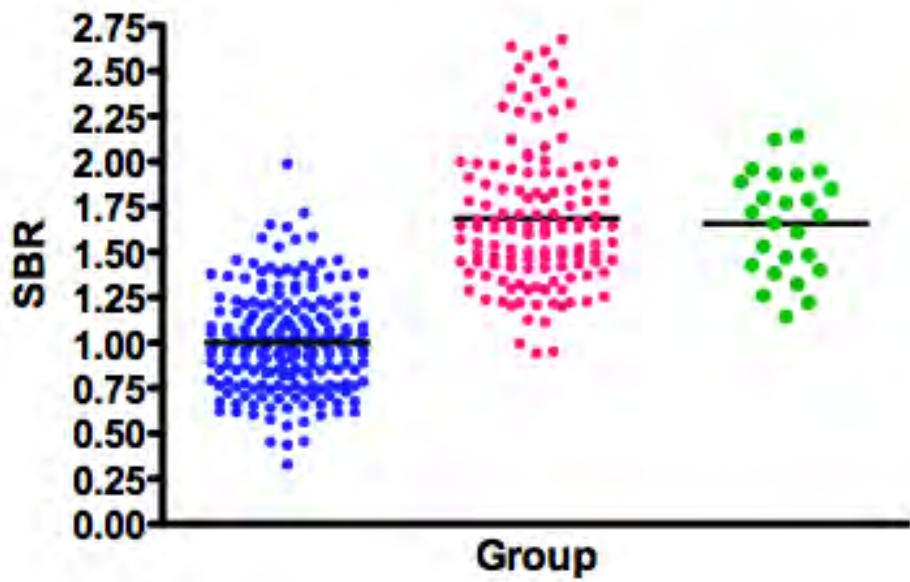
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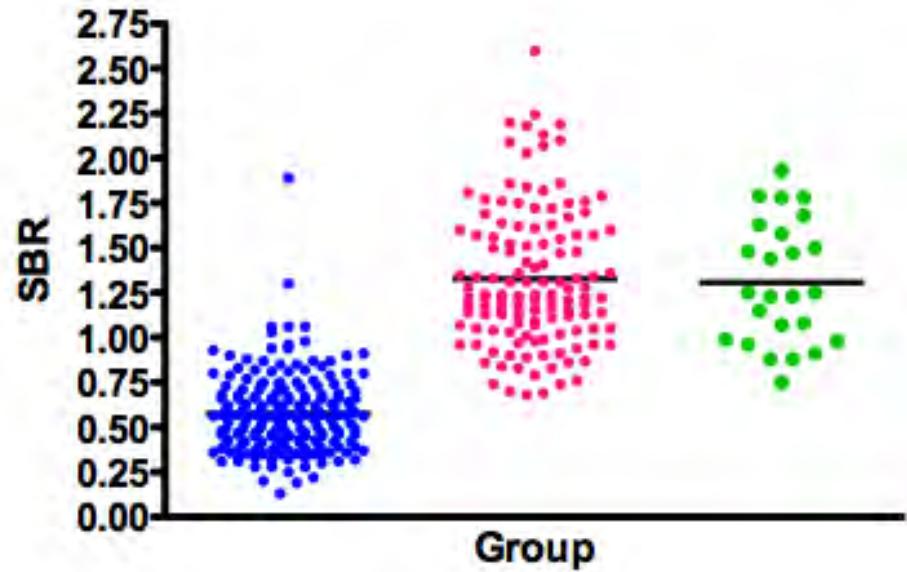
DAT SPECT Striatal Binding Ratios-Baseline Scans

PPMI Avg SBR



PD n=197 HV n= 129 SW n=25

PPMI lowest putamen



PD n=197 HV n= 129 SW n=25

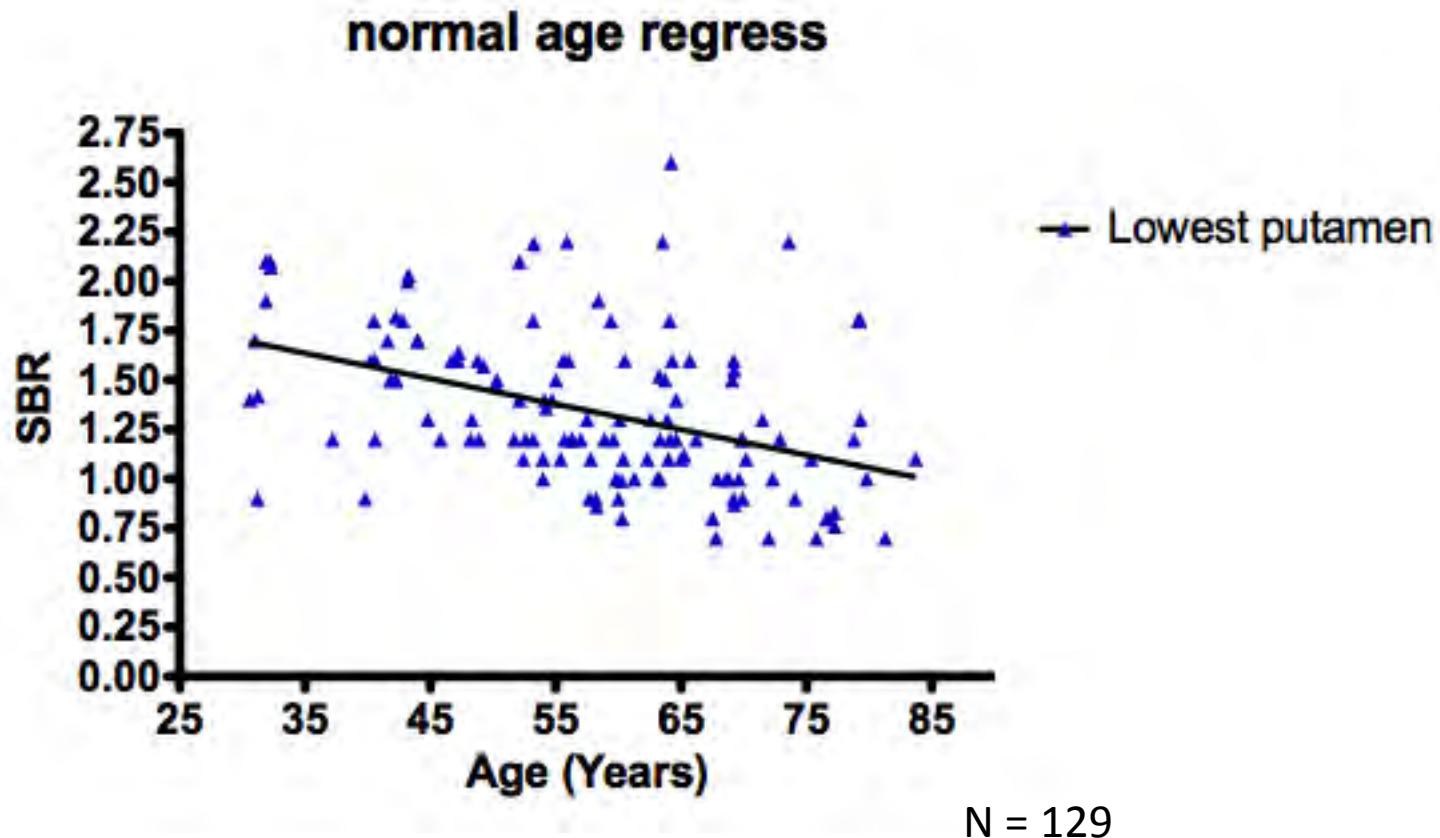


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SBR signal loss is 6.2% per Decade in Healthy Volunteers

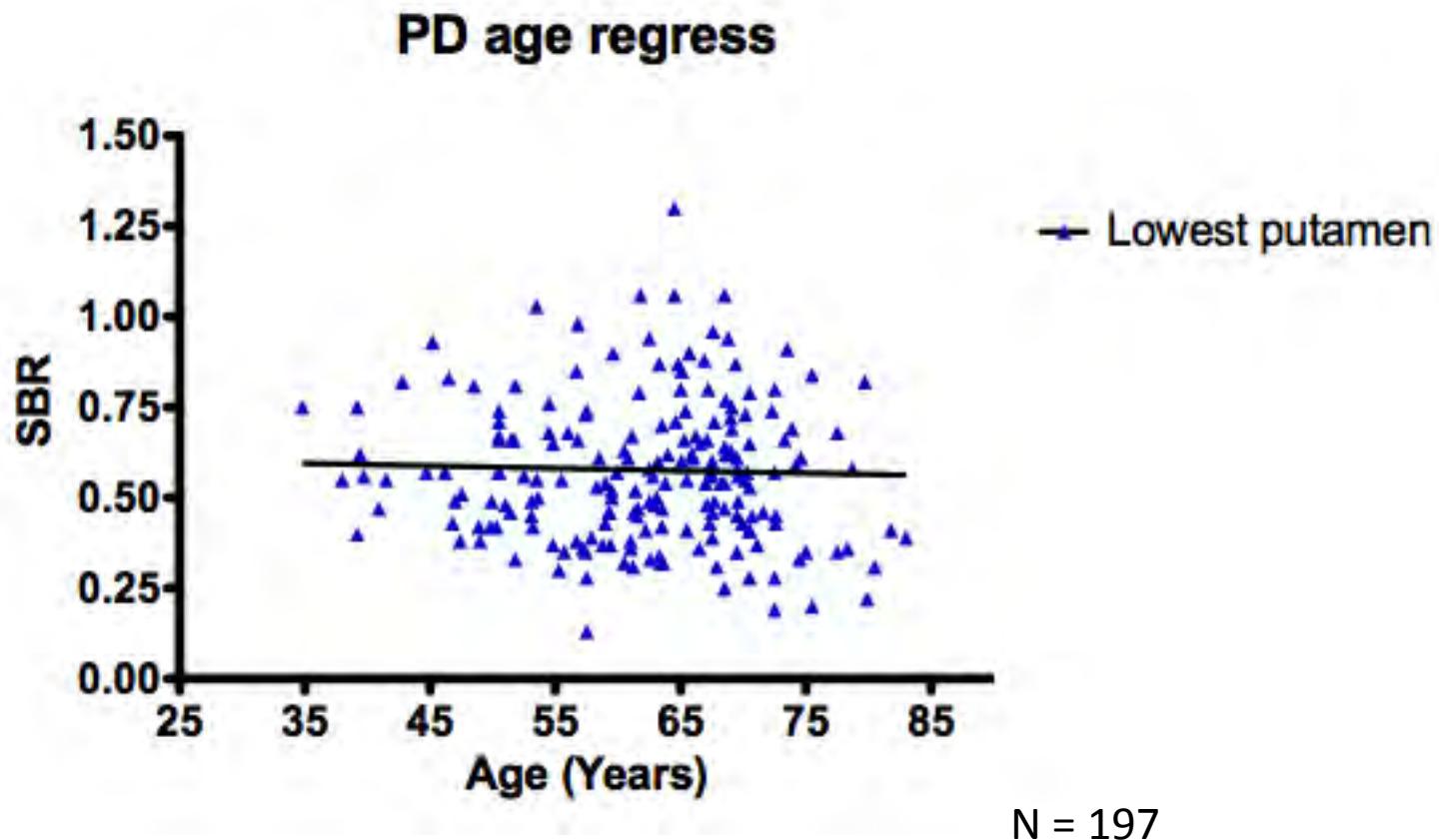


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SBR signal in PD is poorly correlated with age

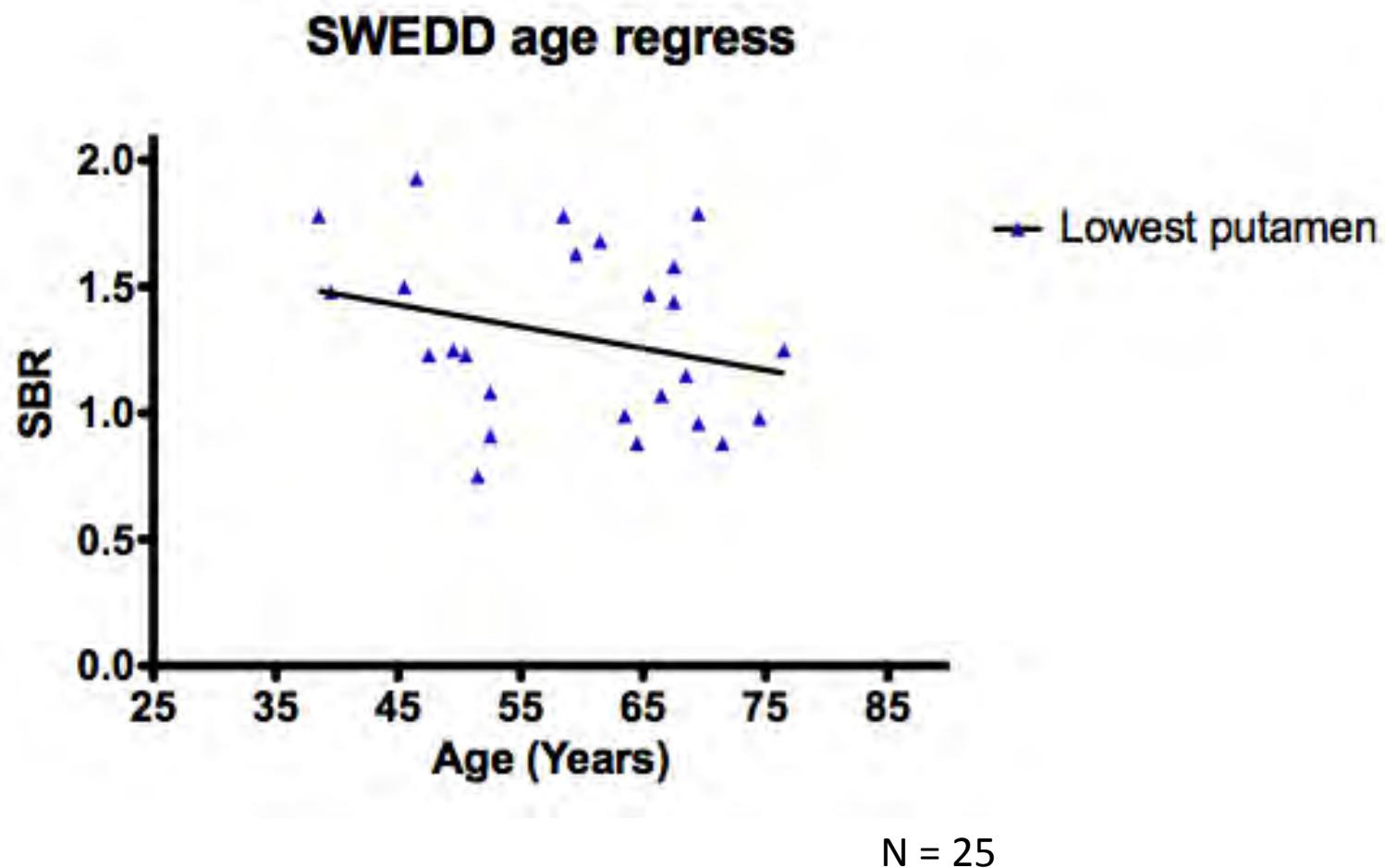


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SBR signal loss is 4.7% per decade in SWEDDs

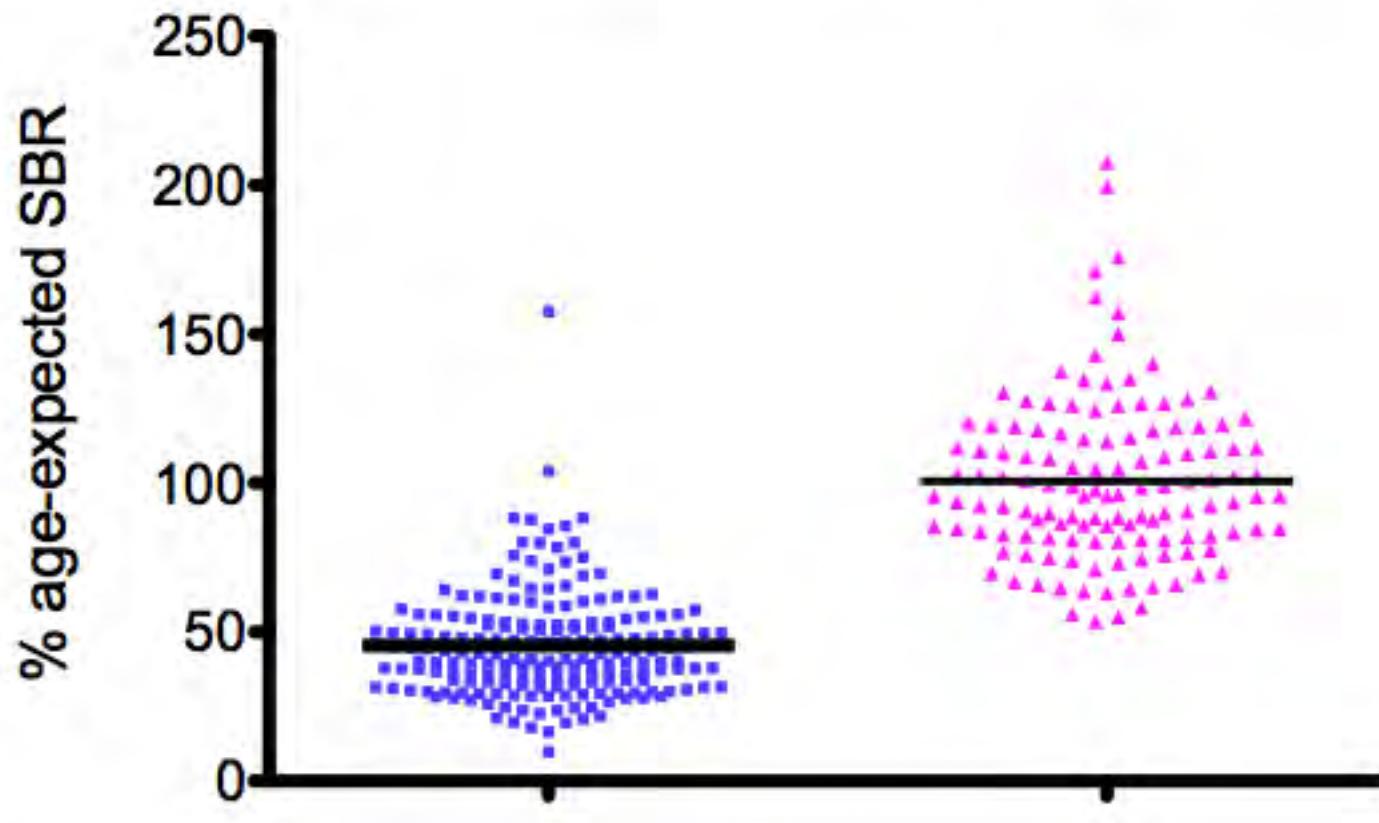


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Age corrected Lowest Put SBR

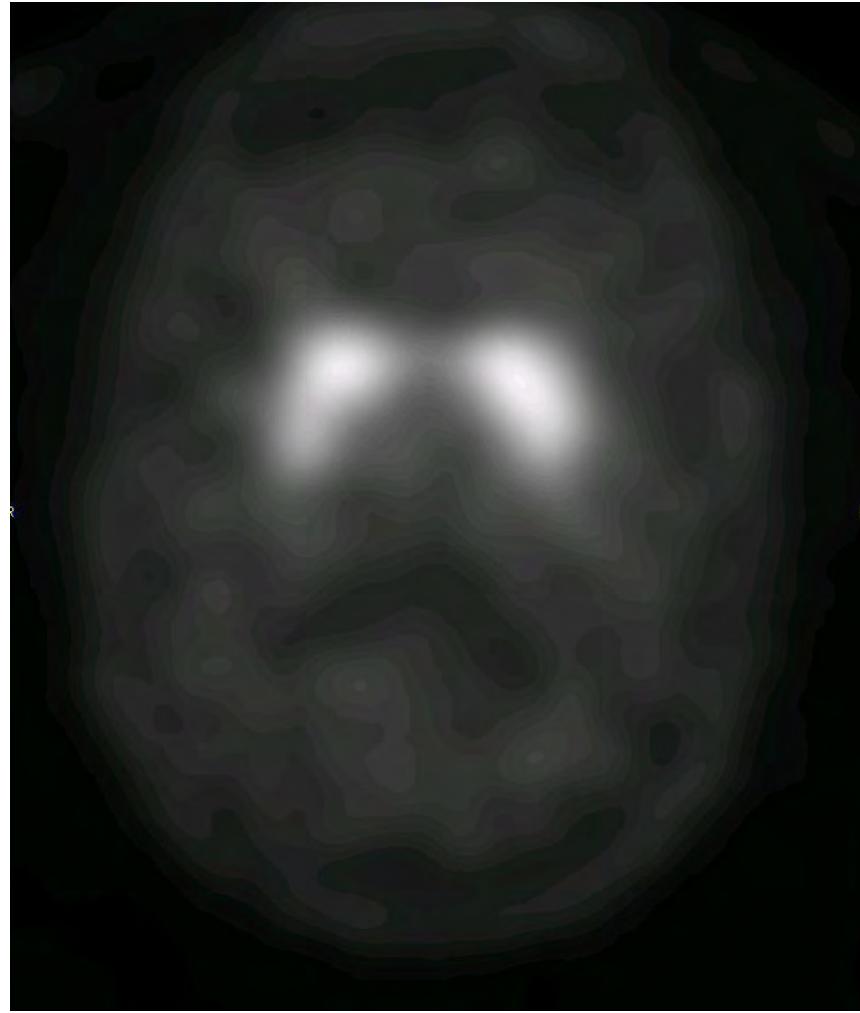


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PD “outlier” scan

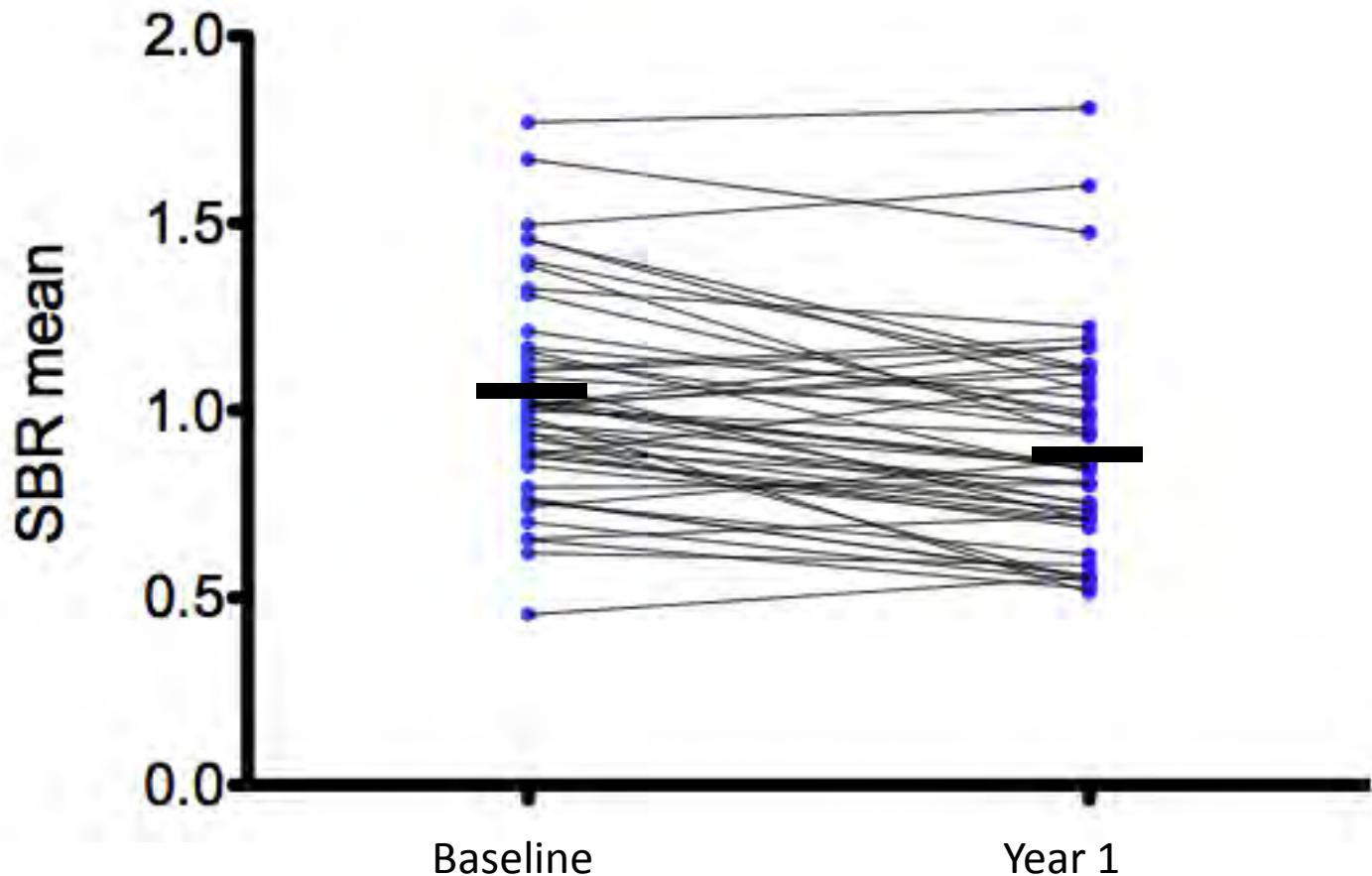


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Longitudinal Assessment of Striatal Binding Ratio in PD



N = 47

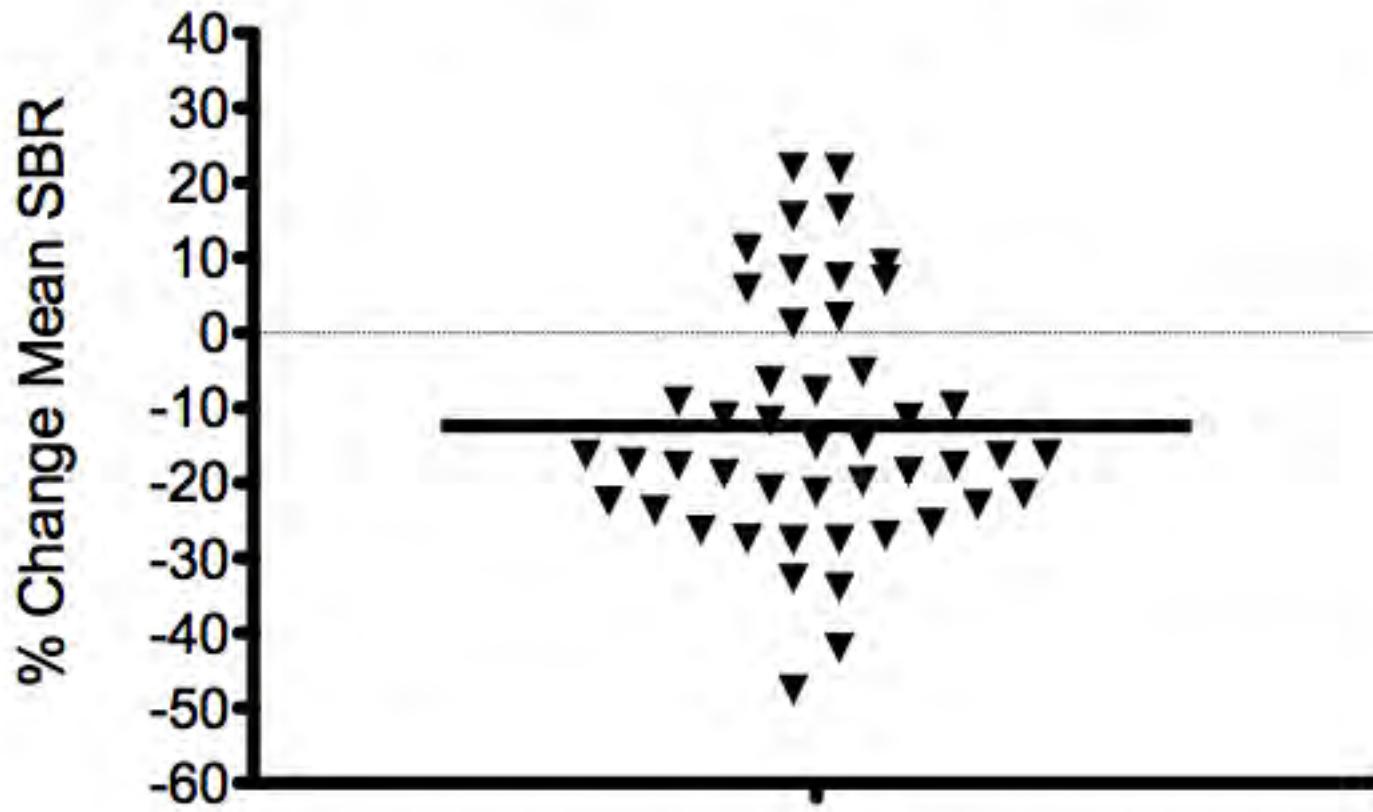


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Percent change over one year (n=47)



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Mean reduction = 12.4 % (%COV= 131%)

DAT Imaging in PPMI

- SWEDDs rate about as expected (15%) in de novo PD, SBR outcomes similar to controls, but limited data
- Normal aging is associated with about 6% signal loss per decade (0.6%/year)
- First longitudinal data suggests SBR reductions over one year approximately 20 times the rate of signal loss seen in normal aging



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Presentations

- Society of Nuclear Medicine Annual Meeting, June 12, 2012. Miami, Florida
- The MDS 16th International Congress of Parkinson's Disease and Movement Disorders
June 19, 2012. Dublin, Ireland



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New DEA 222 Procedure

- GE will no longer accept “open-ended” DEA 222 forms after May 7, 2012
- Those sites using paper 222 forms will need to submit a 222 for each order
- Solution is to obtain digital certificate and order vials electronically from CSOS
- A GE representative can help sort through process of registering for the digital certificate



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DTI Subproject Processing & Analysis

K. Wu, S. Buckley, D. Tosun, F. Ezekiel and N. Schuff

VA and UCSF, San Francisco
May 2012



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Processing Status

Subjects	Baseline (Year 1)	Follow-up (Year 2)
Received	112	6
Processed	85	2
LONI Uploaded	71	0

As of April 27, 2012.

Note: the number of processed images is almost twice as large, since most subjects have two DTI scans in a single session and we process both sets.



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Subject Demographics

Characteristics	Control (n = 52)	PD (n = 54)	SWEDD (n = 6)
Age (year)	58.5 (11.1)	61.7 (9.1)	57.0 (14.1)
Gender: M/F	31 / 21	38 / 16	3/3
Disease duration (years)	NA	1.4 (0.8)	1.0 (0.5)

As of April 10, 2012.

Results are presented as: mean (standard deviation).

n, number; NA, not applicable;

DTI Sites

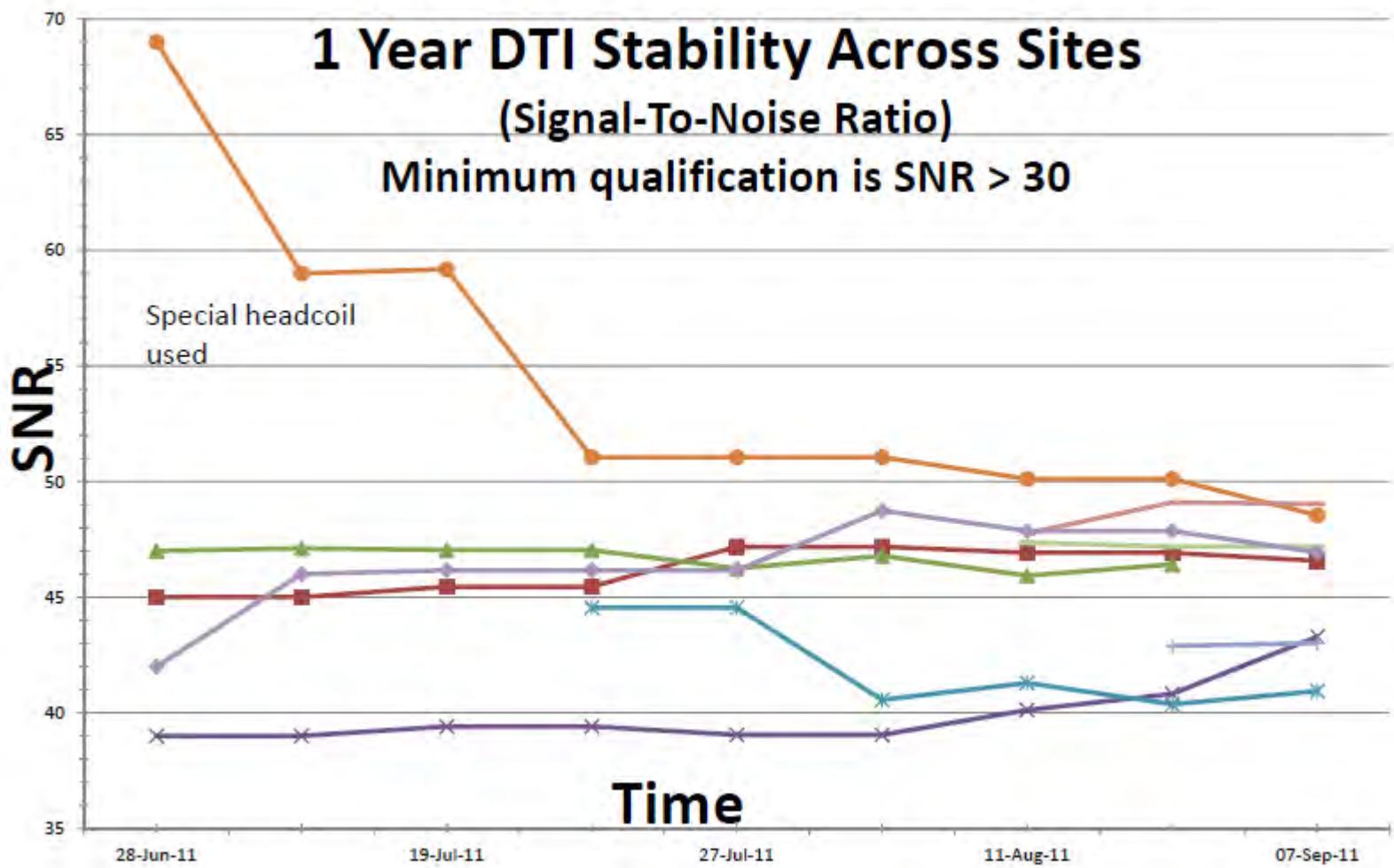
- As of March 6, 2012:
 - 9 active sites
 - Baylor, Parkinson's Institute, John Hopkins, Emory, Northwestern, Mellen Center, Tübingen, Paracelsus-Elena, and Innsbruck

Site	Subjects	DTI sets
Baylor	14	27
Parkinson's Institute	14	28
John Hopkins	9	18
Emory	8	15
Northwestern	17	33
Mellen Center	5	10
Tübingen	12	24
Paracelsus-Elena	12	24
Innsbruck	9	18
Total	100	197



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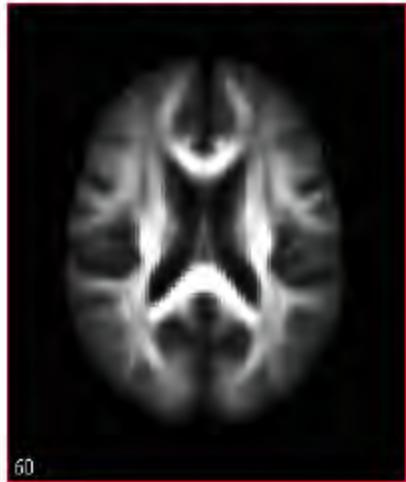


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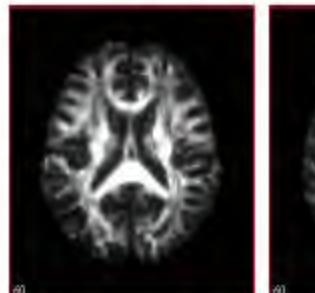
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Representative FA Maps

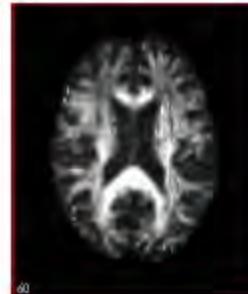
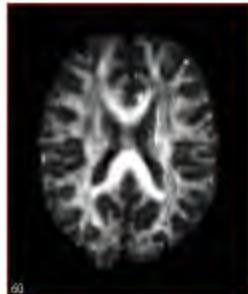
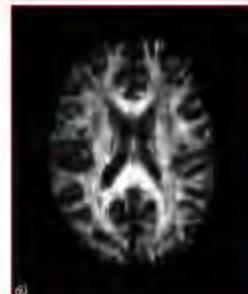
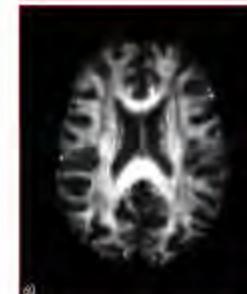
Group Averaged FA



Control



PD

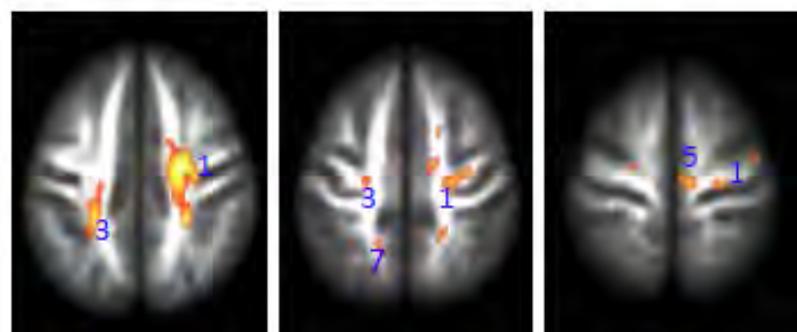
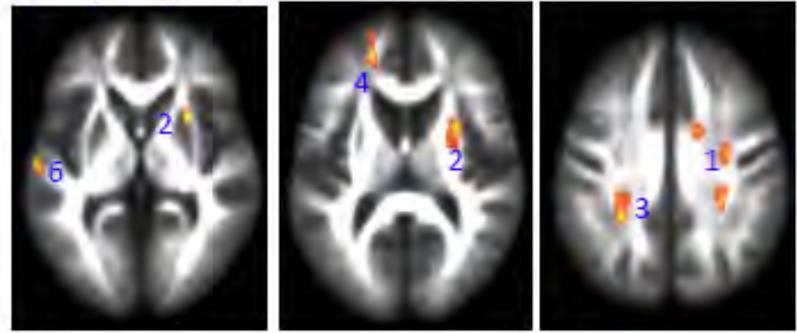
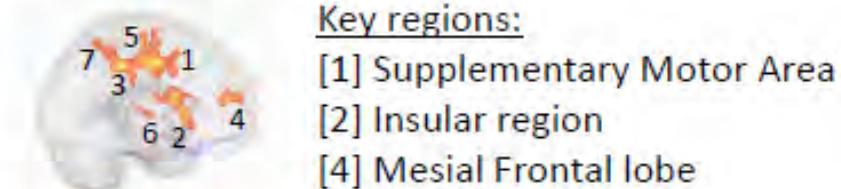
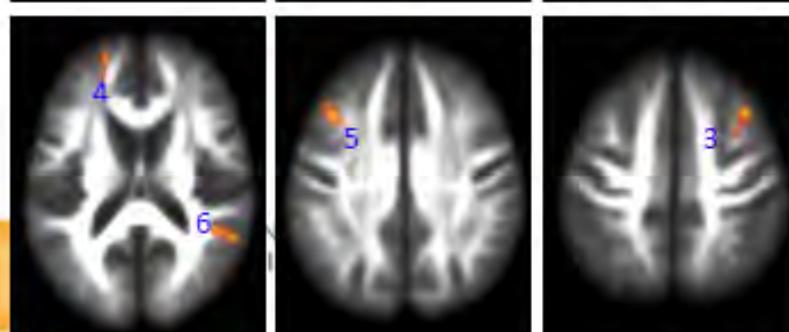
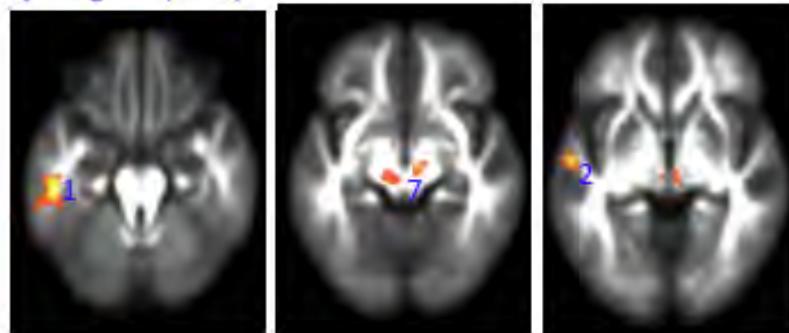
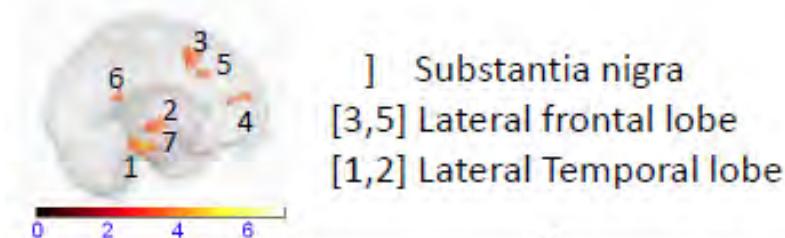


Regional DTI Abnormalities In PD

In Relation to:

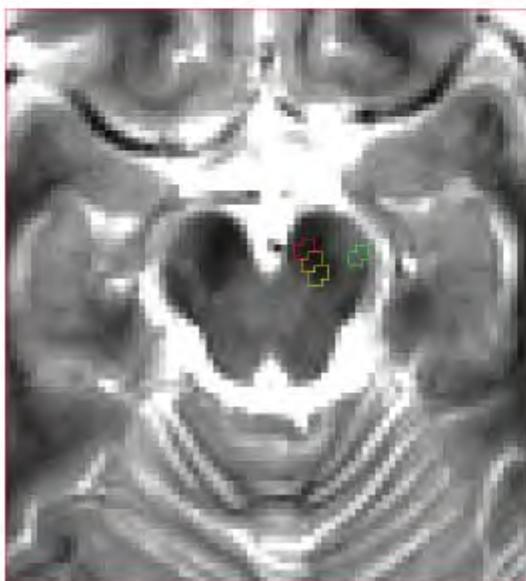
Increased Movement Deficits

Diminished Dopamine Uptake

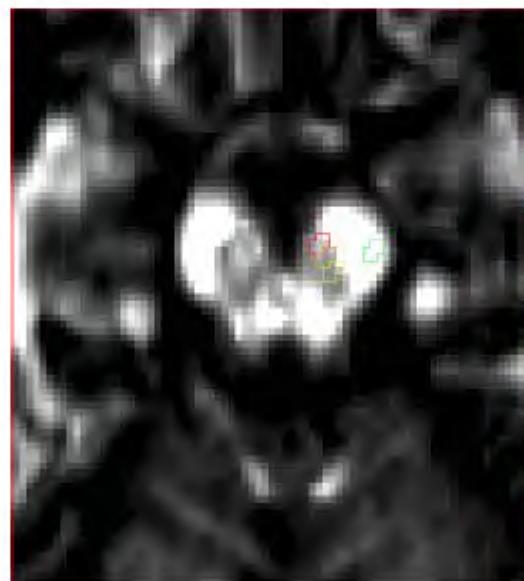


Representative Maps With Markings For Evaluating DTI In The Nigra

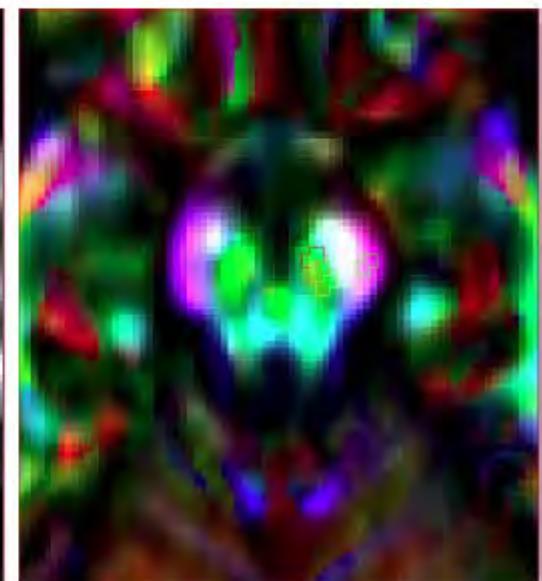
T2



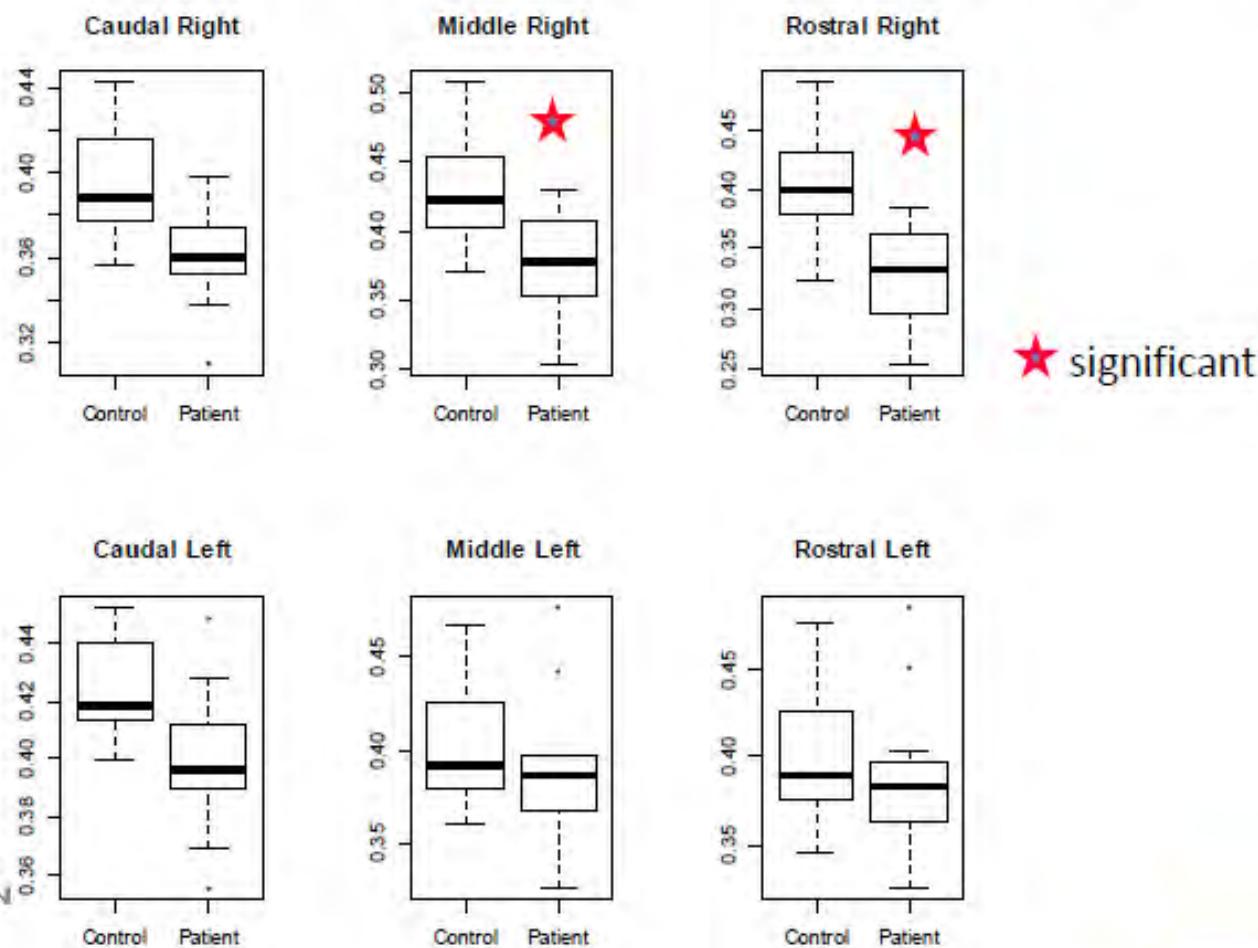
FA



Directional
Diffusion Map



Preliminary Results: FA Variations In The Nigra



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Conclusions

- DTI may have clinical value for the assessment of Parkinson's disease.
- Moreover, DTI provides complementary information to DAT imaging, especially with respect to quantification of severity of symptoms.
- DTI is feasible in a multicenter setting



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Publications

1. *Distribution of diminished brain microstructure in Parkinson's disease:
Abstract AAN, New Orleans

2. Associations between brain microstructural and dopaminergic integrity in Parkinson's disease: A joint diffusion tensor and DAT imaging study:
Abstract MDS meeting, Dublin

* Selected for AAN Scientific Program Highlights Plenary Session.



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Plans

1. Repeat analyses with a larger sample size, especially ROI analysis of FA in substantia nigra
2. Processing and analysis of 1 yr follow-up DTIs
3. Implementation of tractography and tract-based analysis
4. Joint analysis of DTI and structural MRI
5. Joint analyses of DTI, clinical data and biomarkers (with guidance from Christopher)

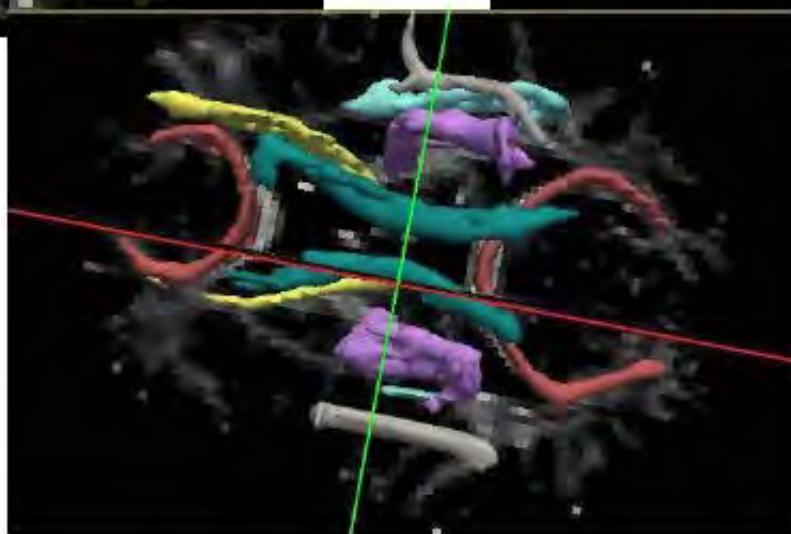
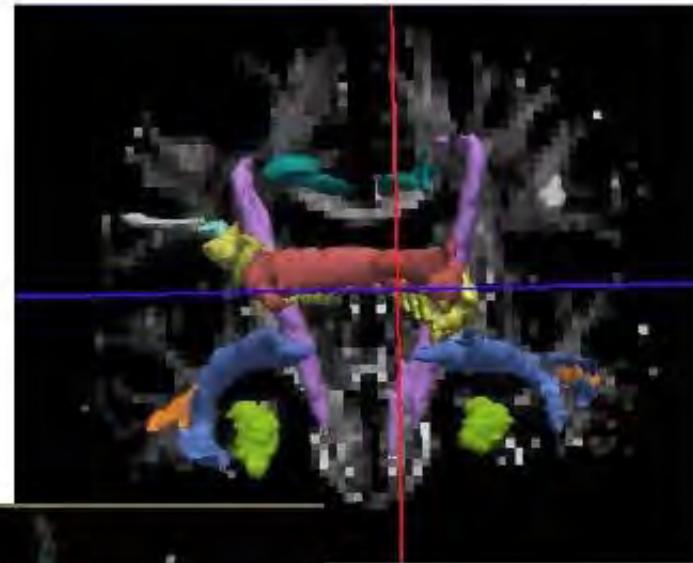


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New Development: Probabilistic Fiber Tracking*



- 5100 Corpus Callosum Forceps Major
- 5101 Corpus Callosum Forceps Minor
- 5102 Left Anterior Thalamic Radiation
- 5103 Left Cingulum - Angular Bundle
- 5104 Left Cingulum - Cingulate Gyrus
- 5105 Left Corticospinal Tract
- 5106 Left Inferior Longitudinal Fasc...
- 5107 Left Superior Longitudinal Fas...
- 5108 Left Superior Longitudinal Fas...
- 5109 Left Uncinate Fasciculus
- 5110 Right Anterior Thalamic Radiat...
- 5111 Right Cingulum - Angular Bundle
- 5112 Right Cingulum - Cingulate Gyrus
- 5113 Right Corticospinal Tract
- 5114 Right Inferior Longitudinal Fas...
- 5115 Right Superior Longitudinal Fa...
- 5116 Right Superior Longitudinal Fa...
- 5117 Right Uncinate Fasciculus

* TRACULA
by Anastasia Yendiki
MGH



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PPMI Biorepository Update

PPMI Annual Meeting

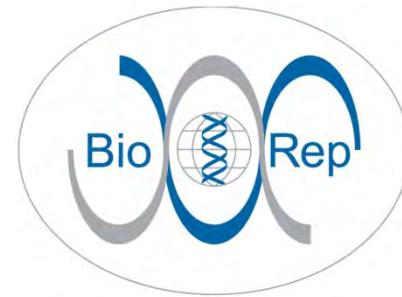
May 2-3, 2012

Alison Scutti, MS

Coriell Institute for Medical Research



CORIELL INSTITUTE
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facilitating research worldwide



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Biorepository Core Team

Coriell

Alison Scutti, MS
Senior Project Manager
Biorepository PI

Emily Giles
Project Manager

Steve Madore, PhD
Director, Molecular Biology

Dara Kusic
Application Developer

BioRep

Paola Casalin
Laboratory Manager

Giulia Malferrari
Laboratory Technician

Marco Teruggi
IT Competence Center

MJFF/CTCC

Mark Frasier, PhD
Director, Research Programs

Emily Flagg
Clinical Project Manager

Alice Rudolph, PhD
Clinical Project Manager



Outline

- Submissions
- Processing
- Issues



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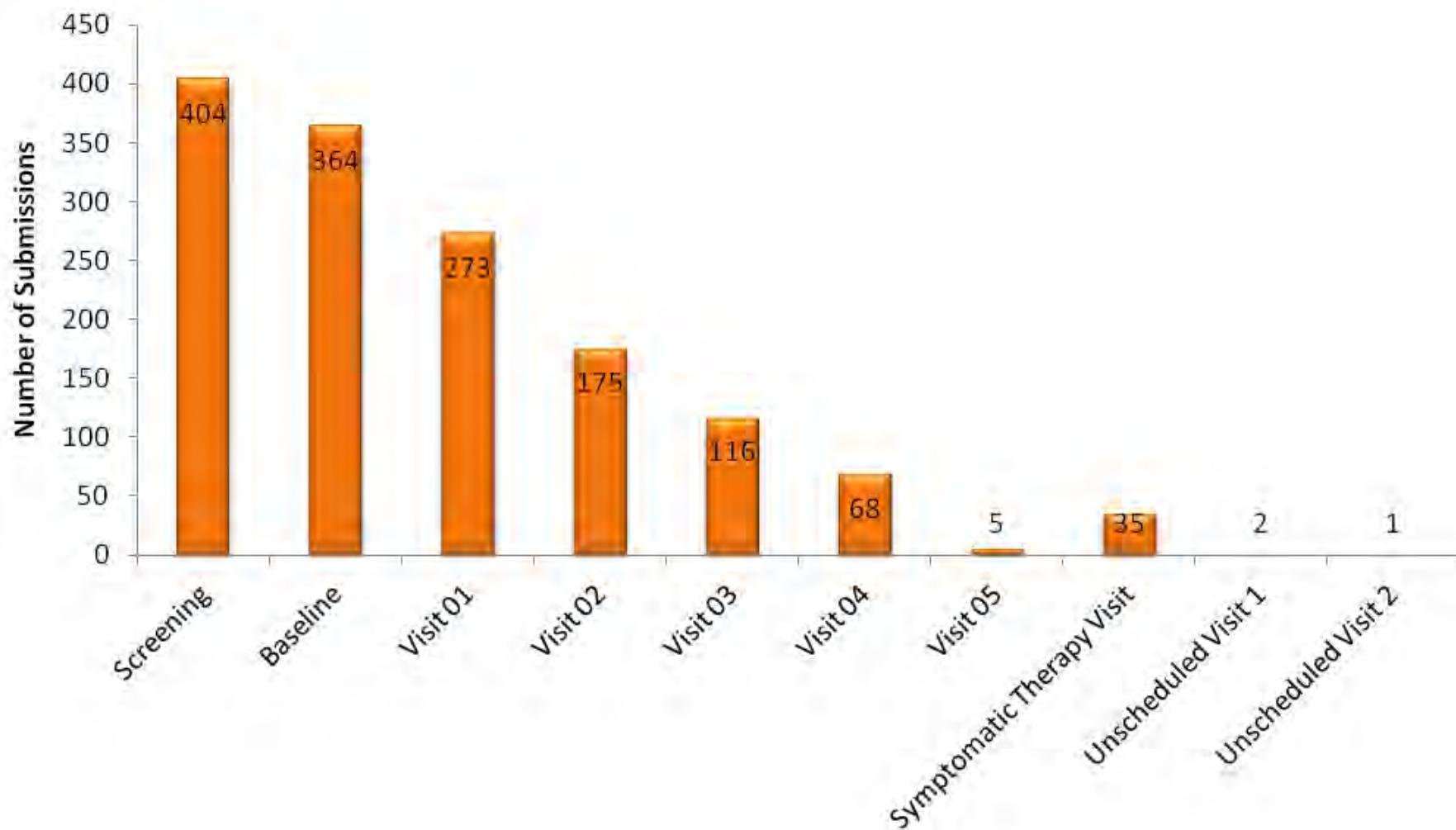
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All data as of 3/31/2012



PPMI Sample Submission Summary

1,443 submissions from 442 unique subjects



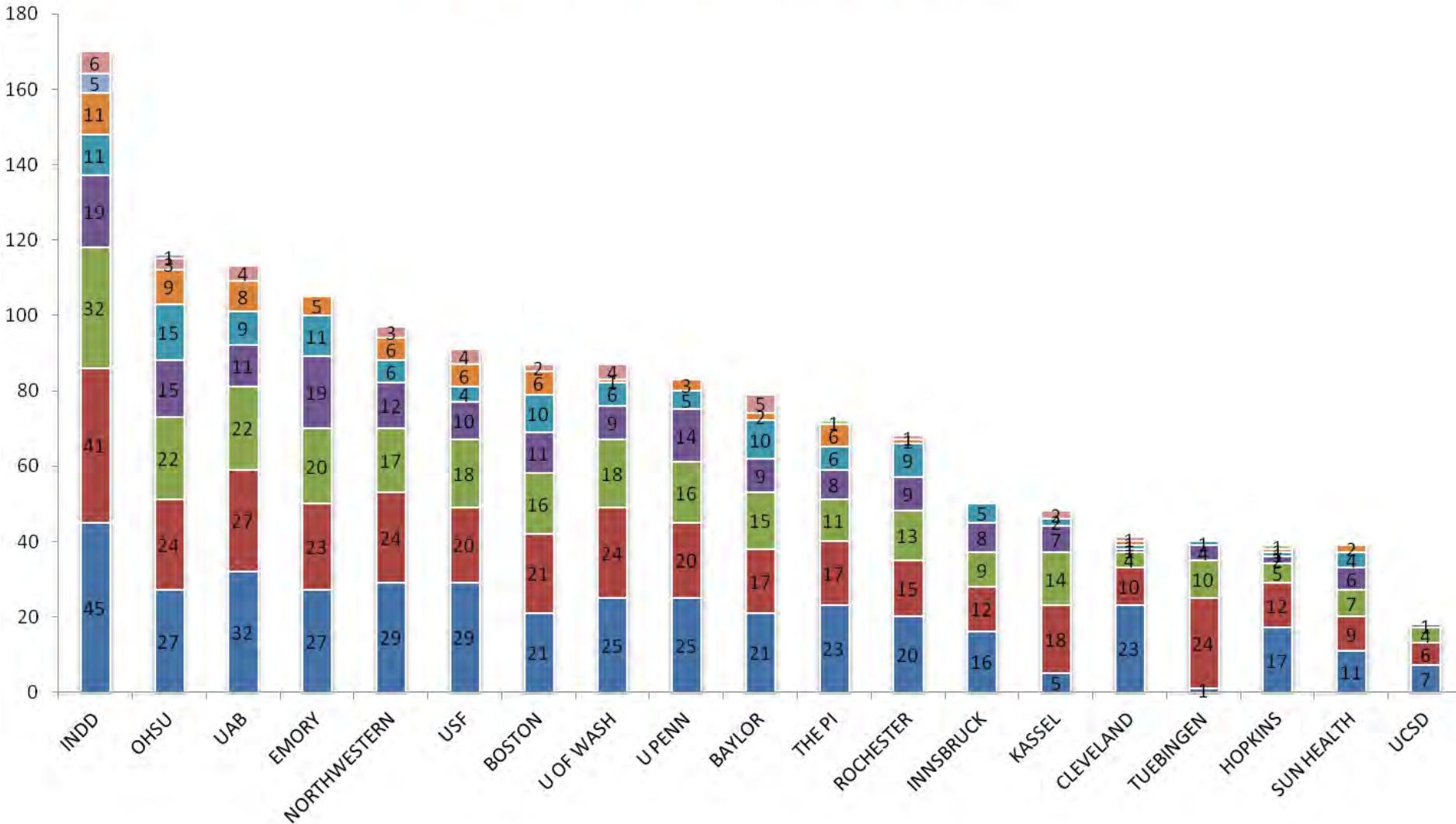
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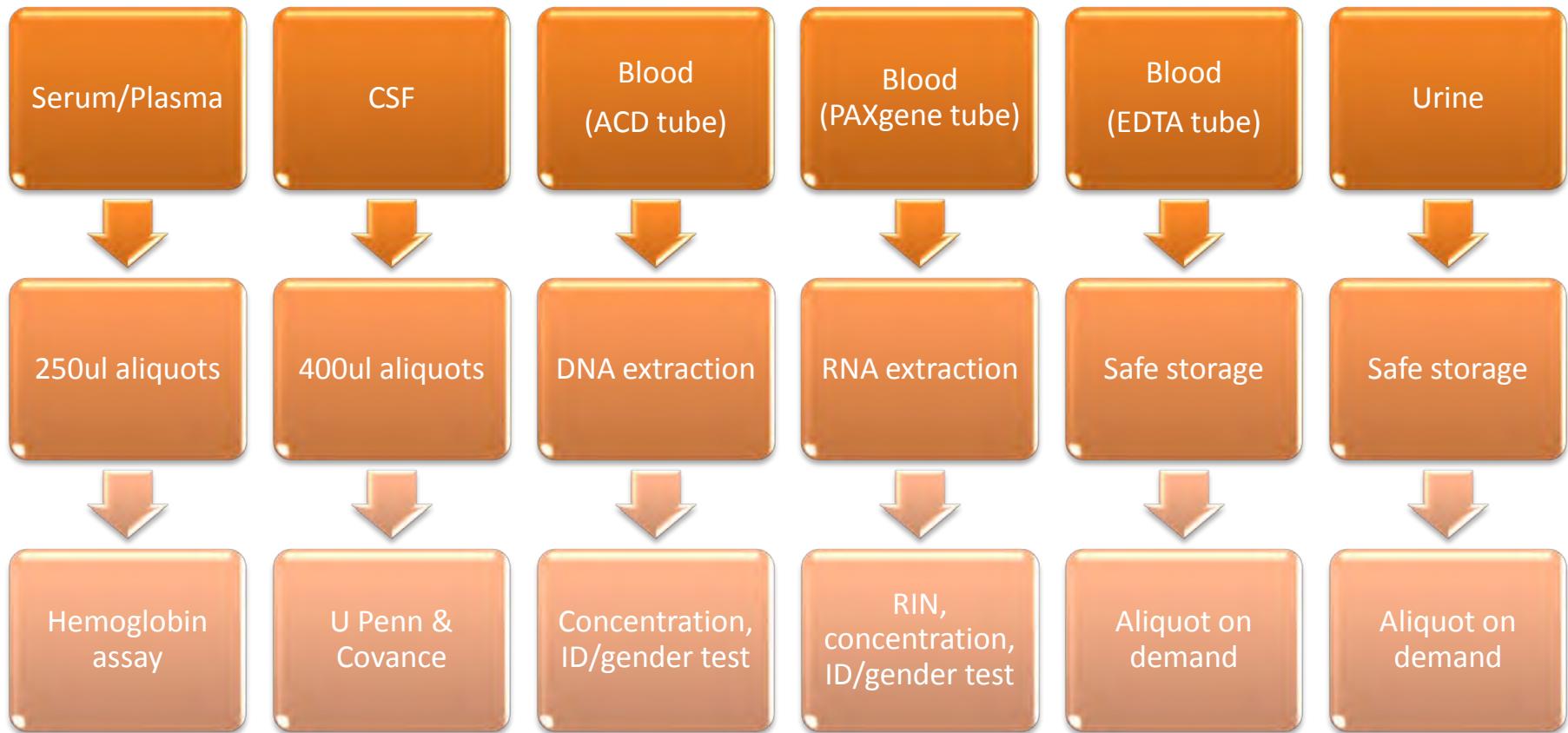


Submissions per Clinical Site

SC BL V01 V02 V03 V04 V05 ST UN1 UN2



Sample Processing Overview



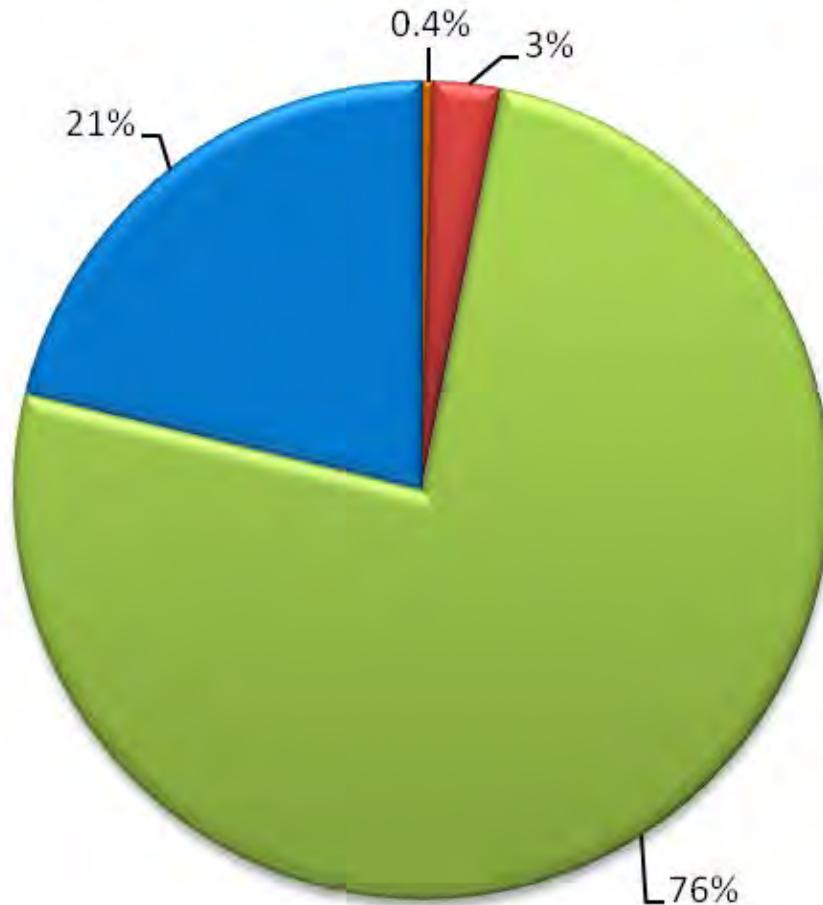
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DNA Extraction Progress

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



Average 260/260: 1.87
Average conc: 0.31 ug/ul
Average total yield: 181.35 ug



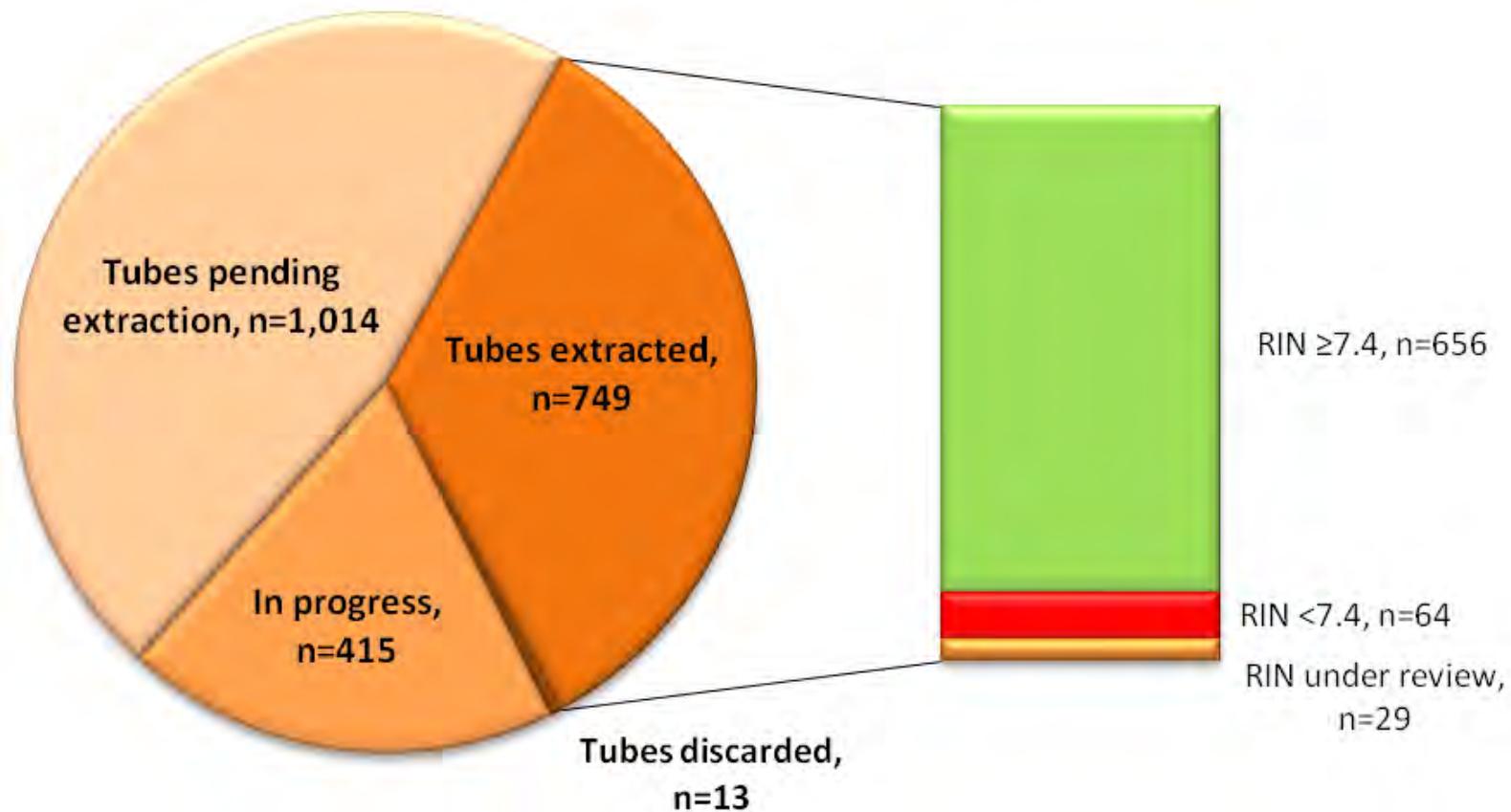
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PAXgene RNA Extraction Progress

Extractions resumed February, 2012



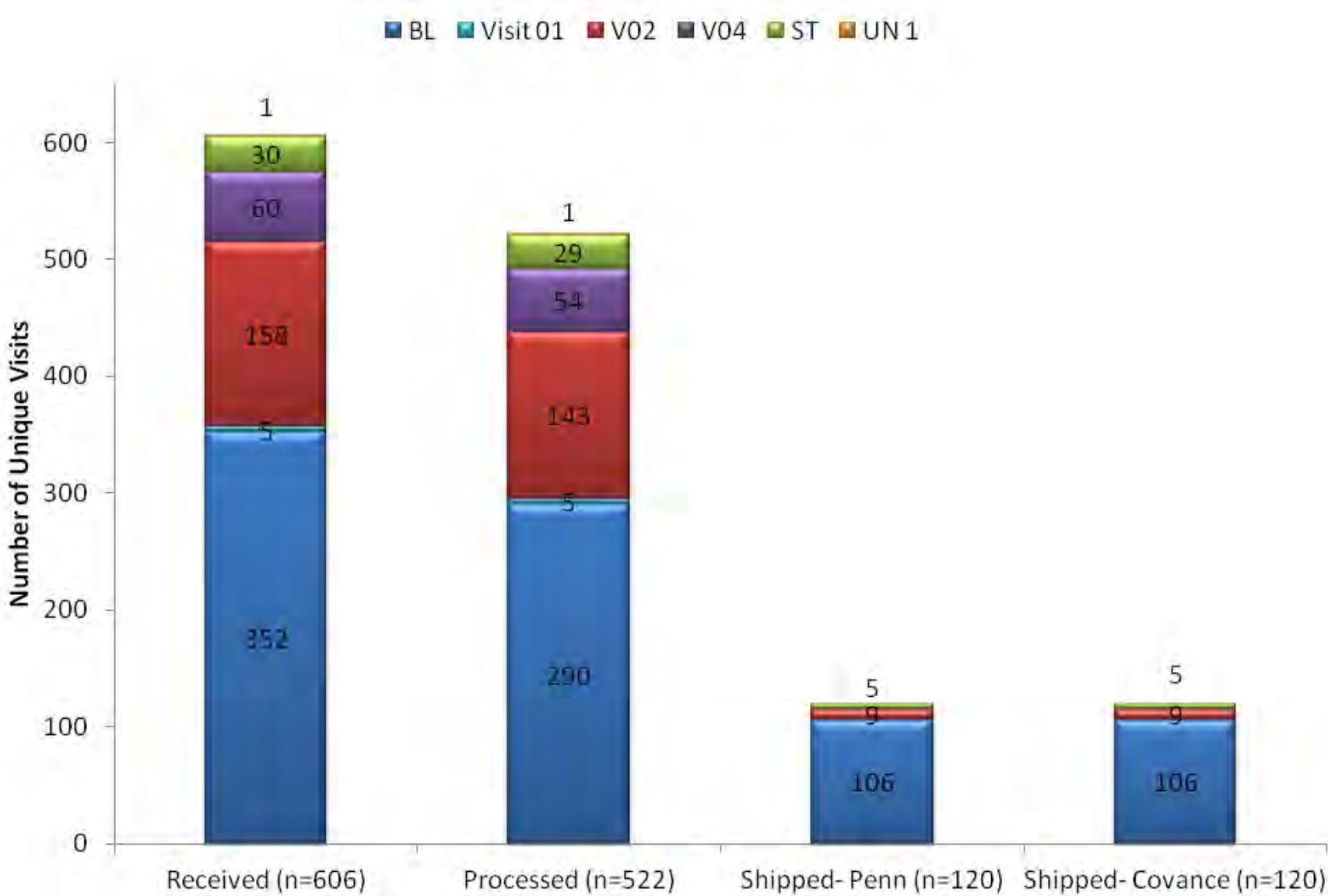
Average 260/280: 2.11
Average concentration: 78.2 ng/ul
Average total yield: 5.47 ug



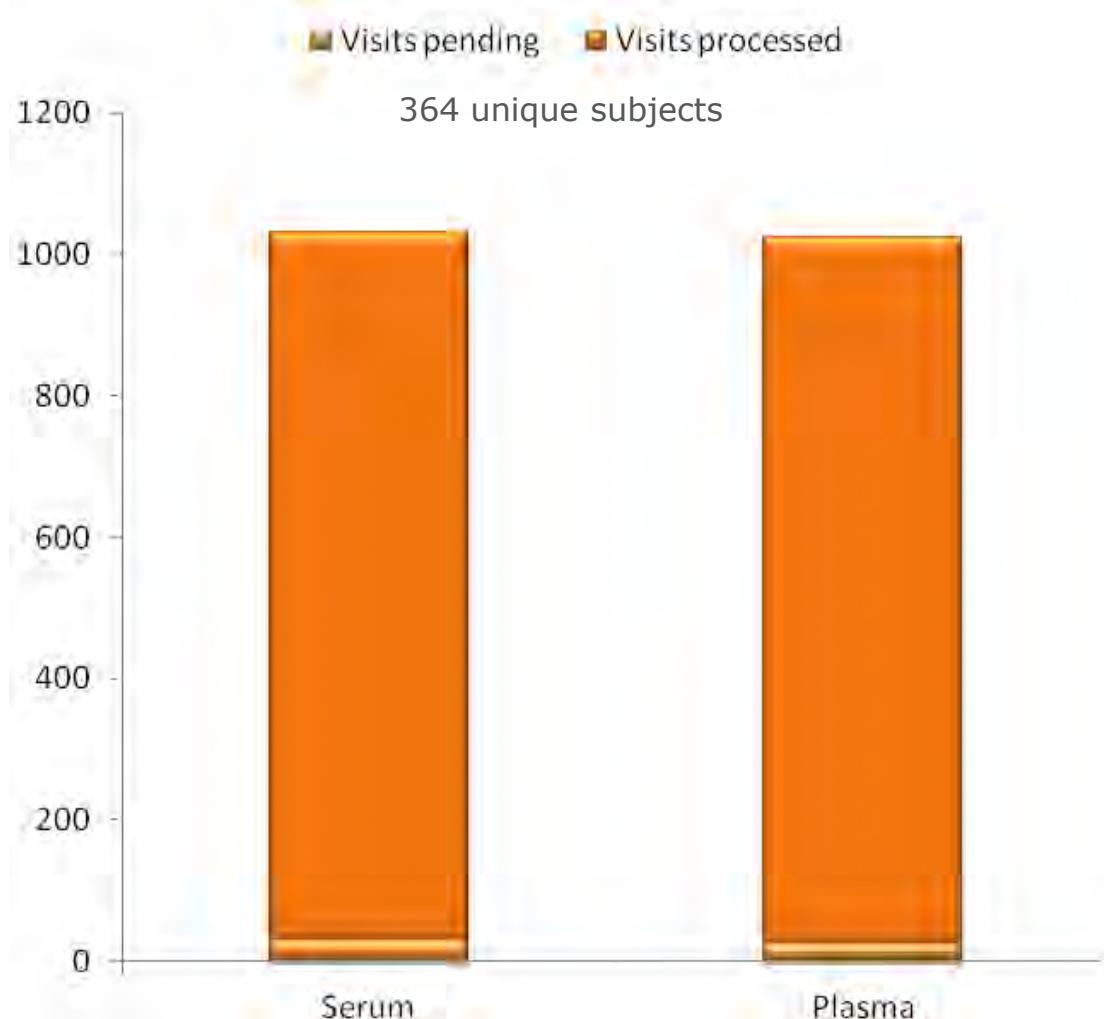
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CSF Processing



Serum & Plasma Progress

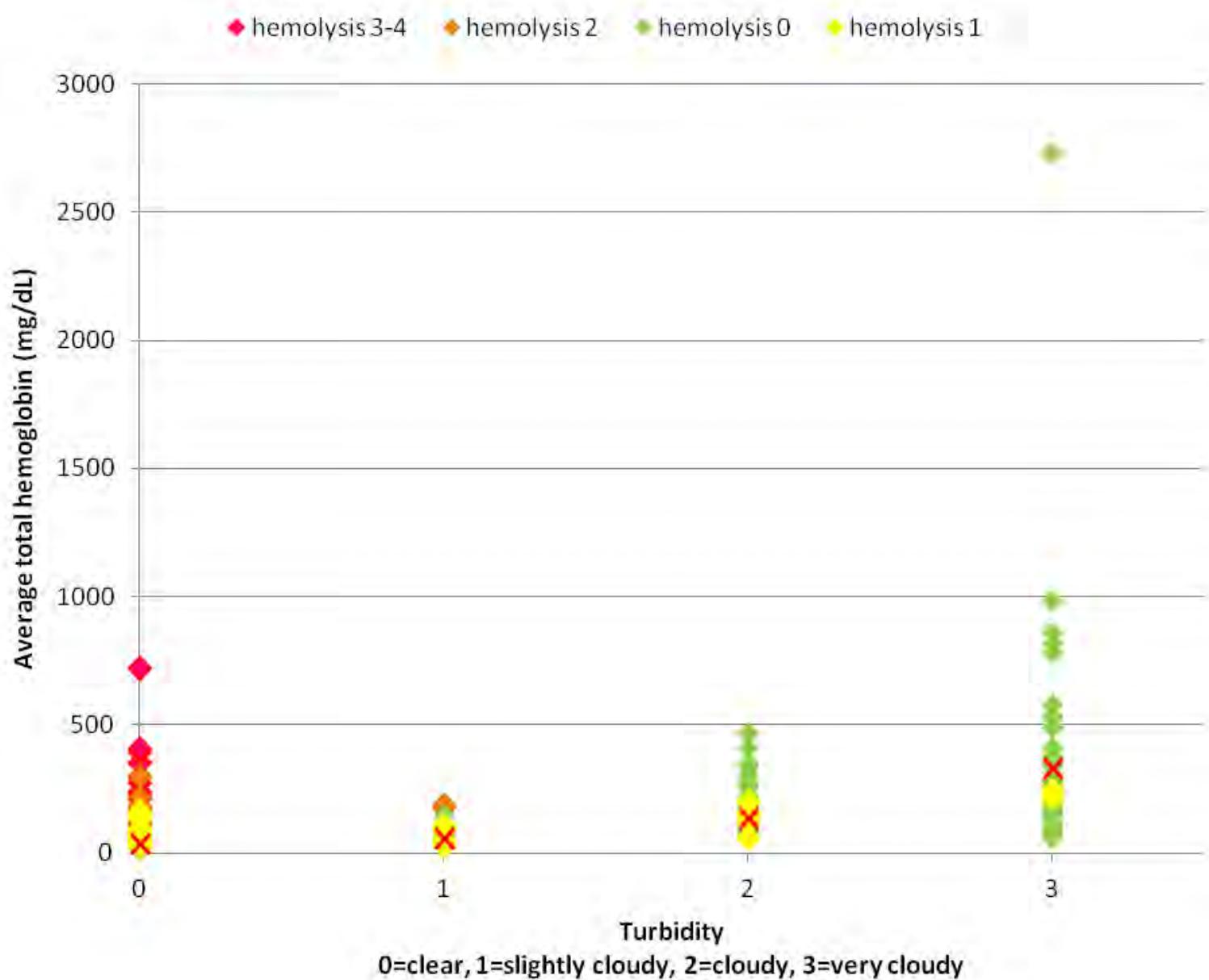


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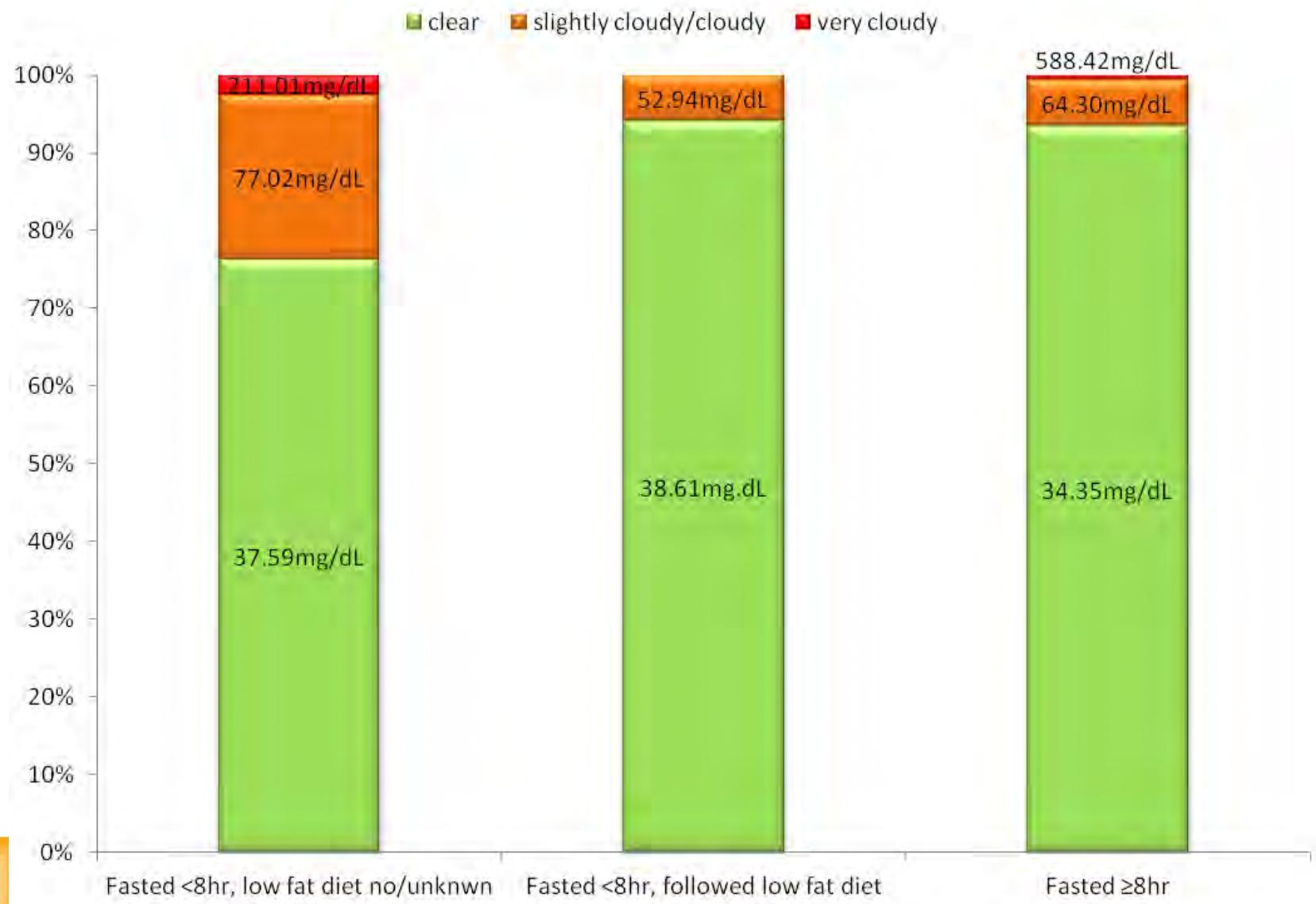
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Serum/Plasma Hemoglobin & Turbidity



Fasting Impact on Serum/Plasma Quality



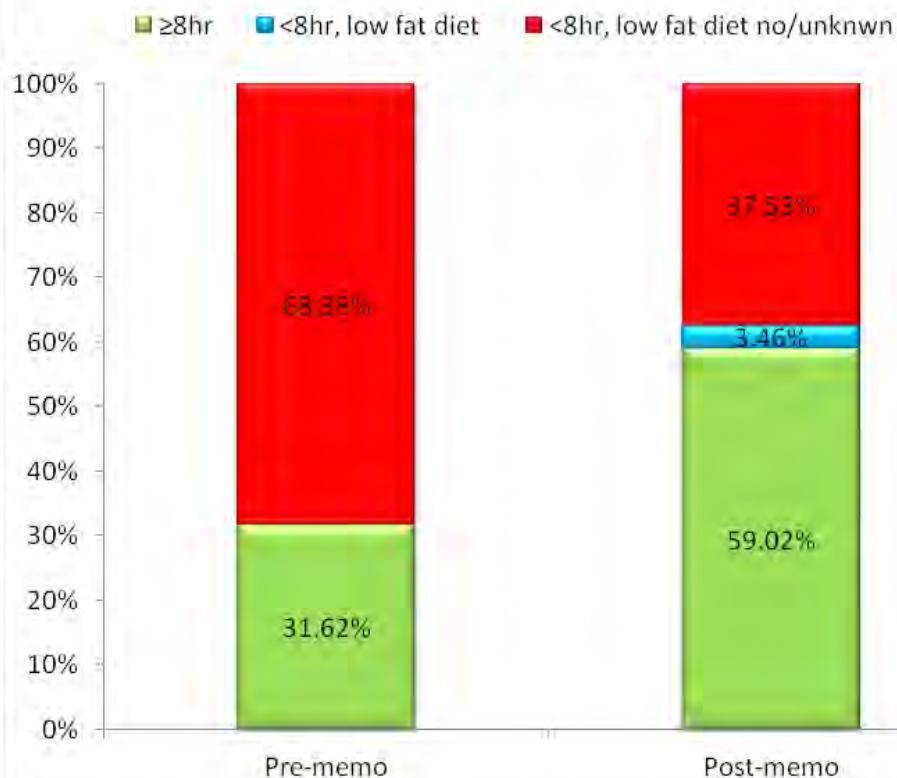
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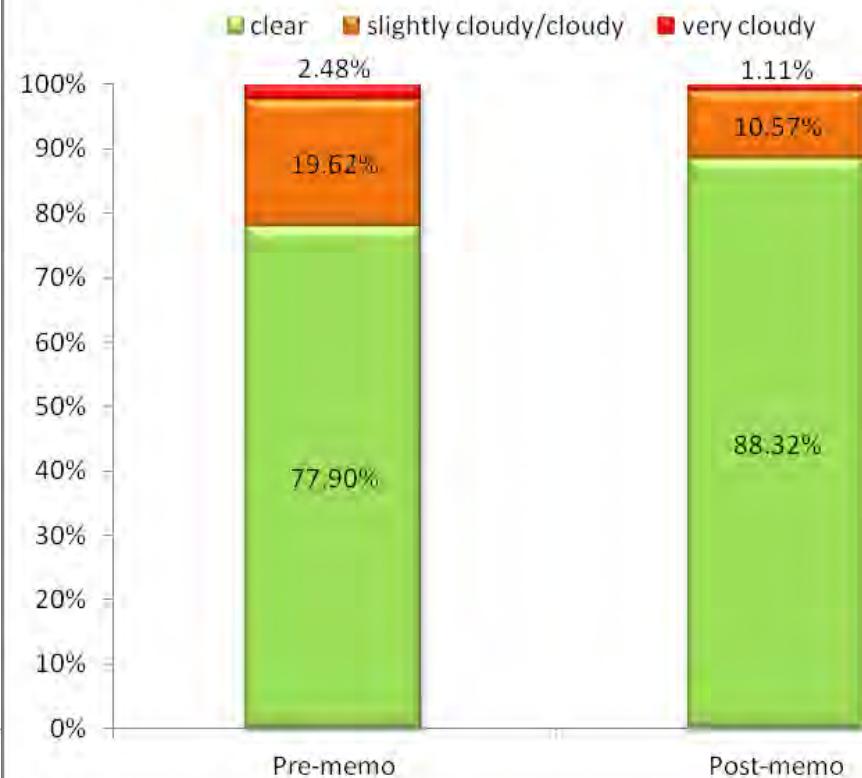
All ser/pl samples to date

Improved Serum/Plasma Quality Since Protocol Amendment 3

Time Elapsed Meal to Blood Collection



Turbidity



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Sample & Submission Issues

Tube labels not adhering well to frozen samples

New labels issued

Cloudy serum/plasma samples

Protocol Amendment: fasting/low fat diet menu

Frozen submissions arriving with low/no dry ice

Alternative shipping methods being considered

RNA with low RINs

Due to single-step extraction method
Electropherograms available upon request



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PPMI Biologics Review Committee

Mark Frasier, PhD
The Michael J Fox Foundation
May 2, 2012



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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
 - Two step proposal process through PPMI website



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Subject Enrollment & Sample Collection

Specimen	Collected Samples (Enrolled patients)							
	BL	V01	V02	V03	V04	V05	ST	
Plasma	370 (372)	280 (284)	178 (182)	114 (116)	79 (79)	5 (5)	37 (37)	1063 (1075)
Serum	BL	V01	V02	V03	V04	V05	ST	Total
	370 (372)	281 (284)	182 (182)	114 (116)	79 (79)	5 (5)	37 (37)	1068 (1075)
CSF	BL	V01*	V02	-	V04	-	ST	Total*
	358 (372)	6 (6)	161 (179)	-	68 (78)	-	32 (36)	625 (671)

*Including 6 CSFs at V01 visit, 93% of CSF were collected
BL 98% of CSF were collected

Plasma (EDTA) Samples for PPMI

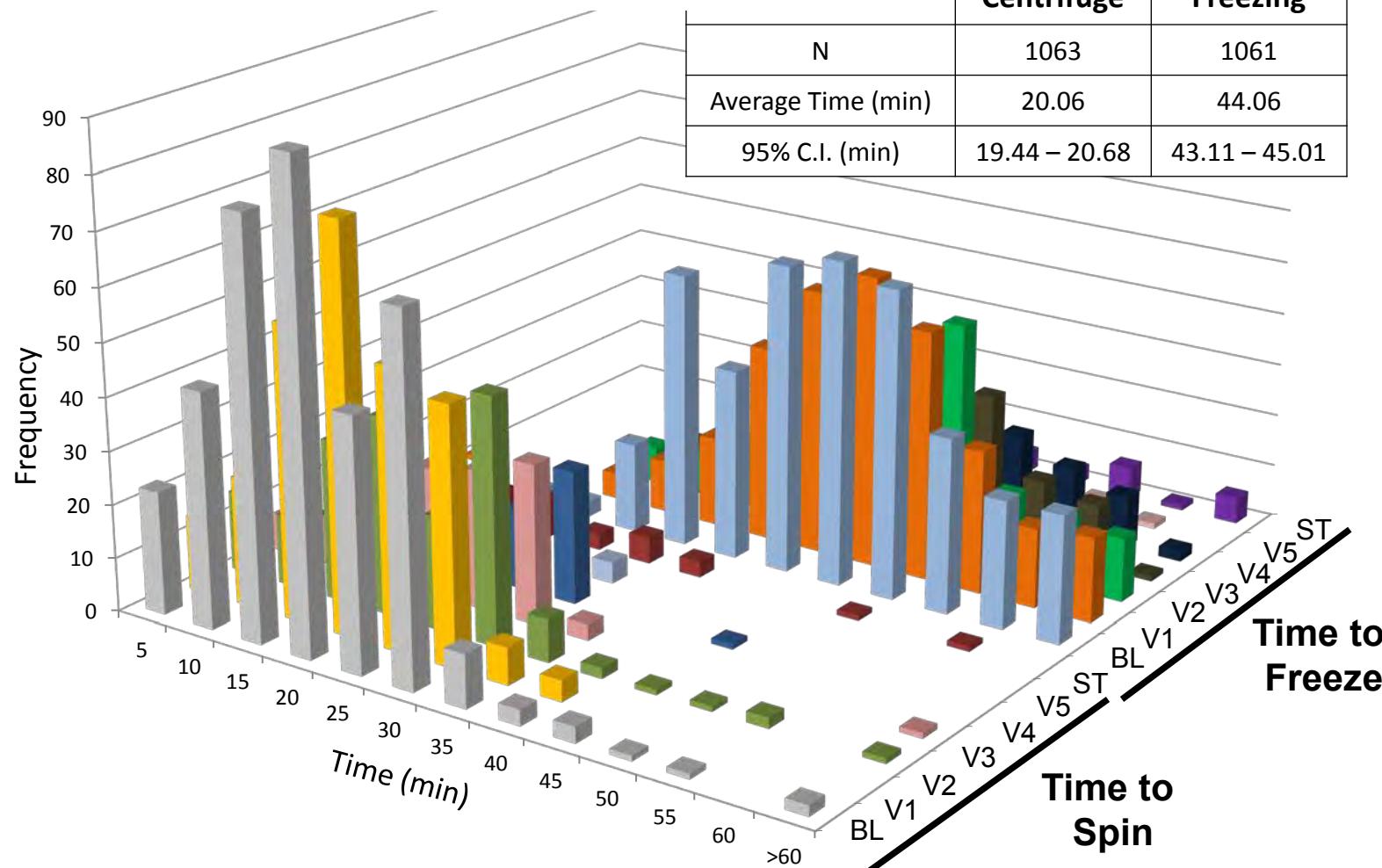
In the morning (8 am – 10 am), preferably fasted

Within 30 min, Cfg. at 4°C for 15 min at 1500×g

Place pre-printed label on 2mL aliquot tube

Aliquot to 2 – 3 tubes

Immediate freezing & storage at -80°C (within 60 min)



Total number of aliquots (4/12/2012) : 3175

Serum Samples for PPMI

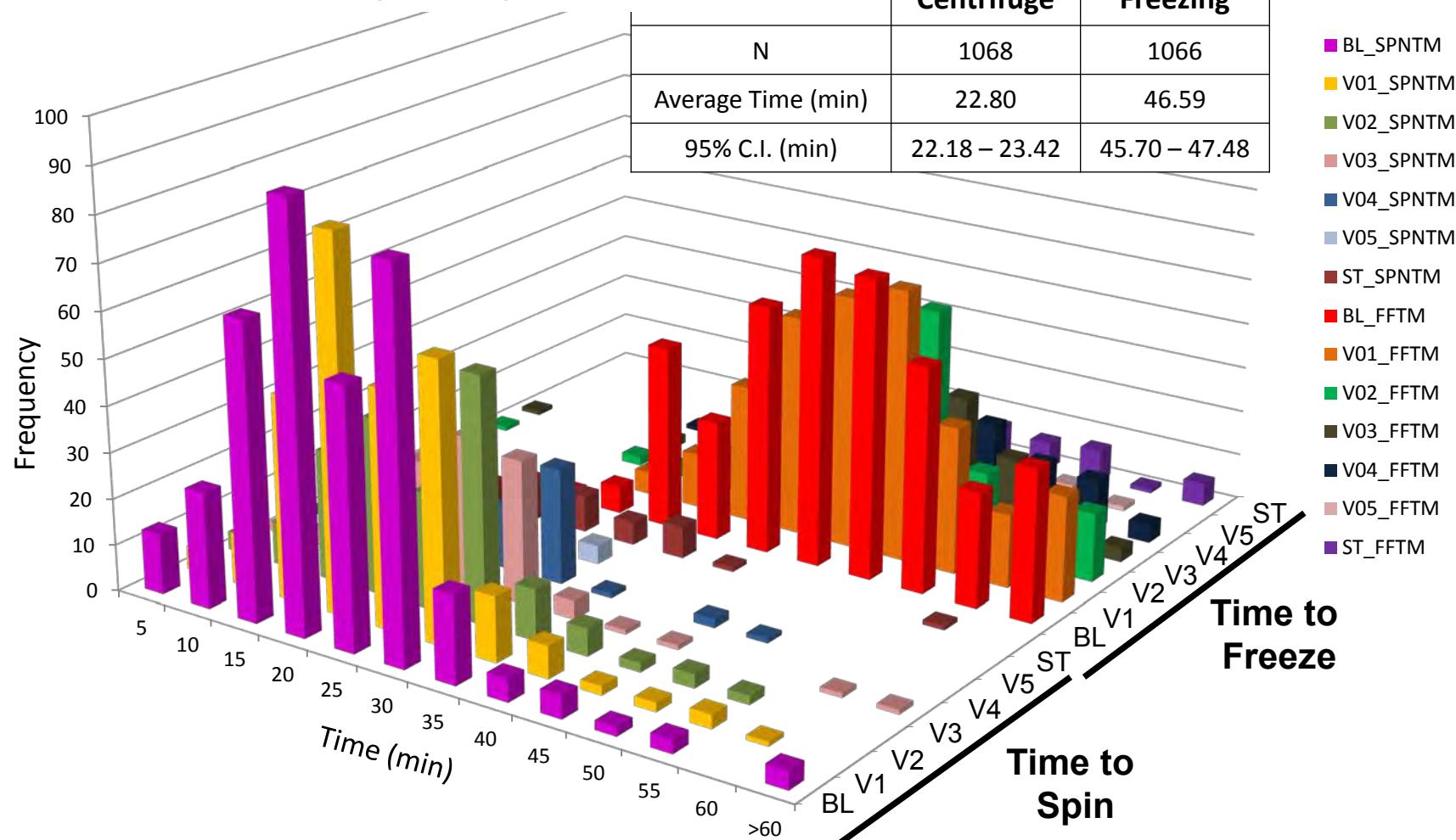
In the morning (8 am – 10 am), preferably fasted

Within 30 min, Cfg. at 4°C for 15 min at 1500×g

Place pre-printed label on 2mL aliquot tube

Aliquot to 2 – 3 tubes

Within 60 min of collection, freezing & storage at -80°C



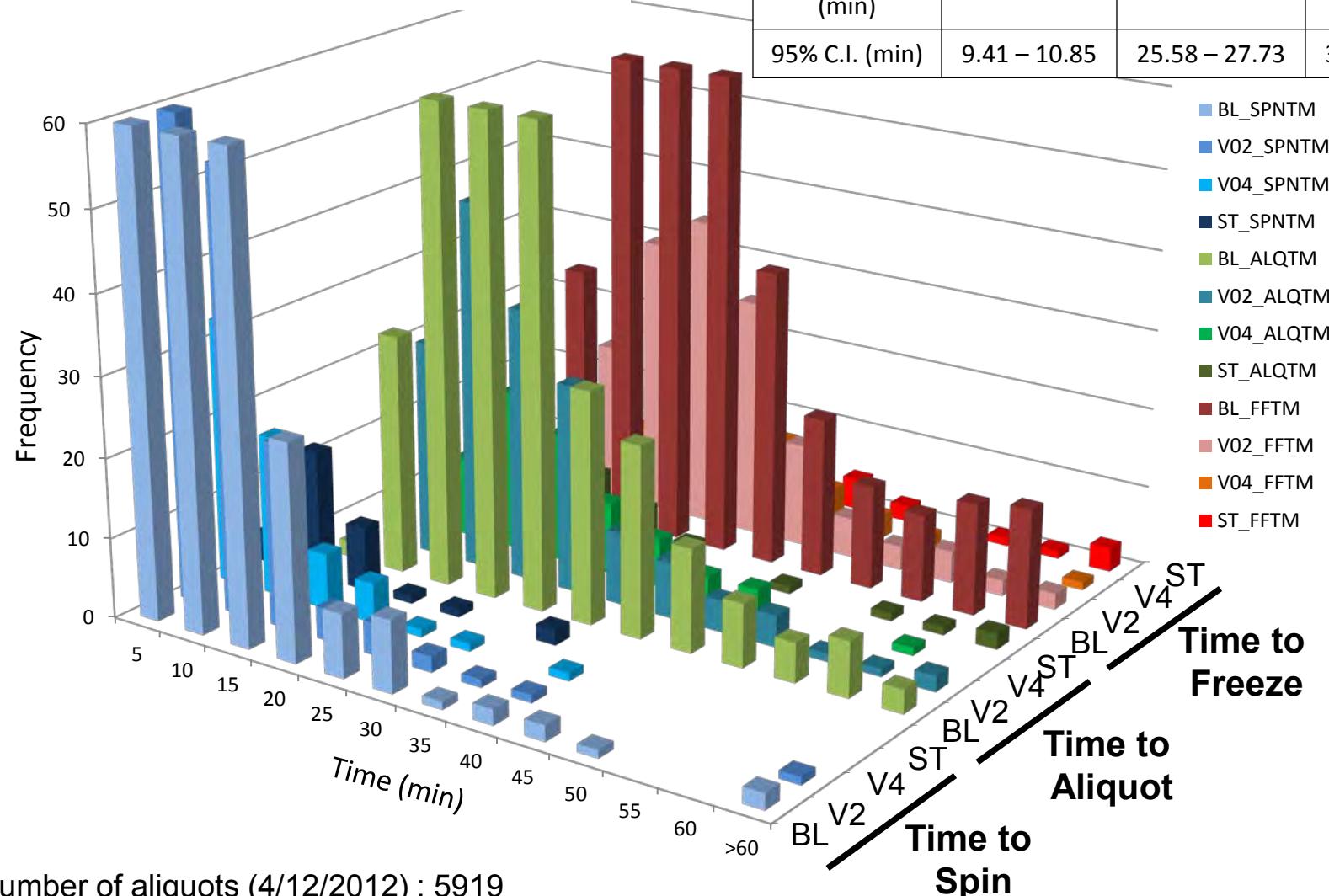
Total number of aliquots (4/12/2012) : 3004

CSF Samples for PPMI

In the morning (8 am – 10 am), preferably fasted
 Within 15 min, Cfg. at RT for 10 min at 2000×g
 Aliquot to pre-cooled & labeled polypropylene tube
 Immediate freezing on dry ice & storage at -80°C

CSF Samples (From Collection to Freezing)

	Centrifuge	Aliquot	Freezing
N	625	625	625
Average Time (min)	10.13	26.66	33.02
95% C.I. (min)	9.41 – 10.85	25.58 – 27.73	31.65 – 34.40



Total number of aliquots (4/12/2012) : 5919

No information for 3, 2, and 3 samples of CFG, ALQ and FRZ

There are 6 samples at Visit 01 (3 mo.): Data not shown in the graph.

Summary

		Time (min) to Spin	Time to Aliquot	Time to Freezing	Volume (mL) after Spin	Number of ALQ
Plasma	Total Mean	20.06	-	44.06	4.37	2.98
	% CV	51.36%	-	35.82%	11.65%	9.65%
Serum	Total Mean	22.80	-	46.59	3.97	2.82
	%CV	45.17%	-	31.79%	17.36%	15.33%
CSF	Total Mean	10.13	26.66	31.65	14.47	9.47
	% CV	90.64%	51.16%	52.82%	18.50%	14.63%

Summary

Specimen		Mean time of procedures (minute)						
	Visit	BL	V01	V02	V03	V04	V05	ST
Plasma	Mean Time to SPN	19.56	19.56	21.17	20.82	20.62	26.20	18.97
	Mean Time to FRZ	43.92	43.64	44.83	43.94	45.16	51.00	42.11
	Visit	BL	V01	V02	V03	V04	V05	ST
Serum	Mean Time to SPN	22.36	22.54	23.63	23.46	22.06	26.20	24.16
	Mean Time to FRZ	46.69	46.23	46.89	46.35	46.39	51.00	47.24
	Visit	BL	V01*	V02	-	V04	-	ST
CSF	Mean Time to SPN	11.15	10.83	8.56	-	7.87	-	11.34
	Mean Time to ALQ	27.84	26.50	24.70	-	23.82	-	29.41
	Mean Time to FRZ	34.96	31.83	29.75	-	29.29	-	35.25

*There are 6 samples at Visit 1 (3 mo.).

Centrifugation

: Compliance with protocol

CENTRIFUGATION		Time	Temperature	Force
Plasma	Protocol Condition	15 min	4°C	1500×g
	Per protocol (%)	1062/1063 (99.9%)	1032/1063 (97.1%)	874/1063 (82.2%)
Serum	Protocol Condition	15 min	4°C	1500×g
	Per protocol (%)	1062/1068 (99.4%)	1034/1068 (96.8%)	872/1068 (81.6%)
CSF	Protocol Condition	10 min	R.T. (18-30°C)	2000×g
	Per protocol (%)	No data	599/625 (95.8%)	500/625 (80.0%)

Genetics in PPMI

Andrew Singleton



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Andrew Singleton: singleta@mai.nih.gov



Genetics in PPMI

- Probably not used as a discovery cohort for genetics by itself
- 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

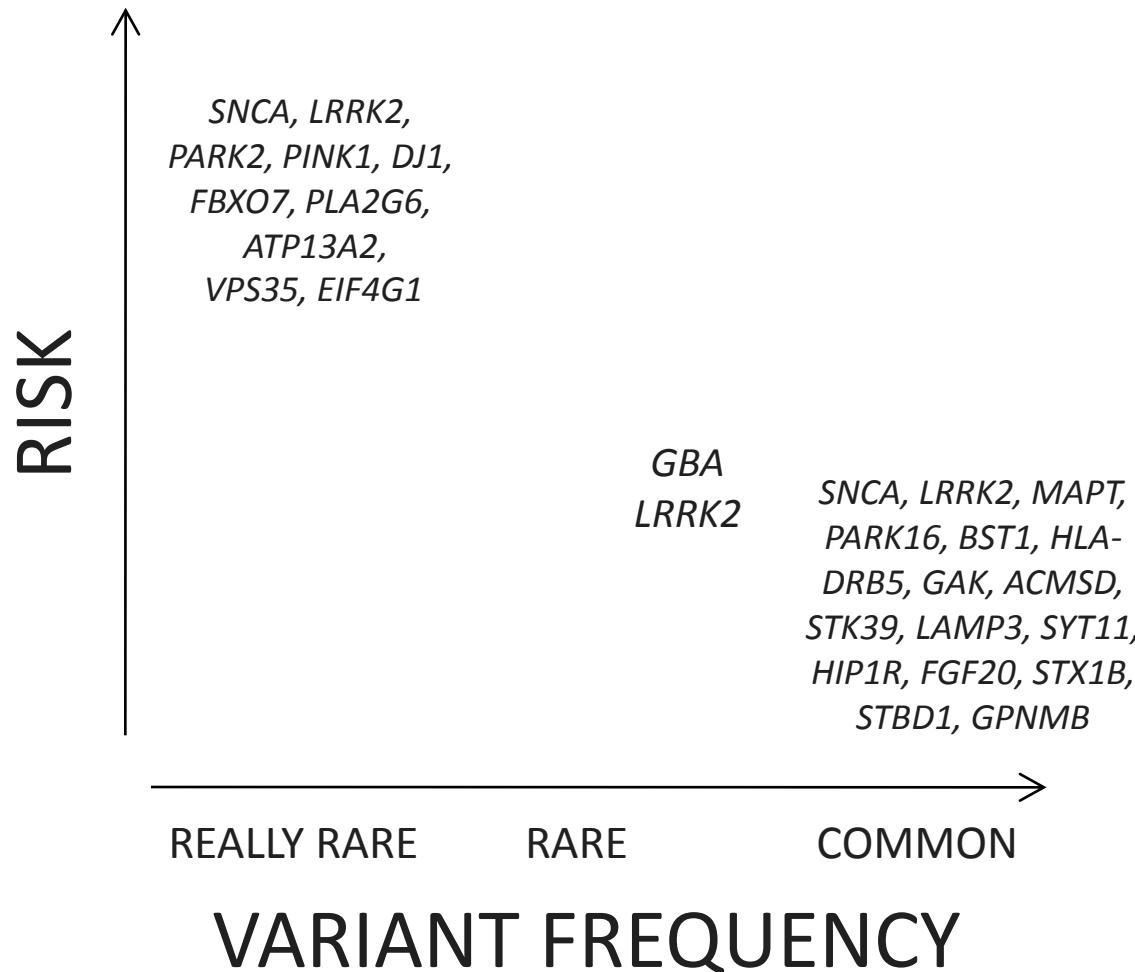


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Genetic Architecture of PD

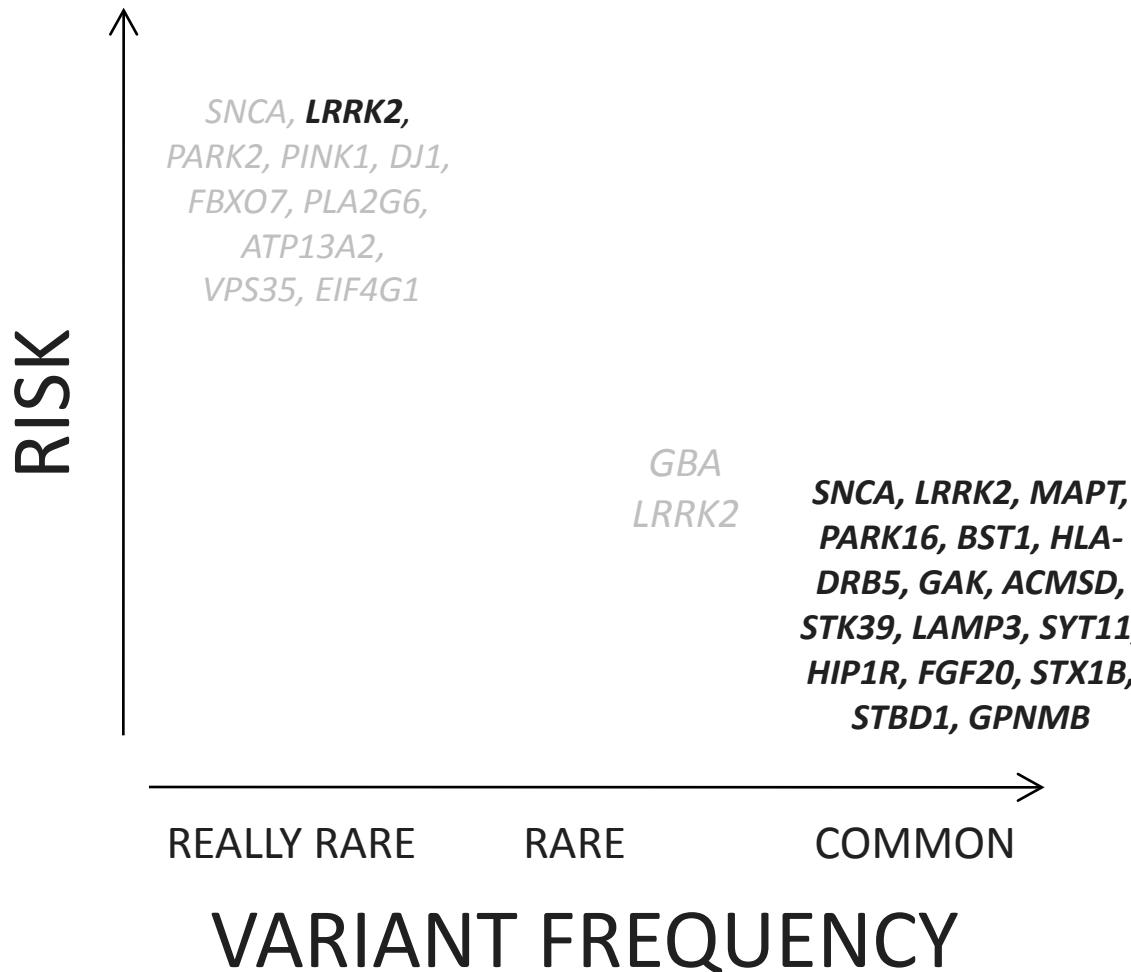


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ImmunoChip



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Data so far

- First 100 samples received in early 2012
- Initial DNA QC all passed
- 96 samples run on the ImmunoChip
- Post genotype QC – 3 samples with mismatched gender (agreed with Coriell QC)
- Sample success rate – 100%
- Genotype success rate – 98.7%
- Data uploaded to LONI

all proceeding as planned



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Andrew Singleton: singleta@mai.nih.gov



Next Steps

- Will continue with ImmunoChip through all samples
- Include individual genotyping (APOE, DAT vntr etc)
- Augment with exome genotyping (neuroX?)
- Likely some addition of sequence data (exome, resequencing, genome)
- Challenge in timing of technology and cohort collection



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Report from Industry Scientific Advisory Board

PPMI Annual Investigators Meeting
May 2-3, 2012

Thomas Comery



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Industry Scientific Advisory Board (ISAB) Membership



Michelle Collins
Katherine Widnell



Mark Mintun



Bernard Ravina,
Chair-elect



Peggy Taylor



Ted Yednock



GE Healthcare

Igor Grachev



Marcel van der Brug



Alastair Reith



Be well

Johan Luthman
David Michelson



Thomas Comery,
Chair



Susanne Ostrowitzki
Paulo Fontoura

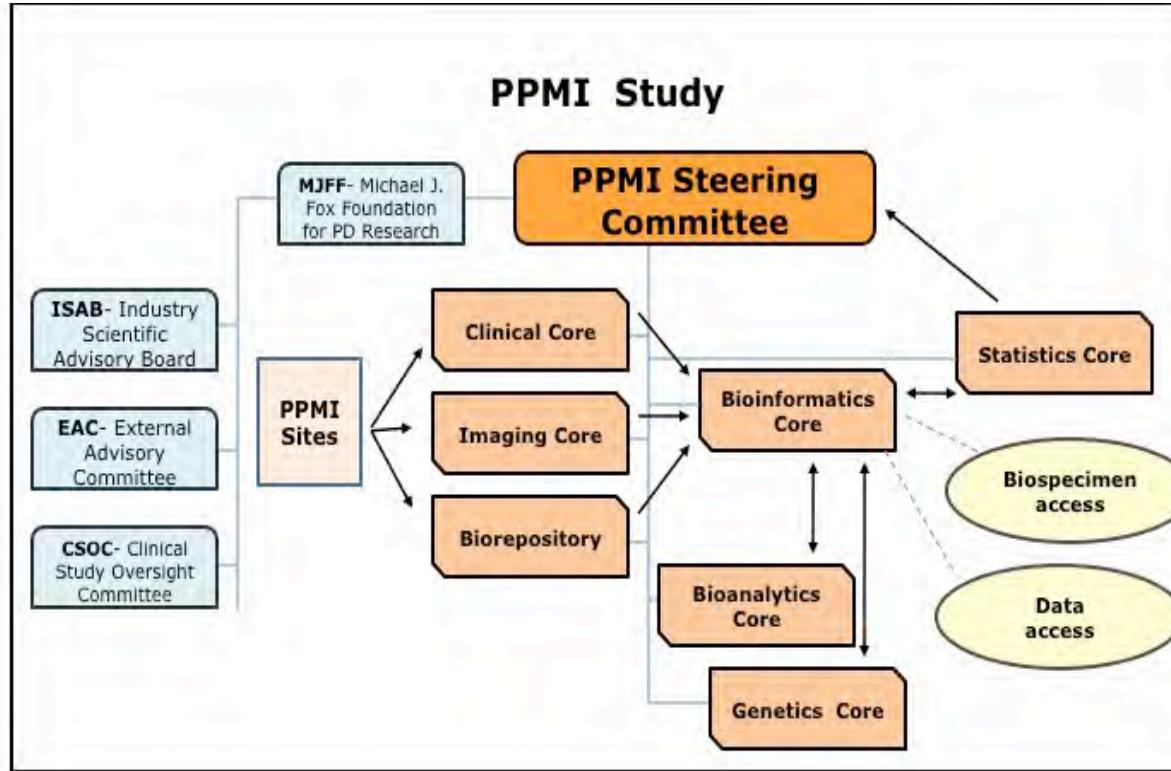


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Industry Scientific Advisory Board Role



- Stakeholder role of the ISAB
 - Support Steering Committee
 - Input in Taskforces/Working groups
 - Participate in Annual Meeting and bi-monthly t-cons
 - Support efforts to identify additional partners
 - Suggest Ancillary Studies



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Ancillary Studies Under Consideration by the ISAB

1. Develop a standard data compilation for use by ISAB members
2. Development of a quantitative Parkinson's disease progression model allowing:
 - simulation of potential trial designs (patient selection, trial size, duration)
 - improved understanding of the effect of drop-outs and placebo response
 - incorporation of biomarker-outcome relationships (neuropsychological, neuroimaging and biofluids)



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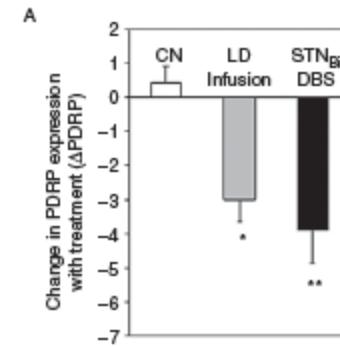
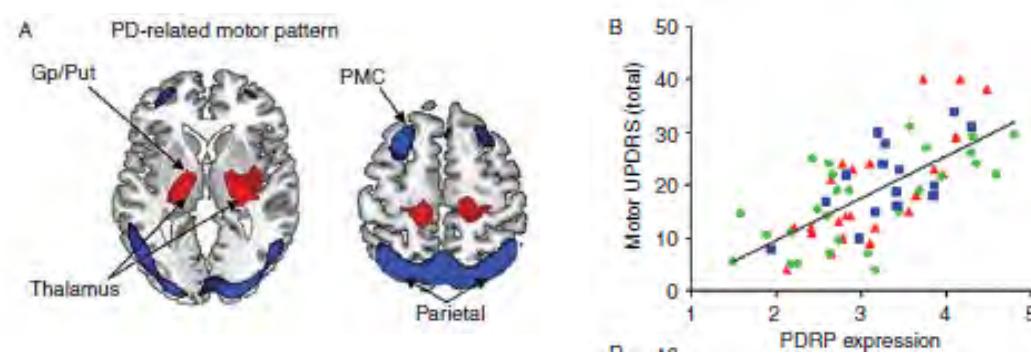
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Ancillary Studies Under Consideration by the ISAB

3. Addition of ASL-fMRI and spatial covariance analysis into PPMI

- Analysis of brain metabolic activity has identified networks associated with motor impairment, cognitive deficits and tremor in PD
- PPMI provides an opportunity to evaluate the robustness of these findings in a multi-center progression trial and correlate the findings with extensive motor and non-motor assessments



Tang et al., 2010

4. Characterization of α -synuclein variants in CSF, plasma and serum as candidate biomarkers for Parkinson's disease

- Establish a profile of α -synuclein variants in biofluids of older healthy volunteers and patients with Parkinson's disease



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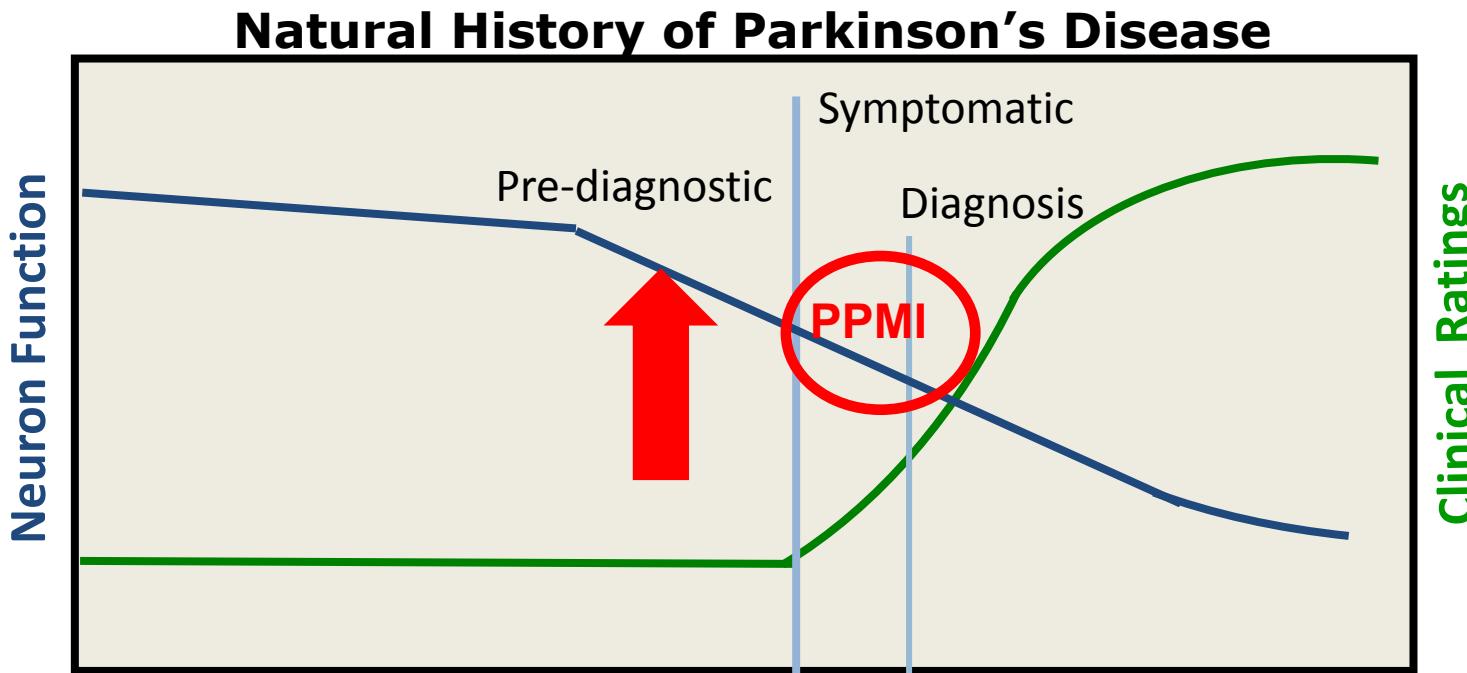
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Ancillary Studies Under Consideration by the ISAB

5. Support the expansion of PPMI to include a cohort at risk for developing PD

- Addition of an at risk population is key as designs and patient identification strategies for potential disease modifying therapies are being developed
- Establish pre-motor biomarker signature



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ISAB Next Steps

- Continue to support the PPMI goals and objectives through ISAB bi-monthly t-cons and participation in working groups
- Formulate and communicate ISAB member's needs as they arise
- Evaluate needs and gaps, recommend new ancillary studies to accelerate drug development in PD, biomarkers acceptance by regulators and develop new indications for approved products
- Support addition of new ISAB members to PPMI



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PPMI

Recruitment, Enrollment and Retention

Update to the PPMI Annual Meeting
May 3, 2012

Danna Jennings, R&R Working Group Chair



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PPMI Recruitment Retention Working Group

- Daniela Berg
- Sohini Chowdhury
- Carey Christensen
- Emily Flagg
- Katharina Gauss
- Christine Hunter
- Danna Jennings (Chair)
- Claire Meunier
- Tanya Simuni
- Carlie Tanner
- Cathi Thomas

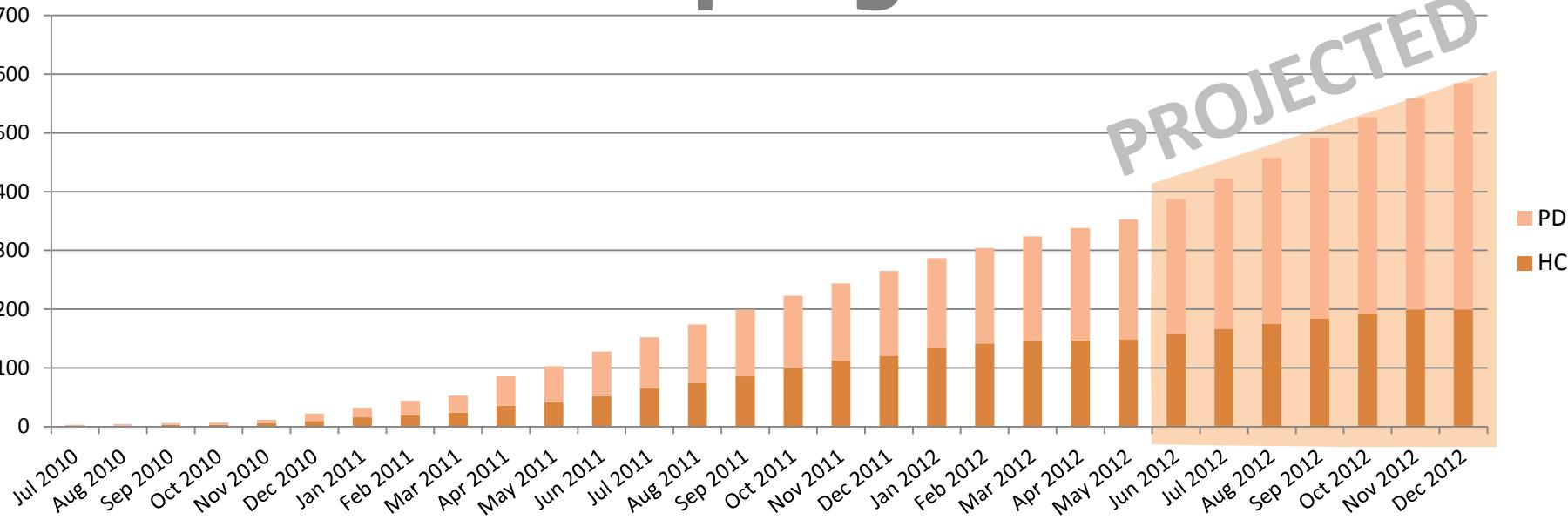


Revisiting our Recruitment and Retention Goals

- **Recruit** 400 *de novo* and 200 control subjects
 - Site Goal: Enroll 1 PD per month and 2 more controls this year
- **Retain** subjects by keeping them engaged to participate in study visits over time
 - Site Goal: Remain connected and continue to cultivate volunteers as key partners in the study



Recruitment progress to date



- Control recruitment has been easier than anticipated, exceeding enrollment projections
- PD recruitment has been more challenging than expected, but progress continues to be made.

With every site enrolling at least one PD subject a month, we can complete PPMI recruitment by the end of the year.

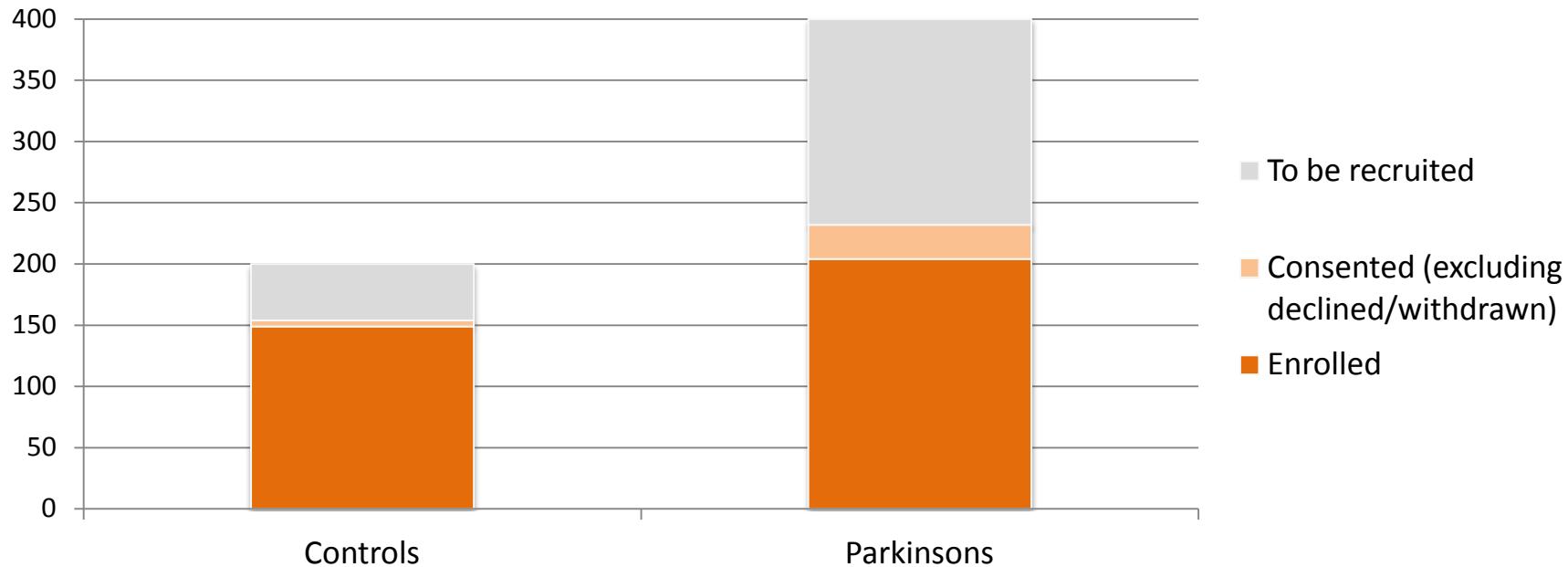


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Recruitment Progress to Date

(as of April 30, 2012)



- 75% (149/200) of controls are enrolled (77% consented*)
- 51% (204/400) of Parkinson subjects are enrolled (58% consented*)



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* Excluded/Declined subjects have been removed from these and all consented calculations throughout this presentation

Site Performance to Date - US

**Meeting PD goal
(>1 PD Enrollments/Month)**

Sites	Enrolled		
	PD	Controls	PD Enr/mon
IND (New Haven)	28	8	1.52
Cleveland Clinic (Cleveland)	11	5	1.45
Emory (Atlanta)	12	12	1.41
U Washington (Seattle)	14	7	1.35
OHSU (Portland)	15	10	1.28
UAB (Birmingham)	14	10	1.26
U South FL (Tampa)	13	8	1.23
U Pennsylvania	11	10	1.16
BU (Boston)	10	9	1.01

**Have not yet met PD goals
(<1 PD Enrollments/Month)**

Sites	Enrolled		
	PD	Controls	PD Enr/mon
U Rochester (Rochester)	10	7	0.94
Northwestern (Chicago)	10	9	0.94
The PI (Bay Area)	8	9	0.91
Baylor (Houston)	10	7	0.86
UCSD (San Diego)	3	3	0.71
Hopkins (Baltimore)	8	4	0.71
Banner Health/APDC	6	3	0.49



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Site Performance to Date - International

**Meeting PD goal
(>1 PD Enrollments/Month)**

Sites	<u>Enrolled</u>		
	<u>PD</u>	<u>Controls</u>	<u>PD</u> <u>Enr/mon</u>
U Tuebingen (Tuebingen)	11	9	1.64
Paracelsus Klinik (Kassel/ Marburg Germany)	7	11	1.22

**Have not yet met PD goals
(<1 PD Enrollments/Month)**

Sites	<u>Enrolled</u>		
	<u>PD</u>	<u>Controls</u>	<u>PD</u> <u>Enr/mon</u>
Innsbruck U (Austria)	3	8	0.75



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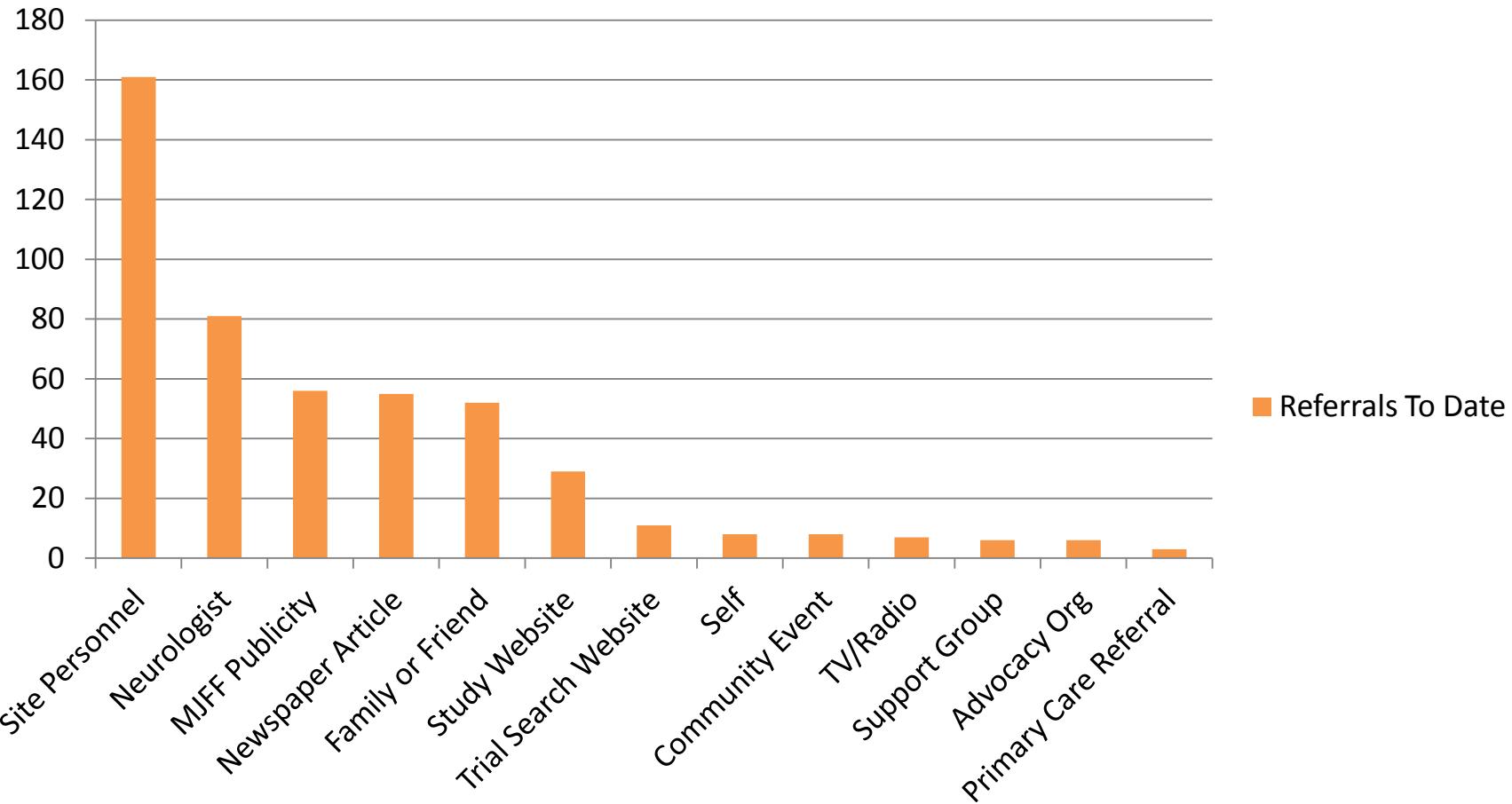


Recruitment Strategies and Activities

- Site Efforts
 - Continued recruitment from clinic practices; consistent outreach and reminders to clinical colleagues and physicians who are affiliated with site, as well as cultivation of colleagues in the community who refer
 - Community outreach continues (support groups, symposia, physician networks, etc)
 - Partnerships with imaging teams to recruit non-site-referred DaT patients
- MJFF strategies
 - Physician salons to cultivate MD relationships at 6 sites; Sites are primary drivers of continuing to foster these relationships
 - Physician mailings sent in 8 markets; additional mailings planned for the rest of recruitment period
 - Veterans mailing to get male controls over 55 resulted in XX enrollments
 - 18 major media stories on the study



Recruitment Sources for Consented PD and SWEDD Participants



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Sharing successful recruitment tactics

- **Physician Outreach and building a referral network**
Zoltan Mari and Jim Leverenz
- **Creating process and structures for recruitment and patient referrals in your own clinic**
David Standaert
- **Building a relationship with an imaging center**
Robert Hauser
- **My role as a PI in boosting recruitment**
Penny Hogarth
- **Coordinator Session: Report back**
Karen Williams



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New Strategies: Focus on PD Recruitment

- Outreach to nuclear medicine facilities
- Consider bringing on a co-investigator at sites when appropriate
- Ambassador toolkit developed to equip PPMI patient committee and MJFF patient council to help spread the word
- Re-tooling web advertisement strategy to reach newly diagnosed who are seeking information online
- Media will continue in select markets where it has proven to result in PD screenings
- Fox Trial Finder is increasingly a resource for subjects as new volunteers register daily
- Working to develop a relationship with the VA system around PPMI and Fox Trial Finder
- Planning a veterans mailing to ask them to share info about the study with friends who are newly diagnosed



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Retention progress to date

	<u>PD</u>	<u>Controls</u>	<u>SWEDDs</u>
% retained	99.0% (n=2 withdrawn)	98.6% (n=2 withdrawn)	96.0% (n=1 withdrawn)

- Sites are doing a great job retaining subjects; Our goal is to maintain this success
- Reasons why subjects have withdrawn:
 - Unwilling to complete full battery of study tests and assessments
 - DaTscan indicated no dopamine deficit; subject did not want to be retained as a SWEDD
 - Subject lives too far away from site
- Tactics to retain subjects include:
 - Continued access to coordinators as primary resources of information for subjects
 - Giveaways at each visit
 - Site retention events (6 held to date; ~10 more planned for 2012)



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Site Awards

Drumroll, please.....



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PPMI Challenge: Recruit 3 PD patients from Jan 22 to now

- IND
- Cleveland Clinic
- Hopkins
- Emory
- Boston University
- OHSU
- U Wash/VA Puget Sound
- Tuebingen
- The PI



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Sites that met the year 1 goal in less than 12 months

- Tie for 3rd place:
IND and OHSU
Met Year 1 Goal in 11.5 months
- Tie for 2nd place:
U South Florida and U Washington
Met Year 1 Goal in 10.75 months
- 1st place:
Cleveland Clinic
Met Year 1 Goal in 9.75 months



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Most PD Consented

- 34 PD subjects have been consented at this site
- And the winner is....



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Most PD Consents in one week

- 5 PD consented in one week
- And the winner is....



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Most improved enrollment rate

- Last year at the meeting had .4* subjects enrolled per month coming into the study and now they have 1.8* per month
- And the winner is....



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*rates from Jan – Apr of 2011 compared to Jan – Apr of 2012

The Road Ahead: Two key challenges for sites

- Recruitment: Keep the pipeline full
 - The study is over half way there
 - What can your site do to build momentum to recruit more PD subjects?
- Retention: Maintaining the stamina and loyalty of enrolled subjects
 - How can we step this up over time?



Questions?



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PPMI Data & Bioinformatics Core

Shirley Lasch

Arthur Toga



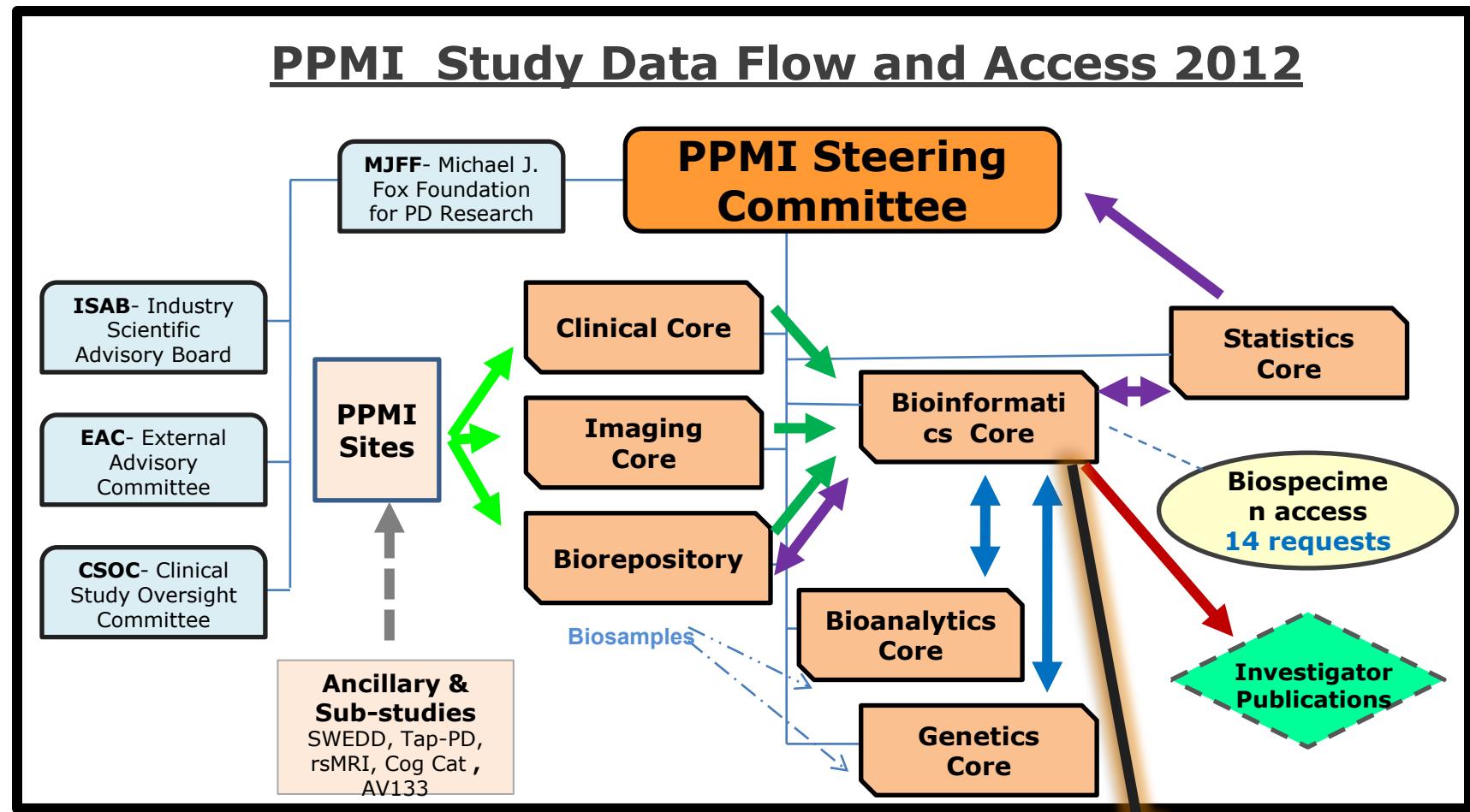
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PPMI Data & Bioinformatics Core

PPMI Study Data Flow and Access 2012



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Apply for PPMI Data Access & Download

Parkinson's Progression Markers Initiative

Subscribe: News

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

About PPMI Study Design Access Data & Specimens PPMI News Get Email Updates Home

OUR MISSION

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

WELCOME

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

DOWNLOAD DATA

REQUEST

DOWNLOAD DATA

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

New Users Apply Now:

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

APPLY FOR DATA ACCESS

Registered Users:

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

Email:

Password:

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

LOGIN

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PPMI Data Access & Download

The screenshot shows the PPMI@LONI website homepage. At the top, there's a navigation bar with links for 'PPMI @ LONI', 'PROJECTS', 'SEARCH', 'ARCHIVE', 'DOWNLOAD', 'EXPLORE', 'MANAGE', and 'LONI Home'. Below the navigation is a banner for 'Parkinson's Progression Markers Initiative' with a link to 'Baseline Summary'. The main content area starts with a 'Getting Started' section containing general information about the repository. To the right is a large data visualization titled 'Participant Research Group and Age Distribution'. It includes a bar chart showing the number of subjects by age group (30-39, 40-49, 50-59, 60-69, 70-79, 80-89) and two pie charts showing the distribution by 'Research Group' (Control, SWEDD, PD) and 'Gender' (Female, Male). The data for the charts is summarized in the following table:

Age Group	Number of Subjects
30-39	10
40-49	25
50-59	62
60-69	90
70-79	37
80-89	8

Below the visualization, there's a 'RELATED LINKS' section with links to 'FREQUENTLY ASKED QUESTIONS', 'PPMI DISSEMINATED DOCUMENTS AND SOPs', 'BIOSPECIMEN ACCESS REQUEST', 'PPMI DATA USE AGREEMENT', and 'CONTACT PPMI TEAM'. At the bottom, a copyright notice reads '© 2012 LONI. All rights reserved.'

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

This diagram illustrates the structure of the PPMI website. It features a central title 'Parkinson's Progression Markers Initiative' and a 'Getting Started' section. Above the title is a horizontal navigation bar with tabs: 'PPMI @ LONI', 'PROJECTS', 'SEARCH', 'ARCHIVE', 'DOWNLOAD', and 'EXPLORE'. Below the navigation bar, there are two specific tabs: 'Home' and 'Baseline Summary'. Three purple arrows point from the text 'data containing tabs' at the bottom to the 'Baseline Summary' tab, the 'SEARCH' tab, and the 'EXPLORE' tab.



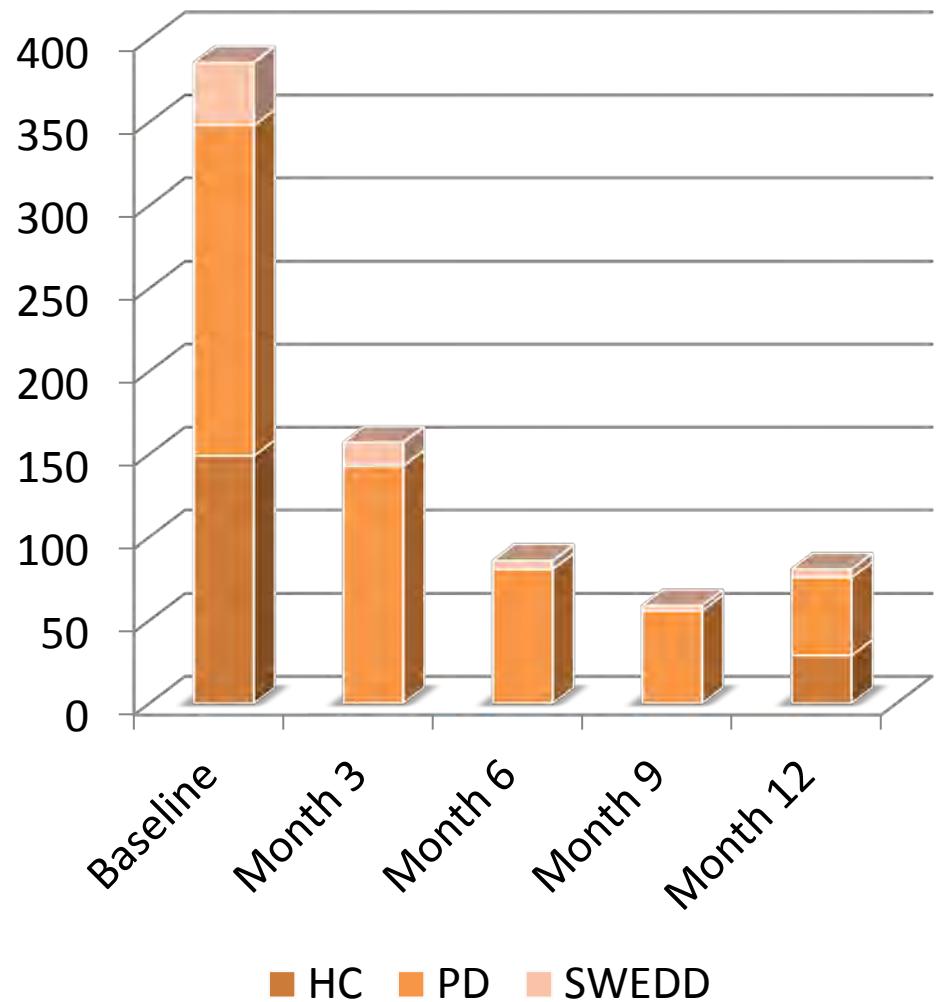
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Available Clinical Data

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



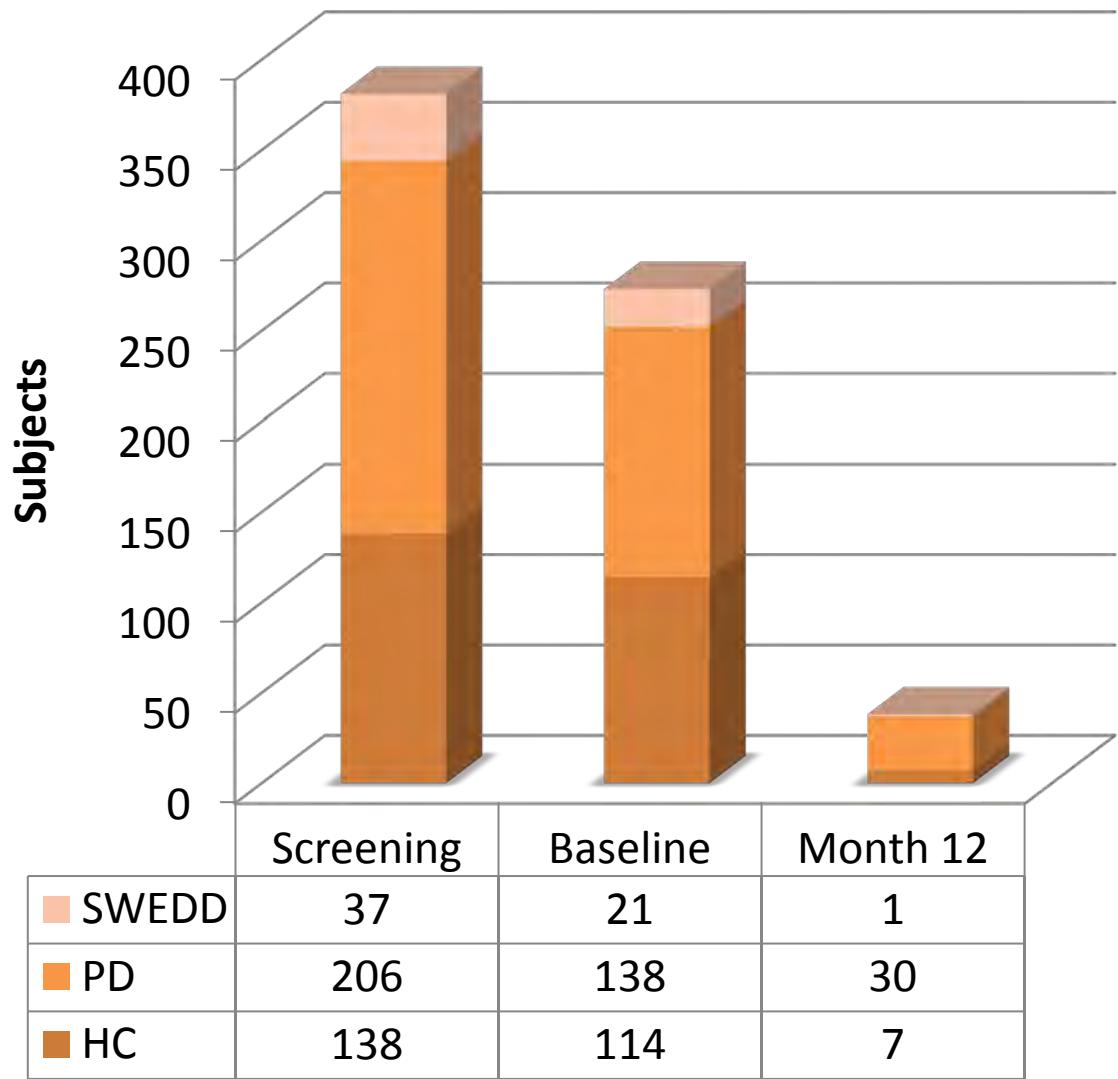
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Available Data

- Structural MR
- SPECT
- Diffusion MR (raw)
- Processed Diffusion MR:
 - FA Maps
 - MD Maps
 - Eigen Vectors



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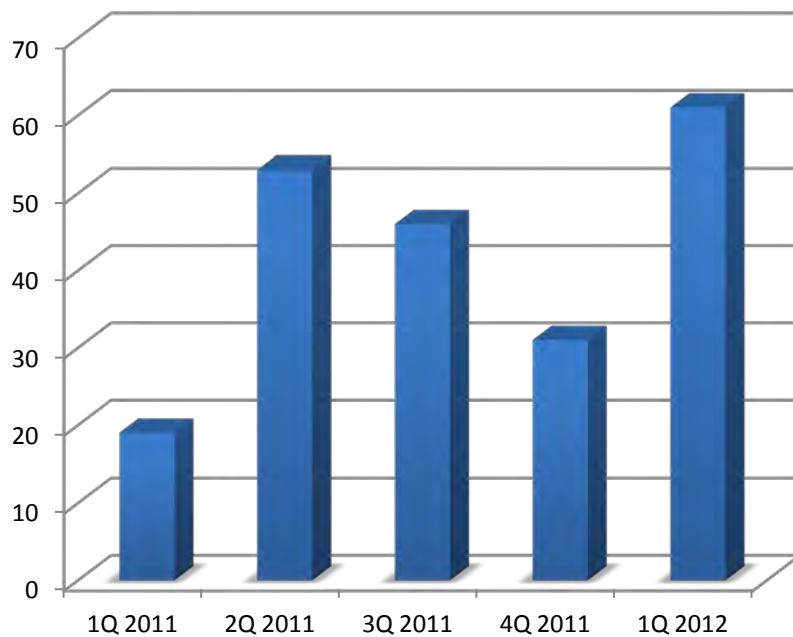
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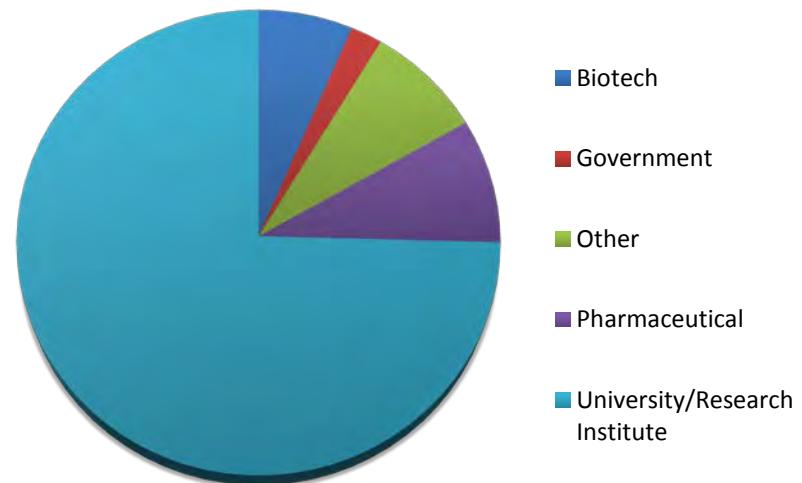
Data Use Applicants

228 Applicants from 28 Countries

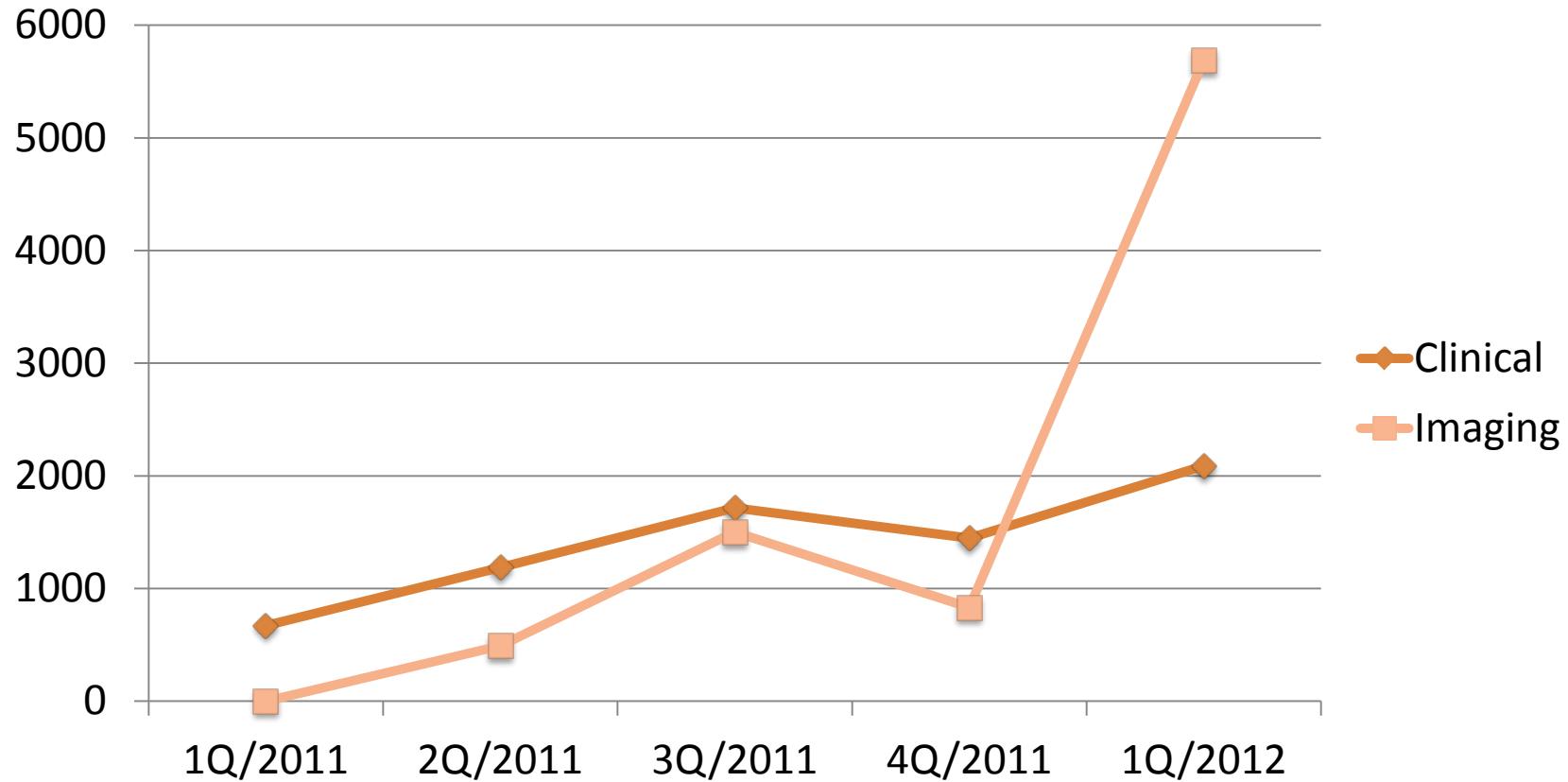
Applicants by Quarter



Applicants by Sector



Download Activity



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PPMI Data & Informatics Core

Highlights of PPMI data availability from 2011 to 2012

2011	2012
PPMI data made accessible to investigators and scientific community - March 2011	Interactive PPMI data access and download platform added- April 2012
Opened on-line registration for authorized users to access PPMI data	Over 228 Registered PPMI Data users from 28 of Countries
17 of 21 PPMI sites activated	22 of 24 PPMI sites activated Added 3 new sites including AUS
Baseline data for 77 subjects (46 PD, 31 HC) reviewed at 2011 meeting	Baseline data for 364 consented subjects (237 PD, 182 HC, 36 SWEDD)
2 Ancillary or sub-studies planned	Data from 2 ancillary studies integrated into database three more expected as part of Amendment 4
Clinical, motor, non-motor, imaging, biospecimen inventory and collection data, and SPECT and MRI scan available for download	Meeting presentations focusing on early data from <i>de novo</i> drug-naive PD patients enrolled in the PPMI study: Association of CSF biomarkers with clinical features DaTSCAN Neuroimaging DTI scanning & DAT uptake Impulse Control Disorder (ICD) Olfactory Function and Cognition Accessibility of PPMI data and biospecimens

What's New?

- Visual Interrogation System
- Dashboard



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Visual Interrogation System

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



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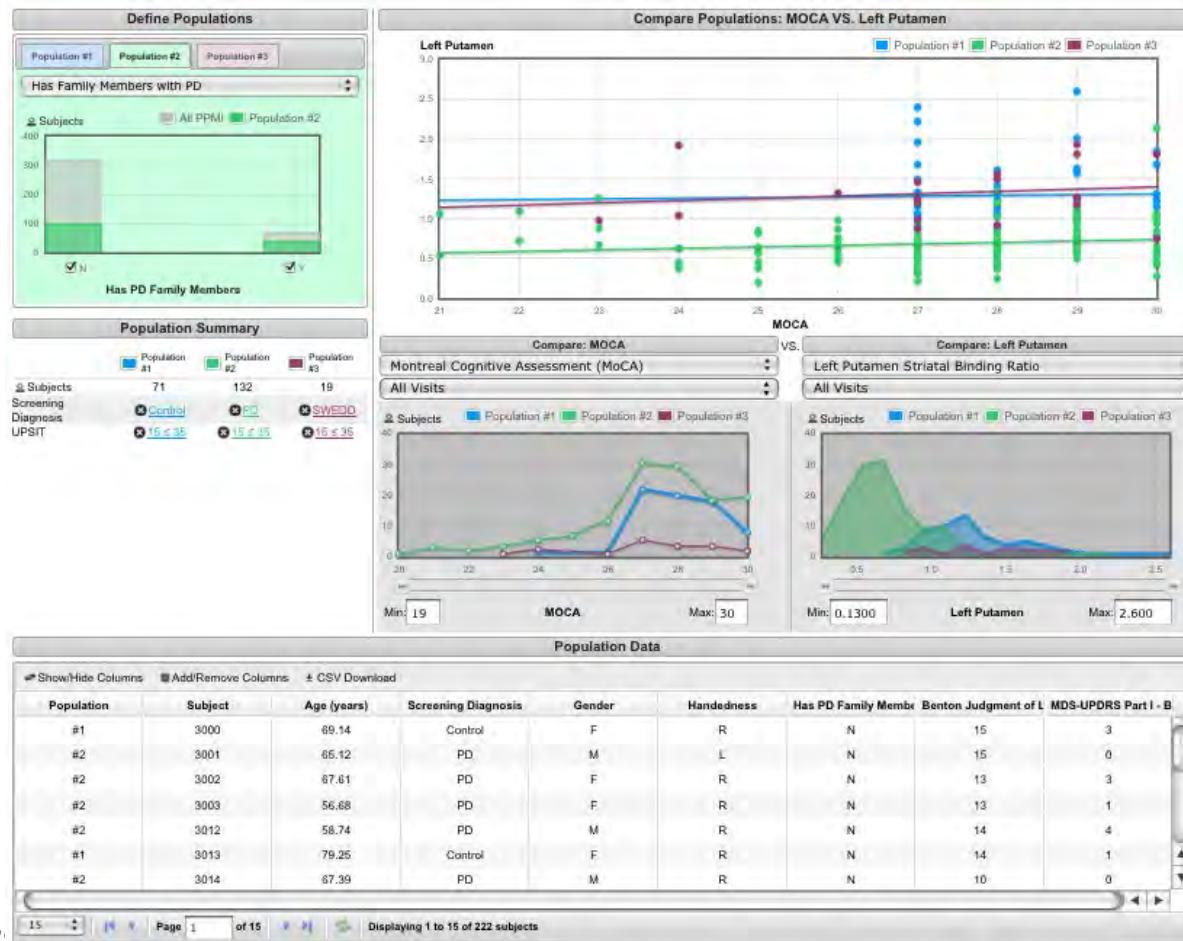


Visual Interrogation System

The screenshot shows the homepage of the Parkinson's Progression Markers Initiative (PPMI) at LONI. The top navigation bar includes links for PPMI @ LONI, PROJECTS, SEARCH, ARCHIVE, DOWNLOAD, EXPLORE (which is highlighted with a large blue circle), and LONI Home. Below the navigation is a secondary menu with Home and Baseline Summary options. The main content area features the PPMI logo and the text "Play a Part in Parkinson's Research". On the right side, there is a "POWERED BY LONI IMAGE DATA ARCHIVE" badge.

This is a footer or sidebar section of the PPMI website. It features the PPMI logo and the text "Play a Part in Parkinson's Research". To the right is a vertical color bar consisting of yellow, orange, and red squares.

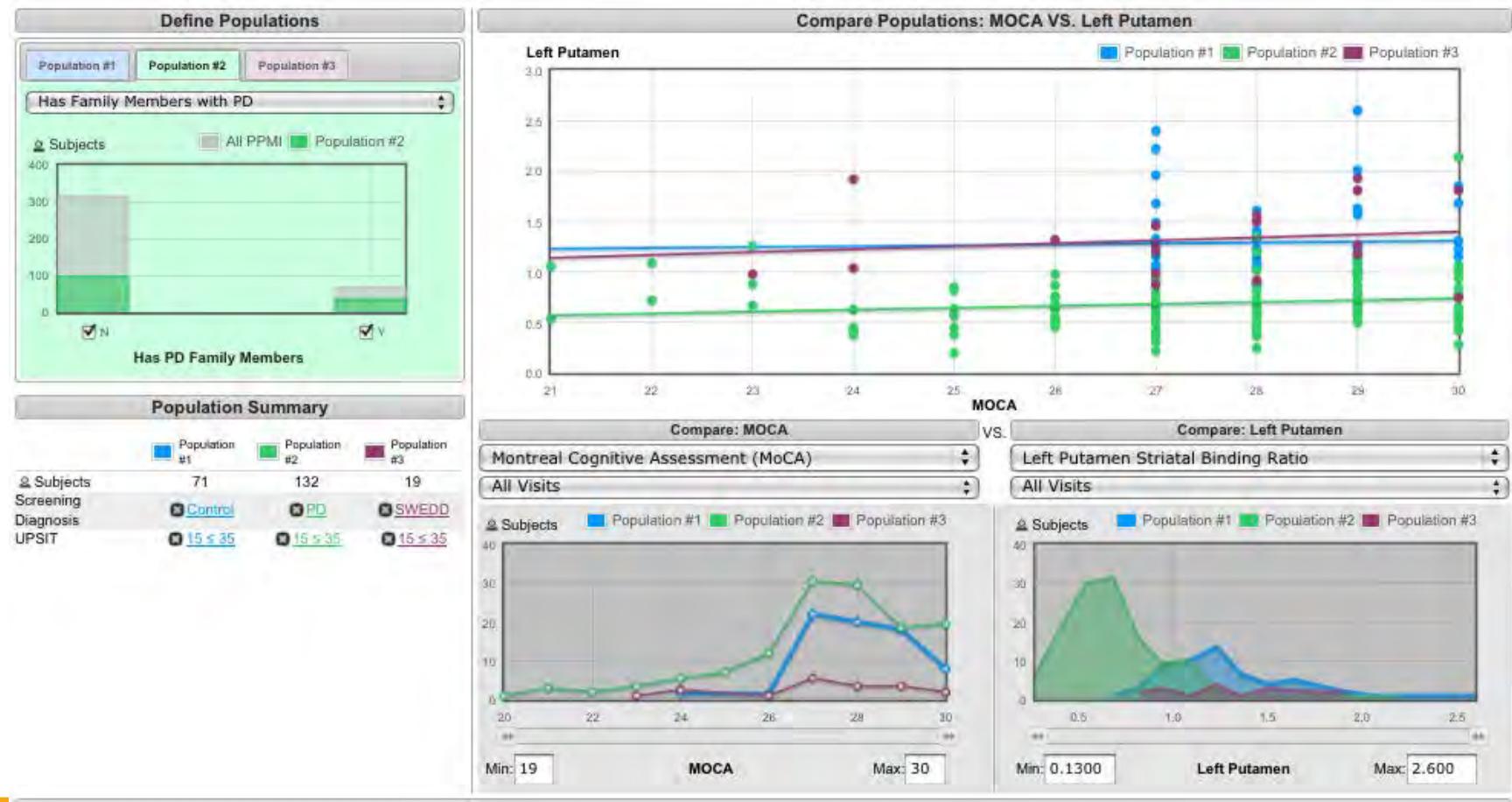
Visual Interrogation System



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Compare User Defined Groups

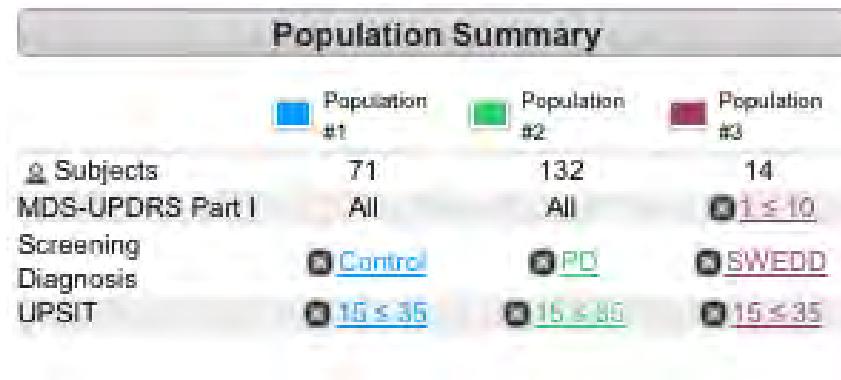
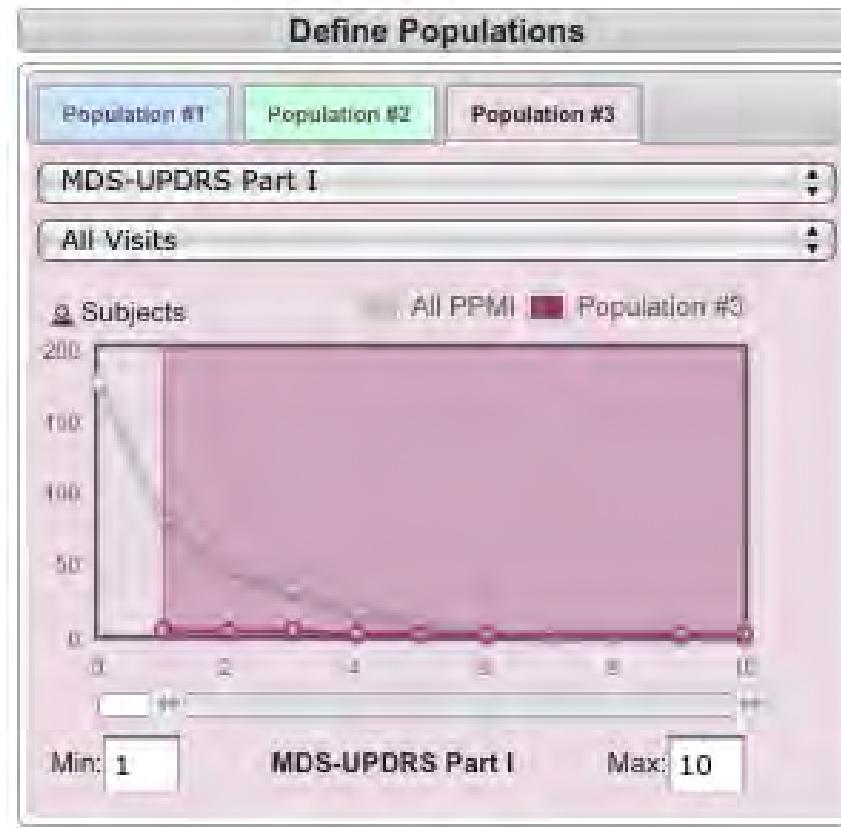


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How to define populations:

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



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Tabular Data

Population Data									
Population	Subject	Age (years)	Screening Diagnosis	Gender	Handedness	Has PD Family Memb	Benton Judgment of L	MDS-UPDRS Part I - B	
#1	3000	69.14	Control	F	R	N	15	3	
#2	3001	65.12	PD	M	L	N	15	0	
#2	3002	67.61	PD	F	R	N	13	3	
#2	3003	56.68	PD	F	R	N	13	1	
#2	3012	58.74	PD	M	R	N	14	4	
#1	3013	79.25	Control	F	R	N	14	1	
#2	3014	67.39	PD	M	R	N	10	0	
#3	3050	51.42	SWEDD	F	R	N	14	3	
15	21	Page 1 of 15	«	»	»»	Displaying 1 to 15 of 222 subjects			

Table – Add Columns

■ Add/Remove Columns

Main

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

Assessments

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

Measurements

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

Visual Interrogation System

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

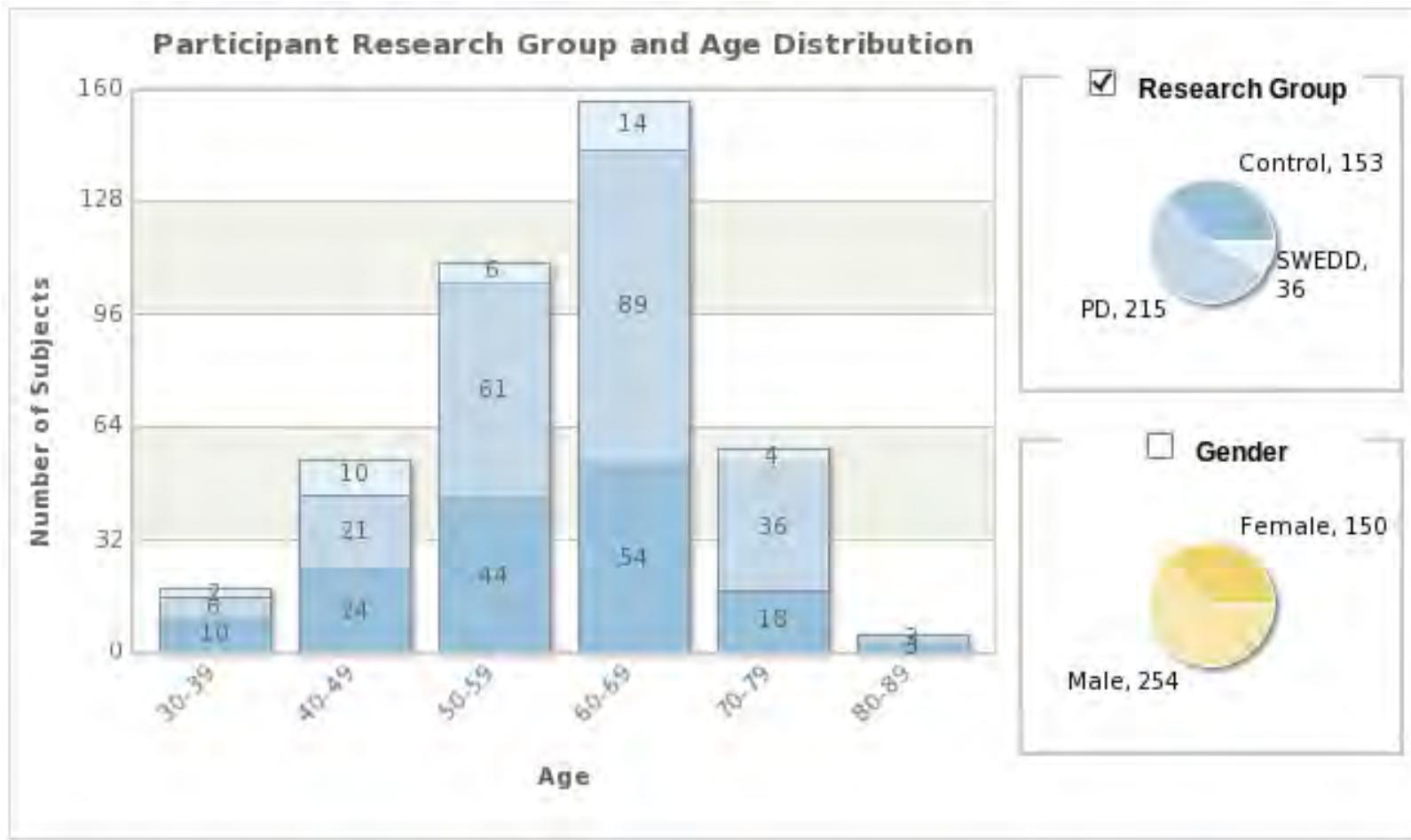


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Dashboard Charts

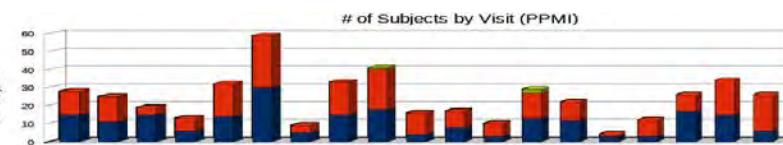
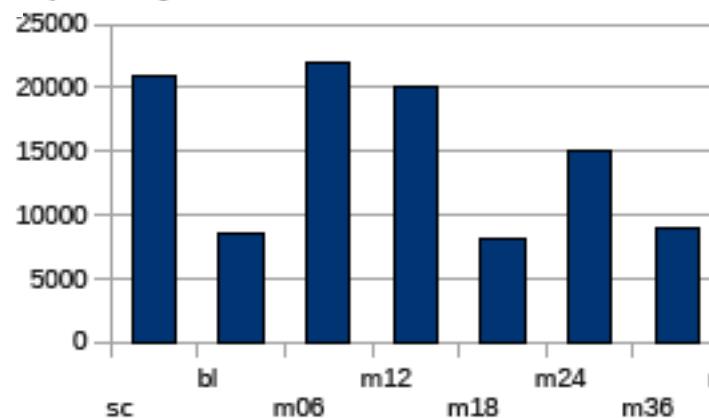


More Coming Soon

Upload By Image type



Upload by visit



PPMI Data Access & Download

Thank you ! Thank you !

PPMI Sites

PPMI Imaging Centers

PPMI Cores

PPMI Data Flow and Integration WG Group

PPMI Working Groups

PPMI Steering Committee

Michael J. Fox Foundation

Industry sponsors and donors

PPMI data users

& most importantly

PPMI study participants !



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Ancillary Studies



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PPMI Ancillary Study Proposals

- Investigators are invited to propose ancillary sub-studies for PPMI
 - initiate the process through the PPMI web site
- These sub-studies may include
 - Analysis of an existing dataset
 - Additional study assessments
 - May involve all or a subset of PPMI participants
 - Should take into consideration progress in PPMI
 - Need for funding



PPMI Ancillary Study Proposals

- Easy access e-Form located on PPMI study website

- Straight forward brief process which allows uploading of an ancillary proposal

- Application process is available 24/7 with submissions sent directly to the committee chair

The screenshot shows the Parkinson's Progression Markers Initiative (PPMI) website with a specific focus on the 'Ancillary Studies' section. The page title is 'Ancillary Studies'. It includes a brief description of what investigators can propose, review criteria, and a two-stage submission process. On the right side, there are five orange buttons with icons and text: 'DOWNLOAD DATA', 'REQUEST SPECIMENS', 'for PROSPECTIVE PARTICIPANTS', 'for PRACTITIONERS', 'for INDUSTRY PARTNERS', and 'for RESEARCHERS'. Below these buttons is a large 'Ancillary Studies Proposal Form' area containing several input fields for the Principal Investigator's contact information, institution details, and location.

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Study Design

Demographic Assessments Methods Assess Outcomes Additional Measures

ANCILLARY STUDIES

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*

DOWNLOAD DATA

REQUEST SPECIMENS

for PROSPECTIVE PARTICIPANTS

for PRACTITIONERS

for INDUSTRY PARTNERS

for RESEARCHERS

PPMI Ancillary Study Proposals

- Proposals are accepted on a rolling basis
- Proposals are reviewed 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
 - Feasibility within the PPMI timeline.



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PPMI Ancillary Study Proposal

- Letter of Intent (LOI) 2 pages and includes
 - brief description of the proposed sub-study
 - 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
 - any potential or available source of funding for the proposal
- Ancillary Study Committee review of the LOI
 - Notification via email within two weeks of submitting the LOI
 - Yes/No decision; Critique not provided
 - Investigator may be invited to submit a Full Proposal
 - Investigators must identify funding: no funds through PPMI. May apply through established MJFF grant programs or other sponsors.



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PPMI Ancillary Study Proposal

- Full Proposals
 - 5 pages in length
 - Follow the format for MJFF research proposals
www.michaeljfox.org/research
 - Reviewed by the PPMI Ancillary Study committee (& subject experts as needed) within 8 weeks of submission date
 - No detailed written critique



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PPMI Ancillary Study Proposal *Review Criteria*

- 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 Study Proposal

Committee members:

Sohini Chowdhuri

Chris Coffey

Danna Jennings

Shirley Lasch

Ken Marek

Todd Sherer

Andrew Siderowf

Tanya Simuni

Carlie Tanner (Chair)

Eduardo Tolosa



Ancillary Studies

Active

Longitudinal follow-up of screen failure due to scan without dopamine deficit (SWEDD)

Feasibility and reliability of home dexterity testing using the OPDM-dexterity measure (TAP-PD)

Assessment of dementia and MCI in PPMI

Proposed

Synuclein and DJ-1 in saliva
(under NIH review)

Resting state MRI
(implementation imminent)

Linking Clinical Data & Molecular Function in using Patient Specific Stem Cells
(Referred to Biologics Working Group)



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SWEDD follow up

Primary Objective

To evaluate the probability of a change in the clinical diagnosis of PPMI PD subjects with a baseline DaTSCAN that shows no evidence for DAT deficit (SWEDD)

Secondary Objectives

To compare baseline characteristics of SWEDD to non-SWEDD PD subjects and healthy controls

clinical characteristics

biomarker characteristics

To evaluate the change in DAT uptake in the SWEDD subjects over a 24-month period and compare it with change in DAT uptake for PPMI PD subjects

To determine the change in clinical markers over a 24-month period compared to PD patients and normal controls



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SWEDD follow up

Subjects

Subjects identified clinically as PD patients for PPMI who do not meet PD eligibility based on a normal DaTSCAN at screening

Assessments

24 month follow up (visits at 6 months, 12 months, 18 months and 24 months)

Clinical (motor, non-motor, neuropsychological)

Biomarker blood draw

DaTSCAN at baseline and 24 months



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Baseline Demographics (SWEDDS)

Characteristic (n = 25)	Mean	Range; s/d
Age (years)	58.4	38 – 75; 10.9
Gender (percent male)	52%	N/A
Symptom duration (months)	9.5	1.0 – 37.0; 9.2
MDS-UPDRS, part III score	16.2	3 – 39; 9.7
Tremor (percent present)	84%	N/A
UPSIT (raw score)	30.8	12 – 39; 6.6
Number of PPMI sites with at least one SWEDD	11	N/A



Home dexterity testing study

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
- Current status: OHSU = 3; INDD = 7; UPenn = 4

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



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TAP-PD baseline demographics

Characteristic (n= 10)	Mean	Range
Age	62	50-81
Gender (% male)	80%	
OMS	41.2	24.1-48.6
Key Down	3.9	3.4-4.3
Peg Cycle	0.9	0.8-1.4



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Current ancillary studies: consistent with review criteria

- Consistent with and furthers the overall goals of PPMI study
- Feasible within parent study
 - Limited additional subject/site burden



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'Learning' Trial Designs

Intended to answer the following questions:

- Does the intervention get to the where it needs to be?
- At a sufficient concentration?
- In a biologically active form?
- Does it engage the target of interest?
- Does it influence downstream biology or pharmacology?
- At what dose?
- With what toxicity?

Early Trial Design Issues

- Dosage Identification
 - Tolerability
 - Target Engagement
- Identification of Failure
 - Non-superiority
- Population Identification
 - Post-hoc
 - Adaptive

Identifying Populations

- All diseases have inherent variability that may predict response to treatment
- Identifying patient factors that may predict response, can better target therapies
- Such 'biomarkers' may not have a known role in disease pathogenesis
- Cancer examples include EGFR mutations in NSCLC and the current I-SPY₂ trial

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 20, 2004

VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

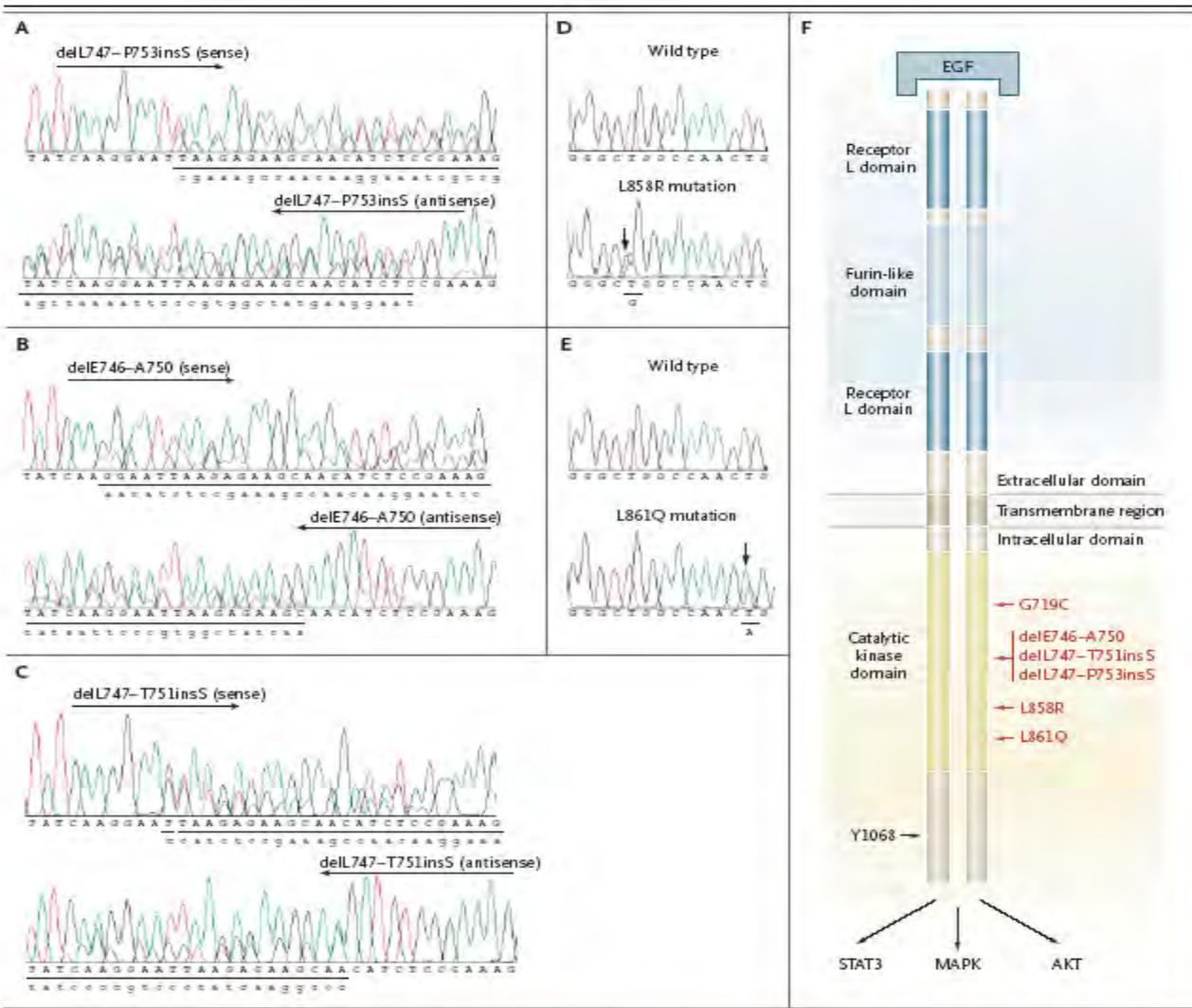
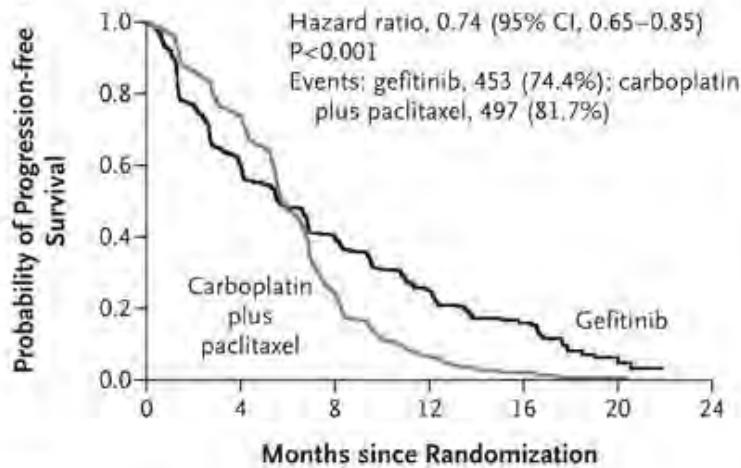
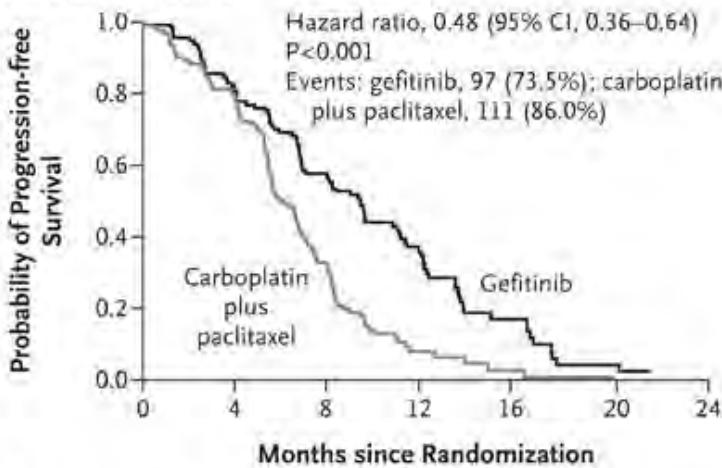
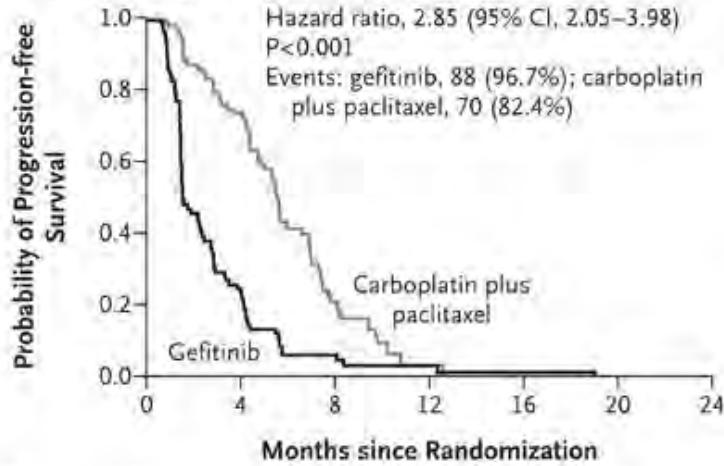
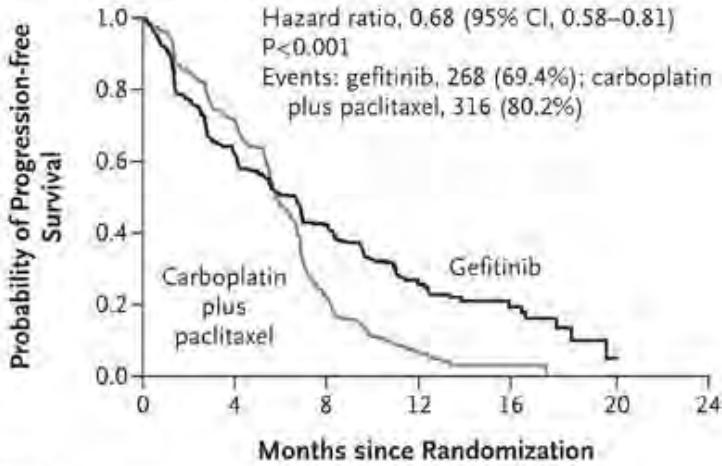


Figure 2. Mutations in the EGFR Gene in Gefitinib-Responsive Tumors.

Panels A, B, and C show the nucleotide sequence of the EGFR gene in tumor specimens with heterozygous in-frame deletions within the tyrosine kinase domain (double peaks). Tracings in both sense and antisense directions are shown to demonstrate the two breakpoints of the deletion; the wild-type nucleotide sequence is shown in capital letters, and the mutant sequence is in lowercase letters. The 5' breakpoint of the delL747-T751insS mutation is preceded by a T-to-C substitution that does not alter the encoded amino acid. Panels D and E show heterozygous missense mutations (arrows) resulting in amino acid substitutions within the tyrosine kinase domain. The double peaks represent two nucleotides at the site of heterozygous mutations. For comparison, the corresponding wild-type sequence is also shown. Panel F shows dimerized EGFR molecules bound by the EGF ligand. The extracellular domain (containing two receptor ligand [L] domains and a furin-like domain), the transmembrane region, and the cytoplasmic domain (containing the catalytic kinase domain) are highlighted. The position of tyrosine¹⁰⁶⁸ (Y1068), a site of autophosphorylation used as a marker of receptor activation, is indicated, along with downstream effectors activated by EGFR autophosphorylation—STAT3, MAP kinase (MAPK), and AKT. The locations of tumor-associated mutations, all within the tyrosine kinase domain, are shown in red.

A Overall**B EGFR-Mutation-Positive****No. at Risk**

	0	3	6	9	12	15	18	21	24	No. at Risk
Gefitinib	609	363	212	76	24	5	0			
Carboplatin plus paclitaxel	608	412	118	22	3	1	0			

C EGFR-Mutation-Negative**D Unknown EGFR Mutation Status****No. at Risk**

	0	3	6	9	12	15	18	21	24	No. at Risk
Gefitinib	91	21	4	2	1	0	0			
Carboplatin plus paclitaxel	85	58	14	1	0	0	0			

No. at Risk

	0	3	6	9	12	15	18	21	24	No. at Risk
Gefitinib	386	234	137	43	12	2	0			
Carboplatin plus paclitaxel	394	251	67	14	1	0	0			



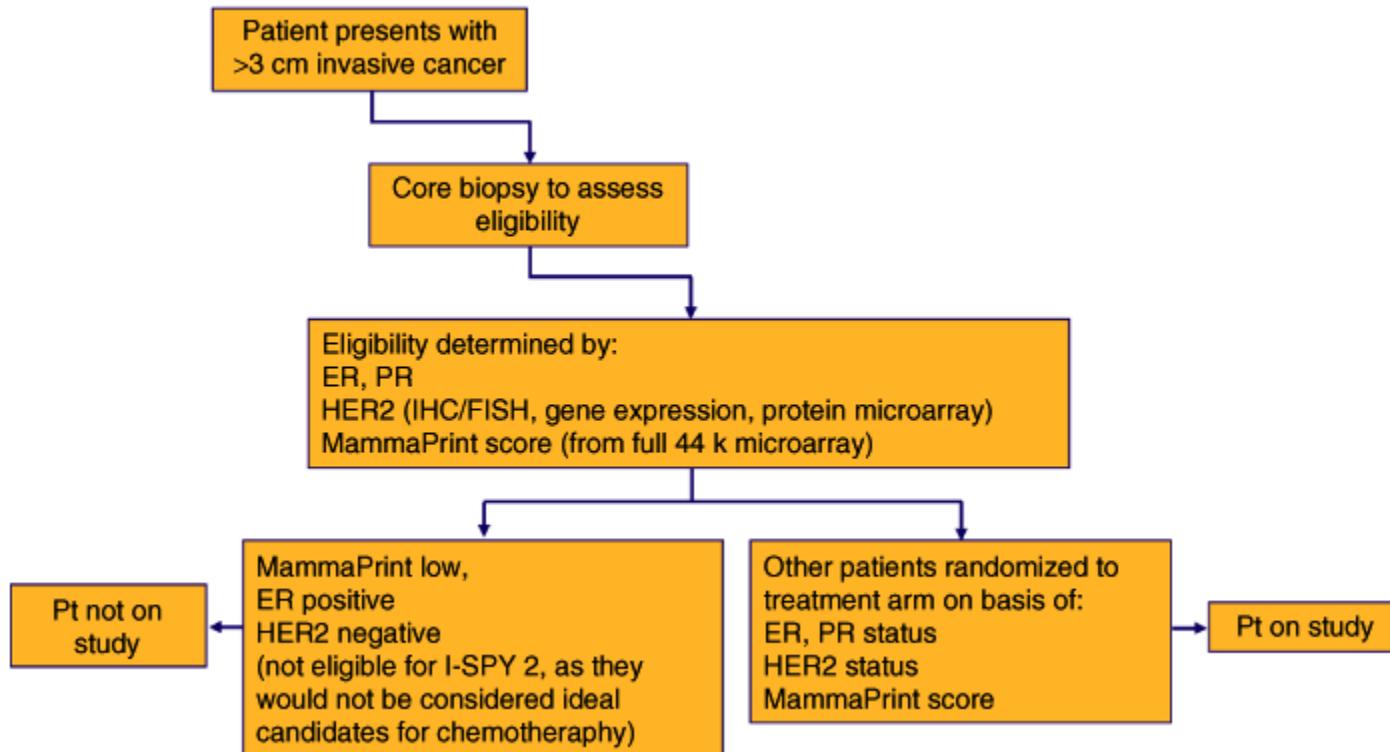
Breast Cancer Example

- I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy
- AD Barker, CC Sigman, GJ Kelloff, NM Hylton, DA Berry and L Esserman
- Clinical Pharmacology & Therapeutics, Vol 86 No 1, July 2009

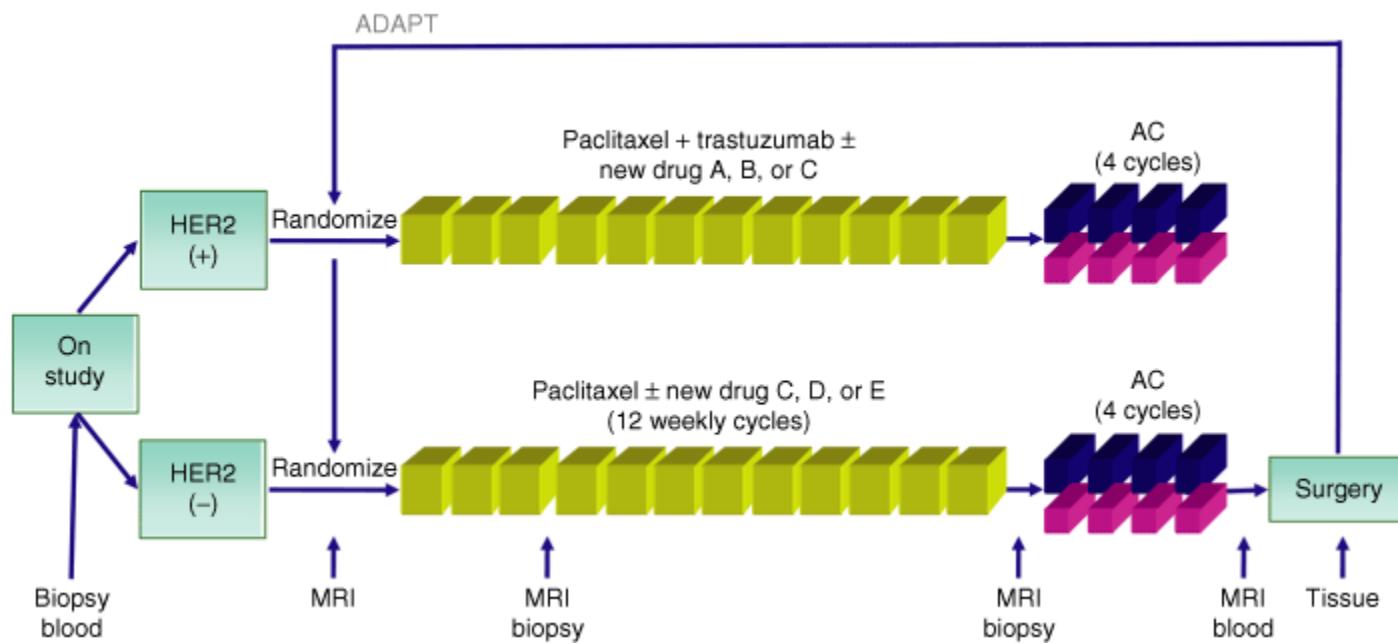
Breast Cancer

- I-SPY2 Adaptive Design Process
- Funded by FNIH: NCI, FDA, industry, academia, philanthropy
- Coordinated with FDA's CDER, CBER, CDRH from get-go
- Drugs from many companies
- Data sharing

Eligibility



Design



Breast Cancer

PERSONALIZED MEDICINE | How redesigning a clinical trial can speed drug development

1 cube = 10 patients

Traditional clinical trial

Takes essentially all patients with a disease being studied and is typically intended to eliminate differences in patient characteristics that could bias measures of drug effectiveness.

New trial design

Uses genetic profiles to highlight 'biomarker' differences among patients and to match drugs to patients with biomarkers that predict a benefit.

Note: In all clinical trials, phase I consists of testing on human subjects to determine toxicity levels.

Graphic by Maryanne Murray/WSJ

PHASE II

Randomized or non-randomized trial: In a randomized trial, about 60 patients are put in two groups: One receives the experimental drug and the other serves as a control group. In a non-randomized trial, about 40 patients receive the experimental drug.



PHASE II

Patients are placed in groups based on genetic profiles and are randomly assigned to either standard therapy or one of five different drugs plus standard care.

Early results increase chances that patients entering the trial later will be assigned to a drug showing benefit against tumors with their genetic profile.

Less successful drugs are eliminated.

It will take up to 120 patients for each drug to determine which ones graduate to phase III studies.

PHASE III

If a drug graduates to phase III, it typically takes 3,000 patients and about three years to determine if it is safe and effective enough for approval.



**HISTORIC SUCCESS RATE
30 TO 40%**

PHASE III

Researchers expect that drugs graduating from I-Spy 2 to phase III can be tested with 300 patients selected according to genetic profiles found to respond to the drug in phase II. It is hoped that this will shorten the time to approval.



**PROBABILITY OF SUCCESS
85%**

Source: Donald Berry, M.D. Anderson Cancer Center

I-SPY 2 Effects

- 40% savings on control arms
- Match drugs & combos with biomarker signatures
- Graduate drug/biomarker pairs to smaller ($n < 300$), more focused, more successful Phase 3
- Descendents of I-SPY 2 in melanoma, colorectal cancer, Alzheimer's, acute heart failure

Behavior/Neuropsychology Working Group



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Membership

- **Andrew Siderowf – WG Chair**
- Alastair Reith**
- Bernard Ravina**
- Chris Dodds**
- Dan Weintraub**
- David Burn**
- David Hewitt**
- Irene Richard**
- Jim Leverenz**
- Keith Hawkins**
- Matt Troyer**
- Michael Ward**
- Paolo Barone**
- Regan Fong**
- Sandeep Gupta**
- Susanne Ostrowitzki**
- Thomas Comery**
- Tony Wei-hsiu Ho**
- William Cho**



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Cognitive and behavioral assessments in PPMI

Cognitive

- Montreal Cognitive Assessment (MoCA)
- Hopkins Verbal Learning Test
- Benton Judgment of Line Orientation
- Letter-number sequencing
- Semantic fluency (animals, fruits, vegetables)
- Symbol-digit modalities test

Behavioral

- UPSIT
- Epworth Sleepiness Scale
- REM Sleep Disorder Questionnaire
- Geriatric Depression Scale (GDS-15)
- State-Trait Anxiety
- Impulse control (QUIP)
- SCOPA-AUT



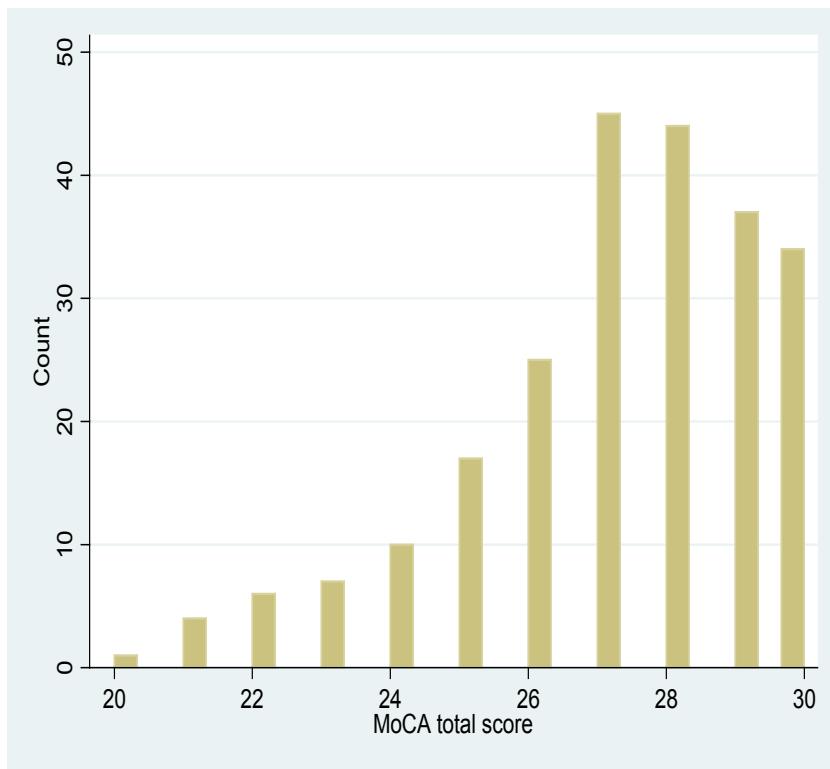
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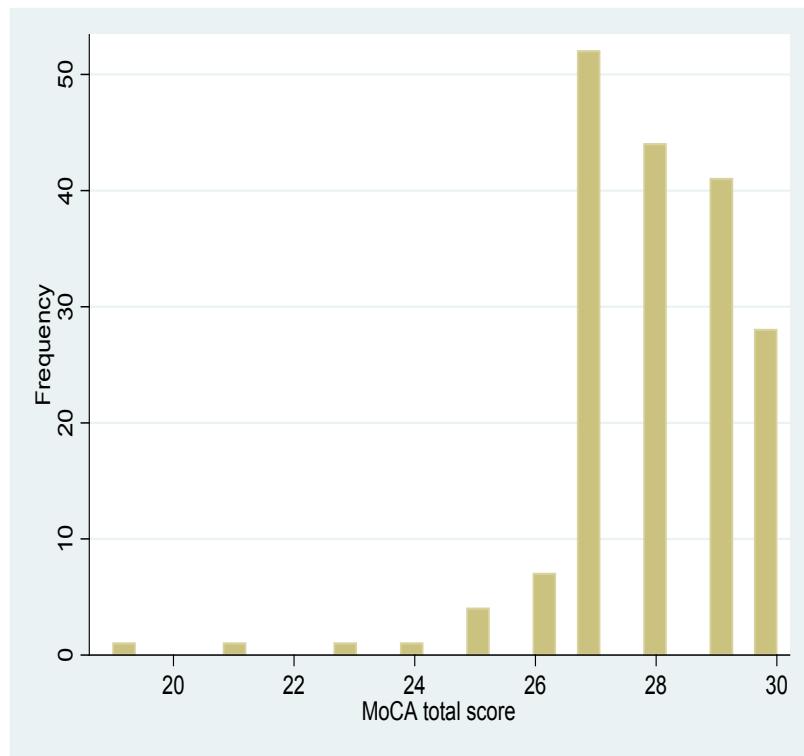


MoCA scores for patients and healthy controls

Patients



Healthy Controls



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Analysis of QUIP in PPMI

- QUIP is self-rated screening questionnaire for ICDs (compulsive gambling, sex, buying, and eating) and related behaviors (punding, hobbyism, walkabout) in PD
 - Short form used in PPMI
- Goal was to determine frequency and correlates of ICD and related behavior symptoms in de novo, untreated PD patients (N=168) and healthy controls (HCs) (N=143)



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Frequencies of Symptoms in PD Patients and Controls

ICD Type (percentage)	PD Patients (N=168)	Healthy Controls (N=143)	Statistic (chi-square)
Gambling	1.2%	0.7%	0.20 (1), p=0.66
Sex	4.2%	3.5%	0.09 (1), p=0.76
Buying	3.0%	2.1%	0.24 (1), p=0.63
Eating	7.1%	10.5%	1.09 (1), p=0.30
Any ICD	10.7%	13.3%	0.49 (1), p=0.49
Punding	4.8%	2.1%	1.61 (1), p=0.21
Hobbyism	5.4%	11.9%	4.30 (1), p=0.04
Walkabout	0.6%	0.7%	0.01 (1), p=0.91
Any ICD or related behavior	18.5%	20.3%	0.17 (1), p=0.68



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Multivariable Analyses in Entire Population

	Any ICD ^a (N=37)	Punding or Hobbyism ^b (N=33)	ICD or Related Behavior ^c (N=60)
Diagnosis (PD versus HC)	-0.48 (0.39), p=0.23	-0.70 (0.42), p=0.10	-0.43 (0.33), p=0.19
Age	-0.02 (0.02), p=0.20	-0.02 (0.02), p=0.40	-0.01 (0.01), p=0.37
Sex	0.07 (0.39), p=0.86	0.14 (0.41), p=0.74	0.01 (0.32), p=0.97
MoCA	-0.08 (0.11), p=0.46	-0.17 (0.11), p=0.10	-0.14 (0.09), p=0.11
GDS-15	0.18 (0.06), p=0.002	0.09 (0.07), p=0.17	0.17 (0.06), p=0.002

^a Chi-square=12.6 (df=5), p=0.03 for model. B (SE), p value presented for each variable.

^b Chi-square=6.8 (df=5), p=0.24 for model.

^c Chi-square=15.2 (df=5), p=0.01 for model.



Correlates in PD Patients

ICD Type	ICD + (N=18)	ICD - (N=150)	Statistic (t test, Mann-Whitney U test, or chi square)	ICD or Related Behavior + (N=31)	ICD or Related Behavior – (N=137)	Statistic (t test, Mann-Whitney U test, or chi square)
Age (mean, [SD])	58.8 (11.2)	61.9 (9.2)	1.3 (166), p=0.19	59.4 (11.0)	62.0 (9.1)	1.4 (166), p=0.15
Sex (% male)	72.2	71.3	0.006 (1), p=0.94	71.0	71.5	0.004 (1), p=0.95
Race (% white)	94.4	96.7	0.2 (1), p=0.63	96.8	96.4	0.01 (1), p=0.91
Education (# years)	16.1 (2.0)	15.8 (2.7)	p=0.54	15.7 (2.1)	15.9 (2.8)	p=0.91
UPDRS motor score (mean, [SD])	21.3 (5.7)	21.7 (8.9)	p=0.80	19.1 (6.0)	22.2 (9.0)	p=0.12
Hoehn & Yahr stage (median)	2.0	2.0	p=0.51	2.0	2.0	p=0.81
MoCA (mean, [SD])	27.1 (2.2)	27.1 (2.2)	p=0.75	26.5 (2.4)	27.3 (2.1)	p=0.11
Semantic Fluency (mean, [SD])	50.1 (11.7)	48.6 (10.9)	p=0.69	48.3 (10.1)	48.9 (11.2)	p=0.68
Letter Number Sequencing (mean, [SD])	10.2 (2.9)	10.9 (2.4)	p=0.47	10.8 (2.7)	10.8 (2.4)	p=0.81
GDS-15 (mean, [SD])	3.8 (3.0)	2.0 (2.3)	p=0.004	3.2 (2.7)	2.0 (2.3)	p=0.005
DaTSCAN striatal :occipital ratio						
Right caudate	1.5 (0.5)	1.4 (0.4)	-1.4 (18), p=0.18	1.5 (0.5)	1.4 (0.4)	-1.1 (37), p=0.26
Left caudate	1.4 (0.5)	1.4 (0.3)	p>0.99	1.4 (0.4)	1.4 (0.3)	p=0.90
Right putamen	0.7 (0.3)	0.7 (0.3)	p=0.48	0.7 (0.3)	0.7 (0.3)	p=0.47
Left putamen	0.7 (0.2)	0.7 (0.3)	p=0.54	0.7 (0.3)	0.7 (0.3)	p=0.63

Conclusions

- PD itself does not appear to confer an increased risk for development of ICD or related behavior symptoms
 - Further reinforces the reported association between PD medications and ICDs in PD
- As ≈20% of de novo PD patients screen positive for ICD or related symptoms, long-term follow-up needed to determine if such patients are at ↑ risk for ICD development once PD medications are initiated



Rationale for Assessment of Cognitive Impairment in PPMI

- Cognitive impairment/dementia important outcome in PD
- Movement Disorders Society Criteria for dementia and MCI recently published
- Previously no mechanism for assessment of MCI or dementia as a clinical diagnosis in PPMI



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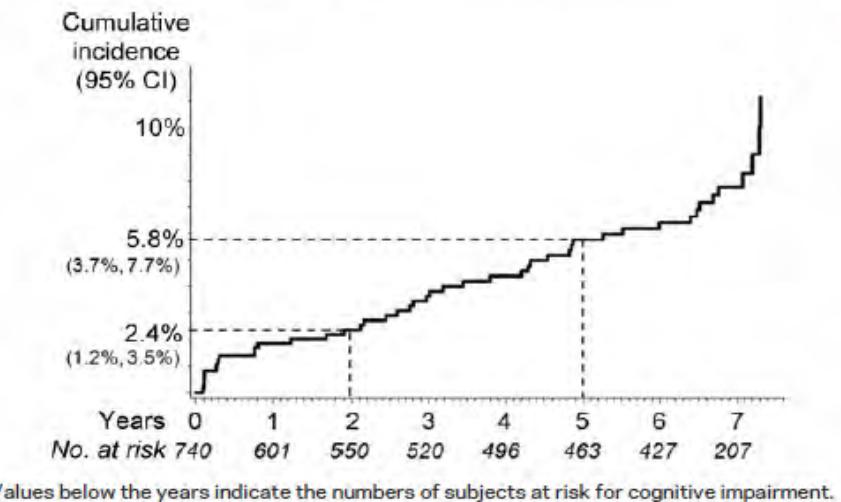
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Cognitive decline in early PD: Frequency and risk factors

- Age
- Education
- “Bulbar” UPDRS
- Frontal cognitive tests
- Hallucinations

Figure 1 Kaplan-Meier curve showing the cumulative incidence of cognitive impairment in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism cohort



MDS definitions of MCI and dementia

PD-MCI

- Report of cognitive decline from premorbid status
- No significant functional impairment resulting from cognitive decline
- Impaired cognitive performance
 - At least 2 test scores >1.0 SD below the standardized mean, regardless of domain

PD-dementia

- Presence of cognitive decline from premorbid status
- Significant functional impairment resulting from cognitive decline
- Impaired cognitive performance
 - At least one test score from 2 domains >1.5 SD below the standardized mean



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Goals of Cognitive Determination in PPMI

- Standardized assessment
- Implement Movement Disorders Society (MDS) definitions of PD-dementia and PD-MCI
- Limited site burden



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Steps for determination of MCI/dementia

1. Investigator determines whether there has been cognitive decline from pre-morbid baseline based on clinical interview and knowledge of patient
2. Investigator determines whether there is functional impairment based on cognitive deficits interfering with performance of routine instrumental activities of daily living (IADLs)
3. Subject has neuropsychological testing at study visit
4. Categorization of MCI/dementia is made centrally based on investigator determinations of #1 and #2 and results of neuropsychological testing
5. Investigator impression of whether MCI or dementia is present is assessed, but is not primary



Case Report Form

DRAFT

PPMI

1	3	2
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COGNITIVE CATEGORIZATION

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

A. Indicate the source of information:
1 = Subject, 2 = Caregiver, 3 = Subject and Caregiver A.

Determining Report of Cognitive Decline

Based on information provided by the subject, the informant, and/or based on the Site Investigator's judgment, determine whether the subject has experienced a decline in cognition compared with pre-morbid abilities (i.e., pre-PD). The following cognitive abilities should be considered:

Attention: Ability to sustain and direct attention, lapses

Memory: Registration, recall of recent events or important dates, new learning ability, misplacement of items, forgetting items

Orientation: Forgetting appointments, estimating time, spatial or geographical orientation

Executive abilities: Reasoning ability, making decisions, following instructions, difficulty with calculations

Praxis: Constructional or mechanical cognitive ability, such as use of tools and appliances

Language: Word finding problems, problems with naming or comprehension

1. Has the subject experienced cognitive decline? (0 = No, 1 = Yes) 1.

Determining Functional Impairment

Based on information provided by the subject, the informant, and/or based on the Site Investigator's judgment, determine whether 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 functional impairment as a result of cognitive impairment? (0 = No, 1 = Yes) 2.

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PPMI

1	3	2
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COGNITIVE CATEGORIZATION

SUBJECT ID	□ □ □	VISIT NO	□ □
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Determining Cognitive Diagnosis

Based on your impression of the subject's current cognitive function, which may include performance on neuropsychological testing, as well as your knowledge of his/her pre-morbid cognitive function and the degree to which cognitive deficits impact his/her ability to carry out daily activities, please rate the subject's current cognitive status. The determination of dementia implies (1) cognitive function that is impaired in more than one cognitive domain, (2) decline from pre-morbid function, and (3) impact of cognitive impairment on daily function. The determination of MCI is based on (1) impairment in at least one cognitive domain, (2) decline from pre-morbid function, and (3) lack of significant impact of cognitive impairment on daily function.

3. Based on your clinical impression, which of the following categories best describes the subject's cognitive state? 3.

1 = Normal Cognition (PD-NC)
2 = Mild Cognitive Impairment (PD-MCI)
3 = Dementia (PDD)

4. What is your level of confidence of this cognitive diagnosis? 4.

1 = 90 - 100%
2 = 50 - 89%
3 = 10 - 49%
4 = 0 - 9%

5. Did you review any neuropsychological tests (including MoCA scores) in making this determination? (0 = No, 1 = Yes) 5.

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Rationale for Emphasizing testing over investigator impression

- Investigator impression still central
 - Cognitive decline
 - Functional impairment
- Minimize site burden
 - Calculate normalized scores
 - Feed back information to PI in real time
- Maintain consistency with MDS definitions



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What about completed visits

- If the subject is not MCI or demented at current visit, a category of normal will be assigned to prior, missing visits
- If the subject is MCI or demented at next visit, determination will be made retrospectively
- Retroactive determinations will be noted in database



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PPMI Biochemical Biomarker Working Group

Les Shaw/John Trojanowski
May 3, 2012



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October 2011: Kickoff Call

- Reviewed inventory and QC issues of PPMI biosamples
- Reviewed alpha-synuclein Round Robin study
- Reviewed initial A β ₁₋₄₂, t-tau & p-tau₁₈₁ data



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Identification of biomarker candidates for inclusion is critical to PPMI

	Tier 1	Tier 2	Tier 3
Criteria	<ul style="list-style-type: none">▪ Markers for which there is some evidence for a disease association▪ Preliminary data around the detection of the marker in a biochemical assay exist	<ul style="list-style-type: none">▪ Putative markers with weak data correlating to PD▪ Standardized assays exist → straightforward to study in PD subjects	<ul style="list-style-type: none">▪ Minimal data available▪ Relationship to PD hypotheses and mechanisms of disease exist
Candidates *	<ul style="list-style-type: none">▪ Alpha-synuclein▪ DJ-1▪ Urate	<ul style="list-style-type: none">▪ Cytokines▪ Glutamine/Glutamate▪ Total Tau and Phospho-Tau (p-181) and Abeta 1-42 species (INNO-BIA AlzBio3 assay)	<ul style="list-style-type: none">▪ ST13▪ J. Zhang's panel of proteins from proteomics▪ Glutathione▪ 8-OHdG

Five biomarker candidates are being actively tracked in PPMI

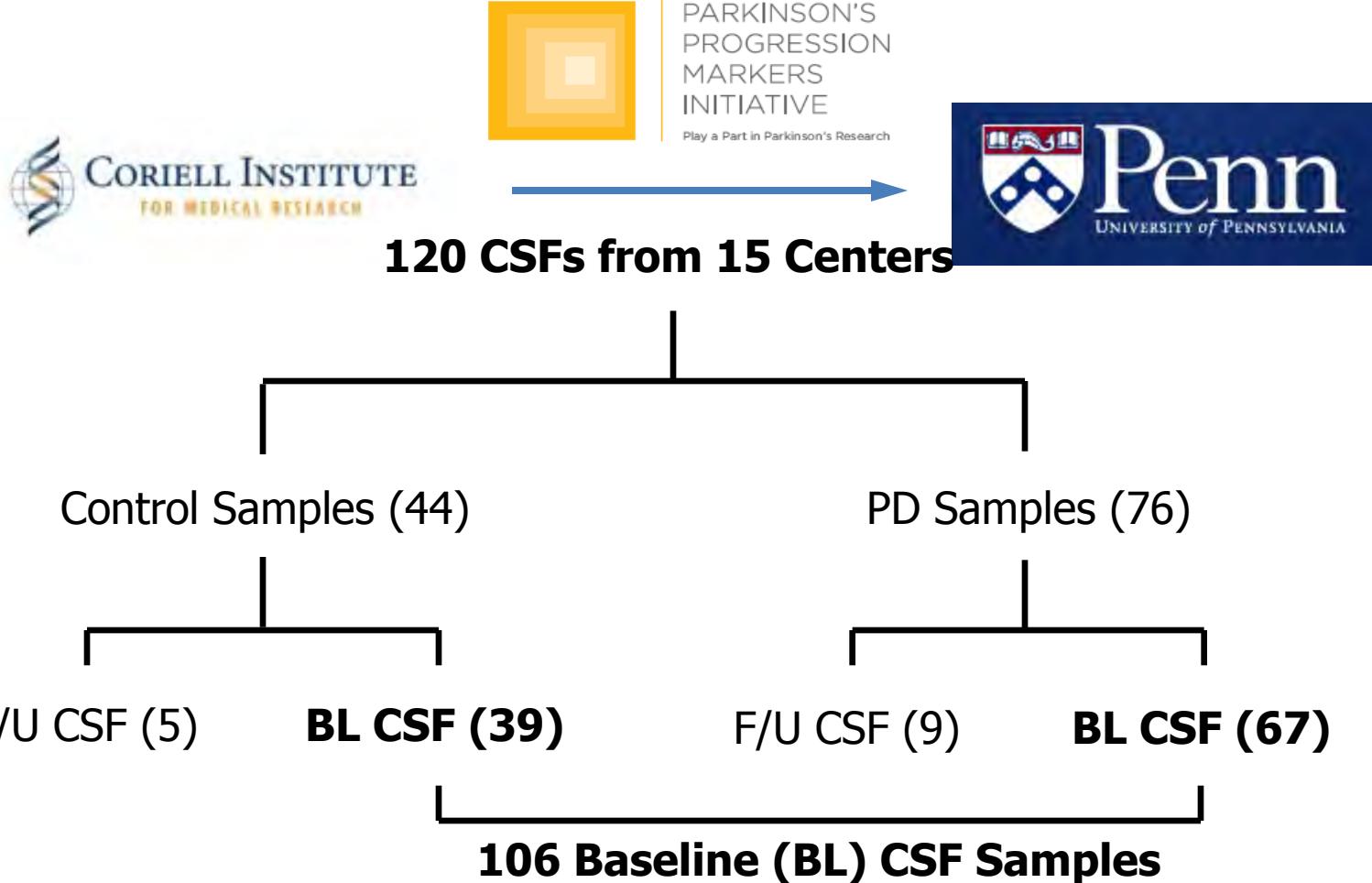


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Transfer of 120 PPMI CSF Samples



Analysis of CSF biomarkers

AD biomarkers analyses : Luminex- platform with AlzBio3 kit,

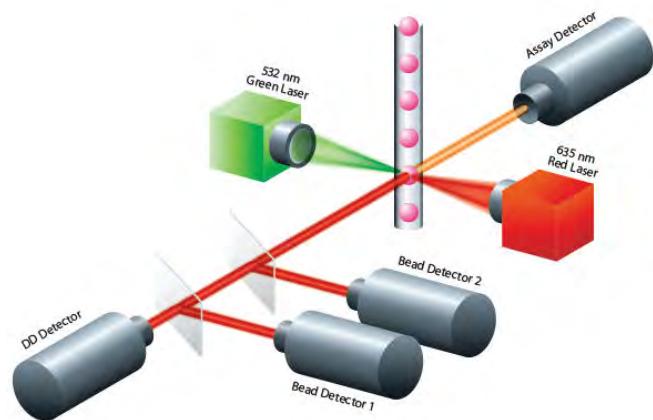
Total of 4 plates (4 runs)

1st plate : Jul. 14 – 15, 2011

2nd plate : Jul. 18 – 19, 2011

3rd plate : Jul. 19 – 20, 2011

4th plate : Jul. 20 – 21, 2011



α -synuclein analyses : ELISA methodology by Covance Inc.

Nov. 15 – Nov. 29, 2011

Characteristics of samples and Analytical performance

Number of subjects	Control		PD	
	40		67	
Number of samples (Total = 120)	Baseline	F/U	Baseline	F/U
	39	5 (VT02)	67	9 (ST: 5, VT02: 4)
Analytical performance	T-tau (%CV)		A β ₁₋₄₂ (%CV)	p-tau ₁₈₁ (%CV)
Aqueous QC controls (n = 4)	ConA	ConB	ConA	ConB
	7.45	3.77	3.60	3.99
CSF pool QC samples (n = 4)	Pool48	Pool52	Pool48	Pool52
	5.09	7.69	9.67	5.37
				3.29
				2.72

Demographics of the PPMI subjects

	HC (N = 39)	PD (N = 63)	<i>P</i> value	SWEDD (N= 4)
Age, years (95% C.I.)	59 ± 13 (55 – 63)	62 ± 10 (60 – 65)	0.2781	67 ± 7 (55 – 78)
Sex, F/M (% of Male)	18/21 (53.8)	24/39 (61.9)	0.4216#	2:2 (50.0)
Education, years (95% C.I.)	16.9 ± 2.4 (16.1 – 17.6)	16.4 ± 2.5 (15.8 – 17.0)	0.1421	14.3 ± 2.1 (11.0 – 17.5)
Age at onset, years (95% C.I.)	-	59.5 ± 10.8 (56.8 – 62.2)	-	63.5 ± 8.2 (50.5 – 76.5)
Mean duration of symptoms, median years (range)	-	1.8 (0.3 – 20.8)	-	2.0 (0.0 – 2.9)
Number of subjects with CSF Hb > 200 ng/mL	6	18	0.1271#	1

#Chi-square test

Clinical characteristics of the PPMI subjects[#]

	HC (N = 39)				PD (N = 63)				p value*	SWEDD (N= 4)			
H & Y stage	0.03 ± 0.16 Texte				1.65 ± 0.51				< 0.0001	1.50 ± 0.58			
UPDRS III motor score	1.6 ± 2.7				22.6 ± 7.6				< 0.0001	17.3 ± 6.2			
Mean tremor score	0.05 ± 0.13				0.46 ± 0.27				< 0.0001	0.50 ± 0.20			
Mean PI GD score	0.01 ± 0.04				0.24 ± 0.26				< 0.0001	0.00 ± 0.00			
UPSIT score	35.1 ± 3.4				21.9 ± 8.1				< 0.0001	33.0 ± 2.9			
Striatal binding ratios (Mean values)	PR	PL	CR	CL	PR [¶]	PL	CR	CL	<0.0001	PR	PL	CR	CL
	1.38	1.39	2.06	2.05	0.61	0.64	1.34	1.33		1.39	1.56	2.00	2.02
MoCA (95% C.I.)	28.4 ± 1.0 (28.0 – 28.7)				27.2 ± 2.0 (26.7 – 27.7)				0.0039	27.3 ± 2.4 (23.5 – 31.0)			
Semantic fluency	53.8 ± 12.1				49.5 ± 10.6				0.0578	40.8 ± 4.1			
WMSIII-LNS test score	12.1 ± 2.8				11.0 ± 2.0				0.0510	10.0 ± 1.4			
SDMT\$	48.6 ± 11.2				41.9 ± 8.9				0.0051	44.8 ± 7.7			
HVLT_total recall	9.0 ± 1.6				8.2 ± 1.5				0.0077	7.8 ± 2.4			
HVLT delayed recall	9.9 ± 2.3				8.3 ± 2.3				0.0004	9.3 ± 4.2			

*Mann-Whitney U test

[¶]PR: Right putamen, PL: Left putamen, CR: Right caudate, CL: Left caudate, N=39 for HC, N=62 for PD, N=4 for SWEDD.

#Data were updated based on PPMI database (04. 12. 2012); Diagnoses of 2 patients were changed.

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

Biomarkers	HC (N = 39)	PD (N = 63)	P value [#]	SWEDD (N = 4)
A β ₁₋₄₂ (pg/mL) (95% C.I.)	242.8 ± 49.95 (226.7 – 259.0)	228.7 ± 45.63 (217.2 – 240.2)	0.0466	276.0 ± 22.99 (239.4 – 312.6)
t-tau (pg/mL) (95% C.I.)	53.9 ± 19.33 (47.6 – 60.1)	46.1 ± 24.71 (39.8 – 52.3)	0.0276	55.0 ± 25.47 (14.47 – 95.53)
p-tau ₁₈₁ (pg/mL) (95% C.I.)	24.9 ± 8.45 (22.2 – 27.6)	21.0 ± 7.83 (19.0 – 23.0)	0.0093	23.5 ± 8.35 (10.22 – 36.78)
t-tau/A β ₁₋₄₂ ratio (95% C.I.)	0.240 ± 0.141 (0.195 – 0.286)	0.215 ± 0.157 (0.176 – 0.255)	0.0451	0.196 ± 0.083 (0.063 – 0.329)
p-tau ₁₈₁ /A β ₁₋₄₂ ratio (95% C.I.)	0.113 ± 0.075 (0.089 – 0.138)	0.099 ± 0.063 (0.084 – 0.115)	0.1482	0.084 ± 0.023 (0.047 – 0.121)
p-tau ₁₈₁ /t-tau ratio (95% C.I.)	0.491 ± 0.160 (0.439 – 0.543)	0.543 ± 0.263 (0.477 – 0.609)	0.6820	0.495 ± 0.230 (0.130 – 0.860)
α -syn (pg/mL) (95% C.I.)	1264 ± 425.7 (1126 – 1403)	1082 ± 611.1 (928 – 1235)	0.0120	1413 ± 750.6 (219 – 2608)
α -syn (pg/mL) (95% C.I.) *	1267 ± 443.5 (1109 – 1424)	1020 ± 456.7 (883 – 1158)	0.0175	1359 ± 909.8 (-901 – 3619)
α -syn (pg/mL) (95% C.I.) **	1269 ± 435.2 (1124 – 1414)	1019 ± 474.8 (886 – 1151)	0.0073	1359 ± 909.8 (-901 – 3619)

*Subjects with CSF Hb < 200 ng/mL. N=33 for HC, N=45 for PD, N=3 for SWEDD.

**Subjects with CSF Hb < 500 ng/mL. N=37 for HC, N=52 for PD, N=3 for SWEDD.

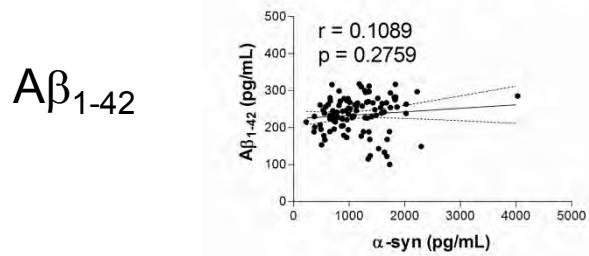
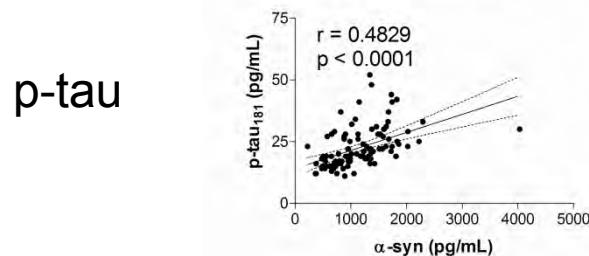
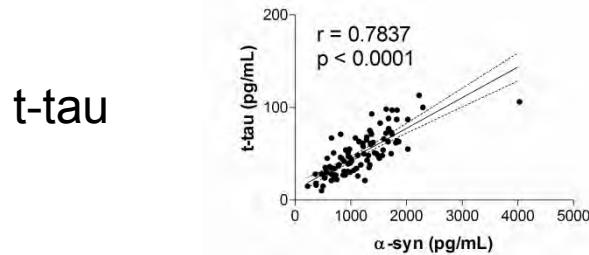
#Mann-Whitney U test

#Data were updated based on PPMI database (04. 12. 2012); Diagnoses of 2 patients were changed.

Summary of multivariate regression analyses

- Multivariate regression analysis: α -SYN is significantly associated with PD diagnosis ($p=0.0019$), but other biomarkers or their ratios are not.
- For clinical variables in PD, p-tau is significantly associated with UPDRS III motor score, ($p=0.0140$), but we could not observe any significant associations between other biomarkers or ratios and other clinical variables.

Correlation between AD biomarkers and α -synuclein



Association of CSF biomarkers with clinical Phenotype of PD

- ✓ Tremor dominant, or Postural instability and gait disturbance (PIGD) dominant phenotype
- ✓ These phenotypes were classified by tremor and PIGD score derived from motor subsection of the UPDRS (Zetusky WJ et al, 1985; Jacovic J et al., 1990)
 - Ratio of tremor/PIGD score ≥ 1.5 : Tremor dominant
 - Ratio of tremor/PIGD score ≤ 1.0 : PIGD dominant
 - Others: Mixed type

UPDRS Subsection used to classify Tremor or PIGD-dominant phenotype

- ✓ Mean tremor score (10 items)
 - : UPDRS II – 1) Tremor
 - : UPDRS III – 2, 3) Postural tremor (both hands), 4, 5) Kinetic tremor (both hands), 6-10) Resting tremor (4 extremities and lip/jaw)
- ✓ Mean PIGD score (5 items)
 - : UPDRS II – 1) Walking and balance, 2) Freezing
 - : UPDRS III – 3) Gait, 4) Freezing of gait, 5) Postural stability

CSF biomarkers according to clinical phenotype in PD patients

Biomarkers	PIGD (N = 22)	Tremor (N = 18)	p value*	Mixed (N = 27)	HC
A β ₁₋₄₂ (pg/mL)	213.9 ± 40.5	241.7 ± 28.1	0.0081	239.1 ± 55.8	242.8 ± 49.95[#]
t-tau (pg/mL)	38.7 ± 25.5	49.6 ± 16.1	0.0187	51.0 ± 27.7	53.9 ± 19.33[#]
p-tau ₁₈₁ (pg/mL)	19.5 ± 8.0	22.0 ± 6.6	0.1697	22.0 ± 8.4	24.9 ± 8.45[#]
α -syn (pg/mL)	905.8 ± 482.1	1149.0 ± 490.1	0.0553	1229.0 ± 758.8	1264 ± 425.7[#]
α -syn (pg/mL), CSF Hb < 500 ng/mL	857.5 ± 495.3	1068.0 ± 447.6	0.0824	1150.0 ± 517.8	1269 435.2[#]
α -syn (pg/mL), CSF Hb < 200 ng/mL	778.9 ± 363.0	1098.0 ± 449.0	0.0291	1186.0 ± 532.9	1267 443.5[#]
t-tau/A β ₁₋₄₂ ratio	0.197 ± 0.176	0.208 ± 0.072	0.0503	0.232 ± 0.175	0.240 ± 0.141[#]
p-tau/A β ₁₋₄₂ ratio	0.096 ± 0.052	0.092 ± 0.030	0.5960	0.105 ± 0.082	0.113 ± 0.075
p-tau/t-tau ratio	0.622 ± 0.338	0.466 ± 0.113	0.2769	0.523 ± 0.248	0.49 ± 0.16

*PIGD vs. Tremor; Mann-Whitney U test

[#]Significant different vs PIGD, but not vs Tremor group

Identification of biomarker candidates for inclusion is critical to PPMI

	Tier 1	Tier 2	Tier 3
Criteria	<ul style="list-style-type: none">▪ Markers for which there is some evidence for a disease association▪ Preliminary data around the detection of the marker in a biochemical assay exist	<ul style="list-style-type: none">▪ Putative markers with weak data correlating to PD▪ Standardized assays exist → straightforward to study in PD subjects	<ul style="list-style-type: none">▪ Minimal data available▪ Relationship to PD hypotheses and mechanisms of disease exist
Candidates *	<ul style="list-style-type: none">▪ Alpha-synuclein▪ DJ-1▪ Urate	<ul style="list-style-type: none">▪ Cytokines▪ Glutamine/Glutamate▪ Total Tau and Phospho-Tau (p-181) and Abeta 1-42 species (INNO-BIA AlzBio3 assay)	<ul style="list-style-type: none">▪ ST13▪ J. Zhang's panel of proteins from proteomics▪ Glutathione▪ 8-OHdG

Five biomarker candidates are being actively tracked in PPMI



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January 2012 Call: Review of PD biomarker literature

- Alpha-synuclein
 - Post translational modifications: phosphorylated, nitrated, aggregated, etc
- DJ-1 modifications (Oxidized)
- MicroRNAs
- Isoprostanes/Oxidative markers
- Neurofilament markers
- Ft3 and Fractalkines
- Neuromelanin



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Next Biologics WG call

- Revisit criteria and data required for inclusion in PPMI
- Invite Jing Zhang to discuss his data around novel PD biomarkers



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PPMI Imaging Core

3 May 2012



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Working Group Discussions and Future Directions

- VMAT2 imaging
- Resting state MRI
- Refining DAT quantification
- New targets

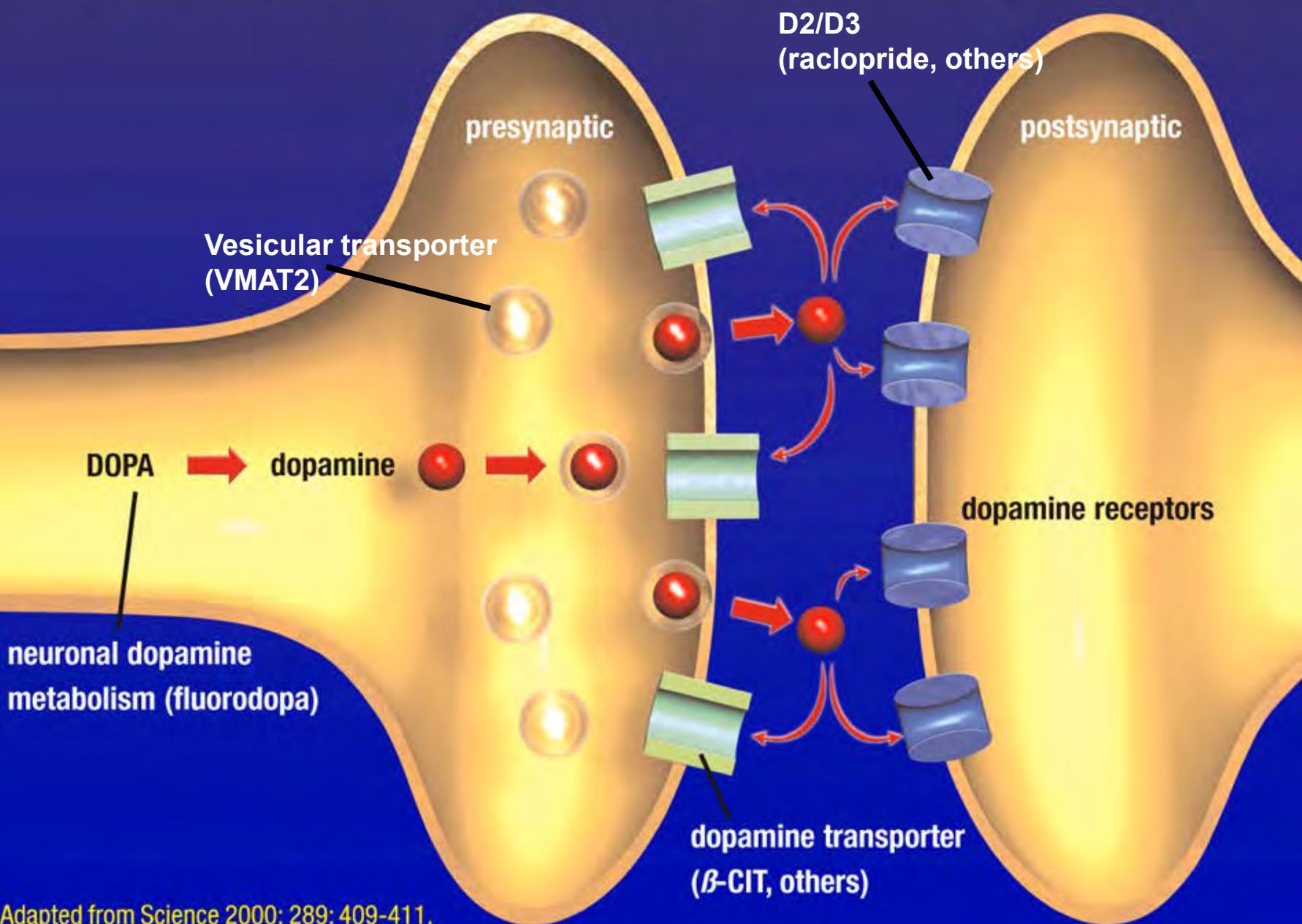


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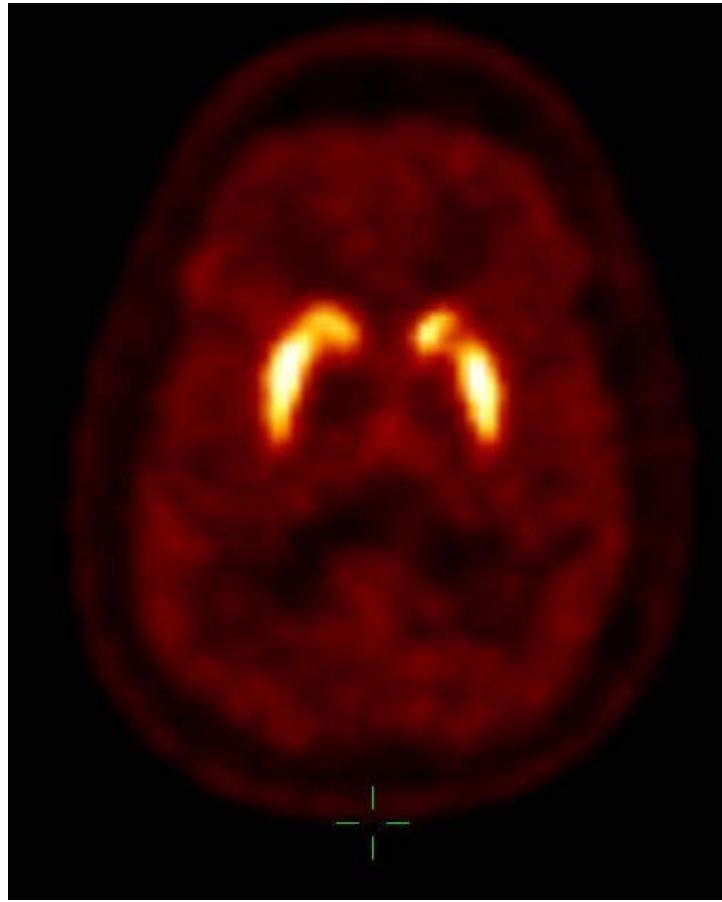
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Imaging in the brain: Molecular targets of radioligands.⁷



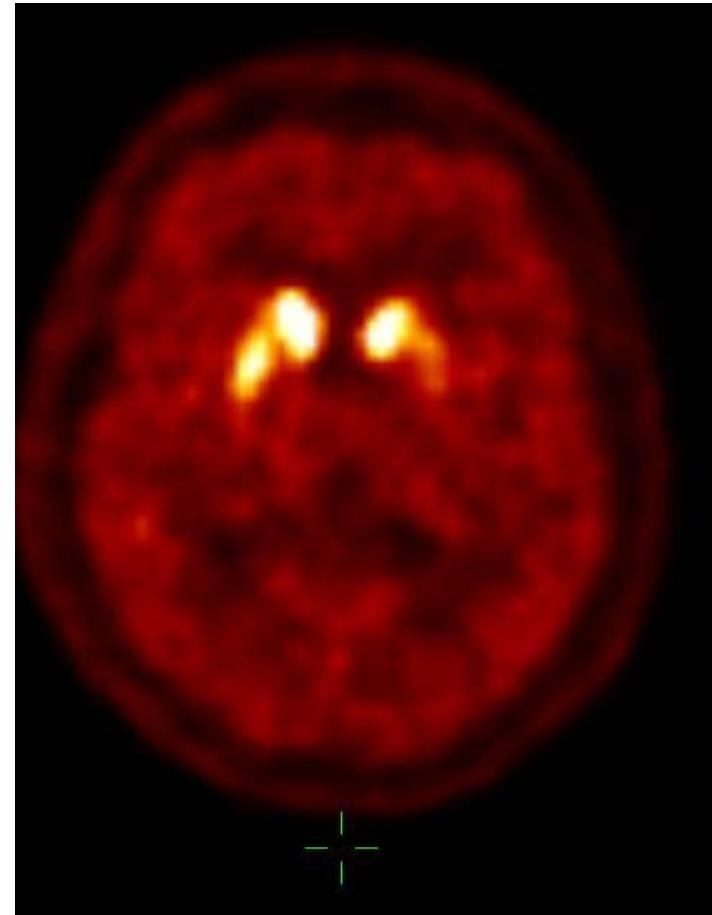
18F-AV-133: Targets VMAT2



Healthy Subject

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AV-133

Mean putamen binding ratio = 3.52



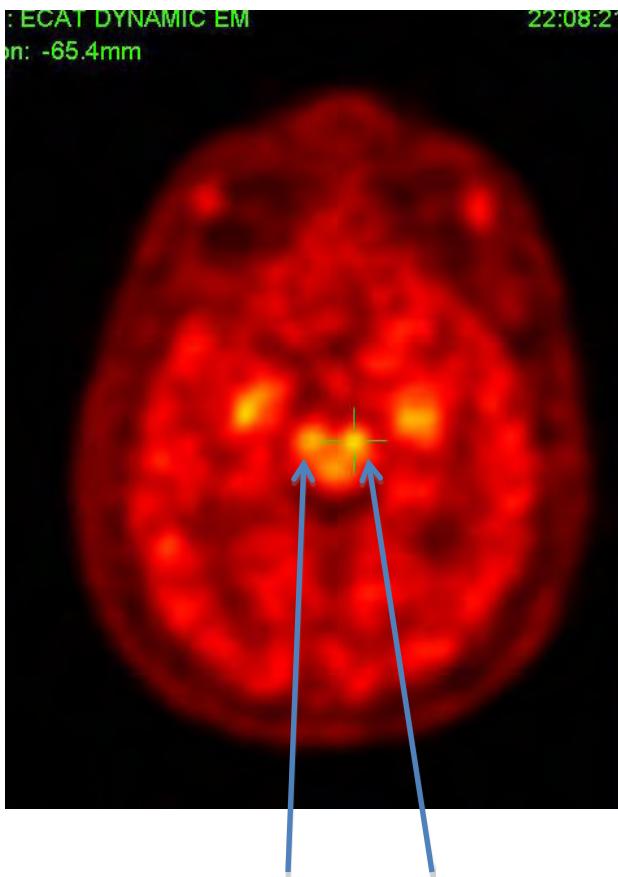
Parkinson's Subject

Mean putamen binding ratio = 1.36

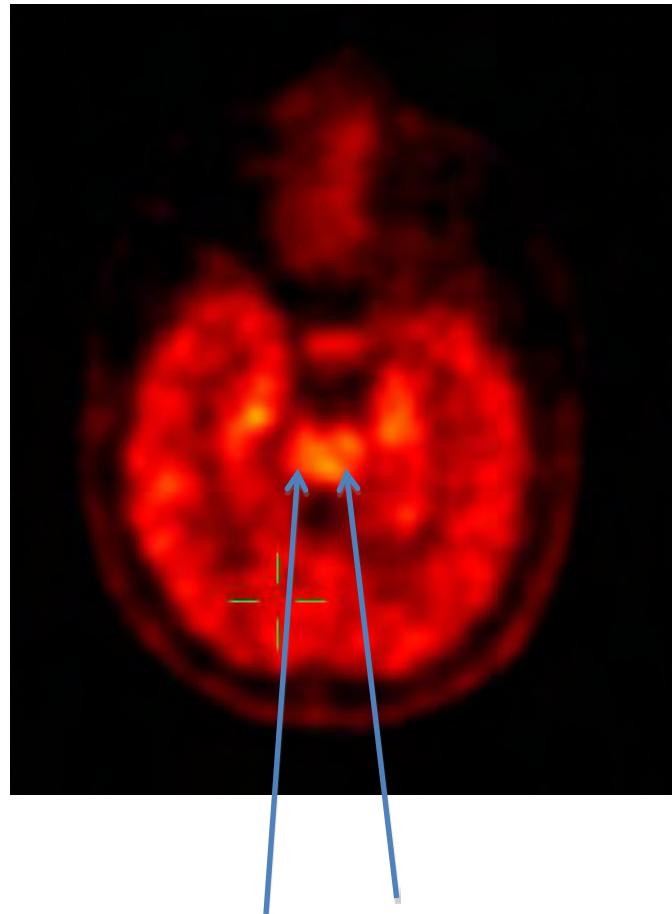


18F-AV133 PET: possible to image the substantia nigra directly

Healthy Subject



PD Subject



Substantia nigra
SN ratio = 1.59

Substantia nigra
SN ratio = 0.91



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PPMI AV-133

PET Imaging sites

- IND
- UPENN
- Johns Hopkins
- Banner
- Baylor
- Sydney- used for enrollment eligibility



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VMAT2 Questions

- Will AV-133 PET differ from DAT as an enrollment scan?
- What analyses should be done in subjects with both AV-133 and SPECT DAT, is higher VMAT2 binding associated with slower clinical progression?
- Analyses could also include locus coeruleus, s. nigra, raphe nuclei



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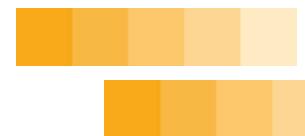
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PPMI Resting State MRI Sub-Study

Darren Gitelman, MD (PI)
Todd Parrish, PhD (physicist)
Xue Wang, PhD (quality control)



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Resting State Sub-Study

- **Aim:** To acquire resting state functional MRI (rsfMRI) data on a subset of patients with Parkinson's disease and controls.
- **Background:** rsfMRI examines the brain's intrinsic functional connectivity by measuring the synchrony of low frequency fluctuations of BOLD (blood oxygen level dependent) MR signal.
 - Changes in rsfMRI activity has been seen in a number of neurodegenerative disorders including PD.



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Methods

- **Sites:** 7 sites with fMRI licenses currently participating in the DTI acquisition.
- **Scanners:** Siemens 3T Trio
- **Subjects:** 30 PD subjects, 30 controls.
- **MR sequence:** TR= 2400 msec, 48 slices, 3 x 3 x 3 mm voxels
- **Quality control:** measures of movement, scan-to-scan and slice-to-slice variance, phantom measurements of noise and stability



Schedule

- **PD participants:** Scanned at entry, then yearly until the end of the study.
- **Controls:** Scanned at entry.



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Analyses

- Data analysis is not formally part of this proposal, but potential analyses listed below.
 - Whole brain correlations
 - Seed-based correlations
 - Independent components analysis
 - Amplitude of low frequency fluctuations (ALFF)
 - ReHo (regional homogeneity)
 - Network measures (e.g., small world networks)

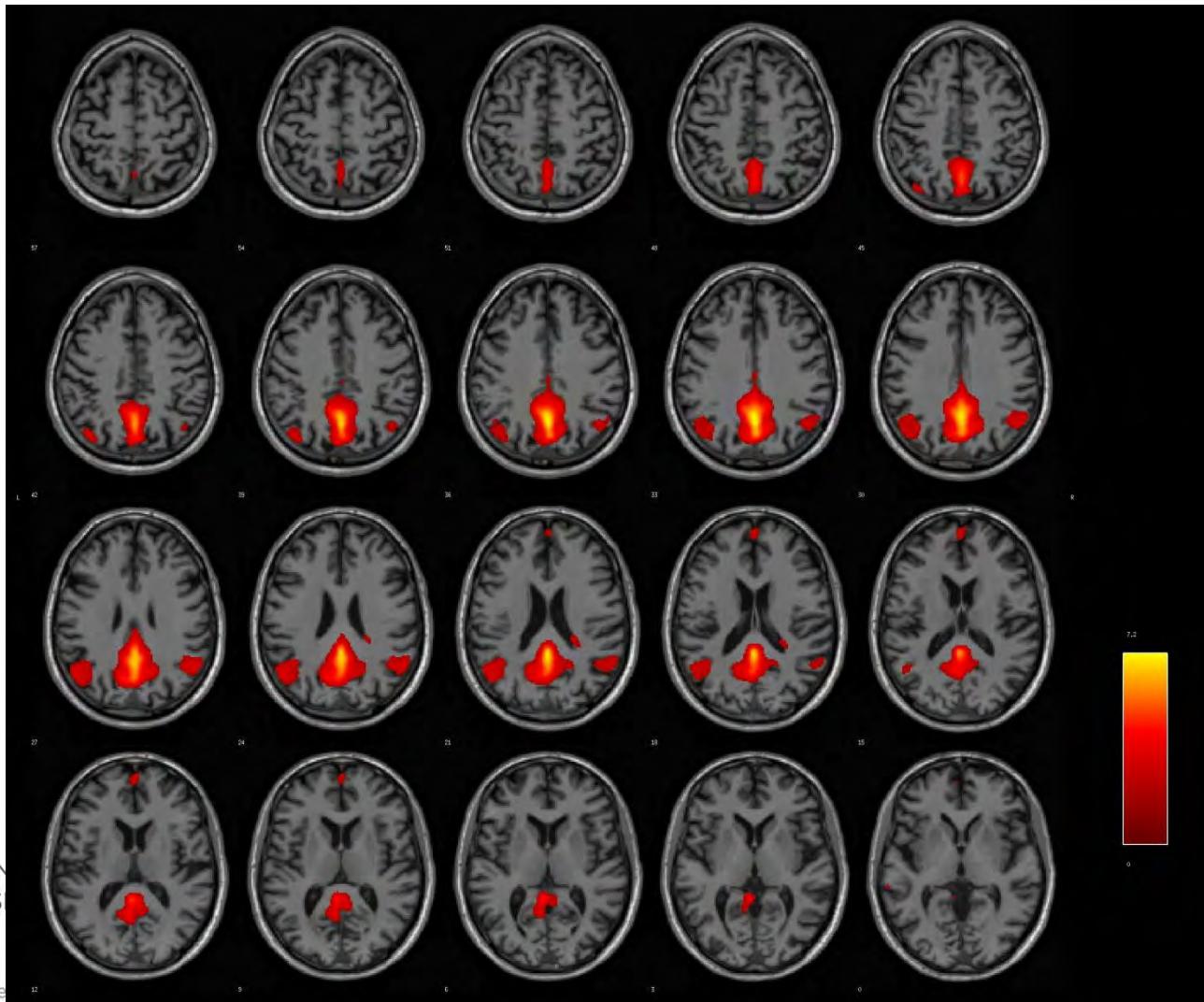


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ICA of rsfMRI data in PD (n=11)



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DATSCAN Analyses

- Normative database(s) for age correction and informing SBR cut-offs for premotor cohort inclusion.
- Biomarker associational analyses, e.g.
 - Does baseline DAT predict rate of change in clinical measures or other biomarkers?
 - Does change in DAT predict longitudinal changes in clinical or other imaging or non-imaging biomarkers?
- Use of 57 Cobalt correction phantoms to reduce variance in within-subject longitudinal SBRs.

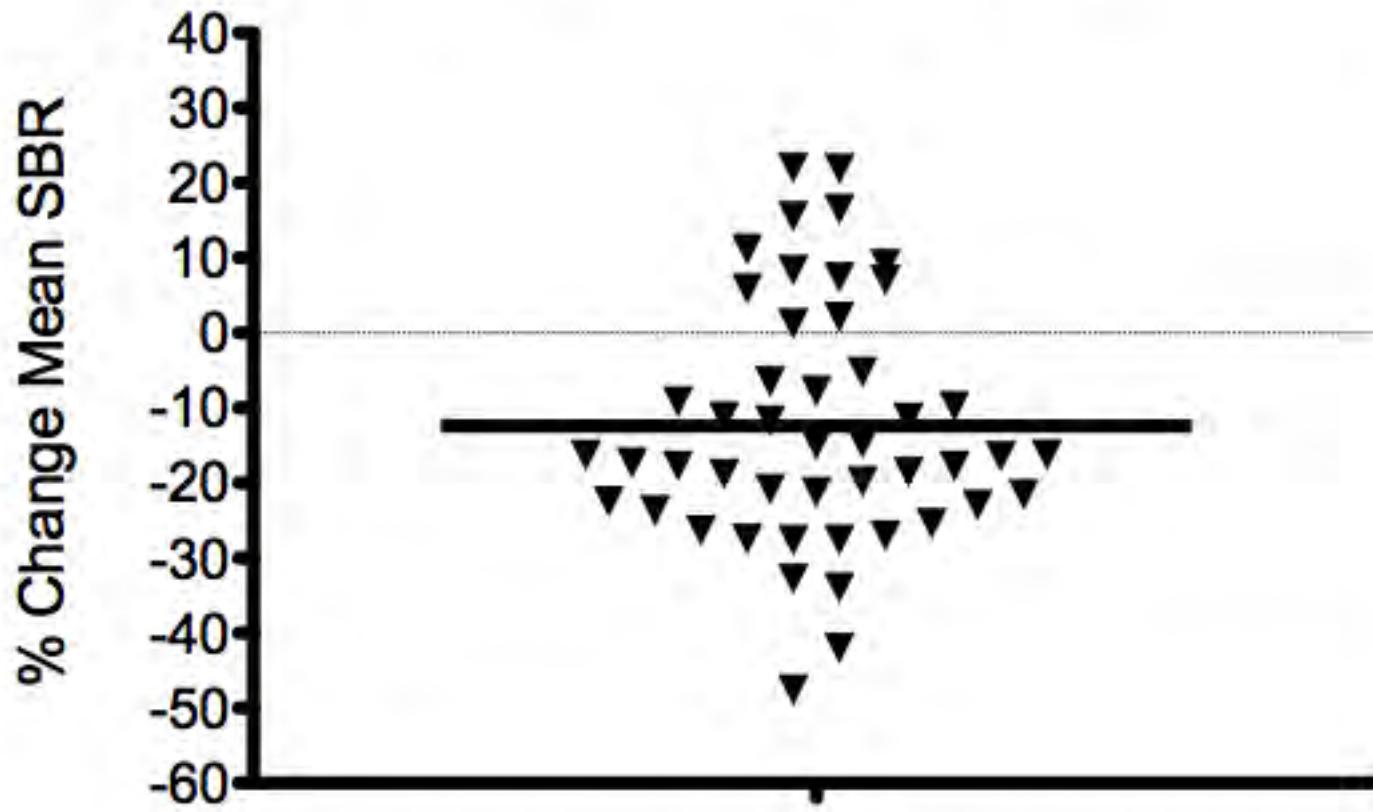


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Percent change over one year (n=47)

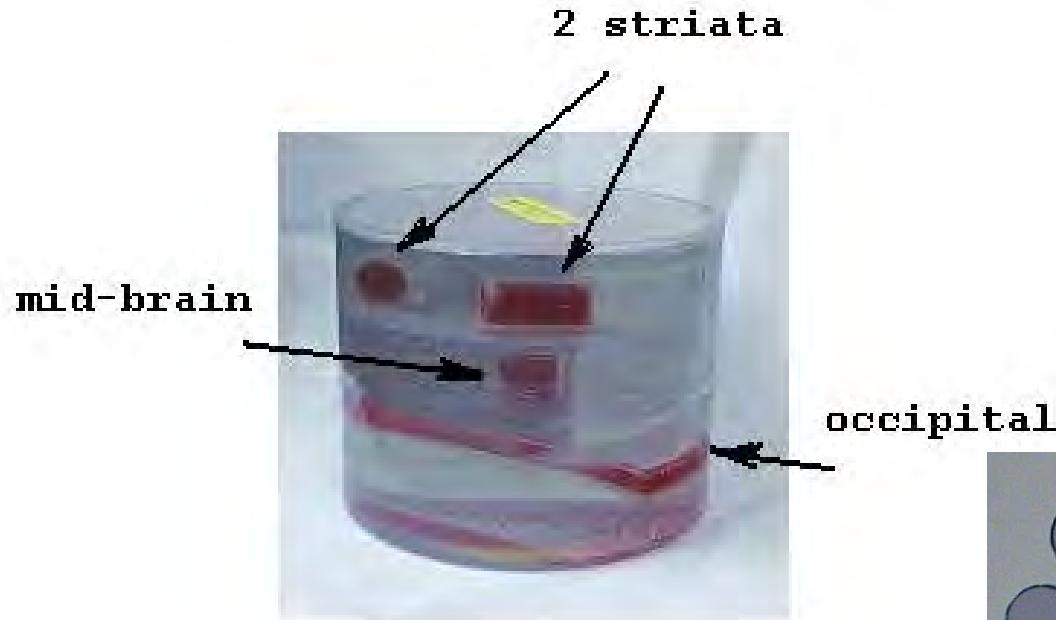


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Mean reduction = 12.4 % (%COV= 131%)

57-Co Striatal Phantom



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Other Imaging Biomarkers

- If funding were available, what other brain targets should PPMI focus on over the next years?
 - Neuroinflammation (e.g. TSPO on activated microglia)
 - Proteinopathy (e.g. alpha-synuclein, tau, amyloid- β)
 - Metabolism (FDG)
 - Other receptor targets (e.g. A2a, mGluR5, 5HT1a, CB1)

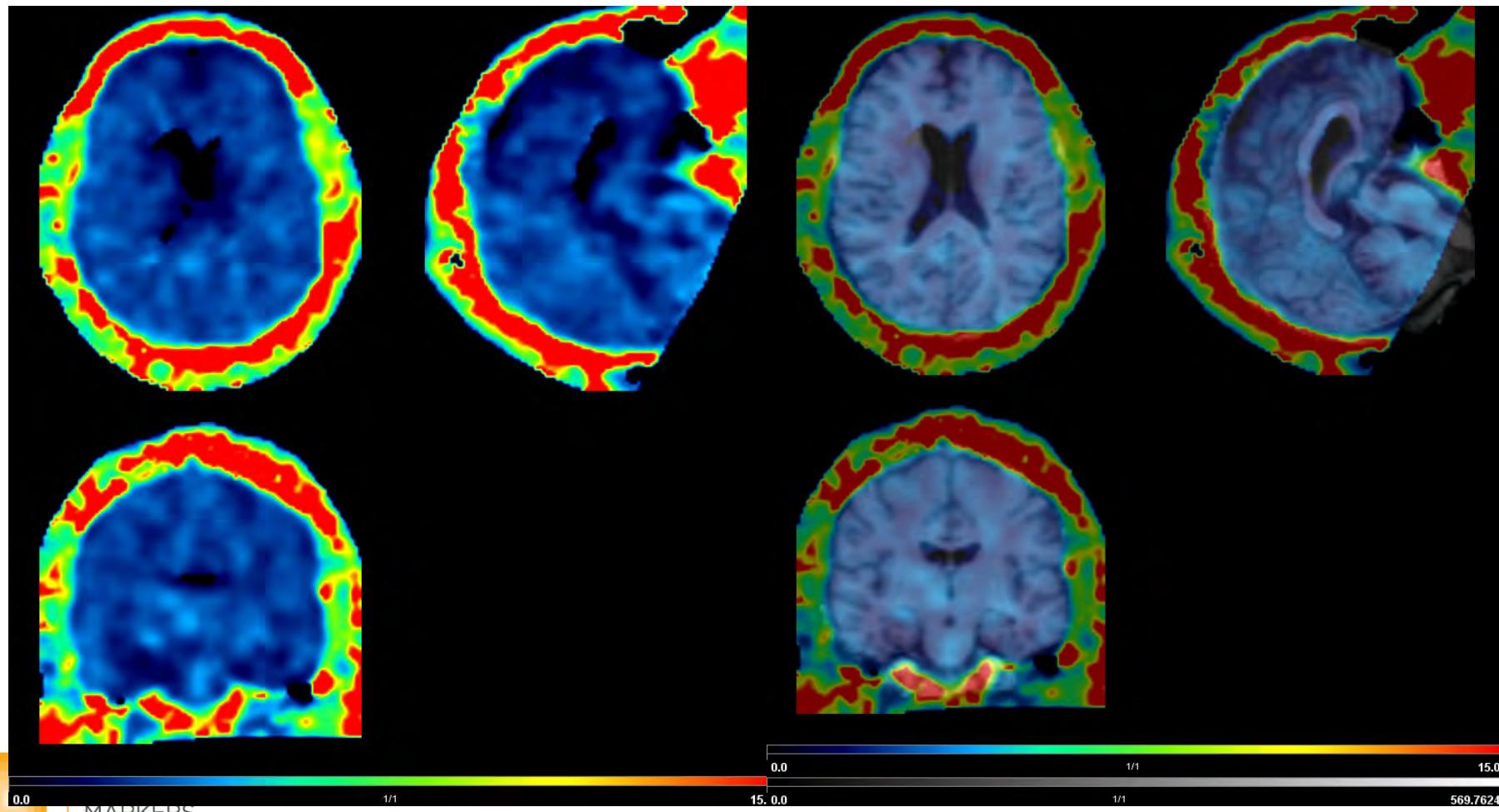


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PBR111-01 First series only (0-90 min post injection) 2 tissue

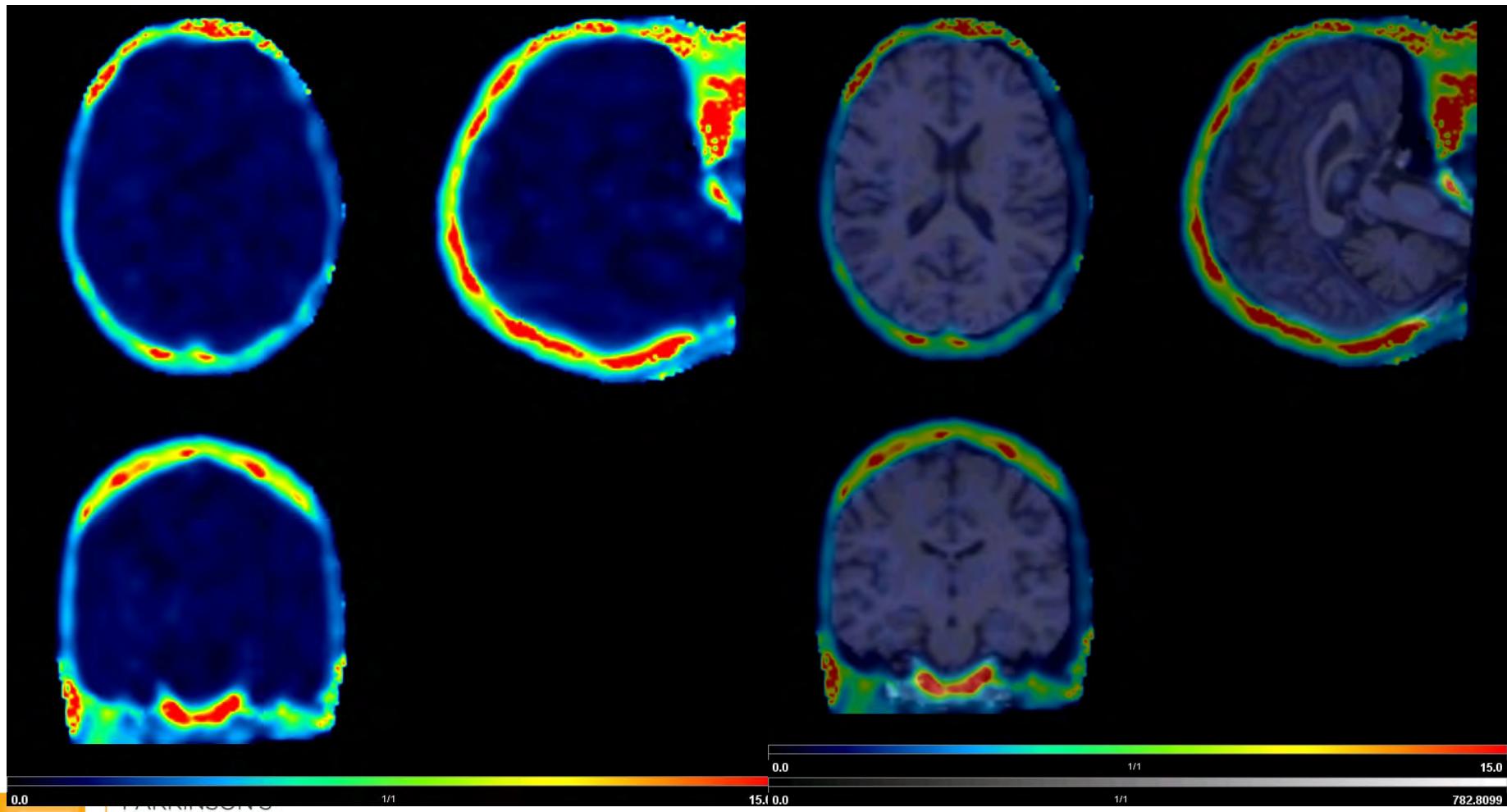


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PBR111-03 2T 1st series



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PPMI Data Analyses

Christopher S. Coffey

The University of Iowa

Karl Kieburtz

The University of Rochester

Ken Marek

The Institute for Neurodegenerative Disorders

PPMI Investigators Meeting

May 3, 2012

New York, NY



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OVERVIEW

Source of data for this presentation:

- All data comes from a data freeze based on data obtained from the LONI website on 04/02/12



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PLANNED ANALYSES

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

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



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PLANNED ANALYSES

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

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



PLANNED ANALYSES

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

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



PLANNED ANALYSES

Planned Analysis #4: Examination of PD Subsets

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



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PLANNED ANALYSES

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

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



PLANNED ANALYSES

Planned Analysis #6: Exploratory analysis of SWEDD subjects

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

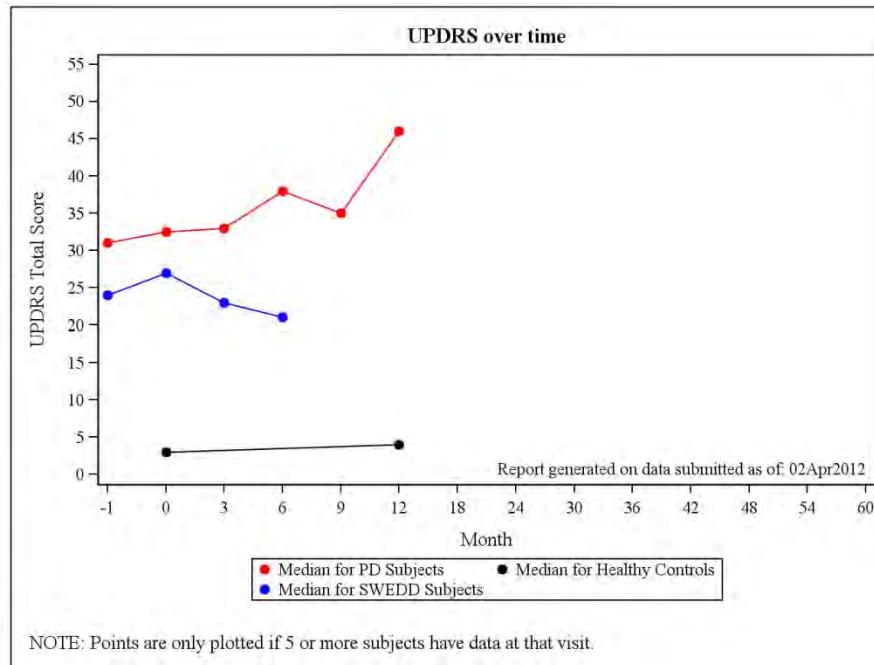


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UPDRS OVER TIME



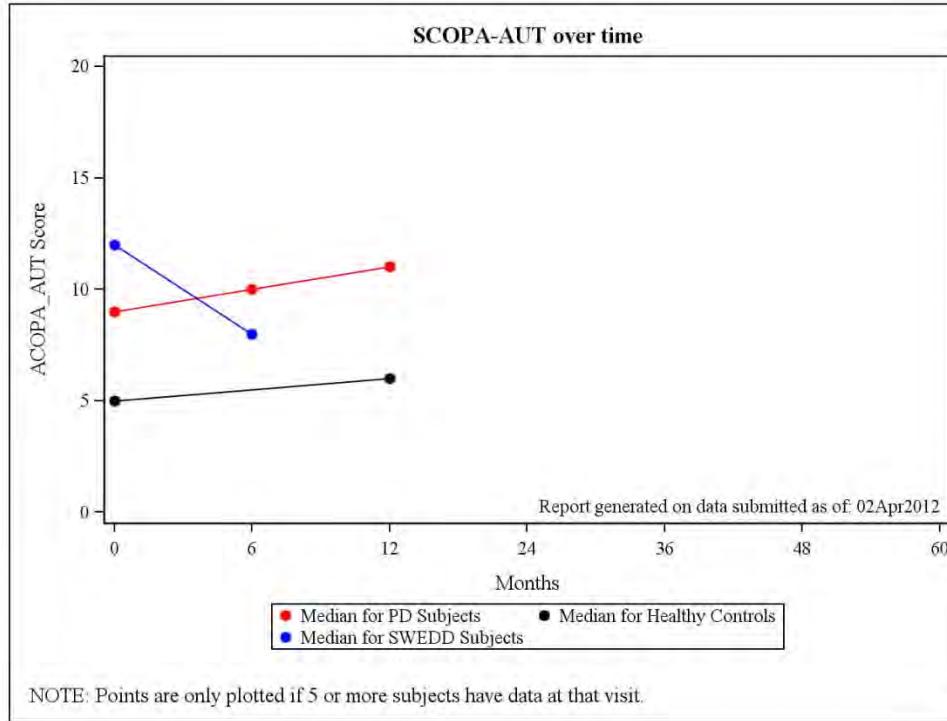
Group	Baseline Median (N) (Min, Max)	Month 3 Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 9 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)
PD	32.5 (188) (7, 72)	33 (140) (7, 72)	38 (112) (9, 94)	35 (54) (9, 63)	46 (50) (13, 84)
HC	3 (147) (0, 20)	N/A	N/A	N/A	4 (27) (1, 14)
SWEDD	27 (25) (7, 64)	23 (11) (6, 57)	21 (5) (13, 40)	13 (3) (12, 21)	17 (3) (15, 37)



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SCOPA-AUT OVER TIME



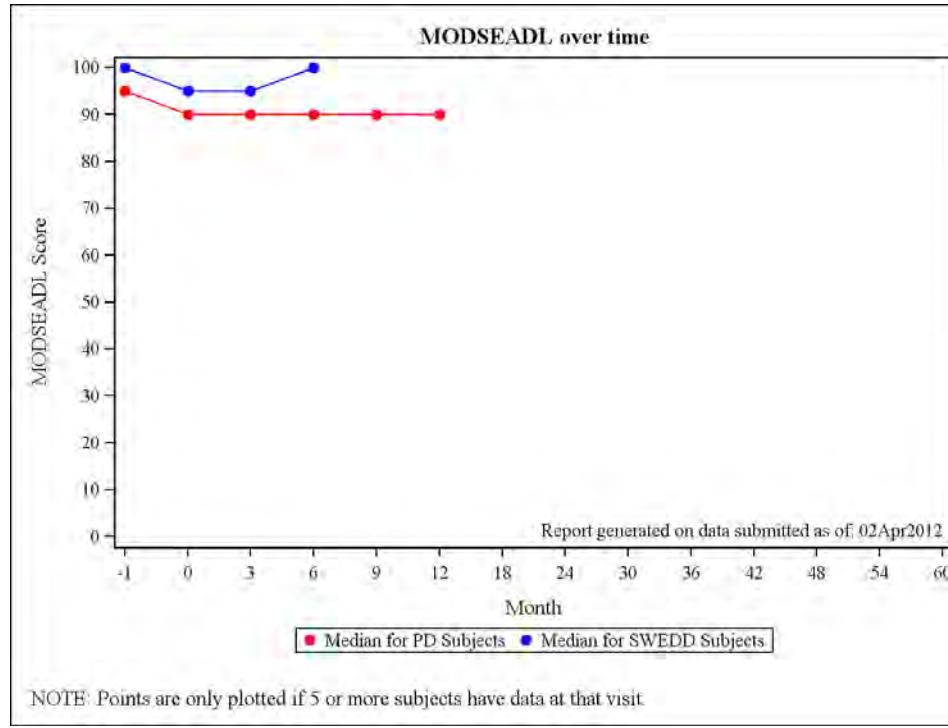
Group	Baseline Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)
PD	9.0 (188) (0, 39)	10.0 (80) (0, 26)	11.0 (37) (2, 30)
HC	5.0 (147) (0, 20)	N/A	6.1 (27) (0, 21)
SWEDD	12.0 (25) (2, 30)	8.0 (5) (6, 20)	9.0 (3) (7, 22)



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MODSEADL OVER TIME

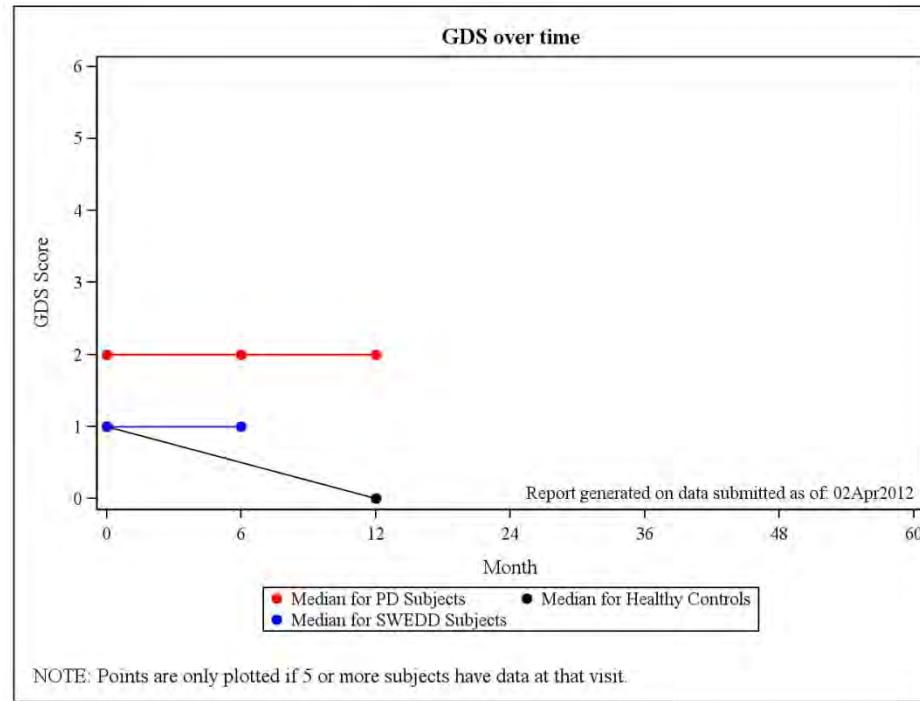


Group	Baseline Median (N) (Min, Max)	Month 3 Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 9 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)
PD	90 (188) (80, 100)	90 (143) (75, 100)	90 (106) (70, 100)	90 (55) (70, 100)	90 (38) (70, 100)
SWEDD	95 (25) (80, 100)	95 (11) (80, 100)	100 (5) (90, 100)	100 (3) (90, 100)	100 (3) (90, 100)



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GDS OVER TIME



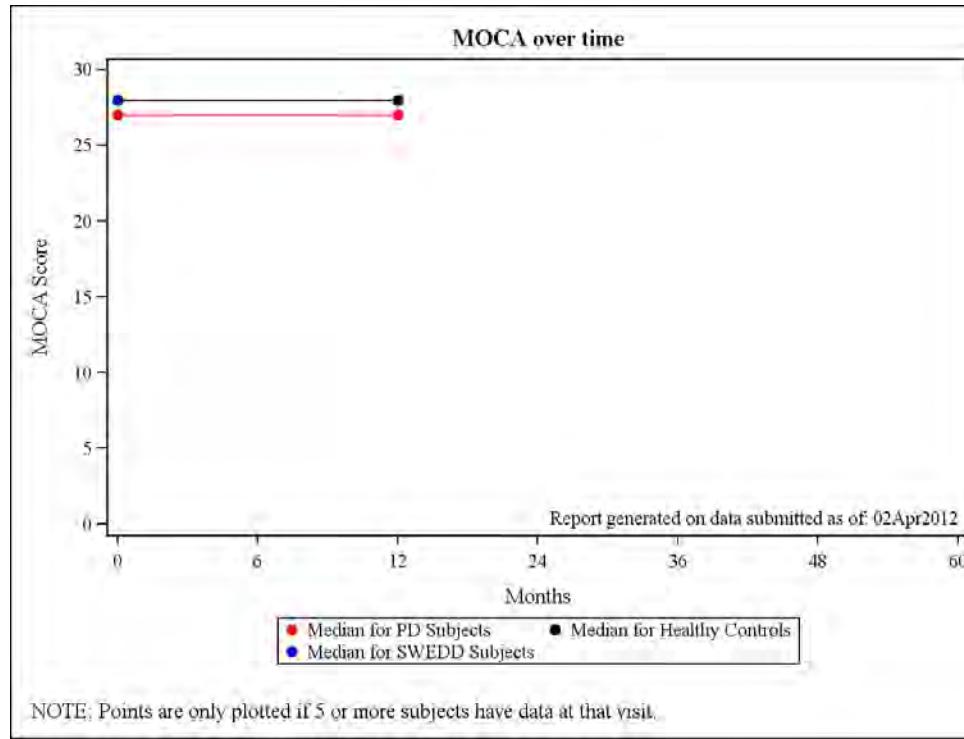
Group	Baseline Median (N) (Min, Max)	Month 6 Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)
PD	2 (188) (0, 13)	2 (114) (0, 10)	2 (38) (0, 10)
HC	1 (147) (0, 15)	N/A	0 (27) (0, 4)
SWEDD	1 (25) (0, 14)	1 (5) (0, 4)	2 (3) (0, 3)



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MOCA OVER TIME



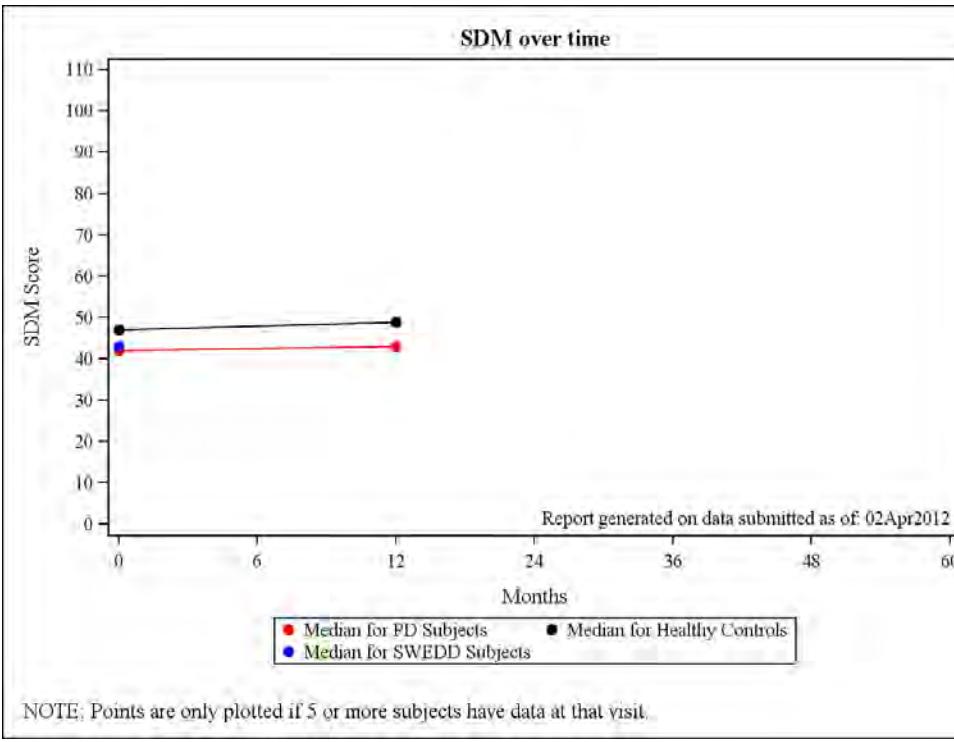
Group	Baseline Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)
PD	26.95 (190) (20, 30)	26.95 (37) (19, 30)
HC	28.05 (147) (27, 30)	28.05 (27) (24, 30)
SWEDD	28.05 (25) (23, 30)	28.05 (3) (24, 28)



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SDM OVER TIME



Group	Baseline Median (N) (Min, Max)	Month 12 Median (N) (Min, Max)
PD	42.0 (188) (16, 76)	43.0 (37) (17, 59)
HC	47.0 (147) (20, 83)	49.0 (27) (27, 79)
SWEDD	43.0 (25) (19, 71)	50.1 (3) (46, 57)



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PLANNED ANALYSES

- Encourage data investigation/mining – know the data
- Propose analyses to working groups, Stats, SC
- What can be done now
 - Correlations of baseline data
 - Study design and assessment question
 - LP
 - Recruitment
 - MDS-UPDRS correlations with non-motor



FUTURE ANALYSES

?????

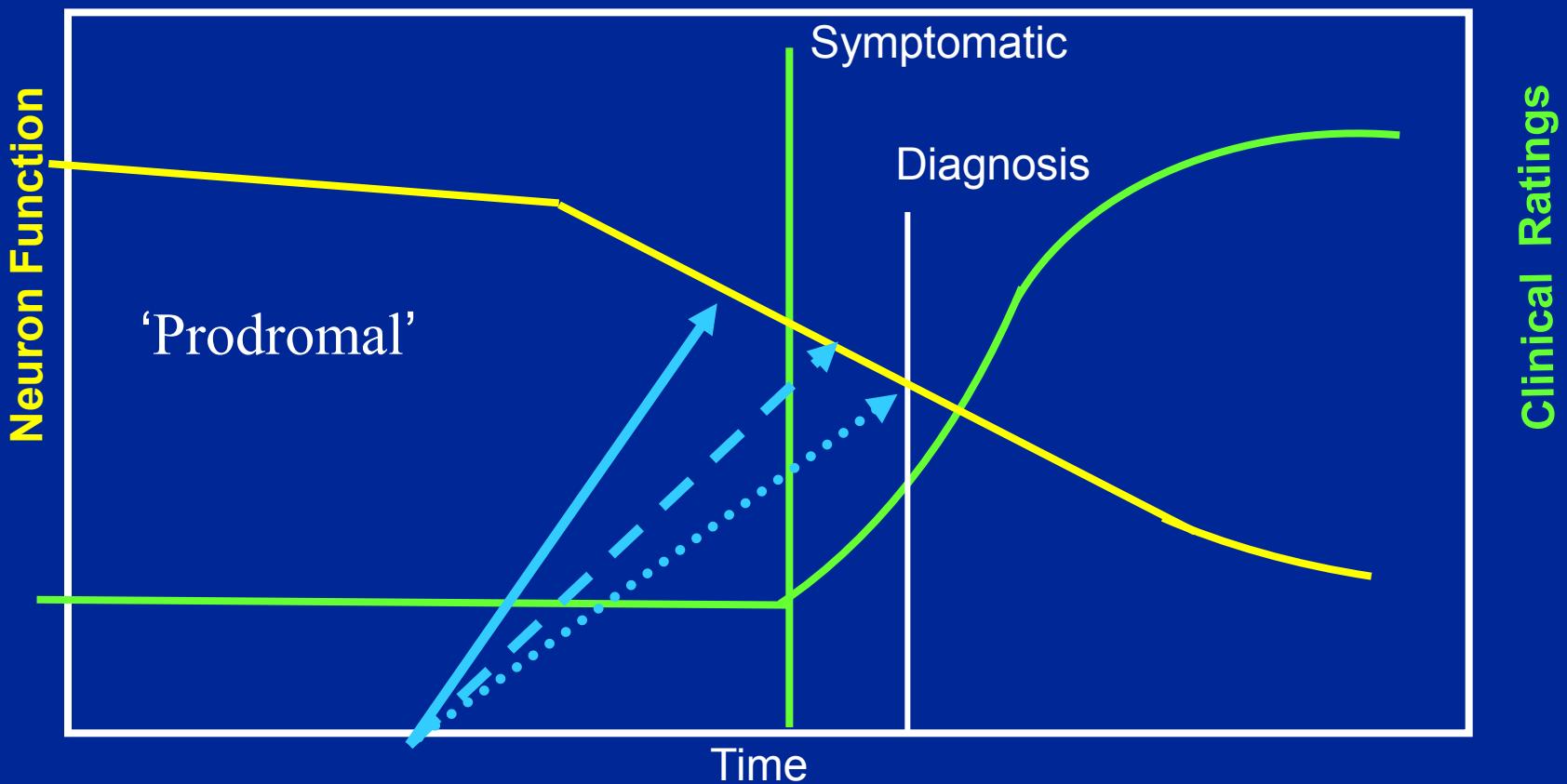


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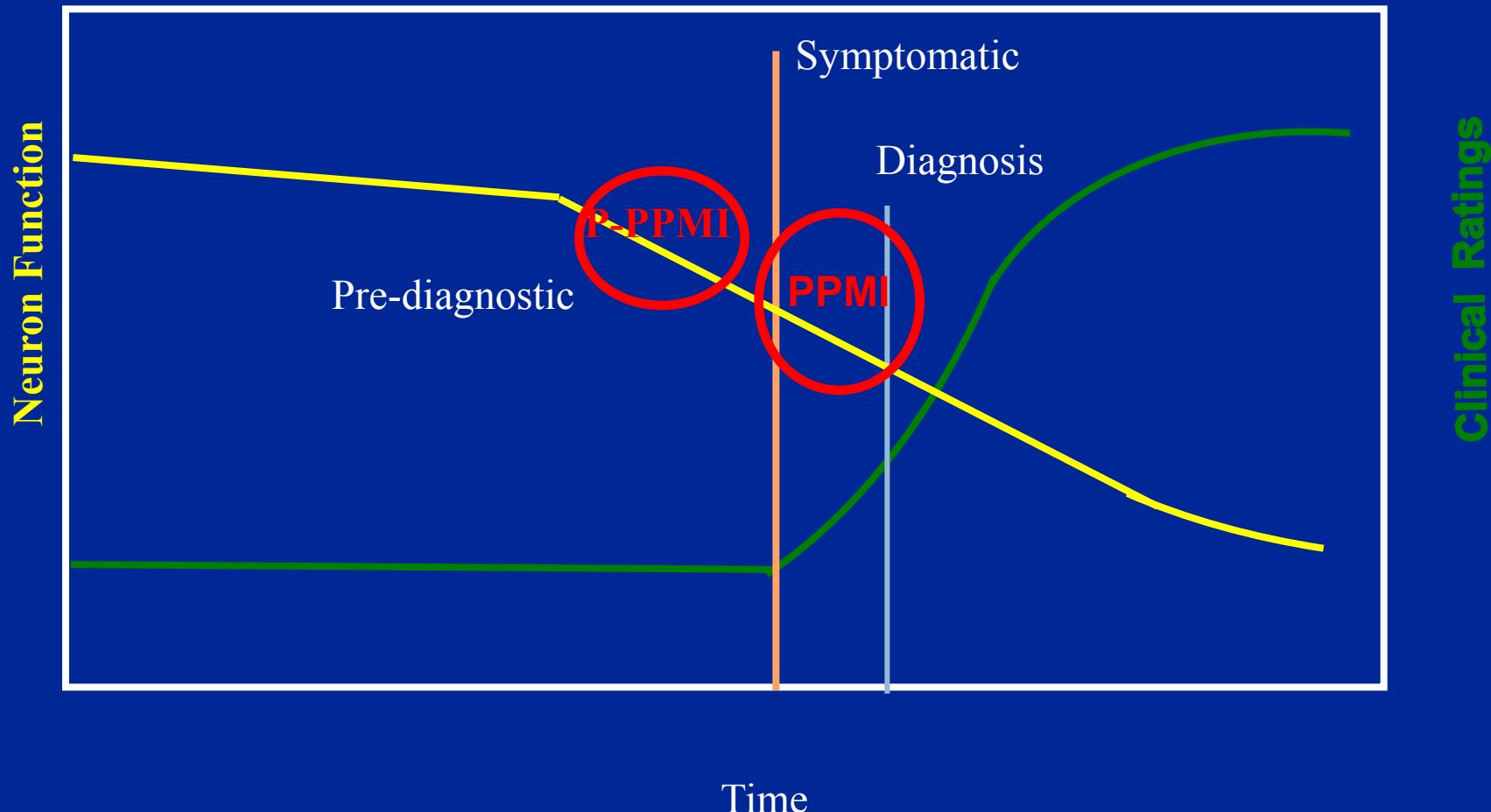
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Natural History of PD



Natural History of Parkinson disease



How to define Prodromal PD

- Enrich a population
- Combine Biomarkers
- Assess biomarker change
- Develop high risk cohort for phenoconversion

Clinical markers

Cognition

Affective

Depression
Apathy
Anxiety

Autonomic

Constipation
Bladder
Sexual
Cardiac

Olfaction

Sleep - RBD

Skin

Motor analysis

Speech

Biomarkers for PD

Imaging –Phenomics

SPECT/PET-Dopamine - DAT, F-Dopa, VMAT2
SPECT/PET-non-dopamine FDG, MIBG, NE, 5HT, Nicotine, Ach, PBR, Amyloid, α -synuclein
MRI-DTI
Functional MRI
Nigral Ultrasound

Genetics

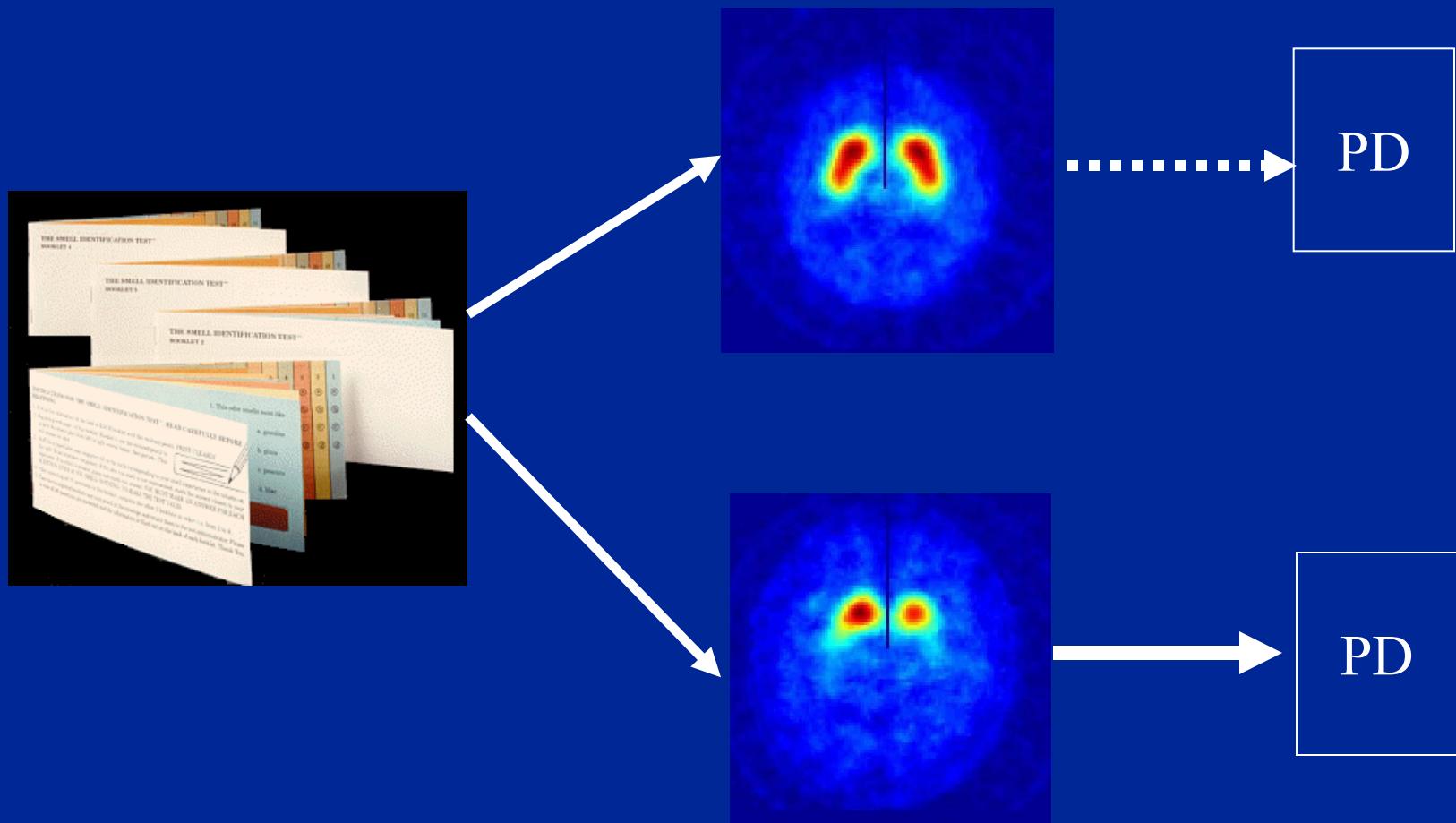
Synuclein, LRRK2, GBA
Parkin DJ-1, Pink1

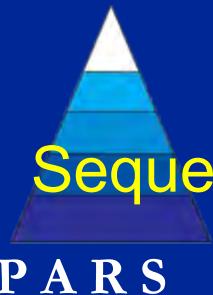
Laboratory

Synuclein, DJ1, Tau, Amyloid, urate

RNA profiling
Metabolomics

PARS: study scheme





PARS baseline –

Sequential and increasingly intensive biomarker assessment

PHASE 1

First degree relatives, non-relatives



Eligible subjects sent UPSIT's ($n = 9,379$)



52% returned

Valid UPSIT's ($n = 4,871$)



(< 15% percentile)

Olfactory loss ($n = 650$)

PHASE 2

Clinic visit - 385

1. UPDRS
2. Diagnostic form
3. SCOPA-aut
4. Non-motor review
5. Neuropsych assess

Imaging visit- 303

1. DAT imaging
2. HRV
3. Blood, CSF sampling

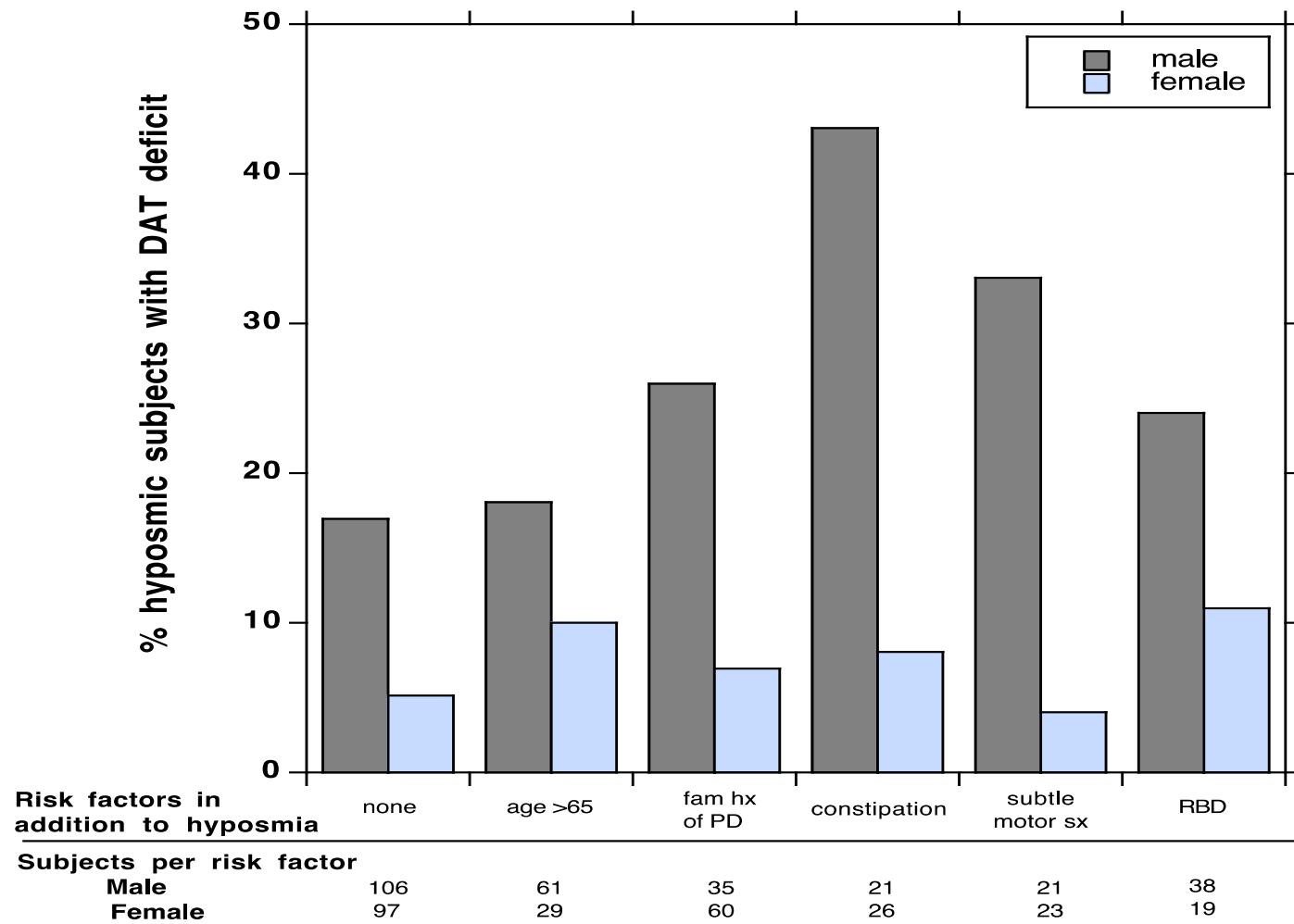
PARS baseline DAT IMAGING -

	HYPOSMIC ($\leq 15\%$) N=203		NORMOSMIC ($> 15\%$) N=100		
Age expected Putamen DAT density	N	Percent of cohort	N	Percent of cohort	
$\leq 65\%$ (DAT deficit)	23	11.3%	1	1.0%	p<.01
$65\% - \leq 80\%$ (Indeterminate)	35	17.2%	7	7.0%	p<.05
$> 80\%$ (NO DAT deficit)	145	71.5%	92	92.0%	

- Hyposmia enriches for DAT deficit (28.5% compared to 8%)
- Severe DAT deficit highly enriches for DAT deficit (11.3% compare to 1%)



Factors influencing the risk of DAT deficit (≤ 65% age expected DAT putamen uptake)



Longitudinal PARS - 2 year interval

84% retention – completion in April 2012

6 of 18 <65% DAT - Parkinsonism

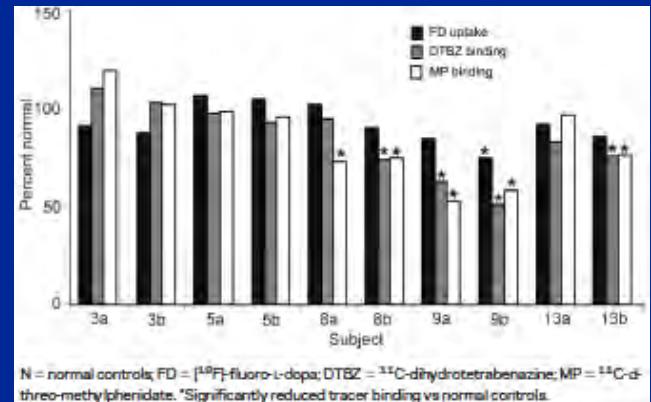
7 of 18 <65% DAT Pre- Parkinsonism

None of >65% (n=220) DAT - Parkinsonism

Start with a genetically defined cohort

Initial studies - Asymptomatic LRRK2 carriers
4 subjects had reduced DAT during a
4 year period
2 of these had abnormal VMAT2
None had abnormal F-dopa

Possible to detect imaging changes in this pre-motor group
Compensation may occur that differentially effects these imaging outcomes



Longitudinal imaging in a LRRK2 family demonstrates progressive loss of imaging outcomes in unaffected mutation carriers

Adams JR, van Netten H, Schulzer M, et al. PET in LRRK2 mutations: comparison to sporadic Parkinson's disease and evidence for presymptomatic compensation. *Brain* 2005;128:2777-2785.

Nandhagopal, R., et al., Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. *Brain*, 2009. 132(Pt 11): p. 2970-9.

LRRK2 AJ consortium

LRRK2 15-20% of PD in Askenazi Jewish population
- 3 sites – Tel aviv, Beth Israel, Columbia, 3 sites in EU

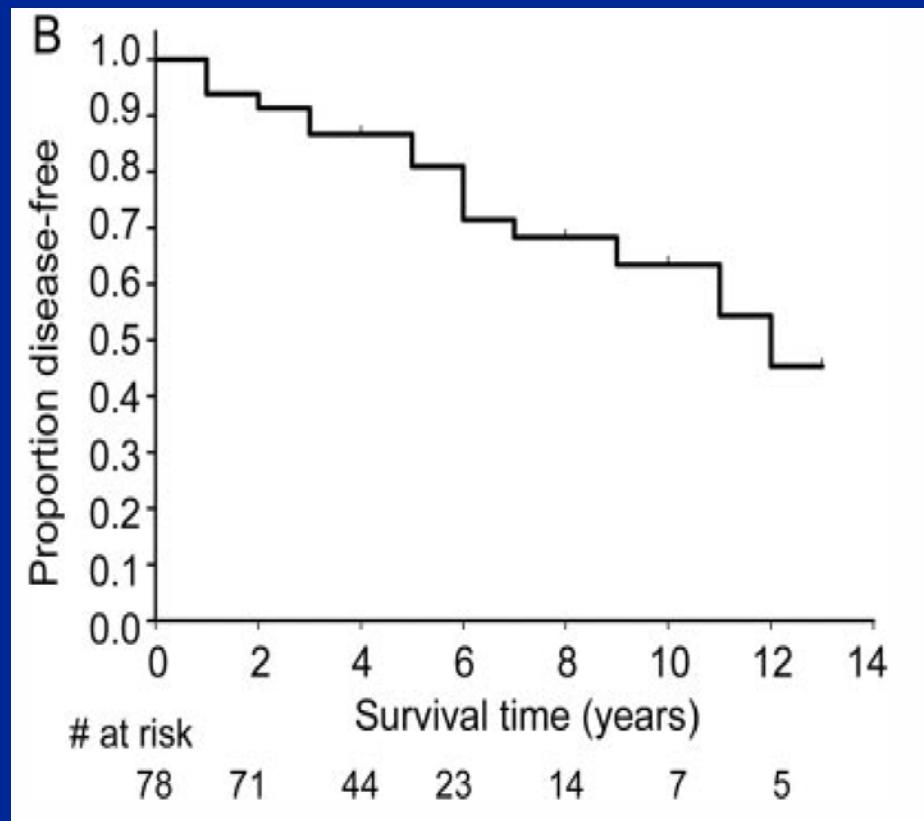
Penetrance uncertain/varied age of onset

Cannot distinguish from IPD

DAT imaging of unaffected carriers to examine pre-diagnostic period.

RBD and Risk of PD

- Risk of PD in patients with idiopathic RBD is about 5%/yr
- Increased risk extends for 10-20 years from RBD diagnosis
- May be related to RBD severity



Decreased striatal dopamine transporters uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eyemovement sleep behaviour disorder: a prospective study

A. Iranzo, F Lomeña, H Stockner, F Valdeoriola, I Vilaseca, M Salamero, JL Molinuevo, M Serradell, J Duch, J Pavía, J Gallego, K Seppi, B Högl, E Tolosa, Werner Poewe, J Santamaría, for the Sleep Innsbruck Barcelona (SINBAR) group

Lancet, 2010

17 of 43 RBD subjects demonstrate reduced DAT uptake

Putamen > caudate reduction

6/17 developed PD or DLB within 2.5 years

Proposal to establish pre-motor PPMI cohort define by DAT deficit

- Utilize existing PPMI infrastructure
 - Sites
 - Cores
 - Database
 - Website
- Utilize LRRK2 cohort
- Utilize Fox Trial Finder
- Utilize existing effort - olfaction, RBD as model

P-PPMI Working group

- Kenneth Marek
- Daniela Berg
- Sohini Chowdhury
- Chris Coffey
- Tom Comery
- Stewart Factor
- Emily Flagg
- Mark Frasier
- Igor Grachev
- Karl Kieburtz
- Danna Jennings
- Shirley Lasch
- Brit Mollenhauer
- Wolfgang Oertel
- Bernard Ravina
- Andrew Siderowf
- Tanya Simuni
- Todd Sherer
- David Standaert
- Carlie Tanner
- Marcel van der Brug

Proposal to establish pre-motor PPMI cohort define by DAT deficit

- Sequential biomarker strategy to identify DAT deficit cohort – olfaction, RBD, LRRK2
- Focus on subjects with < 65% expected DAT
- **Develop a pre-motor risk score**
- Follow group with DAT deficit and normal DAT for 2 years (n=100 subjects)
 - Establish pre-motor biomarker signature
 - Define phenoconversion

P-PPMI Outcome measures

- Change in biomarker signature – Clinical, Imaging, biologic
 - Exploratory comparison of P-PPMI to PD Healthy, SWEDD
- Phenoconversion to motor PD
 - How to define phenoconversion – clinical judgement, existing scales

Prodromal biomarker outcomes

- The mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in Prodromal subjects, and where appropriate the comparison of these rates with PD subjects, healthy subjects at study intervals from 3 months to 48 months.
- Correlations between the rates of change in the mean of clinical, imaging and biomic outcomes in prodromal subjects and between PD, SWEDD and healthy subjects at study intervals from 3 months to 48 months.
- Prevalence of measures of clinical, imaging and biomic outcomes in Prodromal subjects at study intervals from baseline to 48 months.

Definition of Phenoconversion

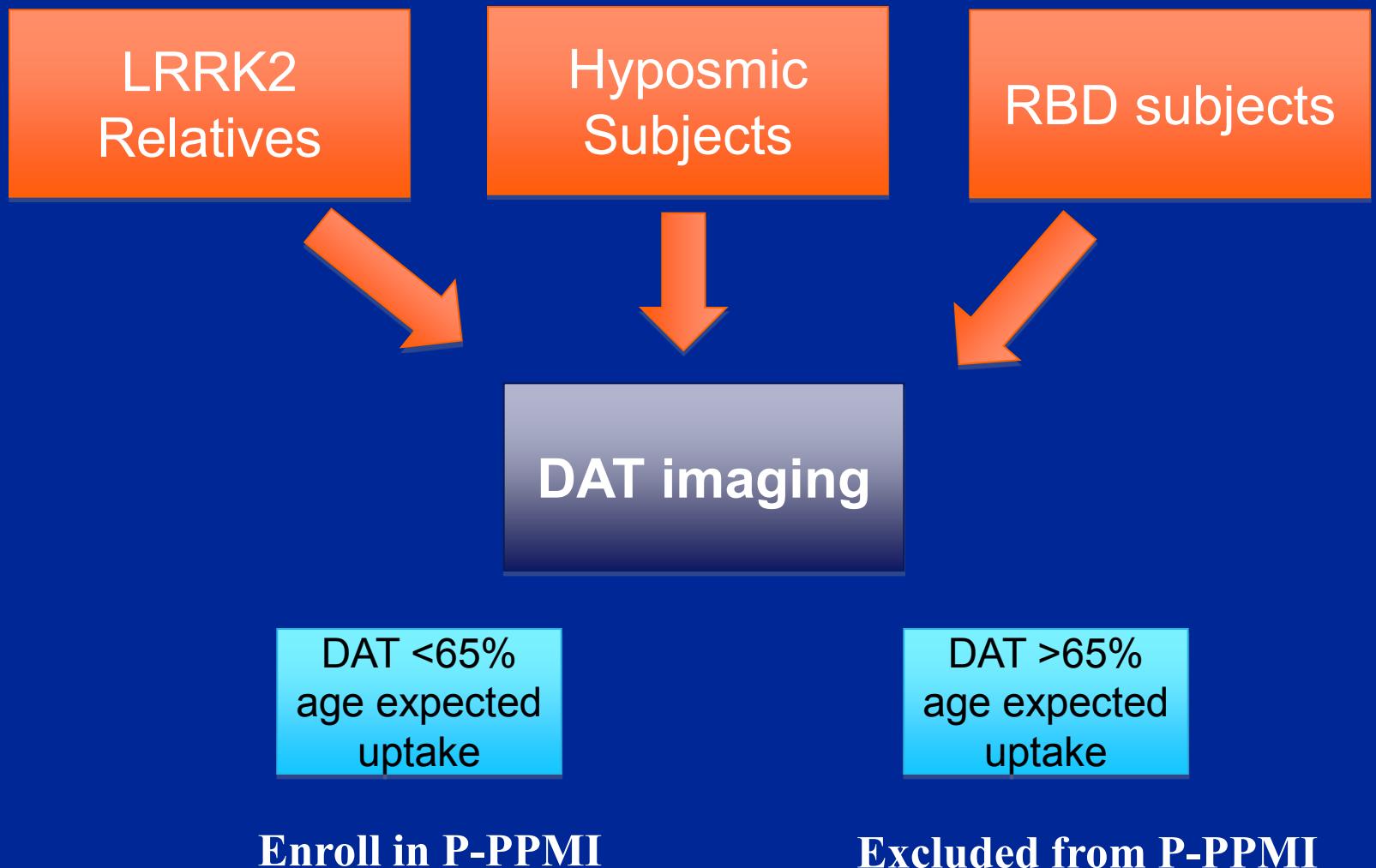
- Clinical Judgement
- Established criteria – GELB, BBB.
- New definition - Adding motor +non-motor symptoms
- Data defined - develop from data

Consensus to utilize robust clinical outcome – ie 2 of 3 cardinal signs of PD +/- asymmetry

P-PPMI Prodromal Recruitment

- Eligibility
 - Combine risk factors to enhance risk of DAT deficit vs
 - Single risk factor to increase number eligible
- From where (cohort dependent)
 - PPMI sites, Fox trial finder, collaborators
- Materials/Media

Eligibility for P-PPMI



Eligibility

- > 60 years
- One or more of following
 - hyposmia <15th percentile for age and gender plus one other symptom + Constipation (<1 BM/day)
 - RBD – defined by PSG
 - LRRK2 mutation

PLUS

- DAT deficit– Putamen binding ratio <65% of age expected

Exclusion

- Dementia or other significant neurological disorder
- Tremor
- Current smoker ?
- Any clear motor sign of PD

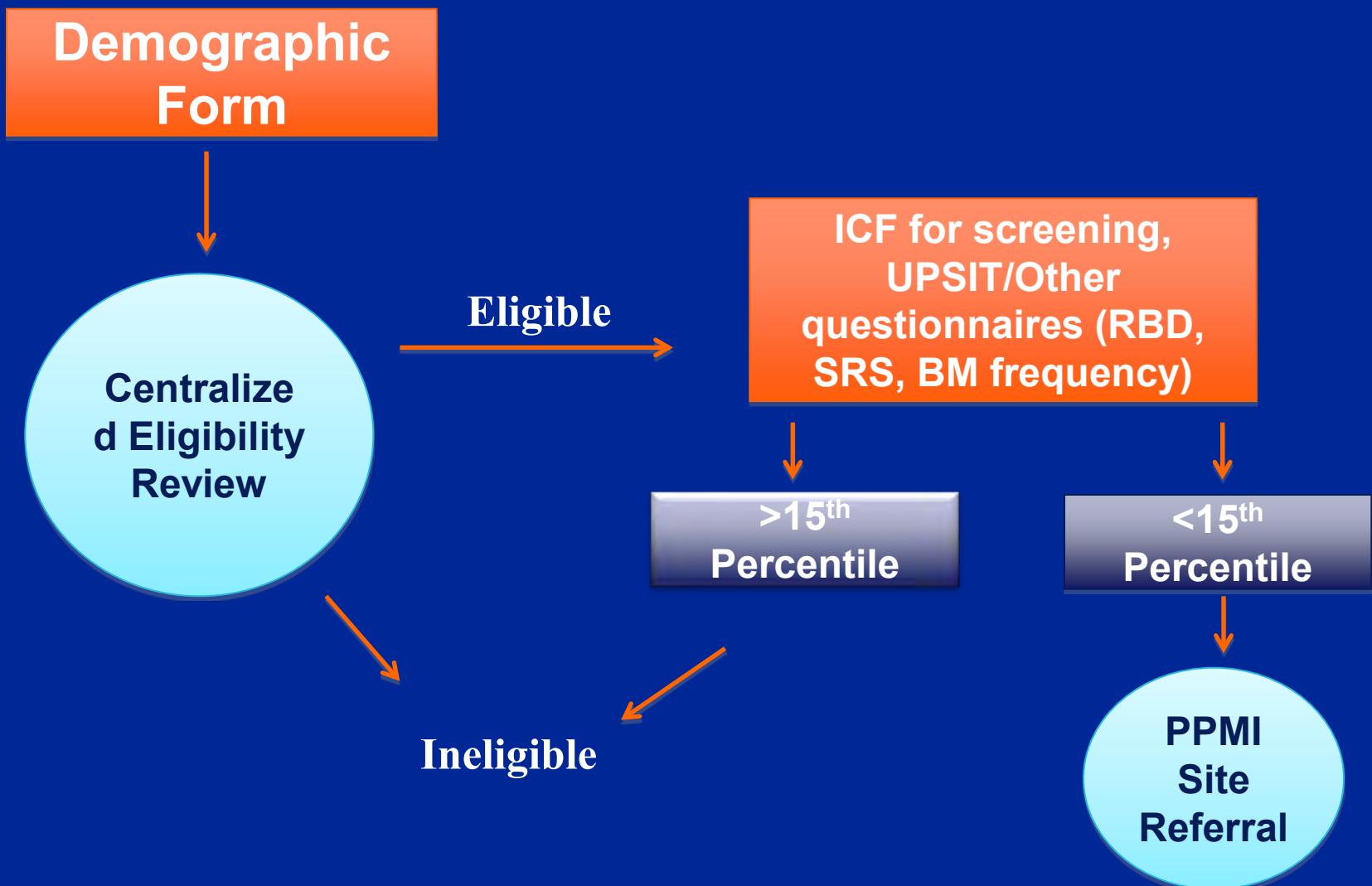
Recruitment Phase

Hyposmic Subjects

Recruitment Sources

- Internet/web-based forms
- Fox Trial Finder
- Location targeted mailings to nurses, veterans
- Family members of clinic patients with PD

Hyposmic Recruitment Schematic



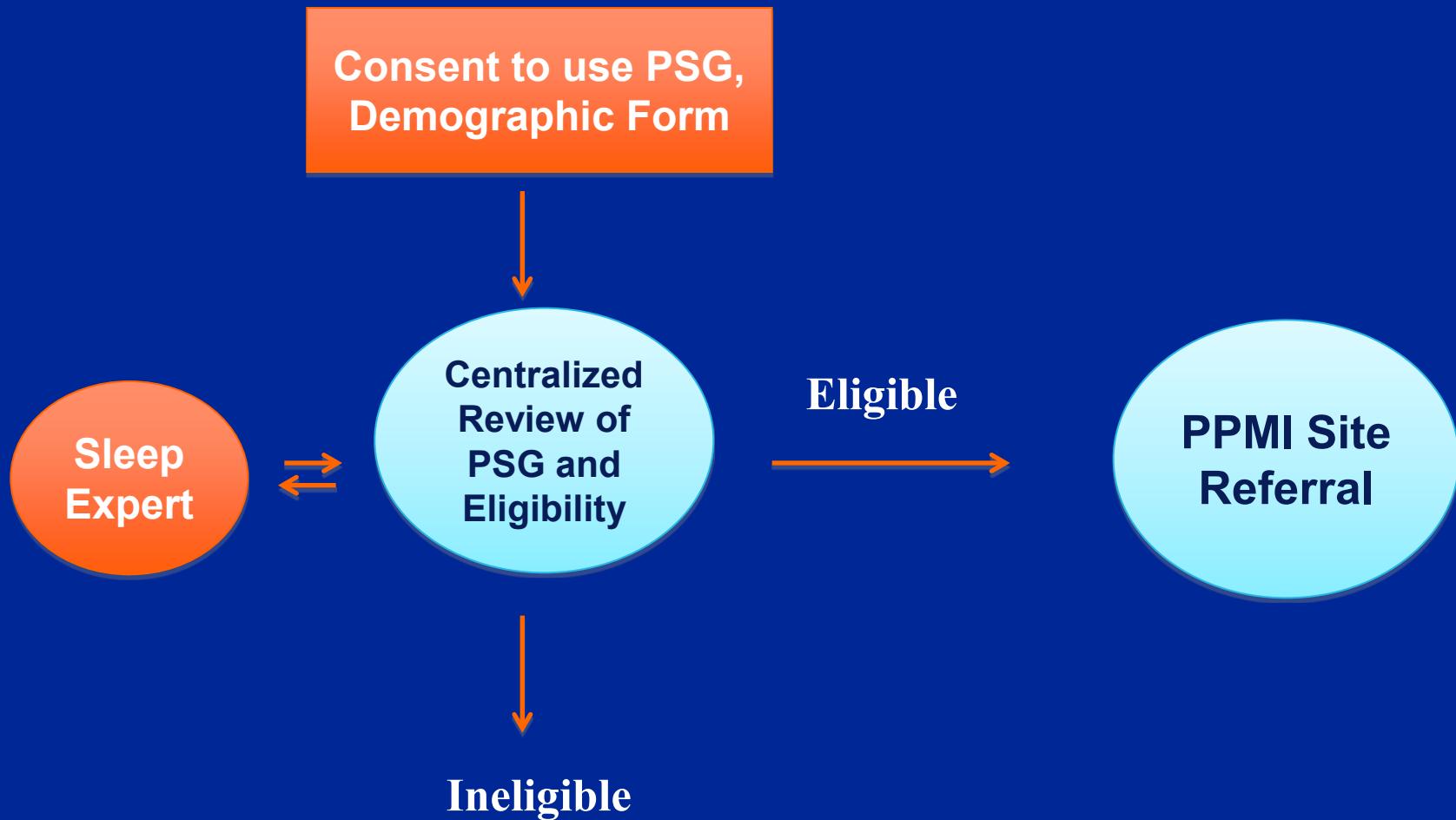
Recruitment Phase

RBD Subjects

Main recruitment source

- Identification of Sleep Center Collaboration at PPMI sites

RBD Recruitment Schematic

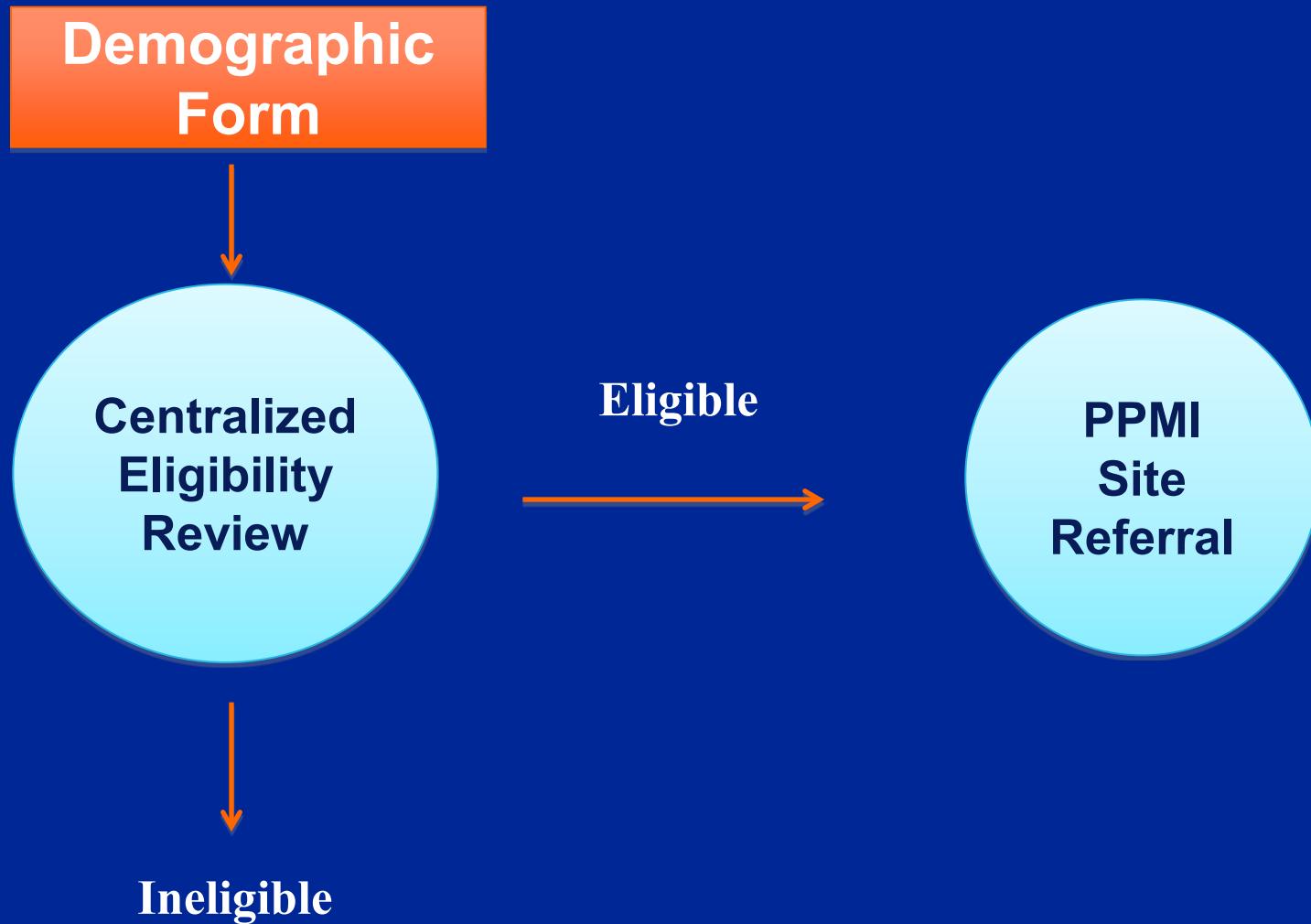


Recruitment Phase

LRRK2 Subjects/Relatives

- Recruitment sources
 - Internet advertising
 - LRRK2 consortia collaborations
 - Referral by LRRK2 subjects in PD clinics
(PPMI sites)

LRRK2 Recruitment Schematic



P-PPMI - Assessments

- PPMI PD schedule of activities
- Modify Primary diagnosis
- Phenoconversion – certainty of Dx
- Wish list of other assessments
 - Annual UPSIT
 - HRV
 - Colon biopsy
 - Skin biopsy
 - Blood/CSF analytes

P-PPMI - Providing info to Subjects

- DAT binding
 - DAT deficit uncertain in prodromal PD
 - Include disclosure of DAT in consent
 - Process underway to establish guidelines for disclosure – Karlawish, AD – A4 study

P-PPMI - Implementation

- Amendment
- CRFs
- Develop recruitment forms
- Need for core recruitment
 - Olfaction – demographics and UPSITs
 - RBD – PSG reading
- Process to refer eligible subjects to PPMI sites

P-PPMI - Operations

- Site training
- IRB submission, management
- Recruitment materials
- Forms and CRF development
- Database development
- Imaging Core: Quantitative rapid response process

P-PPMI - Protecting the core PPMI study

- Continued emphasis on recruitment and retention
- Not all sites need participate in P-PPMI or in all aspects – Site Interest Forms
- Focus on Longitudinal PD data

P-PPMI cohort Timeline

- Protocol development Feb –May 2012
- Introduce to PPMI sites – May 2012
- Site IRB approvals – Sept 2012 – Nov 2012
- Budget approvals – Sept 2012 – Nov 2012
- Implement protocol Dec 2012

Imaging – SPECT and DTI

Society of Nuclear Medicine Annual Meeting, June 12, 2012. Miami, Florida

The MDS 16th International Congress of Parkinson's Disease and Movement Disorders Meeting in Dublin, June 19, 2012

Baseline Neuroimaging Characteristics of the Parkinson's Progression Marker Initiative (PPMI) Parkinson's and Healthy Cohorts

J. Seibyl, MD on behalf of the PPMI Investigators

American Academy of Neurologists in New Orleans LA, April, 2012

Distribution of Diminished brain microstructure in Parkinson's disease:
selected for an AAN Scientific Program highlights Plenary Session

Norbert Schuff, PhD on behalf of the PPMI Investigators

The MDS 16th International Congress of Parkinson's Disease and Movement Disorders Meeting in Dublin, June 19, 2012

Associations between brain microstructure and dopaminergic integrity in Parkinson's disease: A joint diffusion tensor and DAT imaging study
Norbert Schuff,



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Biologics

MEETING PRESENTATION:

PPMI-NYAS, October 26, 2011

PPMI a-synuclein immunoassay interlaboratory study

ABSTRACTS:

Movement Disorders Meeting in Dublin, June, 2012

Association between CSF biomarkers and clinical phenotype of early Parkinson's disease in the Parkinson's Progression Marker Initiative (PPMI) cohort

Ju-Hee Kang, Alice Chen-Plotkin, David Irwin, John Q. Trojanowski, Leslie M. Shaw for PPMI

Alzheimer's Disease International Conference in July, 2012

CSF a-synuclein, Ab₁₋₄₂ and tau proteins; relationships to clinical parameters in early Parkinson's disease

Ju-Hee Kang,¹ Alice Chen-Plotkin,² David Irwin,² Andrew Siderowf,² Chelsea Caspell,³ Chris Coffey,³ Peggy Taylor,⁴ Mark Frasier,⁵ Kenneth Marek,⁶ Brit Mollenhauer,⁷ John Q. Trojanowski,¹ Leslie M. Shaw¹ and the Parkinson's Progression Marker Initiative

Center for Neurodegenerative Diseases Research, UPenn, October 28, 2012

CSF Ab1-42, T-tau and P-tau181 in Early Parkinson's Disease: Predictors of Risk for Disease Progression

Ju Hee Kang, Sarah Pan, John Q Trojanowski, Leslie M Shaw and the Parkinson's Progression Marker Initiative

Clinical and Data Access

PUBLICATIONS:

The Parkinson's progression Marker Initiative- *Progression in Neurobiology 2011*

ABSTRACTS:

American Academy of Neurologists in New Orleans LA, April, 2012

The Parkinson Progression Marker Initiative (PPMI) –A model for Rapid, Comprehensive Data and Biospecimen Access

Parkinson's Progression Marker Initiative

Movement Disorders Meeting in Dublin, June, 2012

Association between olfactory dysfunction and cognition in the PPMI Study

Authors: Siderowf A, Morley JF, Weintraub D, Duda J on behalf of the PPMI Investigators

Frequency of Impulse Control Disorder Symptoms in De Novo Parkinson Disease Patients
Daniel Weintraub, Andrew Siderowf, and the Parkinson's Progression Markers Initiative

Parkinson's Working Group Meeting May, 2012

A Prospective Study for Biomarker Identification in Early Parkinson's Disease

Carlie Tanner and Parkinson's Progression Marker Initiative



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