

# PPMI Status Update

Ken Marek

**PPMI Investigators Meeting**  
**May 5, 2011**  
**New York, NY**



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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”**



# 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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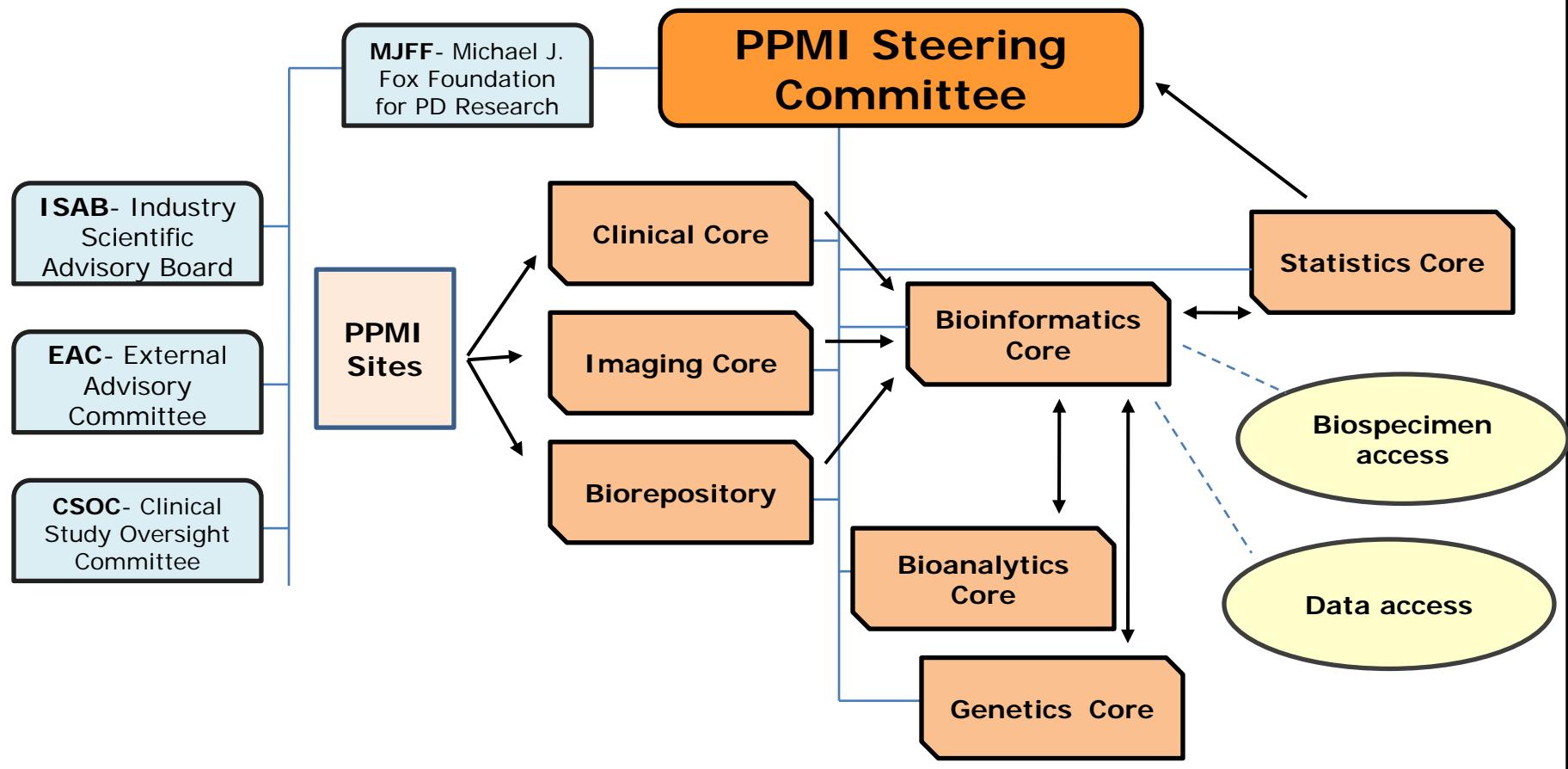


# Establish a Specific Data Set

- Study governance - weekly meetings of the executive steering committee and monthly meetings of the full steering committee consisting of all study cores
- All study cores including clinical, imaging, biorepository, bioanalytics, stats, bioinformatics and genetics – established and working
- Twenty-one clinical sites (16 US, 5 EU)
- Seventeen sites have been trained and activated (14US, 3EU)
- All have fully executed contracts
- Recruitment of PD subjects and healthy controls
- PPMI subjects are successfully undergoing baseline and follow-up assessments including CSF collection



# PPMI Study



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# PPMI Clinical Sites - 2011

- **University of Rochester – Rochester NY**
- **Oregon Health Sciences University – Portland OR**
- **Baylor College of Medicine – Houston TX**
- **The Parkinson's Institute – Sunnyvale CA**
- **University of Pennsylvania – Philadelphia PA**
- **University of South Florida – Tampa FL**
- **University of California San Diego - San Diego CA**
- **Johns Hopkins University – Baltimore MD**
- **Emory University, School of Medicine – Atlanta GA**
- **Institute for Neurodegenerative Disorders - New Haven CT**
- **Boston University – Boston MA**
- **University of Alabama at Birmingham – Birmingham AL**
- **Northwestern University – Chicago IL**
- **Univ. of Wash & VA Puget Sound Health Care System – Seattle WA**
- **Cleveland Clinic – Cleveland OH**
- **Banner Research Institute- Phoenix AZ**
  
- **Innsbruck Medical University – Innsbruck Austria**
- **University of Napoli – Napoli Italy**
- **University of Tubingen – Tubingen Germany**
- **Paracelsus-Elena Klinik – Kassel Germany**
- **Imperial College of London – London England**



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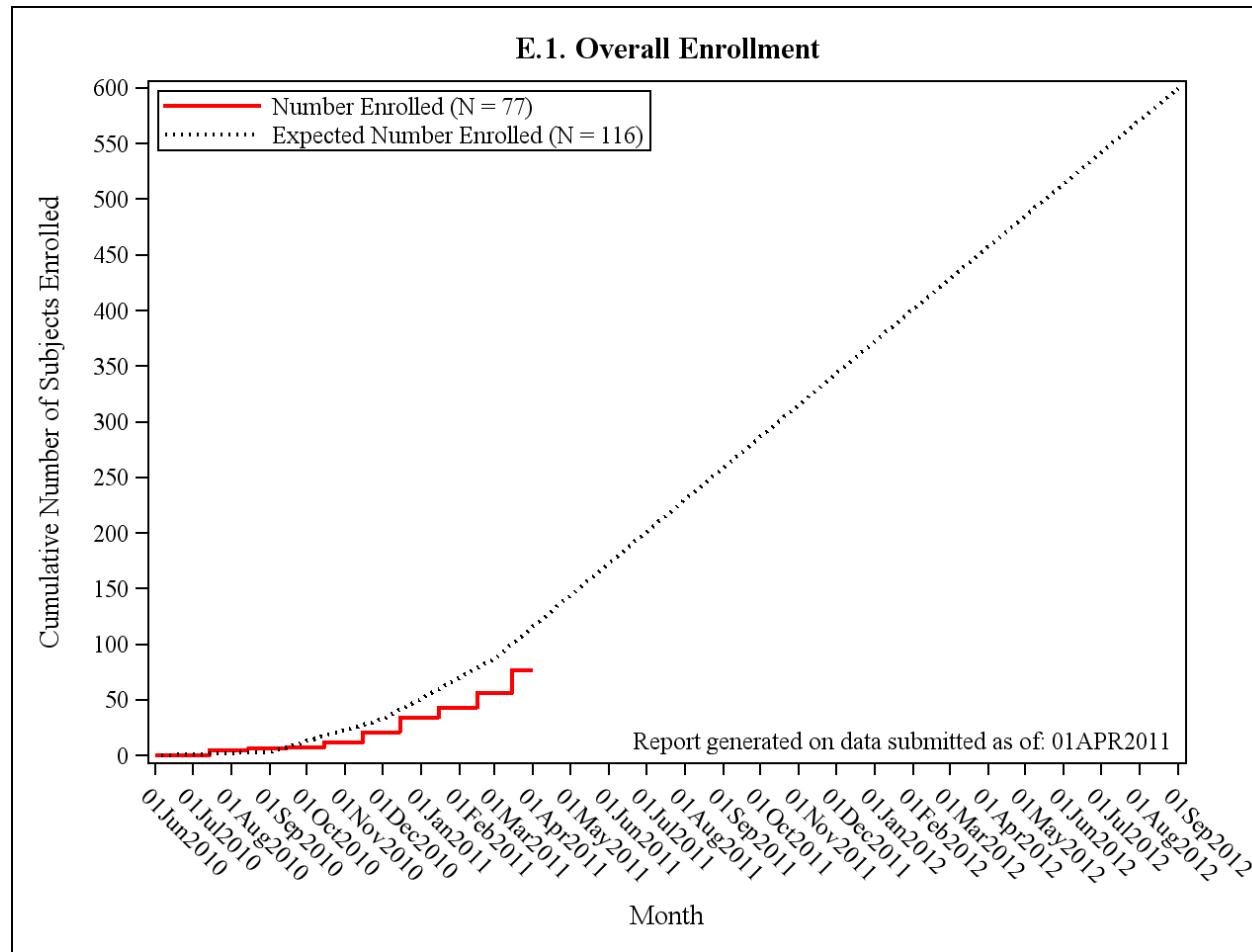


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# ENROLLMENT (through April, 2011)



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# 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
- Control recruitment may be easier than PD recruitment
- LPs are not a major deterrent for potential subjects
- Datscan availability has been a major challenge – DAT imaging as eligibility criteria not fully tested



# **Recruitment – Retention - moving forward**

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



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

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

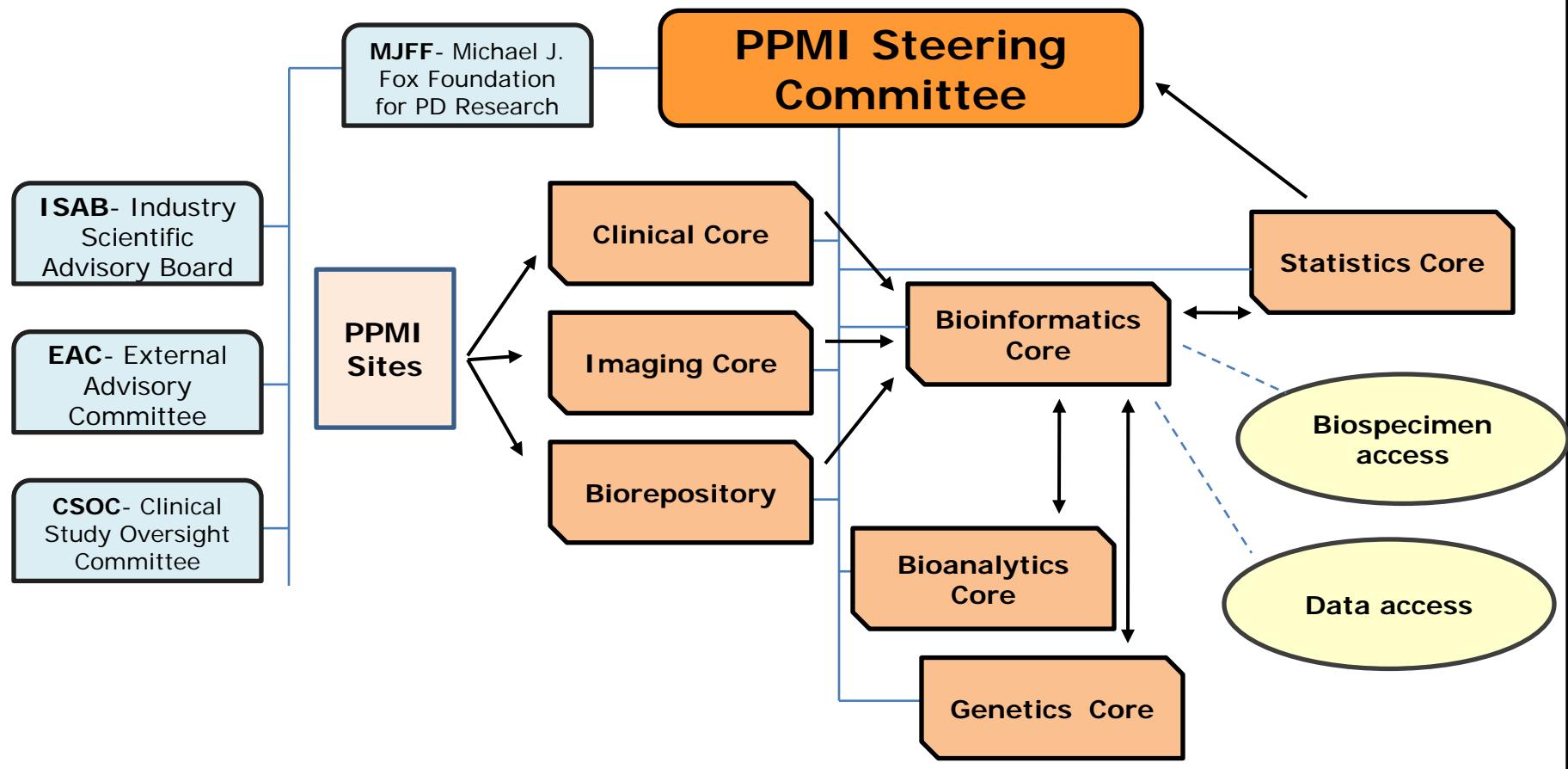


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# PPMI Study



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# PPMI SC and Study Cores

<b>Steering Committee</b>	PI-K Marek, A Siderowf, C Tanner, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, T Simuni, (core leaders, MJFF, ISAB), S Lasch
<b>Clinical Coordination Core</b>	<ul style="list-style-type: none"><li>▪ University of Rochester's Clinical Trials Coordination Center</li><li>• PI: Karl Kieburtz, Emily Flagg, Alice Rudolph, Cindy Casaceli</li></ul>
<b>Imaging Core</b>	<ul style="list-style-type: none"><li>▪ Institute for Neurodegenerative Disorders</li><li>• PI: John Seibyl, Norbert Schuff, Susan Mendick</li></ul>
<b>Statistics Core</b>	<ul style="list-style-type: none"><li>▪ University of Iowa</li><li>• PI: Chris Coffey, Qing Yang</li></ul>
<b>Bioinformatics Core</b>	<ul style="list-style-type: none"><li>▪ Laboratory of Neuroimaging (LONI) at UCLA</li><li>• PI: Arthur Toga, Karen Crawford</li></ul>
<b>BioRepository</b>	<ul style="list-style-type: none"><li>▪ Coriell/BioRep</li><li>• PI: Alison Ansbach,</li><li>• Pasquale De Blasio, Michele Piovella</li></ul>
<b>Bioanalytics Core</b>	<ul style="list-style-type: none"><li>▪ University of Pennsylvania</li><li>• PI: John Trojanowski, Les Shaw</li></ul>
<b>Genetics Core</b>	<ul style="list-style-type: none"><li>▪ National Institute on Aging/NIH</li><li>• PI: Andy Singleton</li></ul>



# PPMI Committees

- **Biologics**
    - John Trojanowski
    - Les Shaw
  - **Imaging**
    - John Seibyl
  - **Neuropsych /Neurobehavior**
    - Andrew Siderowf
  - **Sleep**
    - Wolfgang Oertel
  - **Genetics**
    - Andrew Singleton
  - **Biospecimen review**
    - Gene Johnson
  - **Data and publication**
    - David Standaert
  - **Ancillary study**
    - Carlie Tanner
  - **Recruitment and retention**
    - Danna Jennings
  - **Website**
    - Carlie Tanner
- 
- **CSOC**
    - Ron Pfeiffer
  - **External advisory Board**
    - Guy McKhann
  - **Patient Advisory Board**



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# PPMI MJFF team

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



# PPMI Funding Partners

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



# Early lessons

- We can do this
- PPMI will require a large cooperative efforts form all PD constituencies - there is interest worldwide
- PPMI must continue to be innovative – not a standard clinical study



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# Annual Investigators Meeting

## May 5, 2011

### AGENDA

7:30-8:30 am	<b>Breakfast</b>	All		
8:30-8:45 am	<b>Welcome and Introductions</b>	Marek, Sherer		
8:45-9:15 am	<b>PPMI Status Update</b> <ul style="list-style-type: none"> <li>Sites</li> <li>Recruitment data</li> <li>Enrollment</li> <li>Taskforces, Committees, ISAB</li> <li>Early lessons learned</li> </ul>	Marek	<b>Lunch 12:15 -1:15</b>	All
9:15-9:45 am	<b>Clinical Data Recap</b> <ul style="list-style-type: none"> <li>Demographic Information</li> <li>Collected data (motor, non-motor, neuropsych and neurobehavioral)</li> <li>Data entry and future training</li> </ul>	Coffey, Kieburtz	1:15-1:30 pm	<b>Report from Industry Scientific Advisory Board</b>
9:45-10:05 am	<b>Imaging Recap</b> <ul style="list-style-type: none"> <li>Update and data on DaTSCAN, DTI and MRI</li> <li>Future training</li> </ul>	Seibyl, Schuff	1:30-2:10 pm	<b>Assay Preparation</b> <ul style="list-style-type: none"> <li>Alpha-synuclein Round Robin Study</li> <li>CSF 24-hour collection</li> </ul>
10:05-10:20	<b>DAT Imaging Status</b>	Marek	2:10-3:10 pm	<b>Recruitment, Enrollment and Retention</b> <ul style="list-style-type: none"> <li>Efforts to date, on-going and future plans and strategies</li> <li>Recognition of sites excelling at recruitment</li> </ul>
10:20-10:40 am	<b>Break</b>		3:10-3:20 pm	<b>Break</b>
10:40-11:10 am	<b>Biologics Recap</b> <ul style="list-style-type: none"> <li>Update on inventory/process</li> <li>Data on received samples</li> <li>Future training</li> <li>Biospecimen request process/Biospecimen Review Committee (BRC)</li> </ul>	Scutti, Frasier Shaw	3:20-4:20 pm	<b>Ancillary Studies</b> <ul style="list-style-type: none"> <li>Process</li> <li>Studies</li> </ul>
11:10-11:45 am	<b>Planned PPMI Analyses</b>	Coffey, Marek	4:20-4:50 pm	<b>Future Plans</b> <ul style="list-style-type: none"> <li>Additional sites worldwide</li> <li>Pre-motor cohorts</li> <li>2012 Annual Meeting dates</li> </ul>
11:45-12:10 pm	<b>Data Access Process</b>	Toga, Crawford, Standaert	4:50-5:00 pm	<b>Closing</b>



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# PPMI Clinical Data Recap

Christopher S. Coffey  
The University of Iowa

Karl Kieburtz  
The University of Rochester

PPMI Investigators Meeting  
May 5, 2011  
New York, NY



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# OVERVIEW

Source of data for this presentation:

- Information comes from:
  - Tables produced for CSOC report  
(to be presented during 05/10/11 call)
  - Tables produced for monthly review by steering committee
- All data comes from a data freeze based on data obtained from the LONI website on 04/01/11



# ENROLLMENT (CTCC REPORT)

## PD Subjects:

- 85 consented
  - 50 enrolled
  - 19 pending / 16 declined or excluded

## Healthy Controls

- 56 consented
  - 36 enrolled
  - 12 pending / 8 declined or excluded

**86 Subjects Enrolled**



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# ENROLLMENT (CSOC REPORT)

## PD Subjects:

- 73 consented
  - 46 enrolled
  - 14 pending / 4 declined / 9 excluded

## Healthy Controls

- 45 consented
  - 31 enrolled
  - 7 pending / 5 declined / 2 excluded

**77 Subjects Enrolled**

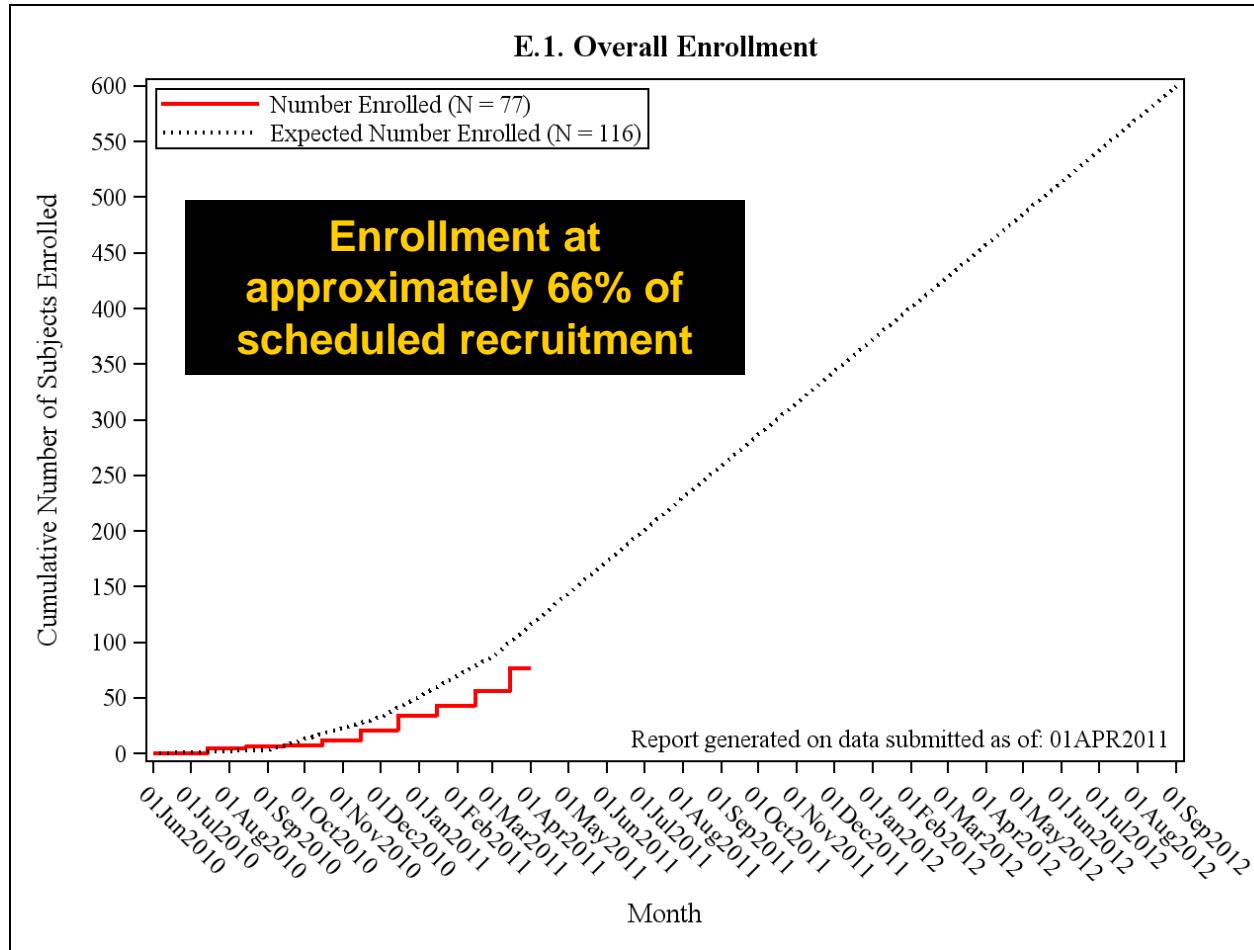


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# ENROLLMENT (CSOC REPORT)



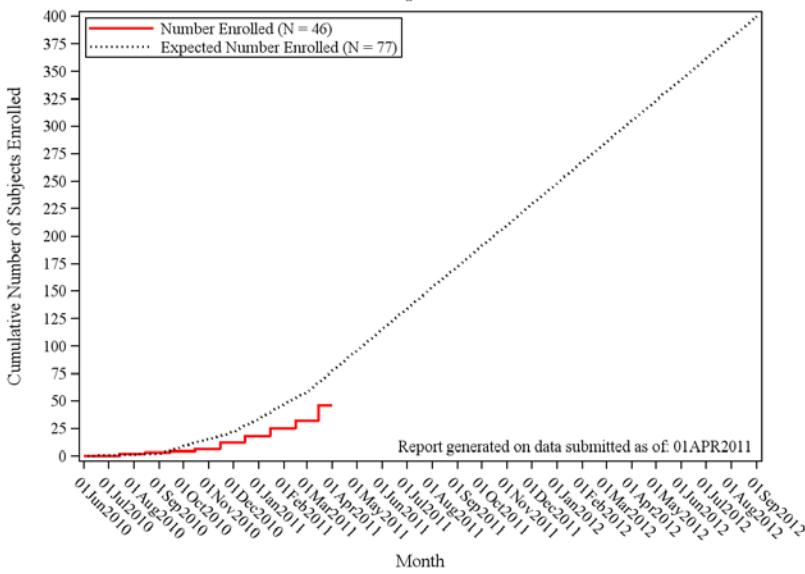
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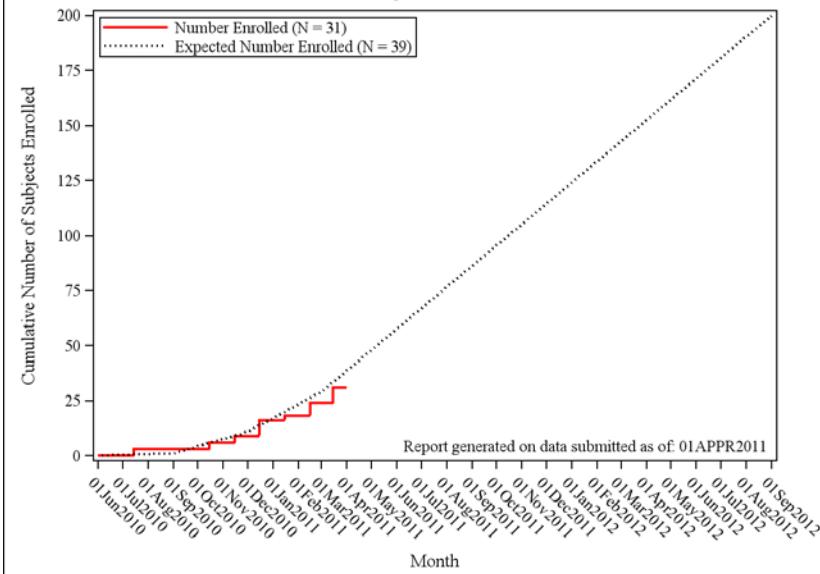


# ENROLLMENT (CSOC REPORT)

E.2. PD Subject Enrollment



E.3. Healthy Control Enrollment



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# REASONS FOR EXCLUSION

## PD Subjects:

- 9 excluded subjects
  - 7 did not meet inclusion criteria (6 due to DaTSCAN)
  - 1 exclusionary medication
  - 1 uncertain diagnosis

## Healthy Controls

- 2 excluded subjects
  - Both did not meet inclusion criteria  
(Low MoCA score & essential tremor)



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# BASELINE DATA COMPLETENESS

Of the 77 enrolled subjects:

- 45 (58%) have all baseline information entered into the publicly-accessible database
  - 72 (94%) have cognitive testing
  - 69 (90%) have a urine sample
  - 69 (90%) have a blood sample
  - 69 (90%) have a lumbar puncture
  - 61 (79%) have all clinical forms entered
  - 58 (75%) have an MRI
  - 55 (71%) have a DaTSCAN

Lag in baseline data completeness is primarily due to time lag between data appearing in clinical database versus the final LONI database.



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# GENDER/AGE DISTRIBUTION

## ➤ PD Subjects:

	Observed	Expected
• Male / <56	5	10.6
• Male / 56-65	9	11.0
• Male / >65	14	8.7
• Female / <56	5	5.5
• Female / 56-65	7	5.5
• Female / >65	6	4.6

p = 0.19

**Non-significant trend towards more older subjects  
than expected.**



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# GENDER/AGE DISTRIBUTION

## ➤ Healthy Controls:

	Observed	Expected
• Male / <56	6	7.1
• Male / 56-65	2	7.4
• Male / >65	7	5.9
• Female / <56	5	3.7
• Female / 56-65	7	3.7
• Female / >65	4	3.1

p = 0.16

**Non-significant trend towards more females than expected.**



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# DEMOGRAPHIC CHARACTERISTICS

	PD Subjects (N = 46)	Healthy Controls (N = 31)
Males	28 (61%)	15 (48%)
Age (mean)	62	60
• <56 years	10 (22%)	11 (35%)
• 56-65 years	20 (43%)	9 (29%)
• >65 years	16 (35%)	11 (35%)
Hispanic/Latino	0 (0%)	1 (3%)
Race		
• Caucasian	41 (89%)	29 (94%)
• African-American	0 (0%)	1 (3%)
• Other	5 (11%)	1 (3%)



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# PD SUBJECT CHARACTERISTICS

## PD Subjects (N = 46)

Family Hx of PD	8 (17%)
Mn duration of disease	9 months
Mn MDS-UPDRS score	
• Total score	35.7
• Part I	7.0
• Part II	7.3
• Part III (Motor Exam)	21.4
Mn Modified Schwab	92
Hoehn & Yahr	
• Stage 1	15 (33%)
• Stage 2	27 (59%)
• Unknown	4 (9%)



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# PROTOCOL DEVIATIONS

## PD Subjects:

- 23 protocol deviations (in 22 subjects)
  - 18 due to eligibility criteria (Most due to DaTSCAN Availability)
  - 1 due to lumbar puncture (CSF testing for hemoglobin)
  - 4 due to DaTSCAN (dosage)

## Healthy Controls

- 14 protocol deviations (in 14 subjects)
  - 8 due to eligibility criteria
  - 1 due to lumbar puncture (CSF testing for hemoglobin)
  - 1 due to MRI not done
  - 4 due to DaTSCAN (dosage)



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# EARLY STUDY TERMINATIONS

## PD Subjects:

- No early study terminations

## Healthy Controls

- 1 early study termination
  - due to ‘other’: “Subject unwilling to comply with all study assessments” Specifically the lumbar puncture
    - as a result completing the screening LP with CSF collection is required before subject enrolls



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# REPORTABLE EVENTS

## PD Subjects:

- 3 reportable events (in 3 subjects)
  - All due to starting PD meds
    - 6 month visit

## Healthy Controls

- 1 reportable event (in 1 subject)
  - Due to early withdrawal
    - subject did not want to complete LP



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# ADVERSE EVENTS

## PD Subjects:

- 7 adverse events (in 3 subjects)
  - 3 LP-related AE's
    - "Back pain" / "Headache" / "Loss of consciousness"
  - No DaTSCAN-related AE's

## Healthy Controls

- 11 adverse events (in 4 subjects)
  - 6 LP-related AE's
    - "Abdominal Pain" / "Back Pain" x 2 / "Headache" x 3
  - No DaTSCAN-related AE's



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# SERIOUS ADVERSE EVENTS

## PD Subjects:

- No serious adverse events observed to date

## Healthy Controls

- No serious adverse events observed to date



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# PD SUBJECTS EXCLUDED BY DaTSCAN

	(N = 6)
Family Hx of PD	2 (33%)
Mn duration of disease	5 months
Mn MDS-UPDRS score	
• Total score	21.5
• Part I	6.7
• Part II	3.0
• Part III (Motor Exam)	11.8
Mn Modified Schwab	96
Hoehn & Yahr	
• Stage 1	3 (50%)
• Stage 2	3 (50%)
• Unknown	0 (0%)



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# PD SUBJECT CHARACTERISTICS

PD Subjects	Enrolled (N = 46)	Excluded (N = 6)
Family Hx of PD	8 (17%)	2 (33%)
Mn duration of disease	9 months	5 months
Mn MDS-UPDRS score		
• Total score	35.7	21.5
• Part I	7.0	6.7
• Part II	7.3	3.0
• Part III (Motor Exam)	21.4	11.8
Mn Modified Schwab	92	96
Hoehn & Yahr		
• Stage 1	15 (33%)	3 (50%)
• Stage 2	27 (59%)	3 (50%)
• Unknown	4 (9%)	0 (0%)



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# PPMI Imaging Core

John P. Seibyl, MD

Institute for Neurodegenerative  
Disorders, New Haven, USA



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# Technical site visits

## Completed

Northwestern  
IND- New Haven  
Johns Hopkins  
Federico II - Naples  
Parkinson's Institute- Sunnyvale  
Univ Pennsylvania  
Univ Rochester  
APDC- Sun City, Az  
Baylor  
Univ Alabama-Birmingham  
Boston University  
Portland  
Innsbruck  
Marburg  
Tübingen  
Univ Washington  
Tampa  
Emory Univ  
San Diego  
Cleveland Clinic

## Pending

London

# PPMI Imaging Studies In-house at IND

- 78 SPECT DAT studies
  - 19 DTI MRI
  - 54 Structural MRI
- 
- 6 potential PD subjects with normal DAT (SWEDD rate about 13%)
  - 1 potential HC subject with abnormal DAT



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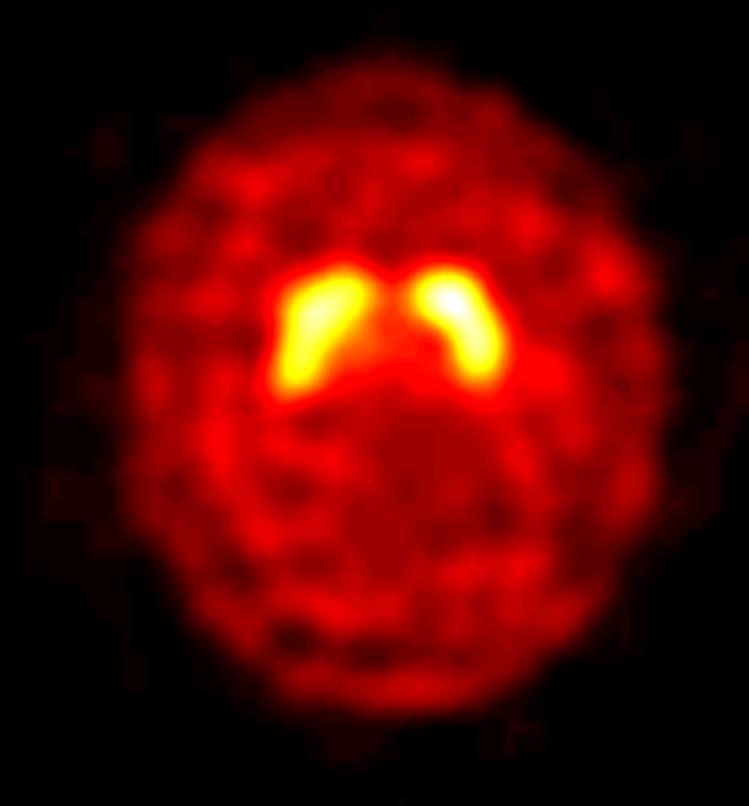
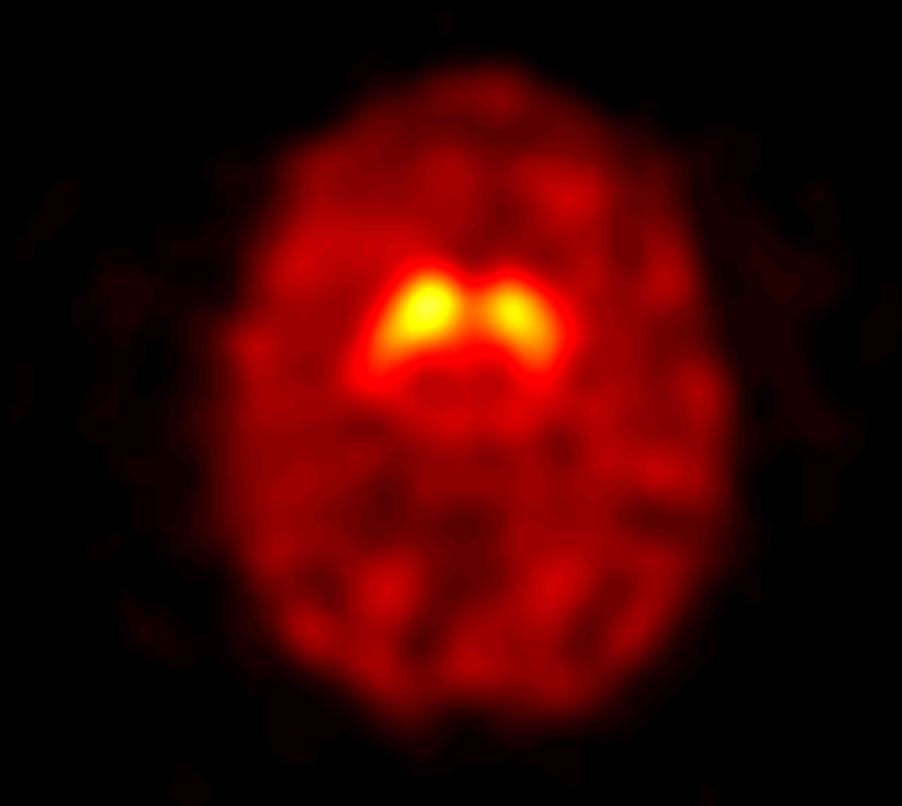
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# DaTSCAN SPECT Imaging

PD

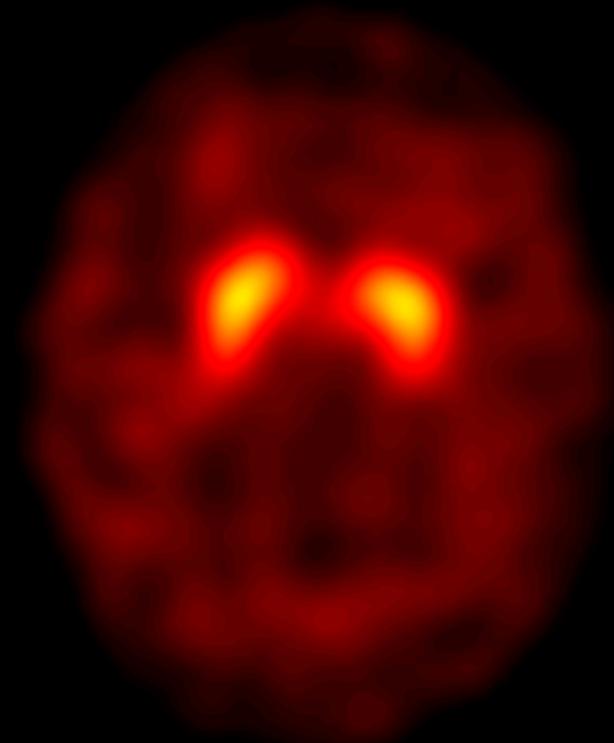
SWEDD



HC



HC excluded



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# 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)



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# Equilibrium Binding Ratio

## Striatal Binding Ratios (SBR)

= Specific striatal binding/occipital reference region

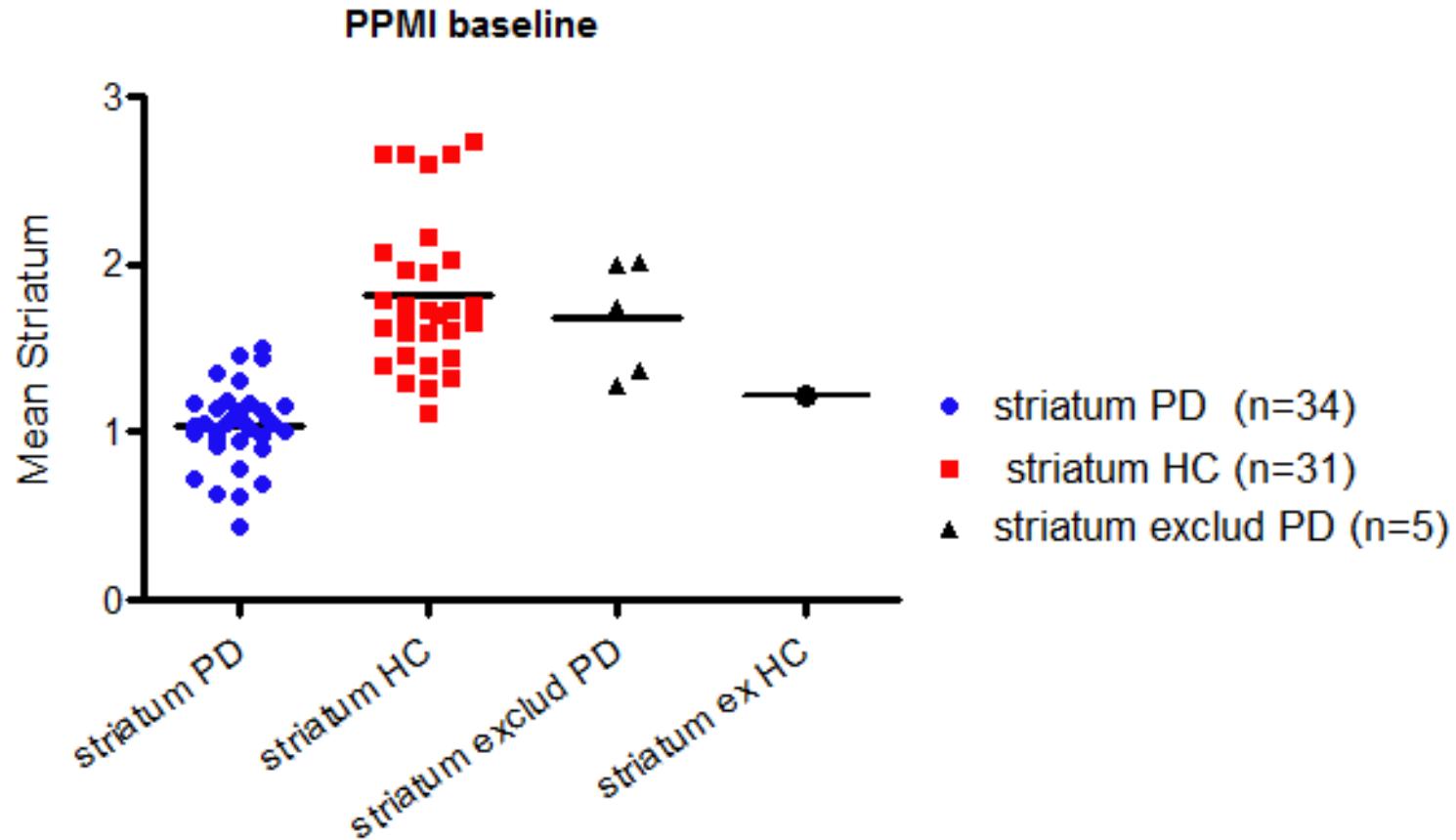
=  $\frac{\text{Total striatal count density} - \text{Occip count density}}{\text{Occip reference count density}}$

= Total striatal density/Occip count density – 1

= Binding Potential (BPnd)



# Mean Striatal Binding Ratio (SBR)

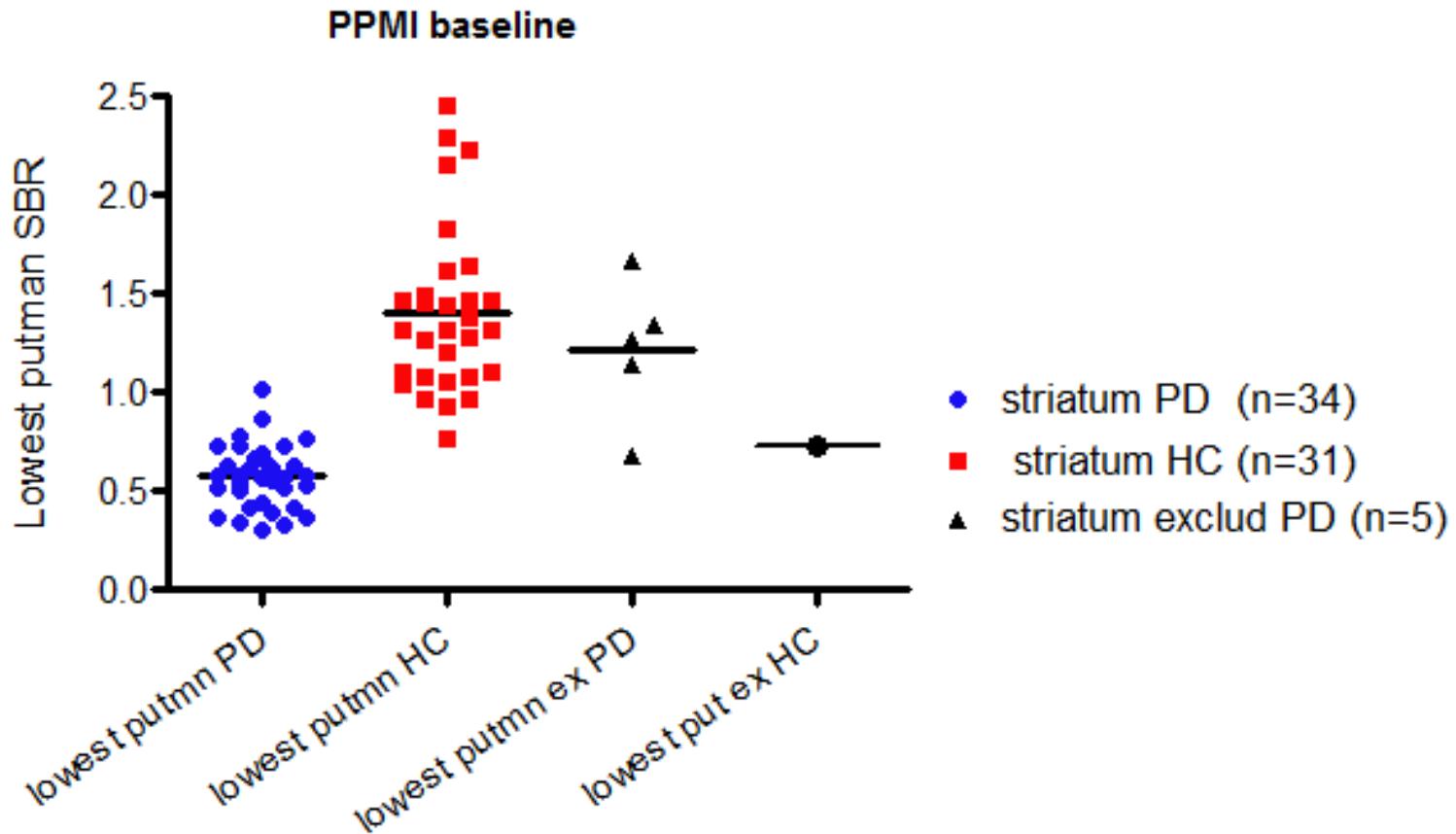


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# SBR Lowest Putamen

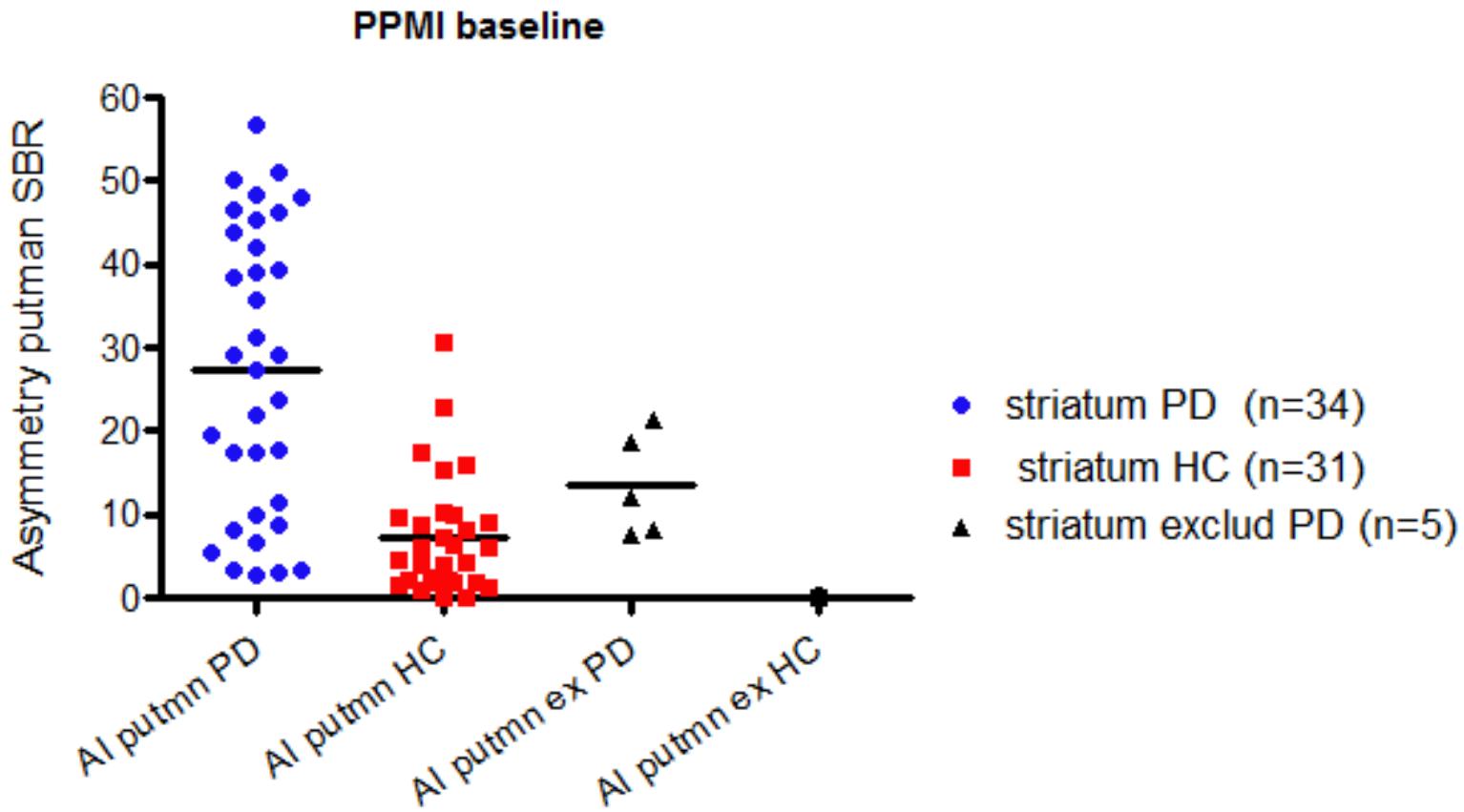


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# SBR Putamenal Asymmetry

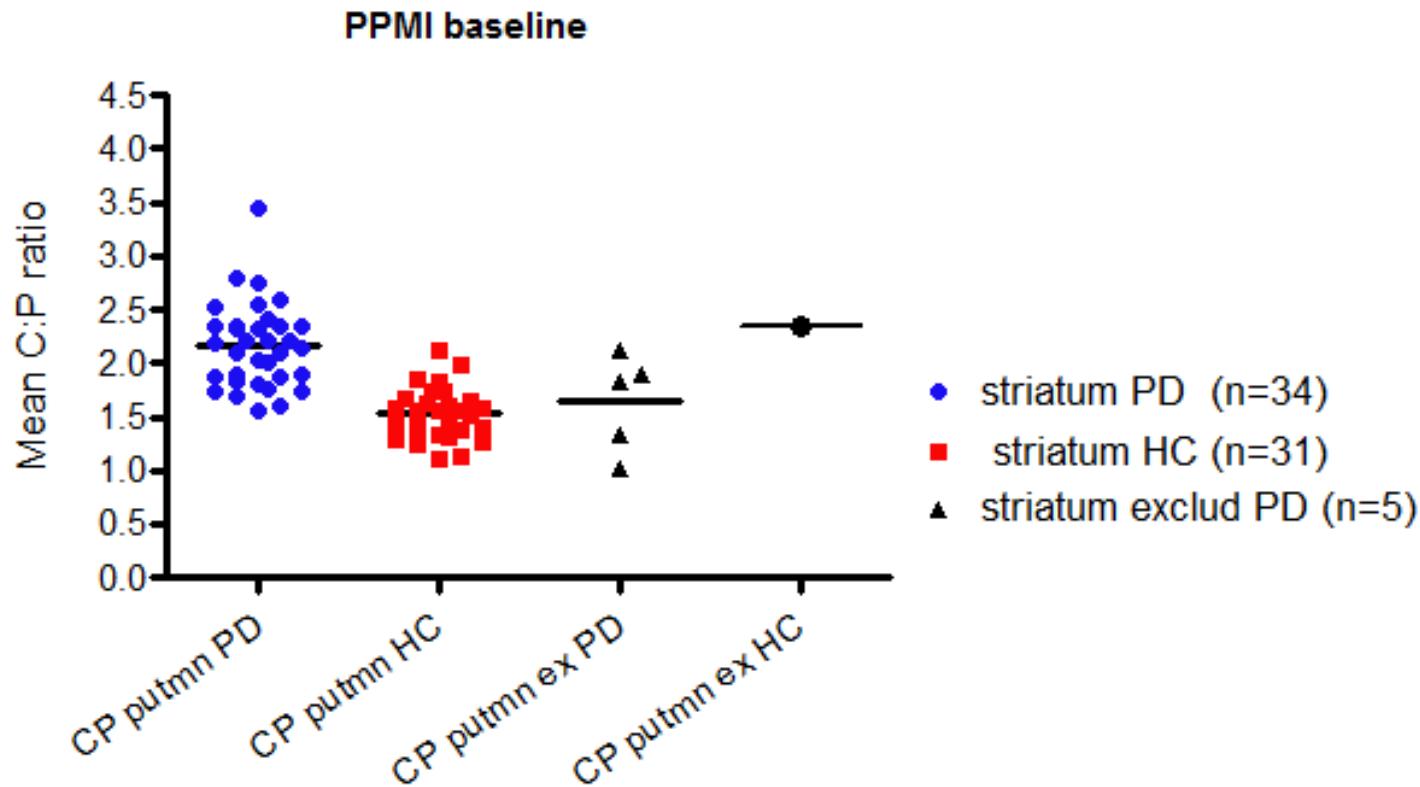


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# SBR Ratio Caudate:Putamen



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# Conclusions

- Initial quantitation consistent with literature SBR values suggesting good between-site standardization of SPECT
- SWEDDs rate about as expected (12-15%) in de novo PD, SBR outcomes more similar to controls, but limited data
- First longitudinal data expected shortly



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# DTI Update

# Future directions/challenges

- Radiotracer availability
- Phantom correction of data-to reduce variance
- Additional imaging biomarkers- e.g. resting state MR, novel scintigraphic targets

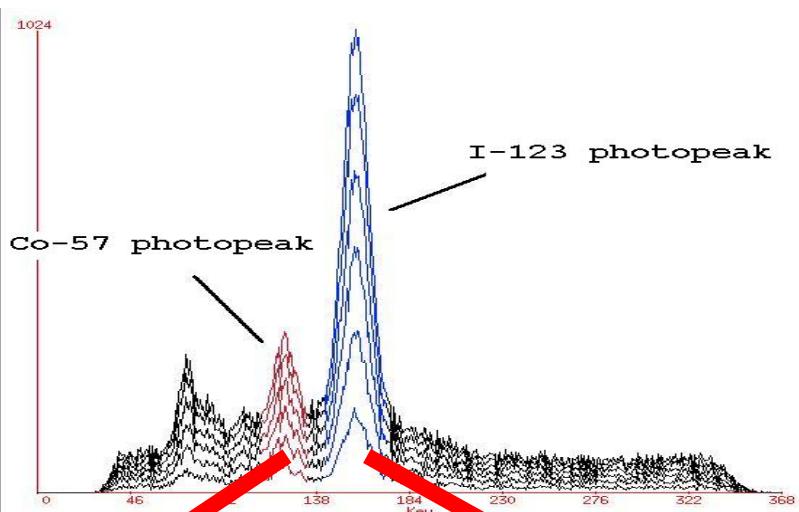


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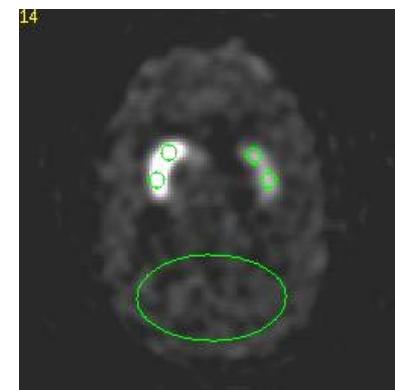
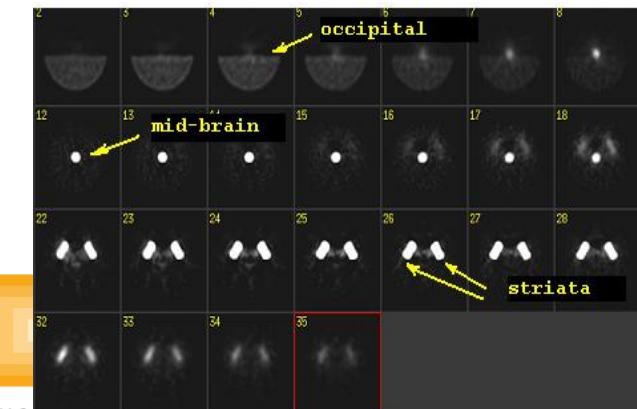
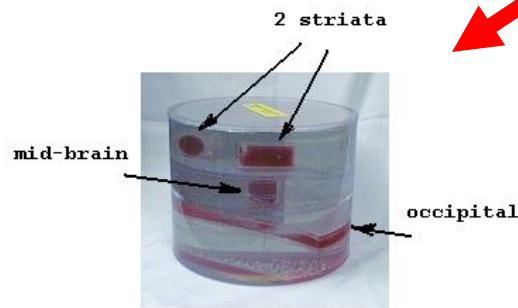
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**$^{57}\text{Co}$**

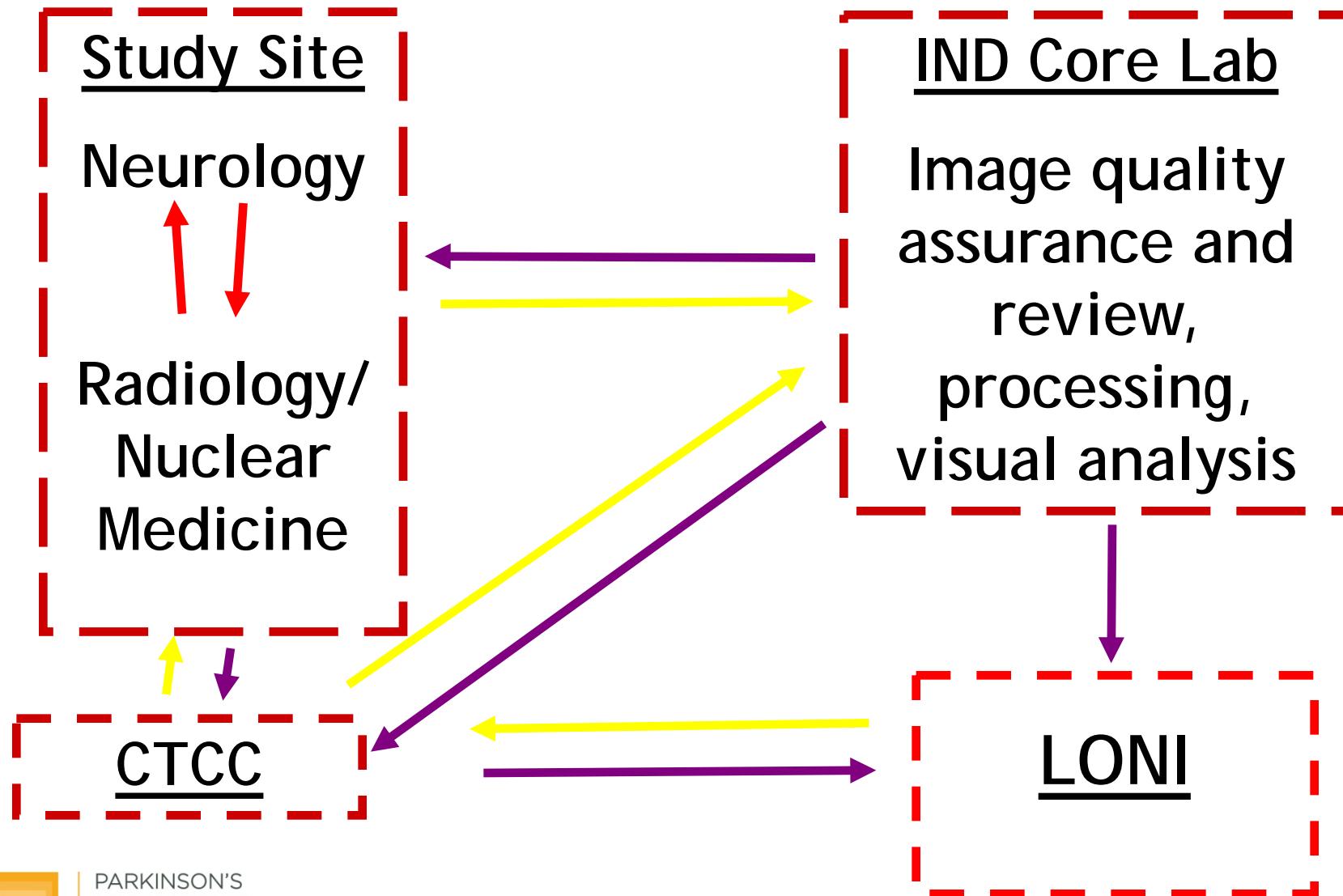


**$^{123}\text{I}$**



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# Imaging Data and Information Flow



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# DTI Subproject Processing & Analysis

Norbert Schuff

VA Medical Center & University of  
California, San Francisco



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# Objectives

- Determine if DTI can:
  - provide a robust marker of PD progression
  - serve as an adjunct to clinical assessment and PET



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# Scope Of Work

- DTI computations:
  - Rigorous quality control
  - Accurate alignment to structural MRI
  - Calculation of:
    - standard DTI measures (FA, MD)
    - advanced DTI measures (geodesic FA, generalized FA)
    - eigenvectors (tractography)
- Exploratory Group Analyses
  - Region-of-interest based
  - Regionally unbiased
  - Joint analyses of DTI with PET



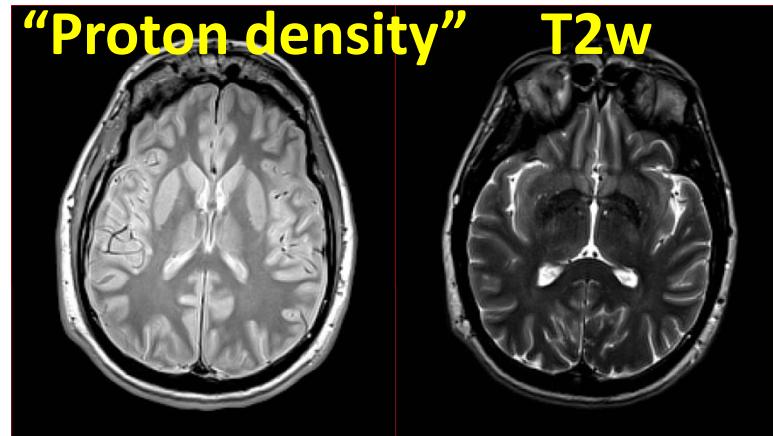
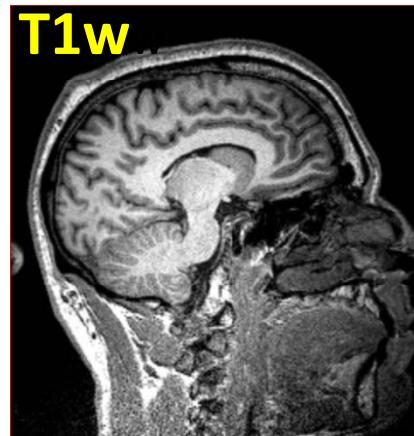
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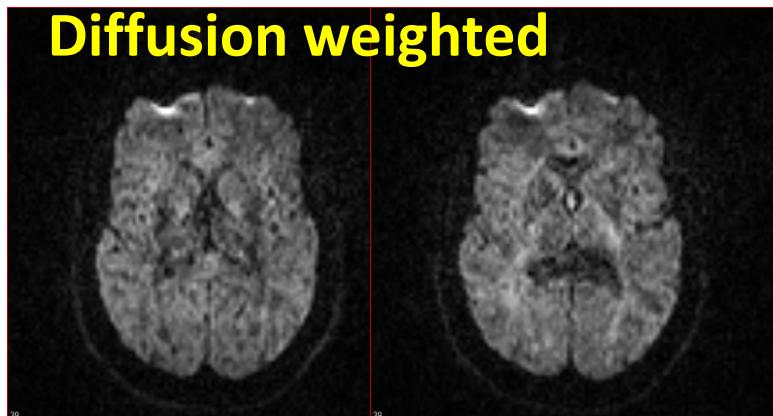
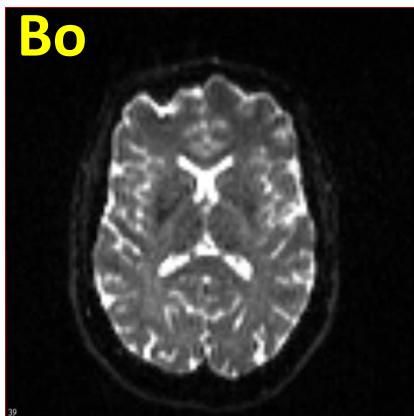


# MRI Acquisitions

Structural  
MRI



DTI



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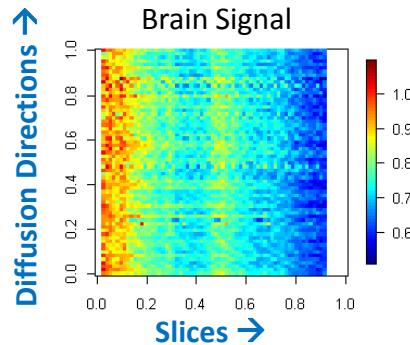
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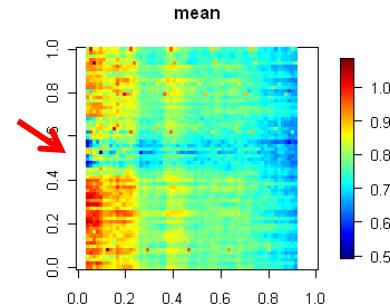
# Automated Quality Control

## Frame-to-Frame Similarity

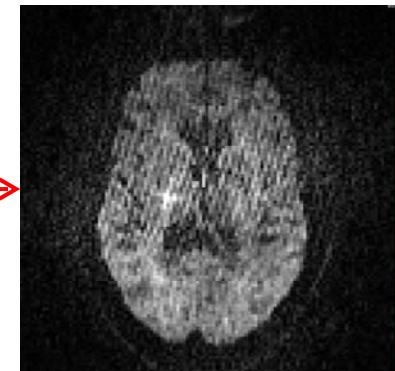
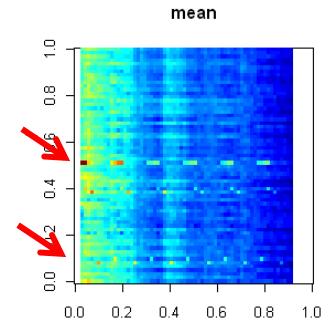
Good Quality



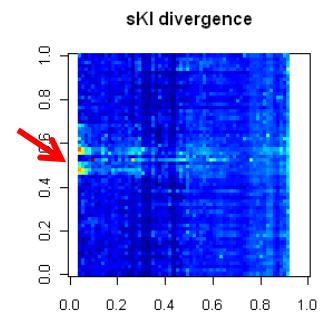
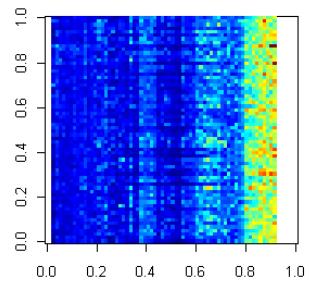
Motion



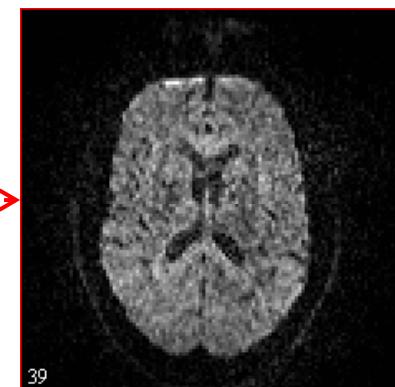
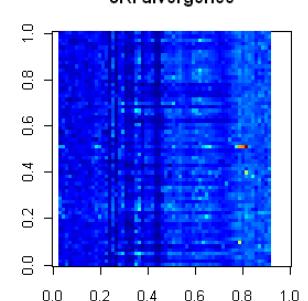
Instability



Noise



sKL divergence



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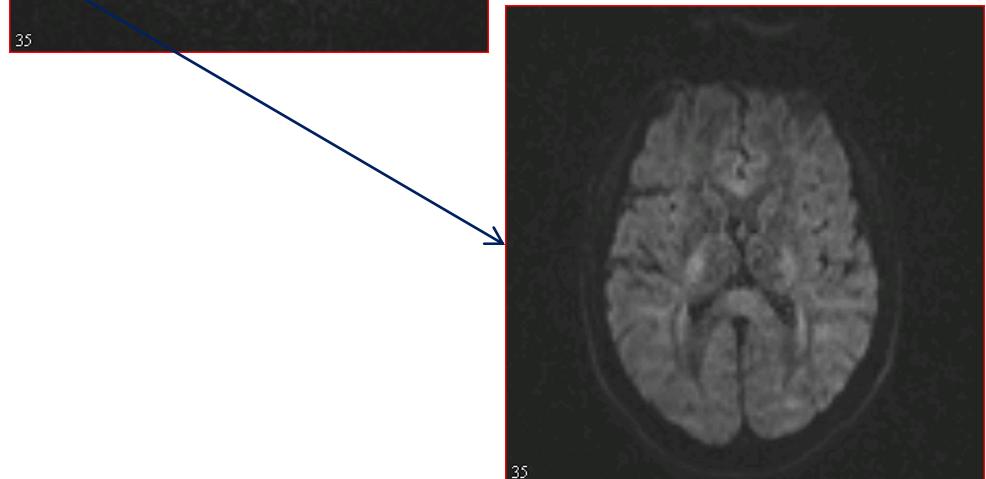
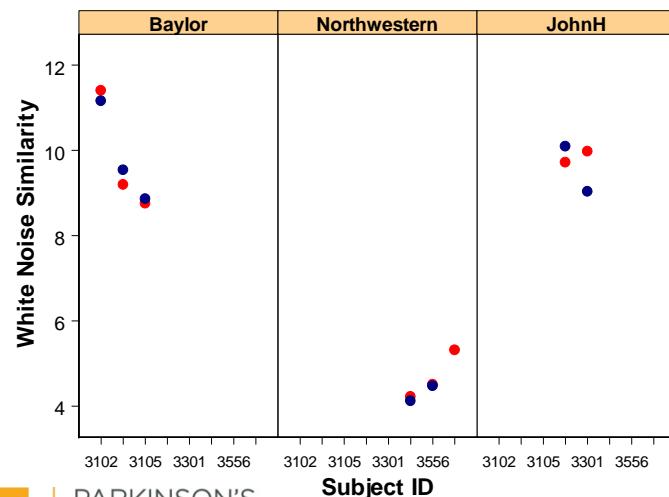
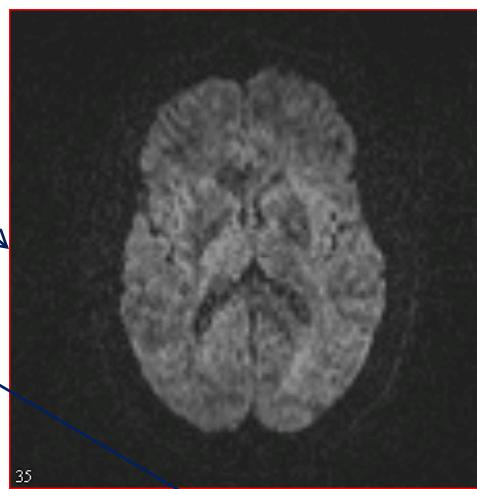
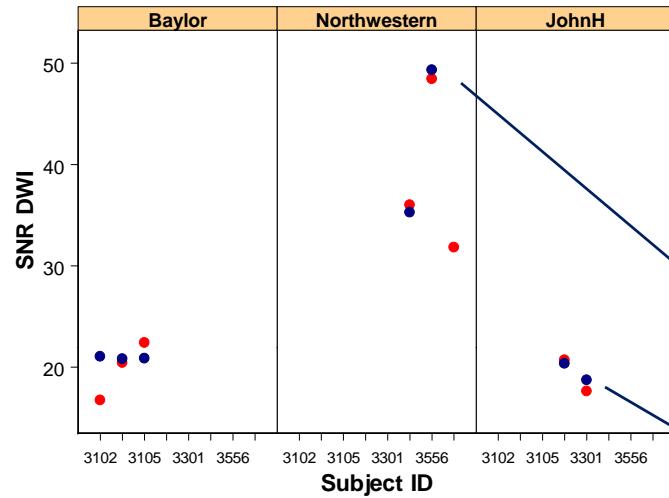


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# DTI Quality Control: First 8 Scans



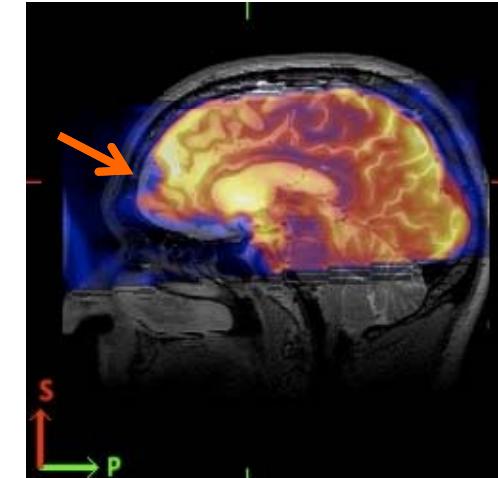
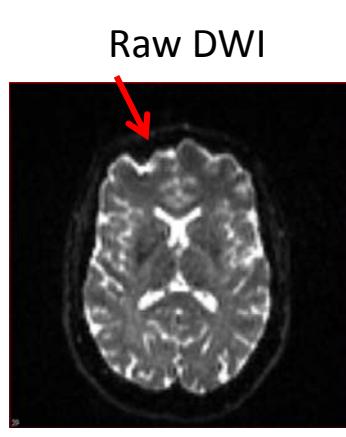
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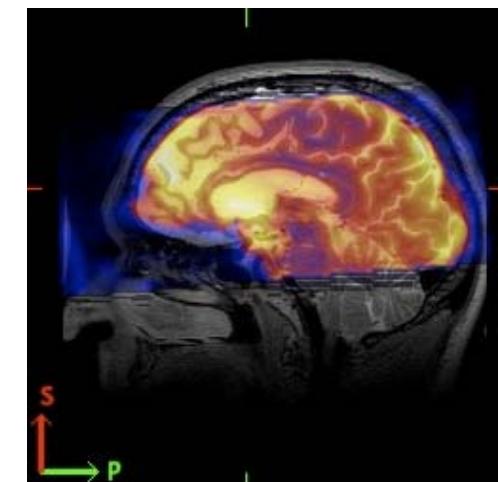
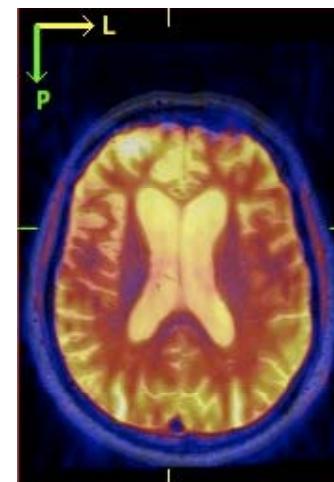
# DTI -MRI Co-registration

Rigid alignment



Nonlinear alignment

(in collaboration with  
Dr. Tom Fletcher, U Utah)



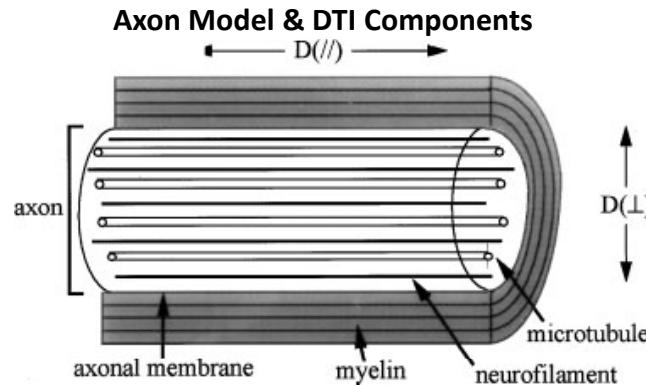
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# DTI Interpretation

## High Sensitivity – Low Specificity



### Summary:

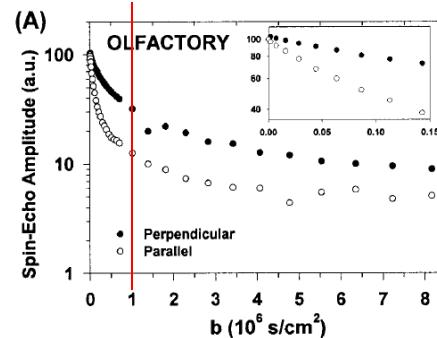
1. Mean displacement distance of tissue water that is captured on DTI using a clinical MRI scanner  $\sim 10\text{-}20 \mu\text{m}$
2. Structural features of axons other than myelin are sufficient to give rise to DTI contrast



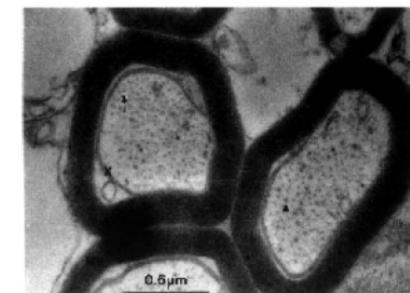
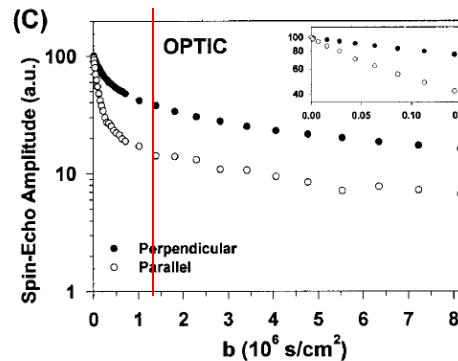
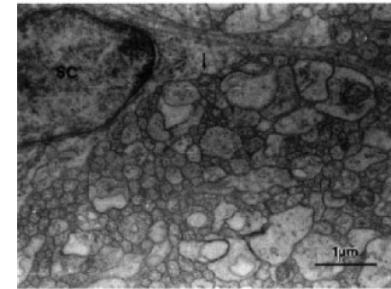
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## DTI Intensity



## Electron Micrographs

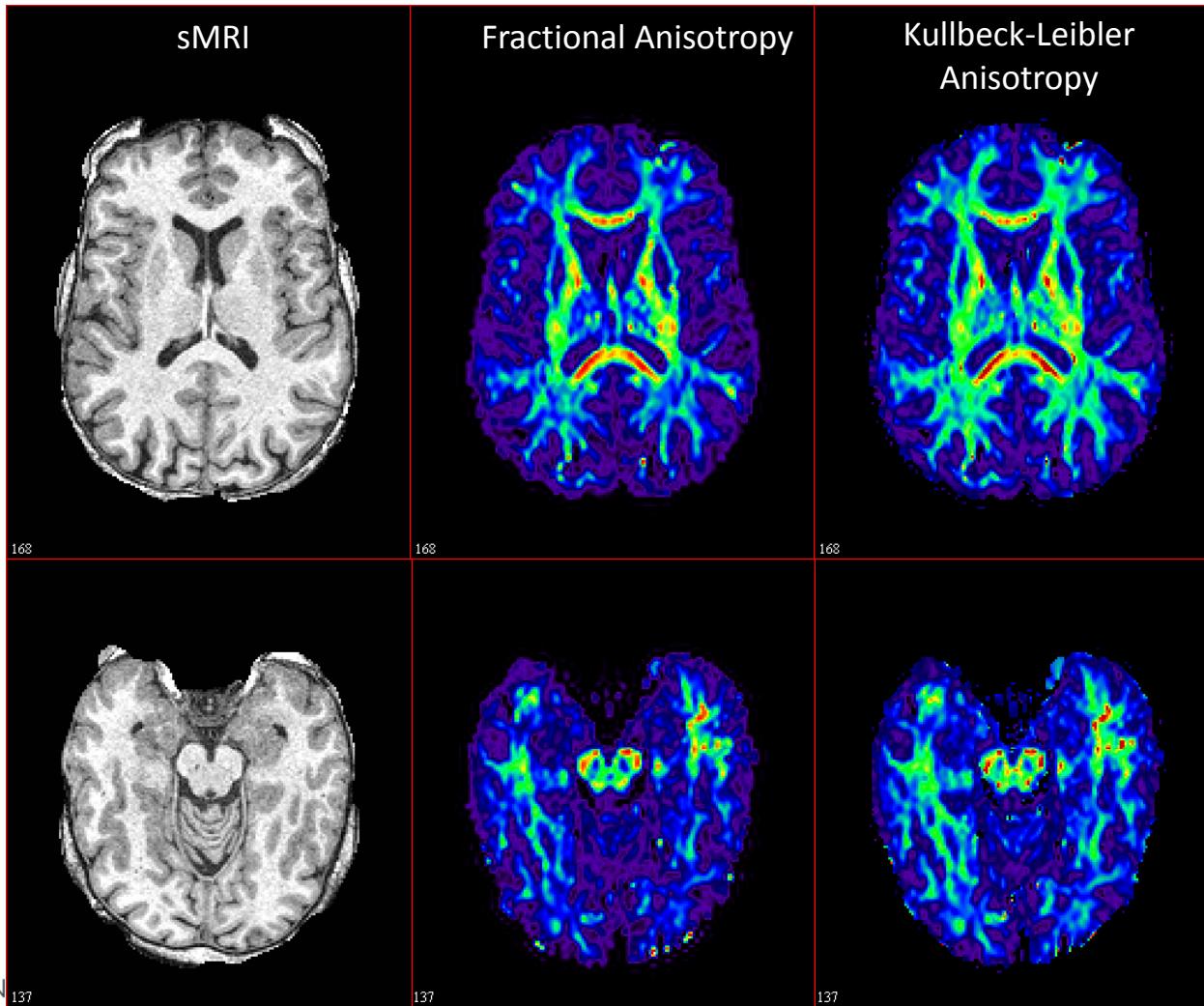


- (A) Non-myelinated olfactory nerve of the garfish  
(B) Myelinated optic nerve of the garfish

C. Beaulieu, NMR in Biomedicine 2002; 15; 435-55



# DTI Computations



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# Summary

- Accomplishments
  - MRI sites were qualified
  - DTI of first 8 subjects QC'ed
  - MRI quality is generally very good
  - Standard and advanced DTI measures implemented
- What needs to be done
  - Format for uploading derived data to LONI
  - Processing of DTI as data arrive
  - Interim group analyses (n=20 per group?)



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# Availability of DAT Imaging

## Current Status:

- **DaTSCAN has not been available since February 2011**
- **Subjects are given waivers to enroll in PPMI until DaTSCAN is available**
- **Subjects enrolled as PD subjects with normal scan will be withdrawn**
- **Current timeline for DaTSCAN production-Uncertain**
- **To date 60 waivers have been given issued - Some site IRB resistant to additional waivers**



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# **Availability of DAT Imaging**

## **Potential solution:**

- **DAT imaging will be produced at the Institute for Neurodegenerative disorder (IND)**
- **Subjects will travel to IND to be imaged**
- **Subjects will be imaged at their sites once DaTscan is available**
- **DAT imaging at IND available JUNE 1**



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# DAT Imaging at IND

- Subjects will consent at the clinical site
- Subject info will be faxed to IND by clinical site
- All travel for the subjects and a companion will be arranged by IND staff
- Subjects will consent at IND and will be imaged at IND (Datscan or  $\beta$ -CIT).
- IND staff will inform clinical site
- IND staff will contact subjects post scan by phone



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# DAT Imaging at IND – Next steps

**IND chemistry team to establish DAT imaging**

**DAT IND modified so that IND can produce DaTscan**

**PPMI protocol and consent modified to allow DAT imaging at IND**

**Site consent modified to allow DAT imaging at IND**

**Logistics established for Site-IND communication**



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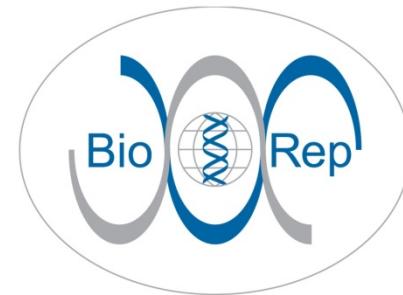
# PPMI Biorepository Update

PPMI Annual Investigators Meeting  
May 4-5, 2011

Alison Scutti, MS  
Biospecimen Repository co-PI  
Coriell Institute for Medical Research



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# Biorepository Core Team

## Coriell

Alison Scutti, MS  
Senior Project Manager  
Biorepository co-PI

Michael D'Andrea, PhD  
Director, Neurosciences  
Biorepository co-PI

Steve Madore, PhD  
Director, Molecular Biology

Sherryann Wert, BS  
Specialized Tissue Culture Supervisor

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



# Outline

- Submissions
- Processing
- Data
- Concerns



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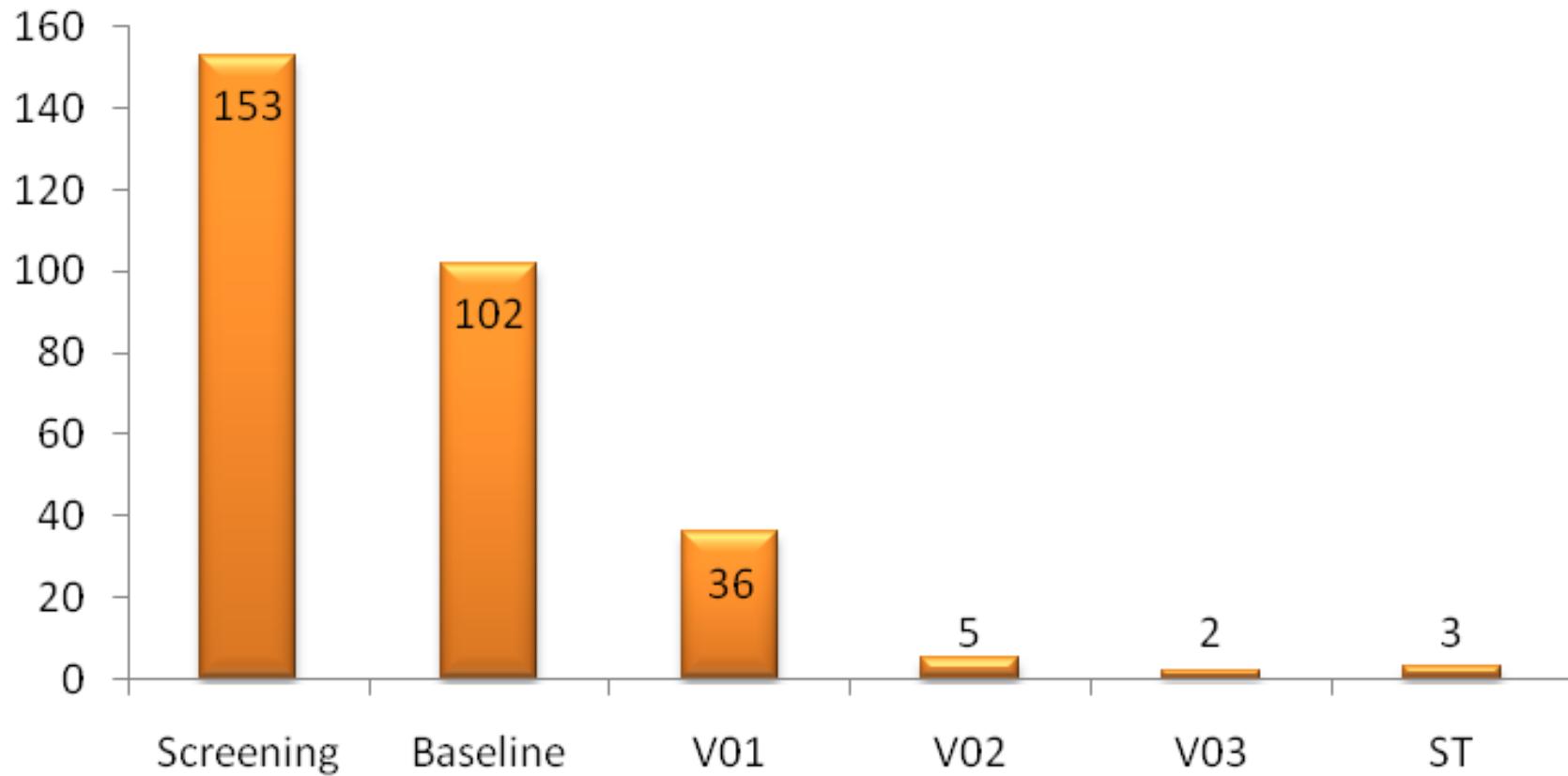
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# PPMI Sample Submission Summary

Total Submissions from Unique Subjects	156
<i>Institute of Neurodegenerative Disorders</i>	21
<i>Northwestern University</i>	16
<i>Oregon Health and Science University</i>	15
<i>University of Alabama at Birmingham</i>	14
<i>Emory University School of Medicine</i>	12
<i>Baylor College of Medicine</i>	11
<i>The Parkinson's Institute</i>	11
<i>Boston University</i>	9
<i>University of Pennsylvania</i>	9
<i>University of South Florida</i>	9
<i>University of Washington and VA Puget Sound Health Care System</i>	9
<i>University of Rochester</i>	8
<i>Sun Health Research Institute</i>	5
<i>Innsbruck Medical University</i>	3
<i>Johns Hopkins University</i>	3
<i>Paracelsus-Elena Klinik</i>	1

# PPMI Submissions by Visit Type



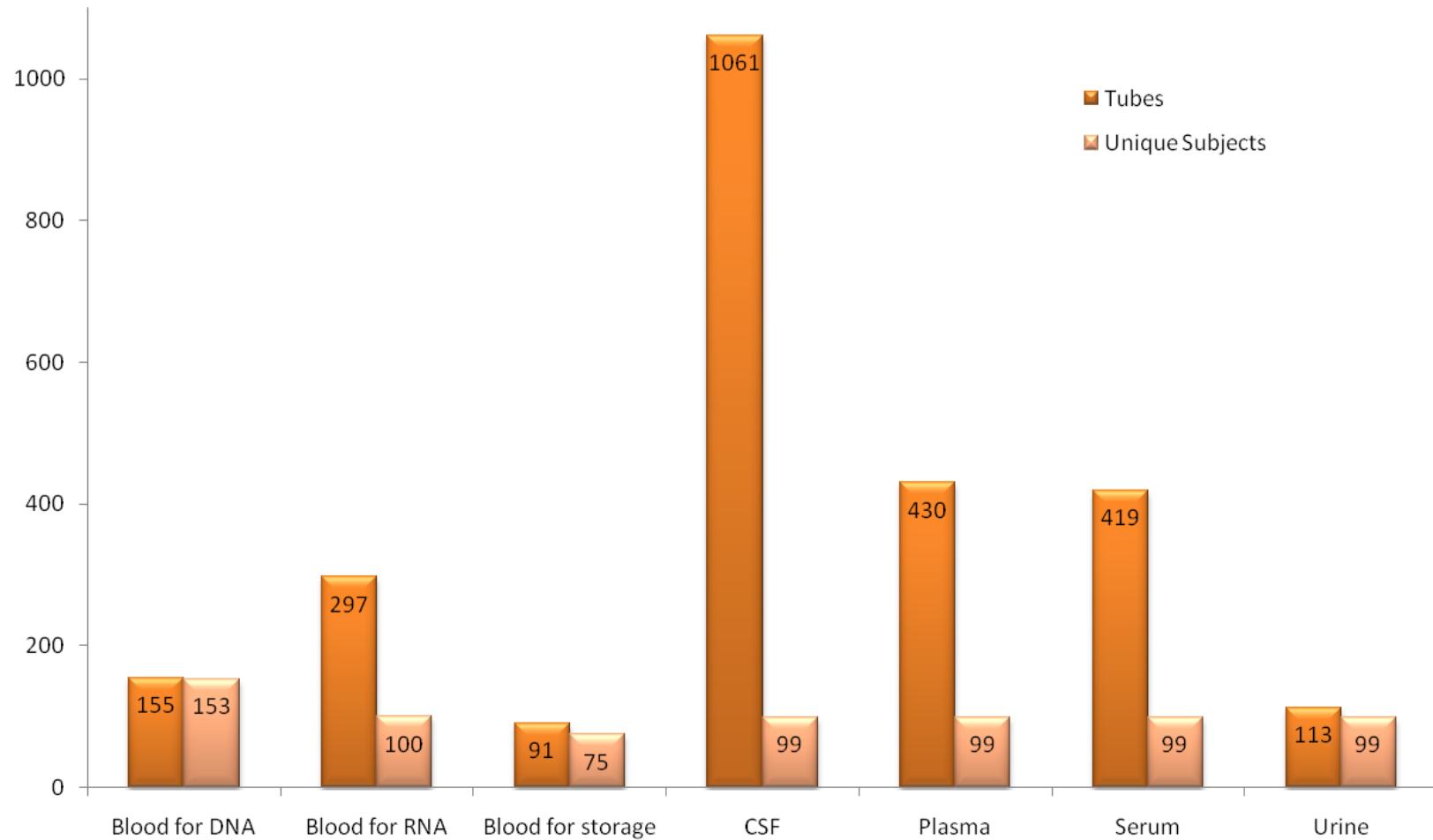
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# PPMI Submissions by Specimen Type

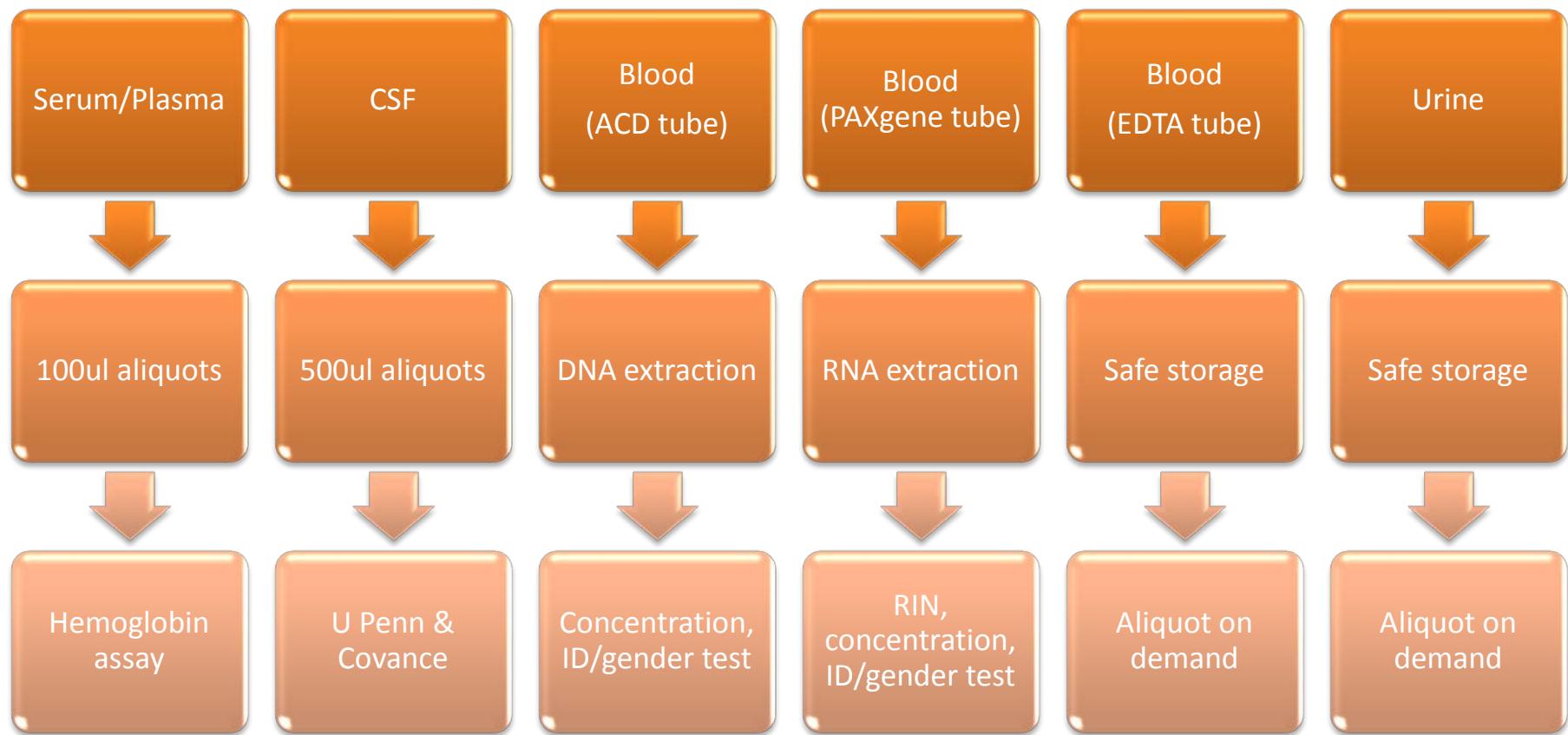


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# Sample Processing Overview



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# Atlas

**Coriell Atlas ALISON ANSBACH ON ATLAS TIME ZONE: EDT**

**Biobanking Sample Management Storage Packages & CDTs Reports**

**Allocated Samples External Submitted Samples Data Entry Samples BioRep Samples Two Weeks Samples Lab Operations Samples Child Confirmation Samples Left Circulation Samples Admin Samples Sample Movement S**

**View Check In Check Out Accessioning Data Entry Pool Sample Make Available**

**Archive 3rd Party Transfer Edit (Lab User) Edit (Admin) View as Excel Print Label Approve**

**Annotation Entry Result Data Entry Add Tests Assign Package Transfer Custody Assign Custodian Create**

1 - 500 of 3882 ( page 1 of 8 ) [ 0 selected ] Group By Storage Status: ▾

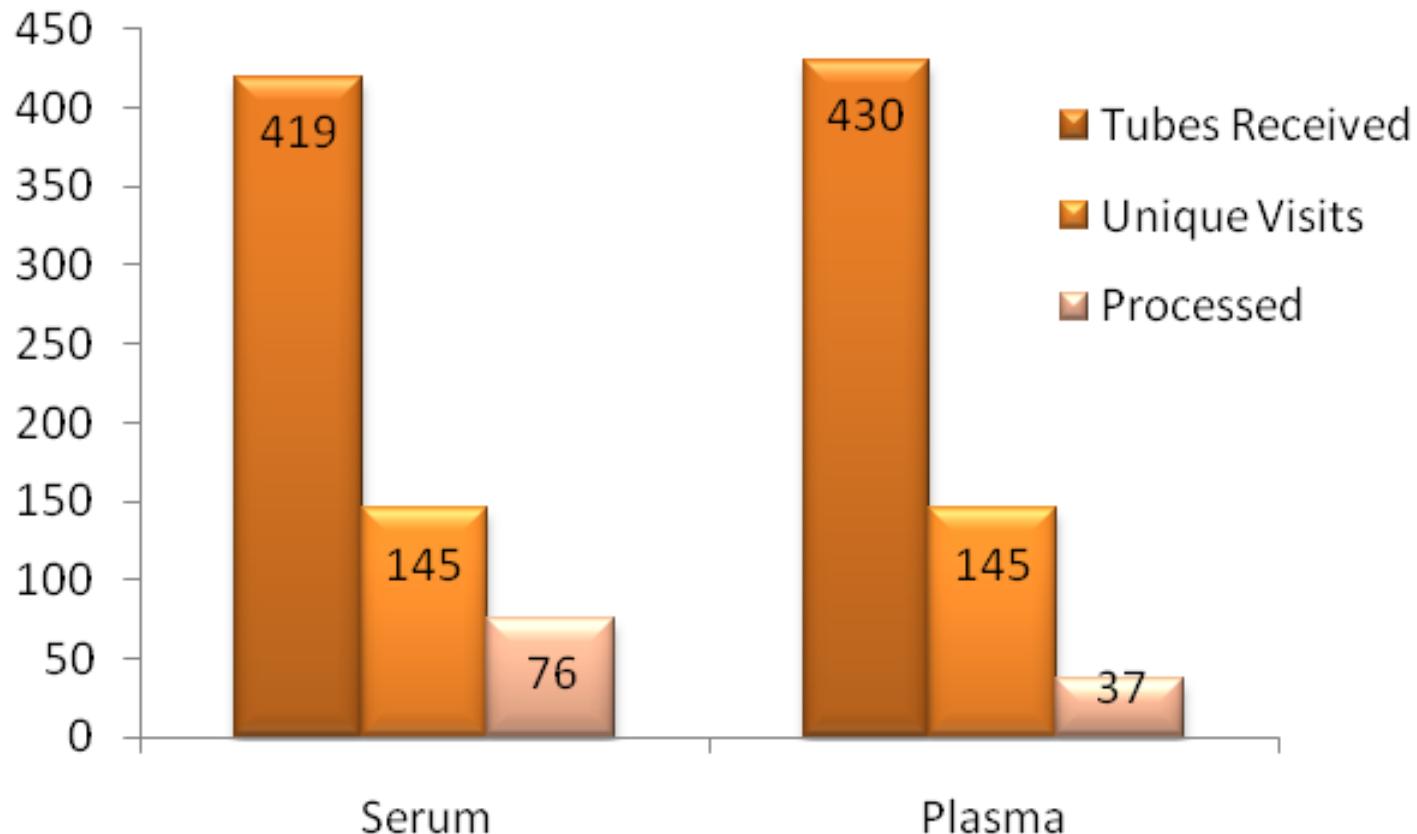
**Storage Status: Disposed**

Sample	Status	Disposition	Sample Type	CD	Custodian	Study	Create Date	Subject	Alias	ClinicalEvent	Study Site	Received With Package	Shipped With Package	Container	CurrentLocation	Previous
<a href="#">PP-00000003</a>	Disposed	Consumed	WB	PPMI	alison	<a href="#">PPMI</a>	6/9/10	<a href="#">ST-00000006</a>	3400	Screening Visit	Institute of Neurodegenerative Disorders	<a href="#">PKG-1006-00004</a>		ACD Tube		
<a href="#">PP-00000005</a>	Disposed	Consumed	WB	PPMI	alison	<a href="#">PPMI</a>	6/10/10	<a href="#">ST-00000007</a>	3401	Screening Visit	Institute of Neurodegenerative Disorders	<a href="#">PKG-1006-00005</a>		ACD Tube		
<a href="#">PP-00000006</a>	Disposed	Consumed	WB	PPMI	alison	<a href="#">PPMI</a>	6/10/10	<a href="#">ST-00000008</a>	3402	Screening Visit	Institute of Neurodegenerative Disorders	<a href="#">PKG-1006-00005</a>		ACD Tube		
<a href="#">PP-00000007</a>	Disposed	Consumed	WB	PPMI	alison	<a href="#">PPMI</a>	6/10/10	<a href="#">ST-00000009</a>	3403	Screening Visit	Institute of Neurodegenerative Disorders	<a href="#">PKG-1006-00005</a>		ACD Tube		
<a href="#">PP-00000008</a>	Disposed	Consumed	WB	PPMI	alison	<a href="#">PPMI</a>	6/10/10	<a href="#">ST-00000010</a>	3404	Screening Visit	Institute of Neurodegenerative Disorders	<a href="#">PKG-1006-00006</a>		ACD Tube		
<a href="#">PP0000-0226</a>	Disposed	Disposed, low volume	WB	PPMI	alison	<a href="#">PPMI</a>	10/5/10	<a href="#">ST-00000024</a>	3500	Screening Visit	University of Alabama at Birmingham	<a href="#">PKG-1010-00031</a>		ACD Tube		
<a href="#">PP0000-0657</a>	Disposed	Damaged, broken	WB	PPMI	alison	<a href="#">PPMI</a>	11/30/10	<a href="#">ST-00000039</a>	3650	Baseline Collection	Sun Health Research Institute	<a href="#">PKG-1011-00104</a>		EDTA tube 5ml		
<a href="#">PP0000-0895</a>	Disposed	Damaged, broken	WB	PPMI	alison	<a href="#">PPMI</a>	12/16/10	<a href="#">ST-00000040</a>	3102	Baseline Collection	Baylor College of Medicine	<a href="#">PKG-1012-00156</a>		PAXgene		
<a href="#">PP0000-1254</a>	Disposed	Damaged, broken	WB	PPMI	alison	<a href="#">PPMI</a>	1/11/11	<a href="#">ST-00000990</a>	3414	Baseline Collection	Institute of Neurodegenerative Disorders	<a href="#">PKG-1101-000228</a>		EDTA tube 5ml		
<a href="#">PP0000-1307</a>	Disposed	Damaged, broken	WB	PPMI	alison	<a href="#">PPMI</a>	1/13/11	<a href="#">ST-00000530</a>	3504	Baseline Collection	University of Alabama at Birmingham	<a href="#">PKG-1101-000236</a>		EDTA tube 5ml		
<a href="#">PP0000-1369</a>	Disposed	Damaged, broken	UR	PPMI	alison	<a href="#">PPMI</a>	1/20/11	<a href="#">ST-00000602</a>	3454	Baseline Collection	Boston University	<a href="#">PKG-1101-000258</a>		Conical - 15ml		
<a href="#">PP0000-1386</a>	Disposed	Damaged, broken	WB	PPMI	alison	<a href="#">PPMI</a>	1/20/11	<a href="#">ST-00000602</a>	3454	Baseline Collection	Boston University	<a href="#">PKG-1101-000258</a>		EDTA tube 5ml		
<a href="#">PP0000-1581</a>	Disposed	Damaged,	WR	PPMI	alison	<a href="#">PPMI</a>	2/4/11	<a href="#">ST-00000001</a>	3301	Baseline	Johns Hopkins	<a href="#">PKG-1102-</a>		EDTA tube		

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# Serum & Plasma Progress

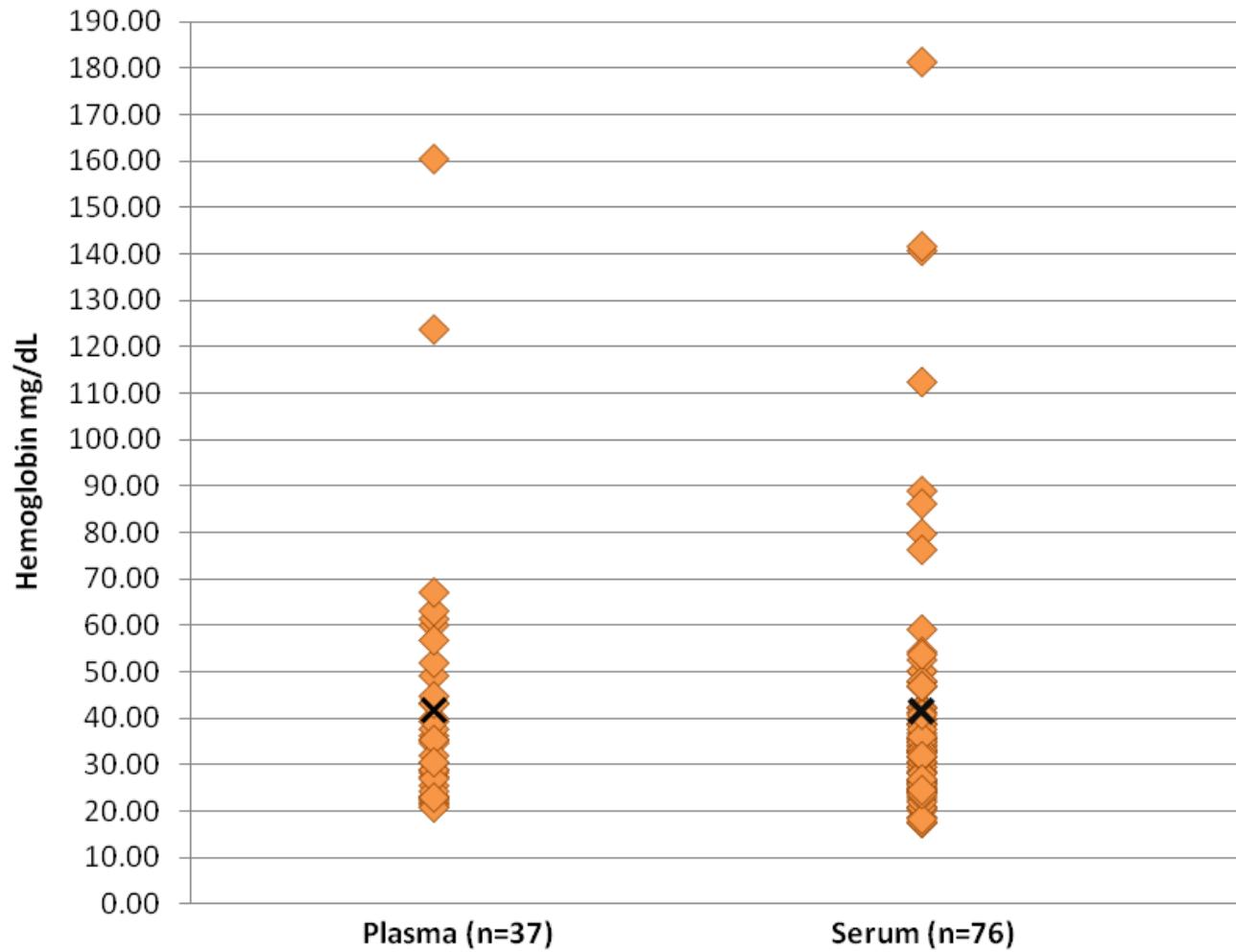


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# Serum & Plasma Hemoglobin Assay Results



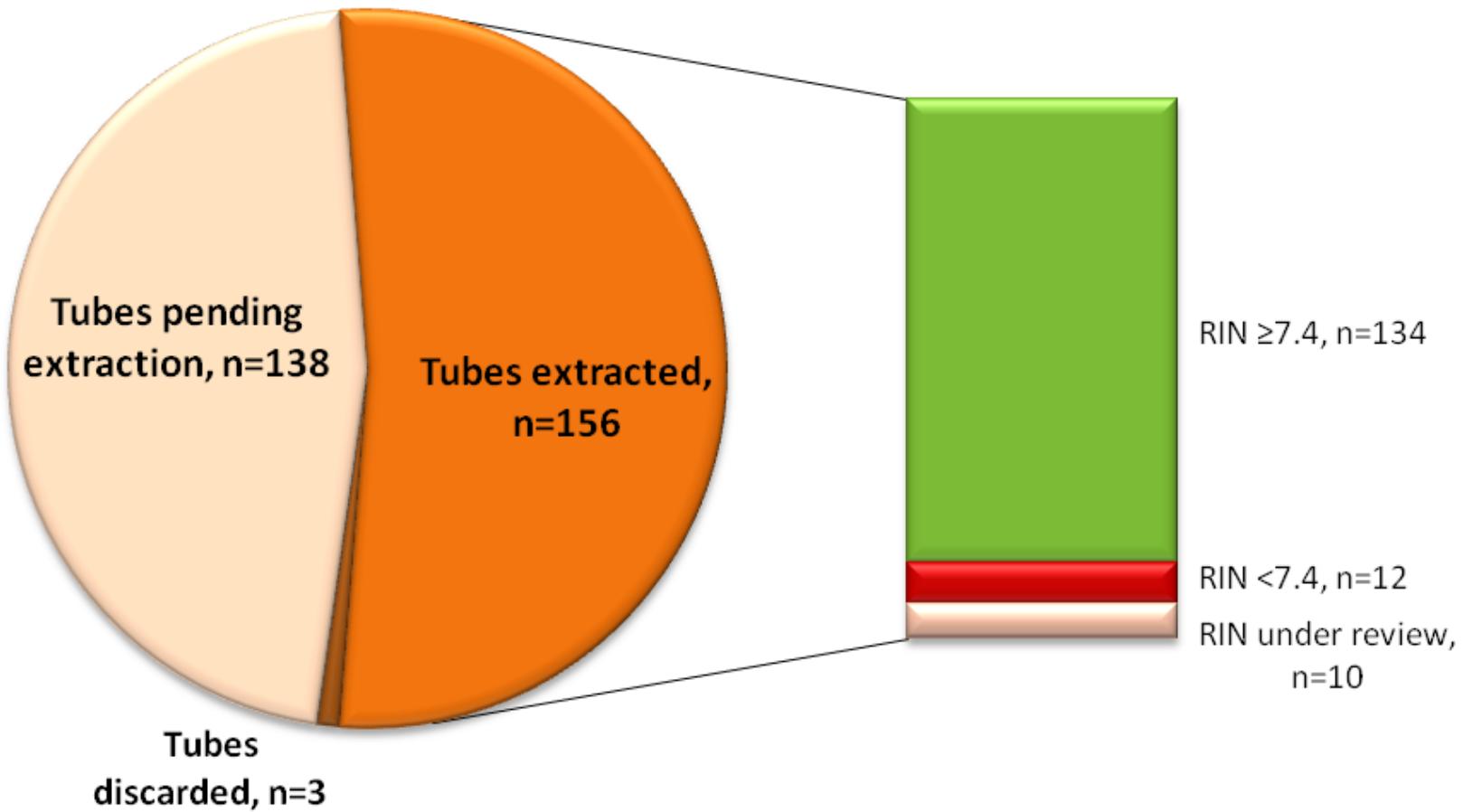
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# PAXgene RNA Extraction Progress



# Sample & Submission Issues

Glass EDTA tubes cracking when frozen

Replaced with plastic EDTA tubes

Tube labels not adhering well to frozen samples

Reminder to sites  
Biologics Manual revised  
Possibility of new label type

Low volume serum, plasma & CSF aliquots

Reminder to sites  
Biologics Manual revised

Sample shipment notifications not being sent

Reminder to sites

Clots/cloudiness present in serum samples

Tracking occurrences



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# In-service Training Planned

- Summer 2011
- Training new staff and re-training current staff on sample collection & processing
  - Highlighting current processing issues common to many sites
- Webinar format



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# Biologics Review Committee Update

- Committee established
  - 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
- Kick-off Call: March 15, 2011
- Bi-monthly calls to evaluate proposals
  - Two step proposal process through PPMI website
- Next call: May 10th



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# Hb cross-val and RNA one-step data



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# Hemoglobin Assay Cross-Validation Study: Purpose & Rationale

- Cross-validate the hemoglobin assay for plasma and serum QC at Coriell and BioRep
- Two different assay formats in use:
  - Coriell – 96-well
  - BioRep – cuvette
- Demonstrate intra- and inter-assay reproducibility using plasma/serum from blood processed at Coriell & BioRep using same methods for PPMI study



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# Hemoglobin Assay Cross-Validation Study: Design

- Use of identical lots of materials to conduct hemoglobin measurements in each lab:
  - Plasma and serum (5 each from Coriell)
  - Hemoglobin assay kits (BioAssay Systems)
  - Eurotrol hemoglobin control ( $75 \pm 30$  mg/dL)
  - Pre-measured hemoglobin (25 mg/dL) from Coriell
- Each lab to use materials stored under same conditions
- Run assays on samples on three different days for inter-assay variability



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# Hemoglobin Assay Cross-Validation Study: Goals

## Achieve cross-validation protocol specifications

- Intra- and inter-assay CVs  $\leq 15\%$
- Standard curve  $R^2$  value  $\geq 0.98$
- Acceptable control ranges
  - $75 \pm 30$  mg/dL for Eurotrol control
  - $25 \pm 5$  mg/dL for hemoglobin control
- Good correlation of plasma/serum hemoglobin values between labs – Pearson's correlation coefficient ,  $R^2 \geq 0.8$

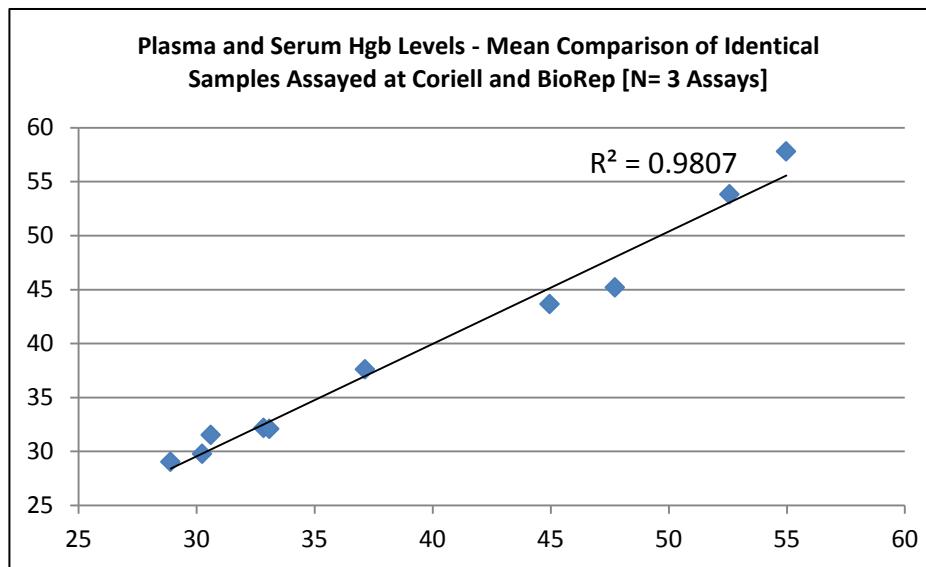
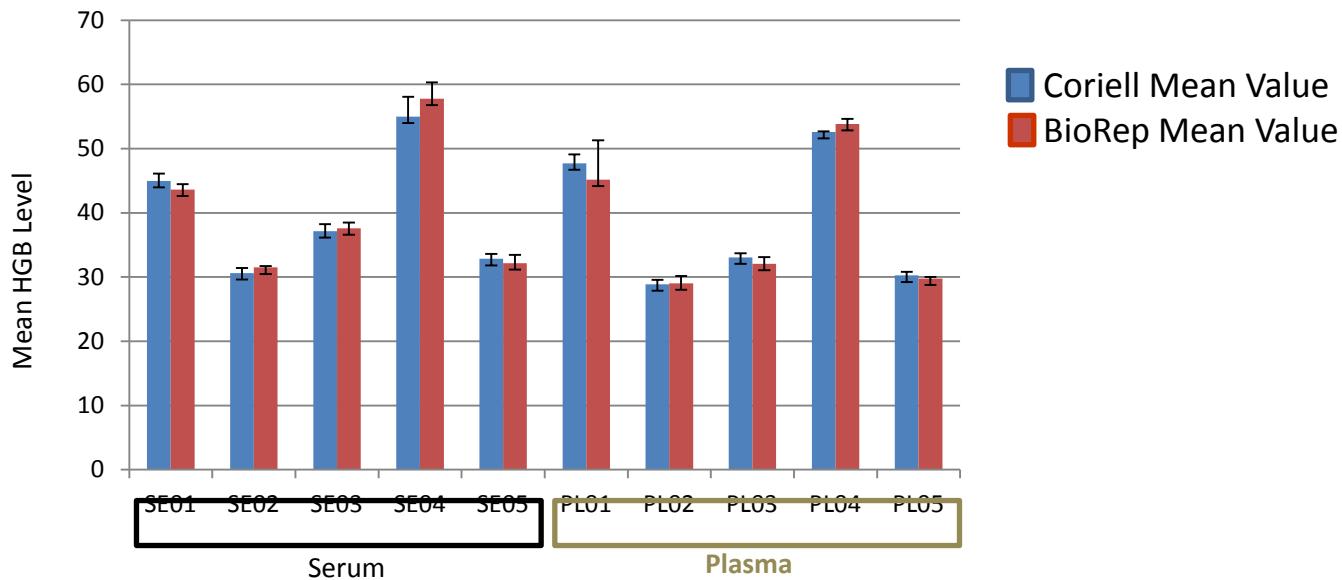


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# Hemoglobin Assay Cross-Validation Study: Results



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# Hemoglobin Assay Cross-Validation Study: Summary

- The hemoglobin assay for plasma and serum QC performed using the different methods by the labs has met the acceptance criteria for the cross-validation procedure.
  - The 96-well plate reader assay used by Coriell and the cuvette assay used by BioRep give very similar results as indicated by the excellent  $R^2$  of **0.98**.
  - Inter-assay CVs between labs are acceptable.
  - Controls fall within the specified range. Some differences were noted between the control values from the labs with a  $p < 0.05$ . Cause undetermined.



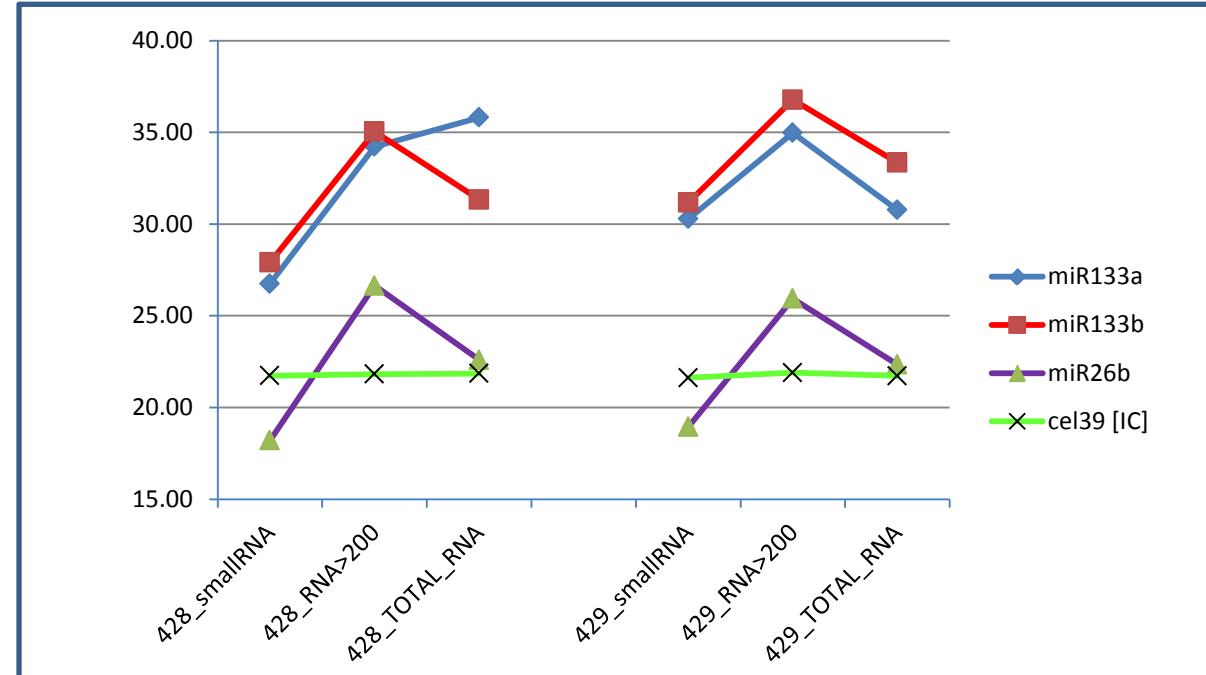
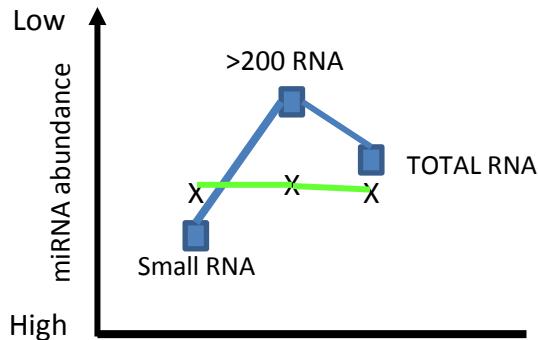
# Experimental Design

- Collect blood in PAXgene tubes from 2 donors
- Isolate RNA using 2-step or 1-step method
  - **2-step:** Standard column purification protocol for large RNA isolation (>200 nucleotides), small RNAs (<200 nucleotides) purified from flow-through on second column
  - **1-step:** All RNAs purified using single column
- 10ng of RNA analyzed for presence of miR133a, miR133b, and miR26b using TaqMan **MicroRNA Assay**
  - All samples “spiked” with synthetic miRNA representing *C. elegans* miR39 as internal reference

**Expect to see enrichment of blood-miRNAs in small RNA fraction from FLOW THROUGH, very little miRNA in >200 RNA fraction, and all miRNAs present in single step method.**



### Expected Pattern



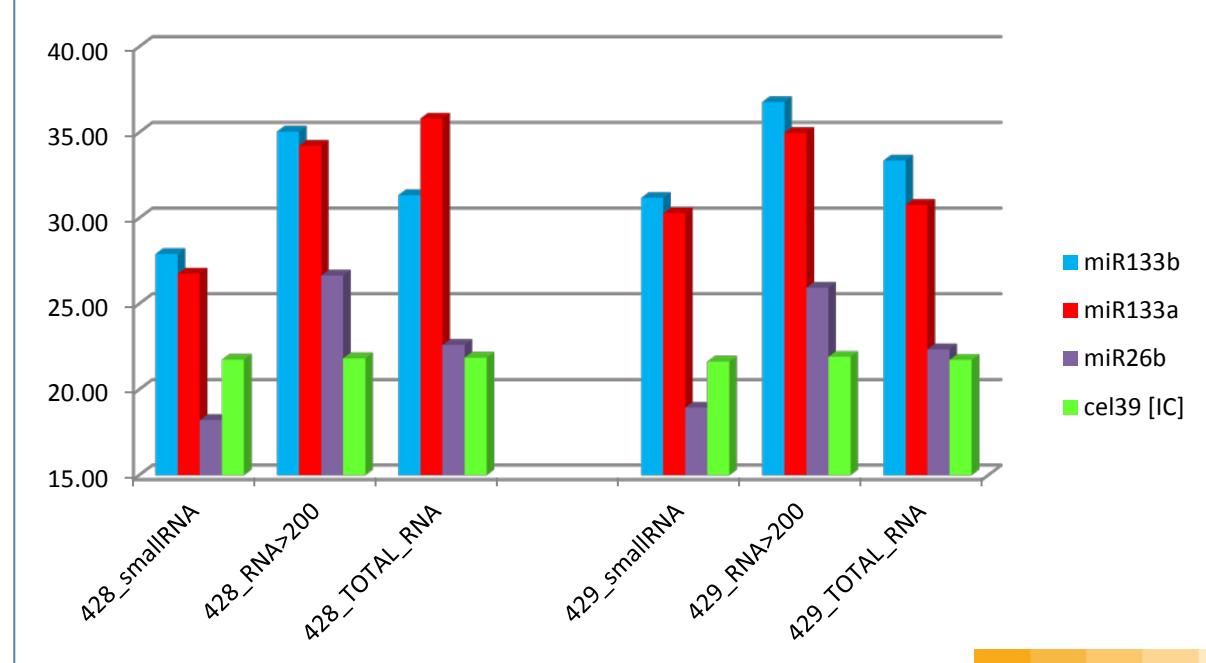
# Graphical Display of Ct Data

In triplicate with %CVs <3.



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# PPMI biofluid collection experience

Leslie M Shaw

Department of Pathology & Laboratory Medicine  
University of Pennsylvania Medical Center



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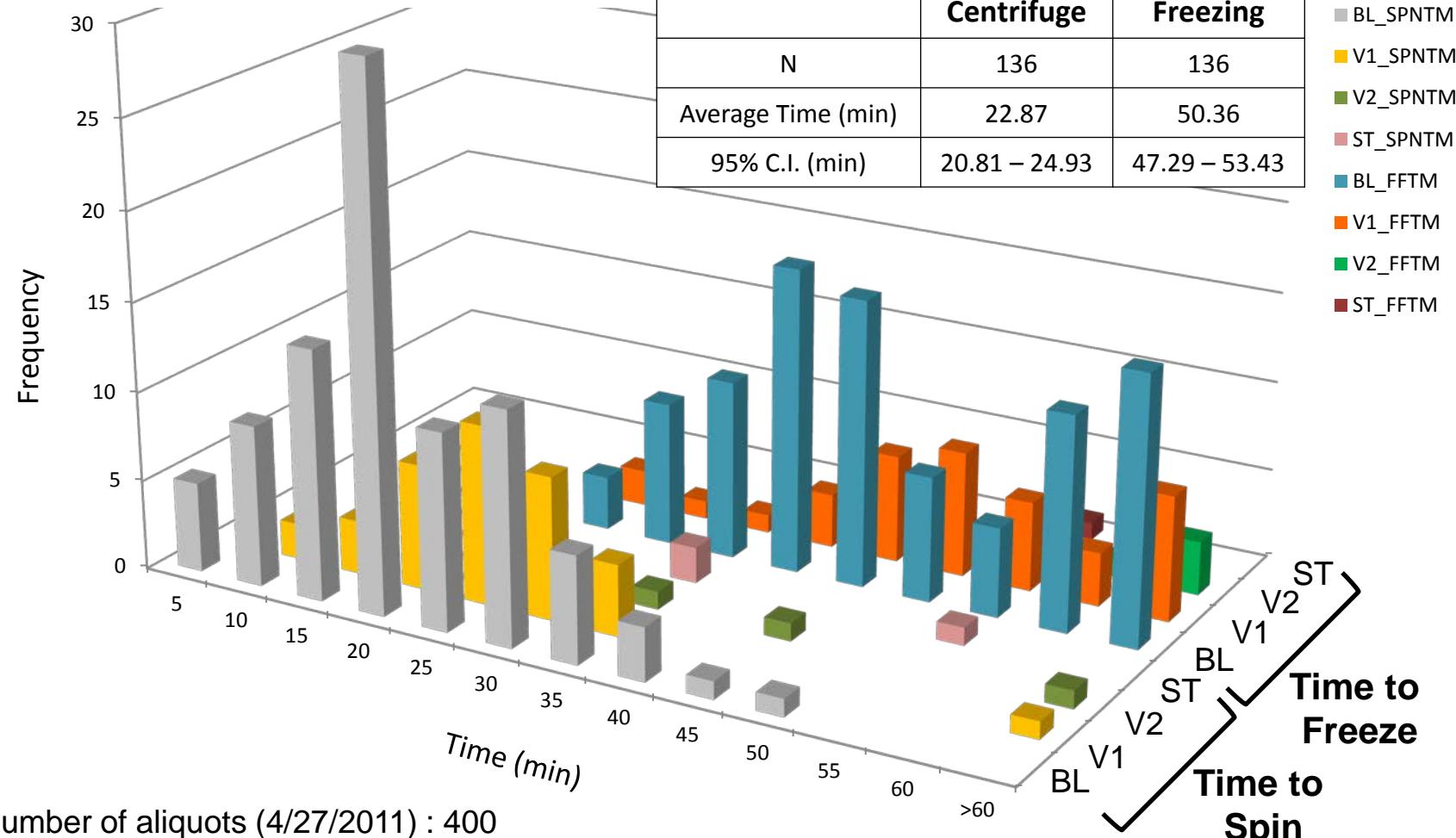


# Subject Enrollment & Primary Sample Collection

				Enrolled Patients				Collected Samples				
Plasma	Total				138				136			
	BL	VT01	VT02	ST	94	36	5	3	93	35	5	3
Serum	Total				135				133			
	BL	VT01	VT02	ST	94	36	5	3	94	35	5	3
CSF	Total				100				97			
	BL	VT02	ST		92	5	3		90	4		3

# 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



Total number of aliquots (4/27/2011) : 400

Number of Pts. enrolled at Baseline & FU

: BL (94), VT01 (36), VT02 (5), ST (3), **VT03 (1\*)**

One patient withdrawal at VT01

\* Data not shown

# CSF Samples for PPMI

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

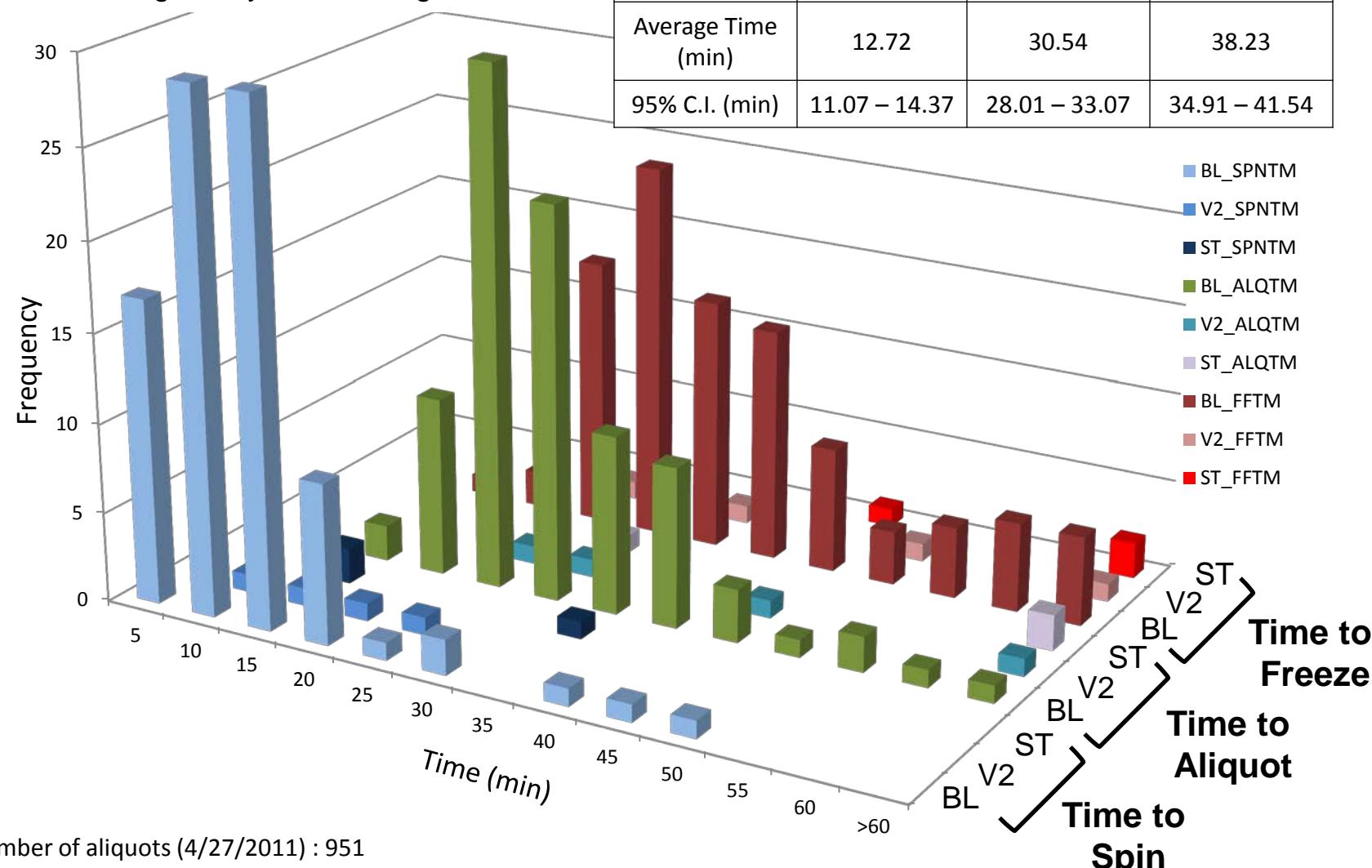
Within 15 min, Cfg. at RT for 10 min at 2000×g

Aliquot to pre-cooled & labeled polypropylene tubes

Immediate freezing on dry ice & storage at -80°C

## CSF Samples (From Collection to Freezing)

	Centrifuge	Aliquot	Freezing
N	97	97 (951)	97
Average Time (min)	12.72	30.54	38.23
95% C.I. (min)	11.07 – 14.37	28.01 – 33.07	34.91 – 41.54



Total number of aliquots (4/27/2011) : 951

Number of Pts. enrolled at Baseline & FU

: BL (90), Visit 2 (4), ST (3)

CSF was unobtainable in two patients at BL, One patient withdrawal at Visit 2

# Summary

		Time (min) to Spin	Time to Aliquot	Time to Freezing	Volume (mL) after Spin	Number of ALQ
Plasma	Total Mean	22.92	-	50.40	4.34 (1 – 6)	2.92 (2 – 4)
	% CV	53.50%	-	36.16%	16.19%	11.03%
CSF	Total Mean	12.72	30.54	38.23	15.3 (7 – 22)	9.8 (5 – 12)
	% CV	65.11%	41.64%	43.62%	15.36%	10.37%

	Visit Code (N of Subjects)			Mean Time to Spin			Mean Time to Aliquot			Mean Time to Freeze		
Plasma	BL (94)	VT1 (35)	VT2\$ (6)	20.2	25.4 <span style="color:red">(23.4)*</span>	42.2	-	-	-	48.2	51.6	70.0 <span style="color:red">(57.5)¶</span>
CSF	BL (90)	ST\$ (3)	VT2\$ (4)	12.3	20.3	16.8	29.1	54.7	45.3	36.9	60.3	50.8

\*When delete 1 sample which might have a recording error (spin time > freezing time)

¶When delete 1 outlier

\$Have outlier influencing on mean values

# Centrifugation

## : Compliance with protocol

CENTRIFUGATION		Time	Temperature	Force
Plasma	Protocol Condition	15 min	4°C	1500×g
	Per protocol (%)	138/138 (100%)	134/138 (97.1%)	97/137 (70.8%)
CSF	Protocol Condition	10 min	R.T. (18-30°C)	2000×g
	Per protocol (%)	No data	89/97 (91.7%)	76/96 (79.2%)

# Sources of variability or delay

- For some centers, the time-delay increased with later visits
- Lack of ready-to-use centrifuge; lack of readily available dry-ice
- Samples left in centrifuge for longer time?
- Other reasons : Require comments

# Informatics Core

Arthur Toga  
May 5, 2011



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# PPMI Online

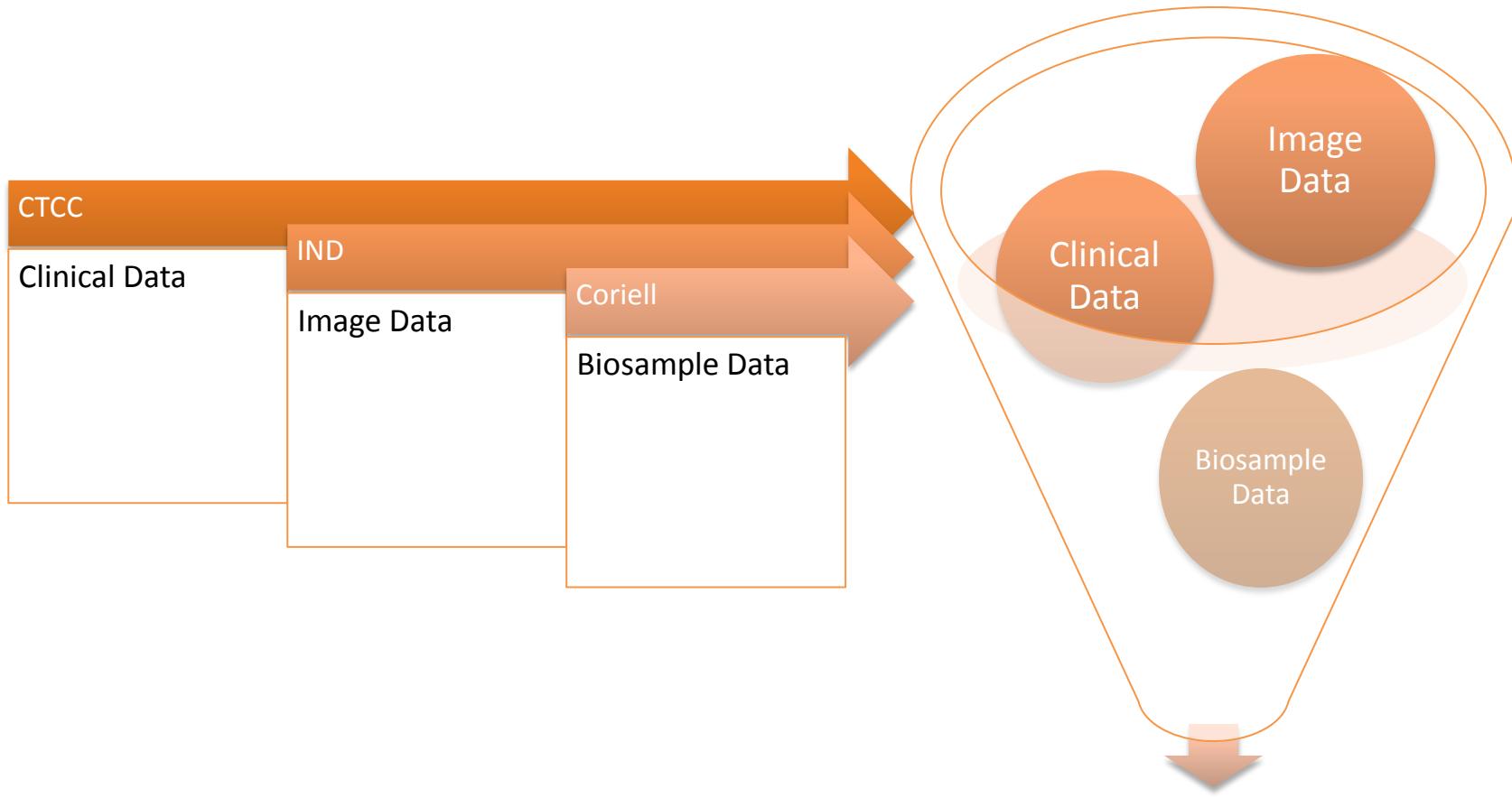


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# PPMI Data Repository



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# Data Ingestion

- Clinical Data from CTCC
  - Demographics & Medical History
  - Assessments & Exams
  - Laboratory Procedures
- Image Data from IND
  - MRI
  - DTI
  - SPECT
- Biospecimen Data to/from Coriell (in progress)
  - Sample distribution requests
  - Inventory updates



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# PPMI Website

## Home Page

- Overview
- Status
- News
- Quicklinks
  - Data Request
  - Biosample Request

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The screenshot shows the PPMI website homepage. At the top, there is a navigation bar with links to 'Most Visited', 'Getting Started', 'Latest Headlines', 'Yahoo!', 'Google Maps', 'YouTube', 'Wikipedia', 'News', and 'iConnectome'. Below the navigation bar is the PPMI logo and the text 'Play a Part in Parkinson's Research'. The main content area has several sections: 'OUR MISSION' (describing the study's goal to identify biomarkers of Parkinson's progression), 'WELCOME' (introducing the study as a landmark observational clinical study), 'PPMI ENROLLMENT STATUS' (showing enrollment goals and current status for Control Participants and PD Participants), 'LATEST NEWS FROM PPMI' (including a proposal process for ancillary studies, a feature on Fox & Friends, clinical data and biospecimens available to researchers, and news about the Cleveland Clinic being added as a site), and a sidebar with links for 'DOWNLOAD DATA', 'REQUEST SPECIMENS', 'for PROSPECTIVE PARTICIPANTS', 'for PRACTITIONERS', 'for INDUSTRY PARTNERS', and 'for RESEARCHERS'. The footer contains copyright information and visitor statistics.

# PPMI Website

## Study Design Page

- Protocols
- Manuals
- SOPs

Screenshot of the PPMI Website Study Design page:

The page features a navigation bar with links to About PPMI, Study Design, Access Data & Specimens, PPMI News, and Get Email Updates. Below the navigation is a secondary menu with Research Documents & SOPs, Stats Forum, and Ancillary Studies.

**RESEARCH DOCUMENTS & SOPS**

**Study Protocol and Schedule**

PPMI was designed with a strong focus on developing standardized protocols for collecting, transferring and storing clinical and imaging data and biological samples. The following documents outline the overall goals, objectives and processes involved in the study to guide the PPMI Clinical Sites in the collection of data and specimens:

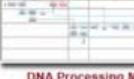
 Study Protocol    Enrolled Subject Schedule of Activities    Case Report Forms

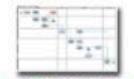
**Data Collection Standards and Processes**

The following documents have been developed to provide step-by-step detail of the sample collection processes to guide PPMI Cores and Clinical Sites in following the study protocol:

 Operations Manual    Biologics Manual    Imaging Manual    DTI Manual

In addition, the study processing maps below outline the path each sample will take through the acquisition, aliquoting, storage and shipping processes from the Clinical Sites to the study biorepository and, eventually, to the researcher.

 CSF Processing Map    DNA Processing Map    RNA Processing Map

 Plasma Processing Map    Serum Processing Map    Urine Processing Map    Whole Blood Processing Map

**Data and Biospecimen Use Agreements and Policies**

The success of PPMI hinges on the sharing of research results from the widespread use of the data and specimens. Below are links to the policies that govern the use of PPMI data and specimens:

 Data Use Agreement    Biospecimen Use Agreement    Publications Policy

[Click here to view PPMI publications and presentations.](#)

On the right side of the page, there is a vertical sidebar with icons for DOWNLOAD DATA, REQUEST SPECIMENS, for PROSPECTIVE PARTICIPANTS, for PRACTITIONERS, for INDUSTRY PARTNERS, and for RESEARCHERS.

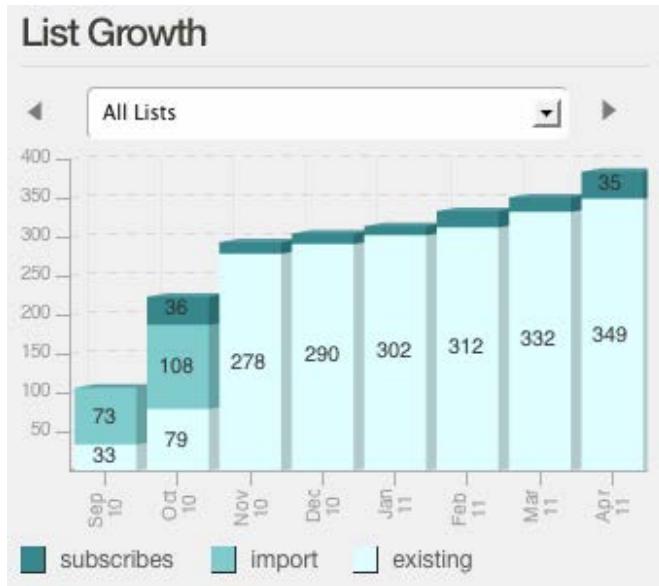


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# PPMI Newsletter

- Email sign-up subscription
- Weekly distribution



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Parkinson's Progression Marker's Initiative News – Deleted Items

Message

Delete Reply Reply All Forward Rules Move Junk Unread Categorize Follow Up

PPMI

Sent: Thursday, April 21, 2011 3:05 AM

To: Web Administrators

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### PPMI News

The following updates were recently posted to the Parkinson's Progression Markers Initiative (PPMI) website. Click on the text links below to read the full story.

**PPMI to be presented on Science/AAAS's webinar**

On April 27th several members of PPMI cores and MJFF's Chief Program Officer, Todd Sherer, will be presenting on biomarkers in PD as part of a webinar organized by Science/AAAS and Science Translational Medicine.

**Qualification of biomarker analyses in ADNI (Acta Neuropathol.)**

Several PPMI steering committee members were recently featured in the German publication, Acta neuropathologica. The paper seeks to determine the precision of assays to measure biomarkers associated with Alzheimer's disease. The results of this paper are pertinent to PPMI since many of the same biomarker analyses will be conducted in PPMI.

**PPMI is featured on Fox & Friends**

Powerhouse couple, Marc and Karen Jaffe, discuss PPMI.

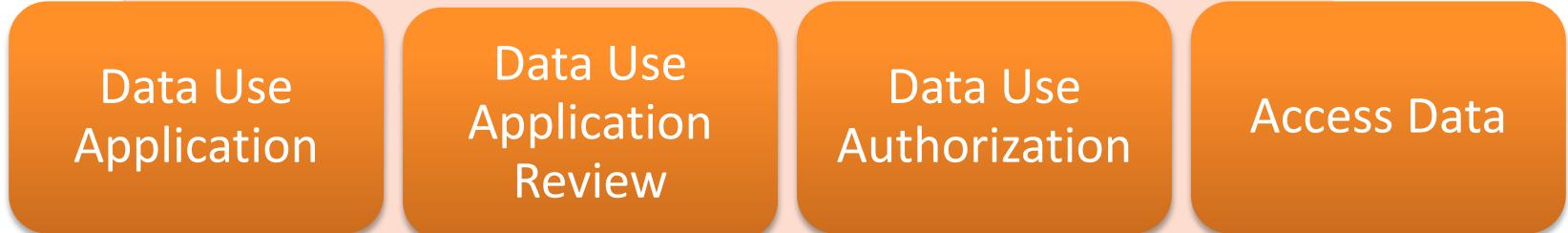
**USF and DATSCAN procedure in PPMI highlighted**

Dr. Joette Giovinco, Fox13 Medical Reporter in Tampa, discusses the DaTscan procedure and PPMI.

**UCSD talks PPMI and biomarkers with the Union-Tribune**

Dr. Douglas Galasko, PI at UCSD, spoke with the San Diego Union-Tribune about the importance of biomarkers for diagnosis, treatment, and research of Parkinson's disease.

# Data Dissemination



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# Data Dissemination

- Data Use Applications
  - Online application
  - Online review
- Biospecimen Use Applications
  - Online application
  - Online review
- Downloads
  - Search
  - Download Data
  - Download Documents



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# Accessing Data

Parkinson's Progression Markers Initiative

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

PPMI Qualification Study Request Specimens Download Data Data & Specimens FAQ

**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](#)

**Ongoing Data Analyses and Other Resources**

Investigators using PPMI data will be asked to provide annual updates on the analyses they have performed. This information will be displayed publicly on the PPMI Web site on an Ongoing Analyses page. Investigators will also be asked to provide new data generated using PPMI data back to the Data and Publications Committee so that it can be integrated into the database for use by future investigators.

To better understand the PPMI database, investigators should refer to the [Data & Specimens FAQ](#). Data users are also encouraged to visit the [Statistician Forum](#) for helpful hints and advice on how to use the downloaded data.

Researchers interested in reviewing the standards and protocols that guide PPMI data collection should refer to the study protocol and manuals posted in the [Research Documents and SOPs](#) section of this site.

PPMI clinical data are complemented by a set of biologic samples. Learn more about how to [request PPMI specimens here](#).

**Database Disclaimer**

Although every attempt has been made to ensure that the contents of the database are correct, errors are provided by multiple parties and occasional errors may occur. All reasonable measures will be taken to ensure that errors are corrected promptly and completely; however, no explicit guarantee is provided regarding the accuracy of any data contained within this database.

Investigators who suspect errors in the database should [contact us](#).

**ALSO IN THIS SECTION**

- PPMI Qualification Study
- Request Specimens
- Data & Specimens FAQ

Enter search keyword  [search](#)

Contact Us [Home](#)

**REQUEST SPECIMENS**

for PROSPECTIVE PARTICIPANTS

for

for

**DOWNLOAD DATA**

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[APPLY FOR DATA ACCESS](#)

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

Email:   
Password:

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[LOGIN](#)

# New Users: Apply

Email | Password | **LOGIN** | Register | Forgot Pas

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LONI > PPMI > Application  
**PPMI Data Use Agreement**

I request access to data collected by The Parkinson's Progression Markers Initiative (PPMI) for the purpose of scientific investigation, teaching or the planning of clinical research studies and agree to the following terms:

1. I will receive de-identified data and will not attempt to establish the identity of, or attempt to contact any of the PPMI subjects.
2. I will not further disclose these data beyond the uses outlined in this agreement and my data use application.
3. I will require anyone on my team who utilizes these data, or anyone with whom I share these data to comply with this Data Use Agreement by registering with the PPMI database and agreeing to these terms.
4. I will accurately provide the requested information for persons who will use these data and the analyses that are planned using these data.
5. I will respond promptly and accurately to annual requests to update this information.
6. I will comply with any rules and regulations imposed by my institution and its institutional review board in requesting these data.
7. I will comply with the PPMI Intellectual Property (IP) policy that states:
  - a. Rights to any non-PPMI IP ("Background IP") that a researcher uses in analyzing or manipulating PPMI data, information, biospecimens, materials or results ("Study Materials") may not be claimed by any other researcher or institution;
  - b. No researcher or institution may claim any IP rights to any Study Materials or inventions arising out of the Study Materials; and,
  - c. Researchers who publish or present analyses of Study Materials will make these freely available without charge to the research community through the PPMI website, when not prohibited by journal copyright terms and conditions.

If I publish abstracts using data from PPMI, I agree to the following:

8. I will cite PPMI as the source of data and the PPMI funding sources in the abstract as space allows.
9. Group authorship of PPMI will not be cited in the authorship line of the abstract.
10. I will upload abstracts onto the PPMI website for registered users to see either as they are accepted or after they are presented.
11. I will prepare 'lay' abstracts to be posted on the PPMI website of analyses that I am performing with PPMI data.

If I publish manuscripts using data from PPMI, I agree to the following:

12. On the author line of the manuscript, after the named authors, I will include the phrase "and the Parkinson's Progression Markers Initiative" with an asterisk referring to the following statement and list of names:

\* Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database ([www.ppmi-info.org/data](http://www.ppmi-info.org/data)). As such, the investigators within PPMI contributed to the design and implementation of PPMI and/or provided data but did not participate in the analysis or writing of this report. PPMI investigators include (complete listing at PPMI site).
13. I will include language similar to the following in the methods section of my manuscripts in order to accurately acknowledge data gathering by the PPMI personnel. Depending upon the length and focus of the article, it may be appropriate to include more or less than the example below, however.

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### Parkinson's Progression Markers Initiative

The mission of the Parkinson's Progression Markers Initiative (PPMI) is the identification of biomarkers of Parkinson's disease progression. Information generated by the study will aid the development of more effective treatments for Parkinson's disease as well as better ways to quantify its progression.

#### Participant Gender Distribution

Research Group	Male	Female
Control	15	17
Patient	29	14

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# Request Specimens Page

Parkinson's Progression Markers Initiative

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**REQUEST SPECIMENS**

A critical component of PPMI is the standardized, longitudinal collection of biospecimens, which include plasma, serum, blood, cerebrospinal fluid (CSF), DNA and RNA. An inventory of the biospecimens is available through the PPMI database and can be reviewed by investigators interested in incorporating PPMI samples in their research. Please note that PPMI samples can only be used for biomarker verification studies.

**Application Process to Request Specimens**

Researchers interested in requesting specimens are encouraged to review the [Process for Requesting Specimens](#). Researchers requesting specimens must agree to the [Biospecimen Use Agreement](#) and the [Publications Policy](#). Click the button below to read more about the Process for Accessing Banked Specimens and to begin the Request Process.

**GO TO SPECIMEN REQUEST PROCESS**

Before starting the specimen request process, [click here to download a template for the Letter of Intent](#).

**Research Funding for Specimen Studies**

Researchers requesting biospecimens may also apply for funding from The Michael J. Fox Foundation (MJFF). The review processes for PPMI biospecimen access and MJFF funding of research are separate processes; approval for use of PPMI biospecimens does not guarantee MJFF funding. MJFF has launched a Biomarker Development Funding Program that may support investigators who are approved to use samples from PPMI. [Click here to learn more about requesting funding from MJFF for biospecimen research using the PPMI samples](#).

**Ongoing Specimen Analyses and Other Resources**

A listing of preliminary analyses specified by the Steering Committee and performed by PPMI cores, as well as analyses performed by additional investigators will be listed in the Ongoing Analyses section of this site (expected to be live Spring 2011). Investigators who are granted samples from PPMI agree to update this information annually, providing the research public with a comprehensive list of the latest findings coming out of PPMI.

Researchers who are interested in reviewing the PPMI collection, processing and storage protocols for biospecimens should review the [Biologics Manual](#) and other [Research Documents and SOP's](#).

 ALSO IN THIS SECTION

- [Download Data](#)
- [Data & Specimens FAQ](#)

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**PROCESS FOR REQUESTING SPECIMENS**  
Investigators should read all of the following information prior to submitting a request for samples. Click the button below to begin the submission process.

**START SPECIMEN REQUEST PROCESS**

**Overview**

The goal of the Parkinson's Progression Markers Initiative (PPMI) is to identify, test and verify markers of progression for early-stage Parkinson's disease. To accomplish this goal, PPMI is collecting biospecimens, including urine, blood and cerebrospinal fluid (CSF) from participants (early stage Parkinson's disease (PD) subjects and healthy subjects). An inventory of PPMI biospecimens available through Coriell, the PPMI biorepository, will be maintained on the PPMI website. Comprehensive clinical and imaging data collected from PPMI research participants will also be available on the PPMI website to enable researchers to develop studies that might correlate biospecimen analysis with relevant subject data.

Several analyses of already identified analytes will be performed by PPMI investigators. Results of these studies will be made available on the PPMI website as soon as laboratory analyses are complete. Planned analyses will investigate the following analytes:

- Alpha-synuclein levels in CSF
- Urine levels in plasma
- DJ-1 levels in blood and CSF
- Tau: Phosphorylated tau, and beta-amyloid 1-42 in CSF

The PPMI study encourages interested investigators, whether associated with PPMI or not, to apply for use of PPMI biospecimens to verify potential PD progression biomarkers. Please note: Stored samples are reserved for verification studies; samples should not be used for biomarker discovery work.

**The PPMI Biospecimen Review Committee (BRC)**  
The BRC has been created to review proposals for access to PPMI biospecimens. Following submission of a Letter of Intent (LOI), the BRC will accept and review Full Proposals and decide a grant award. The BRC will meet every other month (June, August, October, December 2011) to review all Letters of Intent and Full Proposals received in time for the meeting. All proposals submitted to the PPMI BRC will be treated confidentially. [Click here to read our Conflict of Interest statement.](#)

**Procedure to apply for access to Biospecimens**

**Agree to Use Policy** → **Complete Application/LOI** → **Committee Review** → **Submit full Proposal**

Please read the following section carefully to understand the process to apply for use of biospecimens (serum, plasma, DNA, RNA, saliva, urine, CSF) collected as part of the PPMI study. In addition to applying for access to PPMI biospecimens, please note that applicants may also apply to MJFF for funding to perform their own analyses. The review process for biospecimen access and funding are separate. PPMI biospecimen access is determined by the PPMI BRC while MJFF will review all funding requests. Approval for use of PPMI biospecimens does not guarantee MJFF funding.

**Letter of Intent (LOI)**

**Full Proposals**

**Evaluation Criteria**

**Post Review**

**Data Obtained from PPMI Samples**

**Confidentiality**

MJFF and the BRC treat all Letters of Intent (LOI), Full Proposals, research projects and associated research information (collectively, the "Confidential Information") in confidence using no less than reasonable care in protecting such Confidential Information from disclosure to third parties who do not participate in the grant review process and MJFF assessments. All Confidential Information will be handled in accordance with its intended purpose, including its use in the preparation of reviews and assessments, and will be shared only in accordance with its sharing policy stated herein. Notwithstanding Reviewers' obligations regarding such Confidential Information, such obligations cover any information retained in their unaided memories and may not be used without the permission of the disclosing party. Notwithstanding the foregoing, the obligations governing the disclosure and use of Confidential Information do not apply with respect to Confidential Information that it can be demonstrated:

- (a) was generally known to the public prior to the effective date when the LOI was submitted;
- (b) becomes generally known to the public through no unlawful or unauthorized act of omission by any recipient of Confidential Information, or in violation of this review process;
- (c) was independently developed by any recipient prior to the effective date of this review process; or
- (d) was disclosed to a recipient by a third party who has the right to make such disclosure.

If any recipient of Confidential Information is requested to produce any of the Confidential Information pursuant to a legal or governmental proceeding, such recipient shall give the applicant or other owner of such Confidential Information ("the Discloser") as much notice of the proceeding as reasonably possible in order to retain the Confidential Information and shall use its reasonable efforts to assist the Discloser of such Confidential Information in objecting to such request. If a recipient is compelled to disclose any of the Confidential Information pursuant to such legal or governmental proceeding, such recipient shall use its reasonable efforts to assist Discloser in obtaining confidential treatment for such Confidential Information, will disclose only that portion of the Confidential Information which is a proper subject of disclosure, and will provide the Discloser with any copies of Confidential Information so disclosed; provided that such Confidential Information shall remain confidential until it falls into one of the categories specified in this Section entitled "CONFIDENTIALITY".

**Questions**

Contact us with questions about the specimen request process.

**START SPECIMEN REQUEST PROCESS**

# Request Specimens Application

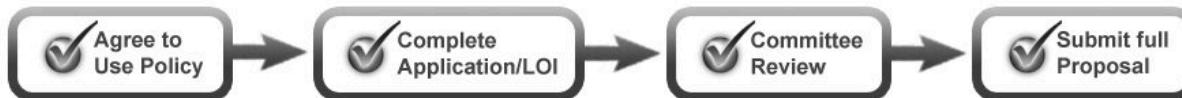


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## Biospecimen Application Form - Stage 1 of 2: Letter of Intent

The biospecimen request process is divided into two stages, the Letter of Intent stage and the Full Proposal stage. Applicants positively reviewed at the Letter of Intent Stage will be invited to submit a Full Proposal. The overall process is summarized in the diagram below.



### Step 1: Biospecimen Use Agreement

Please read the terms of use agreement below and provide your institution email address. After agreeing to the terms of the PPMI Biospecimen Use Agreement you will receive an email with a link to the Letter of Intent application form. Please note: By selecting "I Agree" below, you agree to submit all data generated from analyses of PPMI biospecimens to the PPMI Data and Publication Committee (DPC) upon completion of your analyses. You also agree to allow the DPC to incorporate this raw data into the PPMI database.

I request access to biospecimens collected by The Parkinson's Progression Markers Initiative (PPMI) for the purpose of scientific investigation and agree to the following terms:

1. I will receive de-identified biospecimens and will not attempt to establish the identity of, or attempt to contact any of the PPMI subjects.
2. I will not share or use these specimens beyond the uses outlined in this agreement and my proposal for access.
3. I will require anyone on my team who utilizes these biospecimens to comply with this Biospecimen Use Agreement by signing this agreement.
4. I will accurately provide the requested information for persons who will use these biospecimens and the analyses that are planned using these biospecimens.
5. I will respond promptly and accurately to annual requests to update this information.
6. I will comply with any rules and regulations imposed by my institution and its institutional review board in requesting these biospecimens.

Email Address:

I Disagree    I Agree

**SUBMIT**

### Biospecimen Inventory Summary

(Updated 04-26-2011)

Visit	Patient	Control
Consent	59	41

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# Download Study Data & Docs



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[Study Data](#) [Image Collections](#)



## Download Study Data

- Study Docs
- Biospecimen
- Enrollment
- Imaging
- Medical History
- Motor Assessments
- Non-motor Assessments
- Subject Characteristics
- [ALL](#)

### Filter(s)

Only include data that is new/changed since:

[Download>>](#)

#### Select ALL

- Study Docs**
  - ALL Data & Databases
    - [Code List](#)
    - [Data Dictionary](#)
  - ALL Study Protocol & CRFs
    - [Data Download Content Overview](#)
    - [Study CRFs and Assessments](#)

#### Biospecimen

- ALL Biosample Inventory
  - [Cerebrospinal Fluid Biosamples](#)
  - [DNA Biosamples](#)
  - [Plasma Biosamples](#)
  - [RNA Biosamples](#)
  - [Serum Biosamples](#)
  - [Urine Biosamples](#)
  - [Whole Blood Biosamples](#)
- ALL Lab Collection Procedures
  - [Blood Chemistry & Hematology](#)

# Download Image Data



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Simple Search Advanced Search

## IDA Search

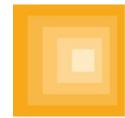
LEGEND: Projects | Research Groups | Modalities | Help | View Collections | Image Status

Search Search Results Data Collections

158 image sets match your criteria: Research Group = All; Sex = Both; Modality = MRI; Image count = 500

Your access level: ADNI (MEMBER), FE (MEMBER), ICBM (MANAGER), NBLP (DBA), PAD (MANAGER), PPMI (GUEST)  
Access to data is controlled by each project's leader. Click the Projects link above for additional information.

(1 of 7) < prev 1 2 3 4 5 6 7 next >											ADD TO COLLECTION	
Subject	Research Group	Sex	Scan Date	Age	Modality	Series Description	Weighting	Slice Thickness	Acquisition Plane	View*	Select All <input type="checkbox"/>	
3000	Control	F	2/01/2011	69	MRI	AX T2 FLAIR	T2	5.0	AXIAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
						sag 3D FSPGR BRAVO straight	T1	1.2	SAGITTAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
3001	Patient	M	3/02/2011	65	MRI	AX T2 AC-PC line Entire Brain	T2	2.0	AXIAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
						AX T2 FLAIR 5/1	PD	5.0	AXIAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
						sag 3D FSPGR BRAVO straight	PD	1.2	SAGITTAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
3002	Patient	F	3/08/2011	68	MRI	AX T2 AC-PC line Entire Brain	T2	2.0	AXIAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
						AX T2 FLAIR 5/1	T1	5.0	AXIAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
						sag 3D FSPGR BRAVO straight	T1	1.2	SAGITTAL	<a href="#">VIEW</a>	<input type="checkbox"/>	
3051	Patient	M	10/26/2010	72	MRI	AX DUAL_TSE	PD	5.0	AXIAL	<a href="#">VIEW</a>	<input type="checkbox"/>	



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# Baseline Data Summary

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## Baseline Data Summary

[Download CSV](#)

Variable	PD Subjects	Healthy Controls		
Female(n)	23	20		
Male(n)	38	23		
Subjects with Family Members with PD(n)	16	(n/a)		
Subjects with No Family Members with PD(n)	45	(n/a)		
	Mean	Range	Mean	Range
Age(Years)	61.0	35 - 83	59.2	31 - 80
Years of Education	16.2	12 - 26	16.7	12 - 20
Duration of Disease (Months)	8.9	0 - 32	(n/a)	(n/a)
MDS-UPDRS Total	35.5	14 - 65	4.1	0 - 17
MDS-UPDRS Part I	1.6	0 - 9	0.6	0 - 4
MDS-UPDRS Part I - Patient questionnaire	5.2	0 - 11	2.1	0 - 7
MDS-UPDRS Part II - Patient questionnaire	6.8	1 - 15	0.2	0 - 4
MDS-UPDRS Part III	21.9	9 - 39	1.2	0 - 10
Hoehn & Yahr	1.7	1 - 3	0.0	0 - 1
Modified Schwab & England ADL	92.6	80 - 100	(n/a)	(n/a)
UPSIT - Total Score	23.2	6 - 39	35.0	21 - 40
MoCA Score*	26.9	0 - 30	28.4	27 - 30
GDS Score	2.3	0 - 10	0.8	0 - 5

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# Baseline Cognitive Data

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Baseline Cognitive Data Download CSV

Variable	PD Subjects	Healthy Controls		
Female(n)	23	20		
Male(n)	38	23		
Subjects with Family Members with PD(n)	16	(n/a)		
Subjects with No Family Members with PD(n)	45	(n/a)		
	Mean	Range	Mean	Range
Age(Years)	61.0	35 - 83	59.2	31 - 80
Years of Education	16.2	12 - 26	16.7	12 - 20
Duration of Disease (Months)	8.9	0 - 32	(n/a)	(n/a)
HVLT Immediate Recall	24.2	13 - 35	26.7	17 - 35
HVLT Delayed Recognition Hits	11.3	7 - 12	11.7	10 - 12
HVLT Delayed Recognition False Alarms	1.2	0 - 4	0.9	0 - 5
Benton Judgment of Line Orientation Score	13.2	7 - 15	13.1	7 - 15
Letter Number Sequencing Raw Score	11.0	6 - 16	12.0	8 - 20
Semantic Fluency Total Score	48.5	29 - 70	53.6	31 - 75
Symbol Digit Modalities Score	43.3	20 - 63	49.9	30 - 76
MoCA Score*	26.9	0 - 30	28.4	27 - 30
	PD Subjects	Healthy Controls		
QUIP Positive-Gambling(n)	1	0		
QUIP Positive-Sex(n)	1	0		
QUIP Positive-Buying(n)	2	0		
QUIP Positive-Eating(n)	6	4		
QUIP Positive-Hobbies(n)	5	2		

# Baseline Specimen Data

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Baseline Specimen Collection Download CSV

Variable	PD Subjects	Healthy Controls		
Female(n)	23	20		
Male(n)	38	23		
Subjects with Family Members with PD(n)	16	(n/a)		
Subjects with No Family Members with PD(n)	45	(n/a)		
	Mean	Range	Mean	Range
Age(Years)	61.0	35 - 83	59.2	31 - 80
Years of Education	16.2	12 - 26	16.7	12 - 20
Duration of Disease (Months)	8.9	0 - 32	(n/a)	(n/a)
	Number of Subjects	Mean Volume	Number of Subjects	Mean Volume
CSF(ml)	54	17.8	40	15.8
DNA(ml)	0	0.0	0	0.0
RNA(ml)	30	5.0	28	6.2
Plasma(ml)	52	8.6	41	8.0
Serum(ml)	52	10.6	41	10.8
Urine(ml)	53	13.4	41	12.5

# What's Next

- **ppmi-info.org**
  - Searchable publications page
  - Data analysis methods page
  - Improving ppmi-info.org based on analytics and surveys\*\*\*
- **PPMI repository**
  - Data Exploration interface
  - Additional biospecimen sharing components



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- Ongoing Analysis

# What's Next

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ONGOING ANALYSES

Search for projects using the Investigator's Name, Institution, or Keywords

Search for projects using the Investigator's Name, Institution, or Keywords

Investigator	Institution	Project Title
Ken Marek	Yale University	AMADEUS consortium
Alison Ansbach	Coriell Institute for Medical Research	NINDS Repository
Sohini Chowdhury	The Michael J. Fox Foundation for Parkin....	Research Programs
Christopher S. Coffey	University of Iowa	CTSDMC
Mark Frasier	The Michael J. Fox Foundation for Parkin....	Research Programs
Danna Jennings	Institute of Neurodegenerative Disorders	Clinical Research
Karl Kieburtz	University of Rochester Medical Center	Neurology and Communi...

for PROSPECTIVE PARTICIPANTS

for PHYSICIANS

for INDUSTRY PARTNERS

for RESEARCHERS

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For more information, please contact the LONI Webmaster



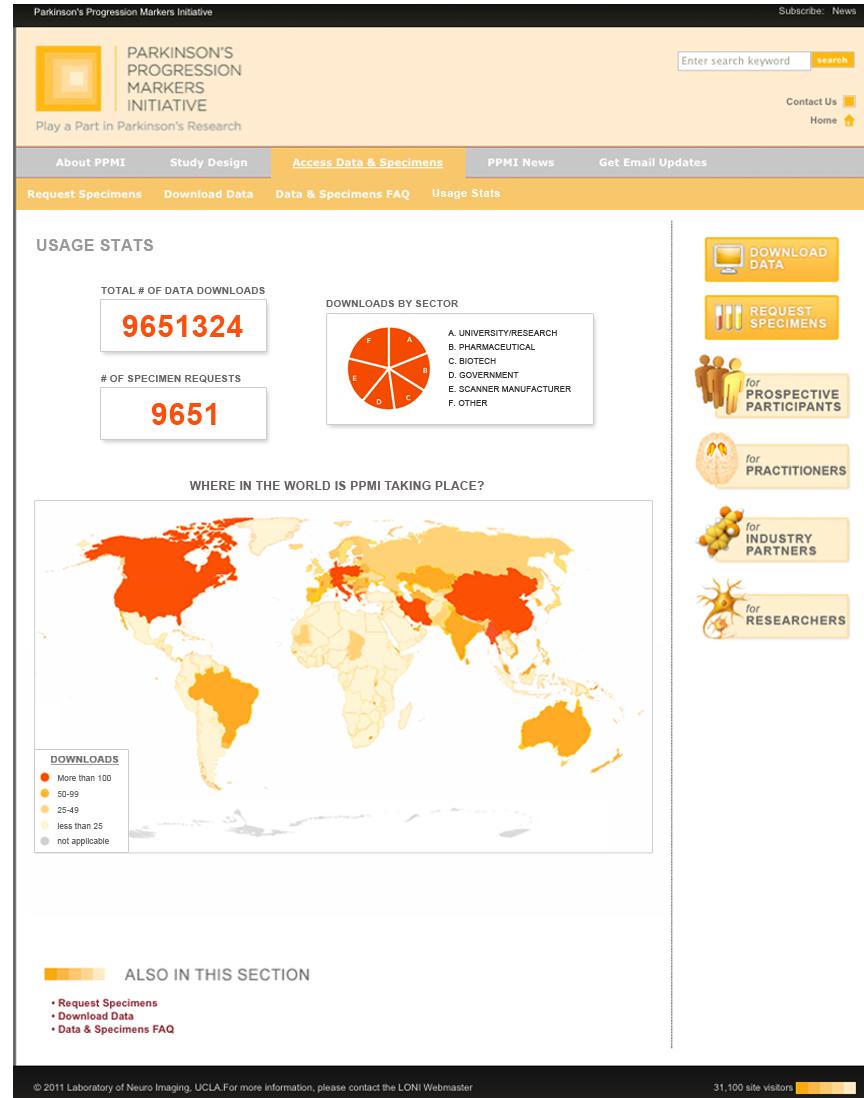
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# What's Next

- Usage stats



# Data Access & Publication



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# PPMI Data Access & Publication

PPMI study data access – goal to make data rapidly and widely available via the PPMI-info.org

PPMI publications – encourage publication of PPMI data



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# PPMI Data Access & Publication committee

- David Standaert (Chair)
- Arthur Toga
- Chris Coffey
- Robert Hauser
- Werner Poewe



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# PPMI Data Access & Publication

## Data & Publication Committee (DPC)

- Oversight of access to PPMI Database
  - Simple online process
- Review publications using PPMI data
  - Review that the author/s have followed the the PPMI Data Use Agreement
  - Meet PPMI publication standards
    - Properly cite and acknowledge the PPMI study
  - Not a review of scientific merit
  - Track PPMI publications



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# PPMI Data Access & Publication

- PPMI data was publicly available after first 50 subjects were enrolled - March 2011
  - Subject data is available in close to 'real time'
  - functionality and content continues to expand and improve
- Data from PD & healthy subjects acquired at PMI sites
  - Clinical data
    - demographic, motor and non-motor, cognitive and neurobehavioral
  - Imaging data
    - DAT, DTI and MRI
  - Blood chemistry and hematology
  - Subject assessments
  - Biospecimen inventories
    - serum, plasma, whole blood, CSF, DNA, RNA and urine
- Acquiring access to PPMI data is a quick & simple online process



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# Data Access & Publication

## Getting Access to the PPMI data



- Click on the DOWNLOAD DATA button on PPMI website
- Complete a very brief e-form
- Process is available 24/7 with a quick turnaround & grants access to most people

The screenshot shows the PPMI website's main navigation bar with links for About PPMI, Study Design, Access Data & Specimens, PPMI News, and Get Email Updates. Below this is a secondary navigation bar with links for PPMI Qualification Study, Request Specimens, Download Data, and Data & Specimens FAQ. The main content area features a yellow header 'DOWNLOAD DATA'. Below it, a text block explains that researchers can obtain access to all clinical, imaging, and biomarker data collected in PPMI, including raw and processed MRI and SPECT images. It emphasizes de-identification to protect patient privacy. Two forms are shown: one for 'New Users Apply Now' and one for 'Registered Users'. The 'New Users' form includes a link to 'APPLY FOR DATA ACCESS'. The 'Registered Users' form includes fields for 'Email' and 'Password', a 'LOGIN' button, and a link to 'Forgot your login and password? Click here.'. To the right, a vertical sidebar lists icons for REQUEST SPECIMENS, PROSPECTIVE PARTICIPANTS, PRACTITIONERS, INDUSTRY PARTNERS, and RESEARCHERS.

Sign – up Today ...Sign – up Today...Sign – up Today....Sign – up Today...



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# **SUMMARY OF DATA ANALYSIS PLAN**

## **Parkinson's Progression Markers Initiative Statistics Core**



**Christopher S. Coffey  
Department of Biostatistics  
University of Iowa**

# OUTLINE

In this presentation, we will:

- Summarize the planned analyses
- Provide the justification for the sample size
- Discuss steps that can be taken by investigators to address future questions of interest

# **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

# 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

## SAMPLE SIZE JUSTIFICATION

Because of exploratory nature of the planned analyses, it is very difficult to provide a formal sample size justification for the entire model building process.

However, we examined the ability of proposed sample size (400 PD patients/200 healthy controls) to detect meaningful effects of interest.

# SAMPLE SIZE JUSTIFICATION

Total Sample Size	Detectable Correlation	Detectable Difference in Prevalence	Detectable Difference in Means (Standardized)
300	0.16	17%	0.33
400	0.14	14%	0.28
450	0.14	15%	0.28
600	0.11	13%	0.24

Last two rows correspond to first set of comparisons  
(PD patients vs. healthy controls)

First two rows correspond to second set of comparisons (among PD subsets)

## **ADDITIONAL ANALYSES**

In addition to the planned analyses summarized above, the PPMI trial will involve the creation of a rich database.

It is hoped that the data from this trial will also allow assessing a number of additional questions.

Investigators are encouraged to bring possible future analyses to the table.

## ADDITIONAL ANALYSES

There are two scenarios for future analyses:

- 1) Investigators can request the data needed to address the question and conduct their own analyses.
- 2) Investigators can propose a research question and work with the statistics core at Iowa to conduct analyses.

# Report from Industry Scientific Advisory Board

PPMI Annual Investigators Meeting  
May 4-5, 2011

Igor Grachev, MD, PhD



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# ISAB Update

- What is ISAB?
- Who we are?
  - Chair: Igor Grachev, GE Healthcare
  - Kim Gallagher, GE Healthcare (secondary representative)
  - Michelle Collins, Abbot
  - Tom Comery, Pfizer
  - Susanne Ostrowizki, Roche (primary representative)
  - Paulo Fontoura, Roche (secondary representative)
  - Johan Luthman, Merck (primary representative)
  - Tony Ho, Merck (secondary representative)
  - Marcel van der Brug, Genentech
  - Bernard Ravina, Biogen Idec
- Stakeholder role of the ISAB
  - Strategic arm of Steering Committee
  - Input in Taskforces/Working groups
  - Participate in Annual Meeting and bi-monthly t-cons
  - Support Steering Committee
  - Suggest Ancillary Studies
- Why industry involvement is important and next steps?

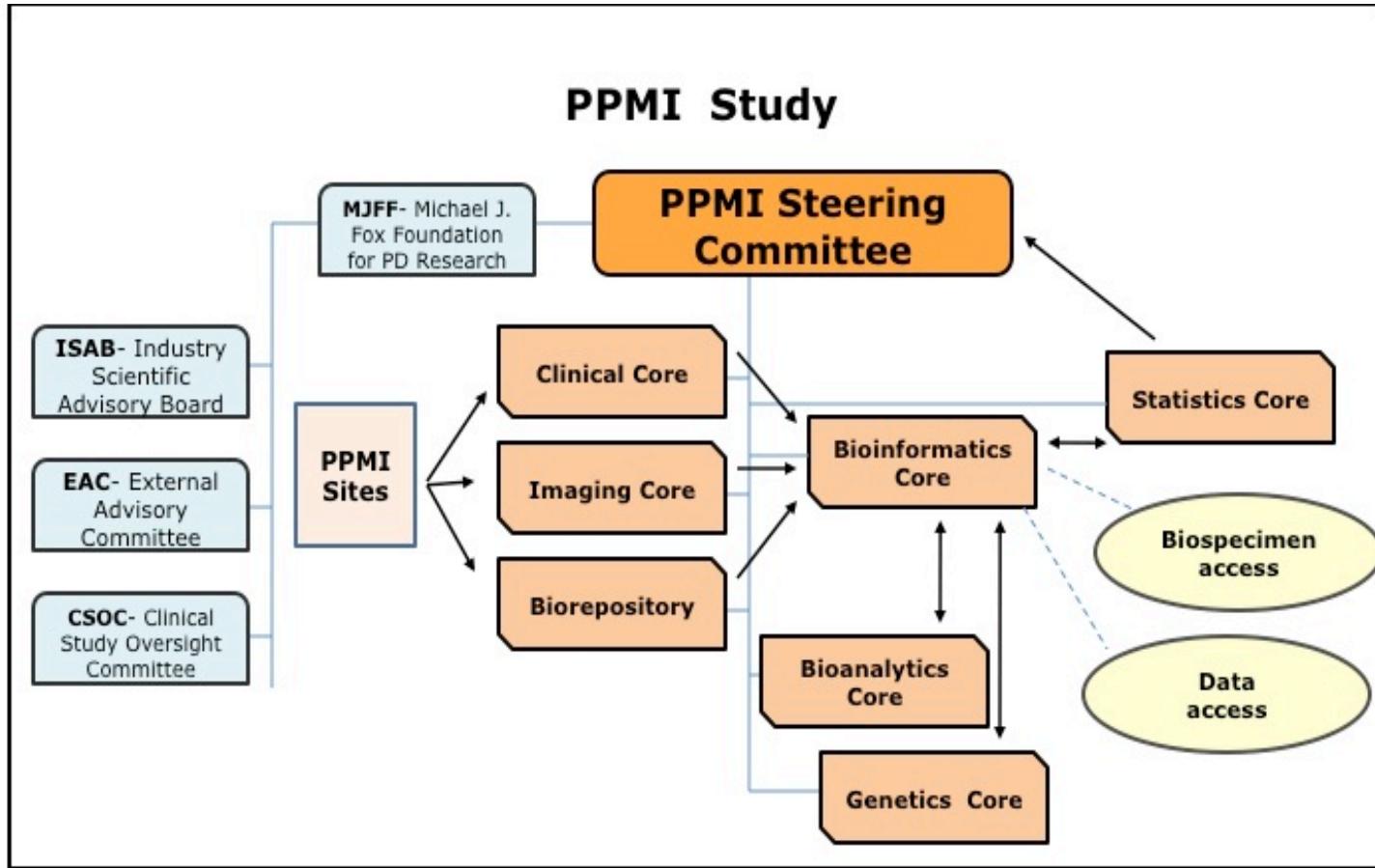


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# PPMI Study Organization and Governance



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# Stakeholder Role of ISAB

- ISAB plays a critical role in providing input and strategic advice on study parameters and goals
- All partner companies can have one primary designate and one secondary designate (to fill in when the primary cannot attend) to the ISAB
- ISAB Chairmanship will rotate on an annual basis; Chairs are to be selected by the ISAB
  - 1<sup>st</sup> Chair – GE Healthcare as first industry partner to sign up
  - 2<sup>nd</sup> Chair - Pfizer
- Acting and future chairs will participate in monthly Steering Committee calls and report back to ISAB colleagues
- Each company can assign one primary and one secondary to Taskforces/Working Groups of interest
- Each company can have two attendees at the Annual Meeting of the study
- Support Steering Committee
- Suggest Ancillary Studies



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# ISAB Next Steps

- ISAB bi-monthly t-cons to formulate Goals and Objectives to support PPMI mission.
- Identify individuals within partner companies to integrate into taskforces/working groups. Ensure partner representation in working groups.
- Formulate and communicate ISAB members needs.
- Evaluate needs and gaps, and recommend new ancillary studies to accelerate drug development in PD, biomarkers acceptance by regulators, and develop new indications for approved products.
- Support PPMI in adding new ISAB members and in closing funding gaps.
- Finalize ISAB organization/working groups.



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# PPMI $\alpha$ -synuclein interlaboratory study

Leslie M Shaw

Department of Pathology & Laboratory Medicine  
University of Pennsylvania Medical Center



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# PPMI $\alpha$ -synuclein interlaboratory study

- Purpose: evaluate precision of 4 immunoassays, including within-run and between-run precision for each participating center
- Samples:
  - 12 aliquots each for 7 patient CSF samples
  - 12 aliquots each for 3  $\alpha$ -SYN standards (rPeptide synthetic  $\alpha$ -SYN)
- Analyses: each center ran these samples together with a series of standards, prepared at each center, all in quadruplicate
- Statistics:
  - Statistical analyses will characterize for each center the precision within-run, between-run and total
- Lab ID: each laboratory was assigned a letter, A, B, C or D, randomly assigned, to preserve anonymity. Only the individual laboratory will know their id letter.

# PPMI interlaboratory study participants

<u>Centers performing immunoassays &amp; investigators</u>		<u>Data analysis</u>	
Covance/Univ of Ottawa	Peggy Taylor, ScD Michael Schlossmacher, MD	UPenn	Leslie M Shaw, PhD John Q Trojanowski, MD, PhD Michal Figurski, PhD
University of Washington	Jing Zhang, MD, PhD Jeff Armaly		
Innogenetics	Eugeen Vanmechelin, PhD Hugo Vanderstichele, PhD	Ulawa	Christopher Coffey, MD Ying Zhang, PhD
Elan	Jennifer Johnston, PhD Ruth Motter		

Patient CSF sample aliquots provided by Britt Mollenhauer; distributed by UPenn biomarker laboratory in sets of 3 aliquots per patient sample.

$\alpha$ -SYN QC sample aliquots provided by Eugeen Vanmechelin

# Plate layout for analytical runs

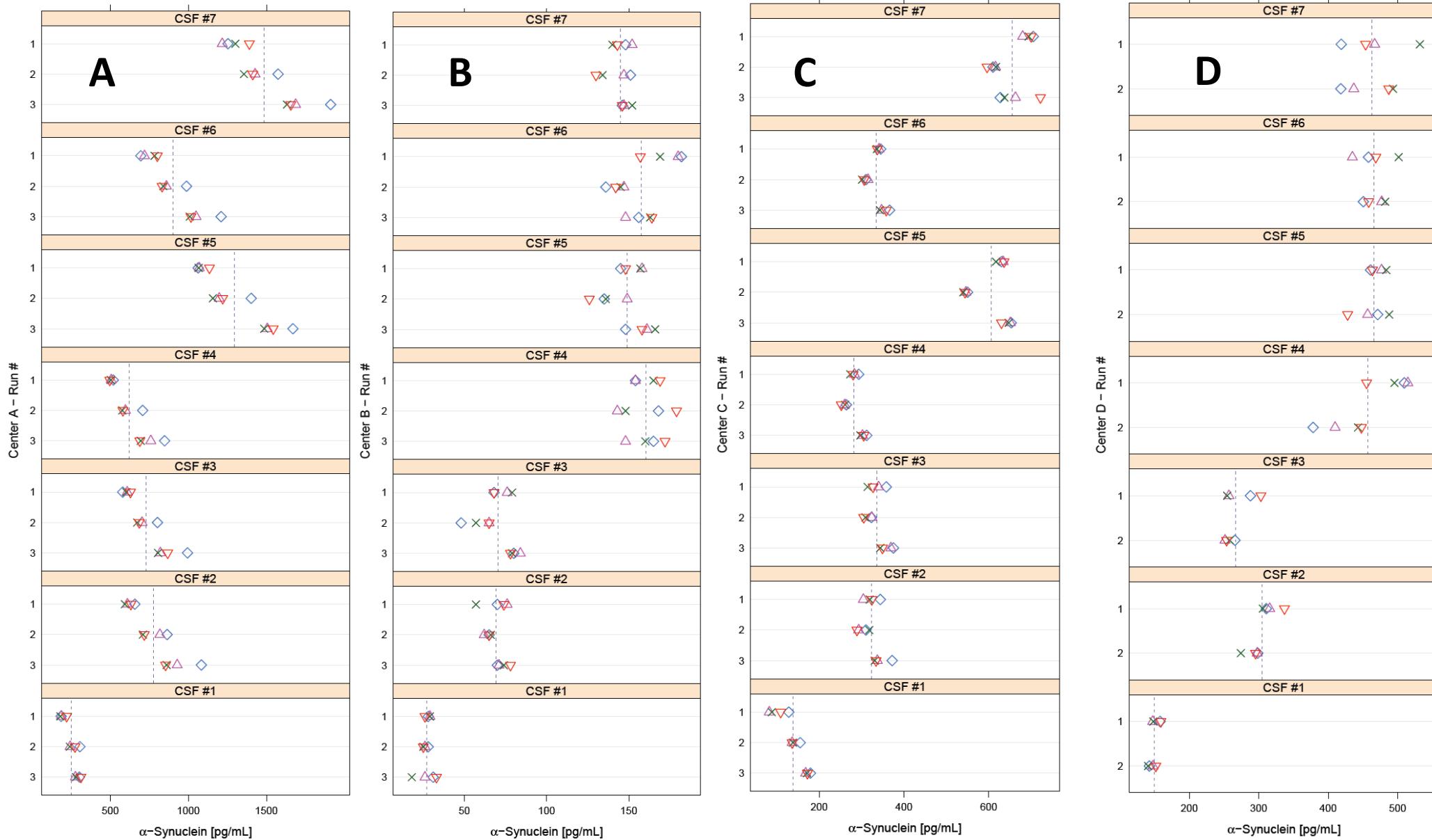
plate 1	$\alpha$ -syn*	rep1		rep2		rep3		rep4		MFI/OD			$\alpha$ -syn conc** pg/ml			
		conc pg/ml	MFI /OD	conc pg/ml	Avg	STDEV	%CV	AVER	STDEV	%CV						
standard 1																
standard 2																
standard 3																
standard 4																
standard 5																
standard 6																
standard 7																
standard 8																
Blank																
Control 1	333pg/ml															
Control 2	111pg/ml															
Control 3	12 pg/ml															
CSF #1																
CSF #2																
CSF #3																
CSF #4																
CSF #5																
CSF #6																
CSF #7																

\* conc standards theoretical

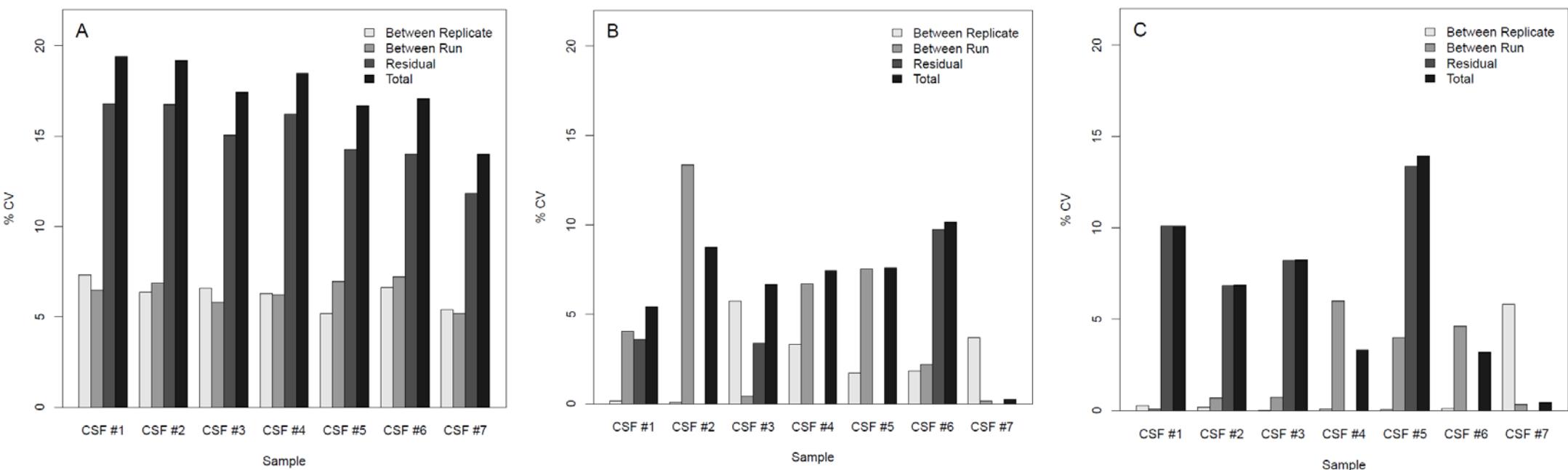
\*\* conc calculated

Each patient CSF sample and control sample was run in quadruplicate, in 3 different runs.

# Data points for each run for each of 4 participating laboratories for 7 patient CSF samples

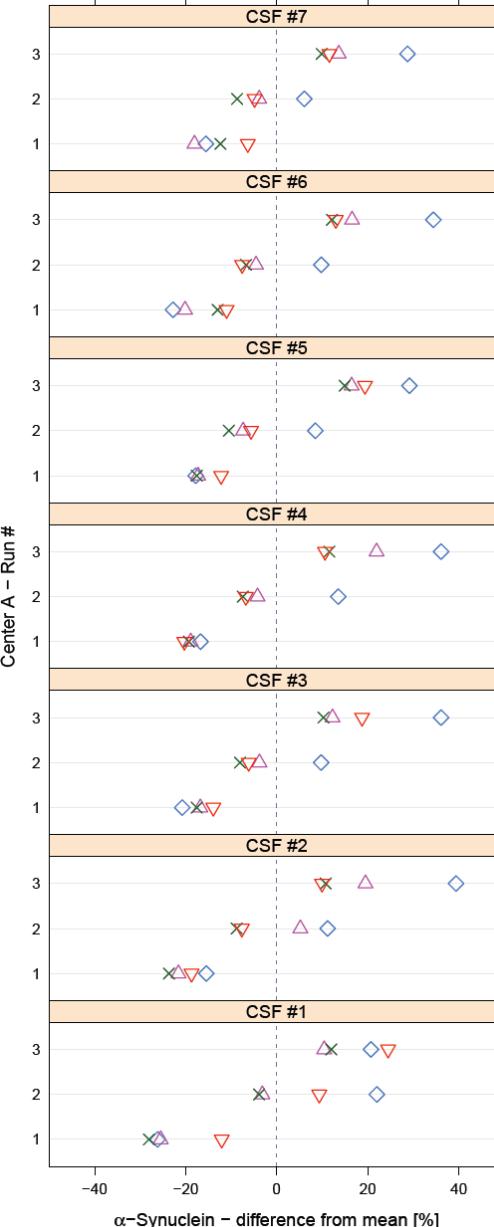


# Mixed-model precision analyses for Labs A, B & C

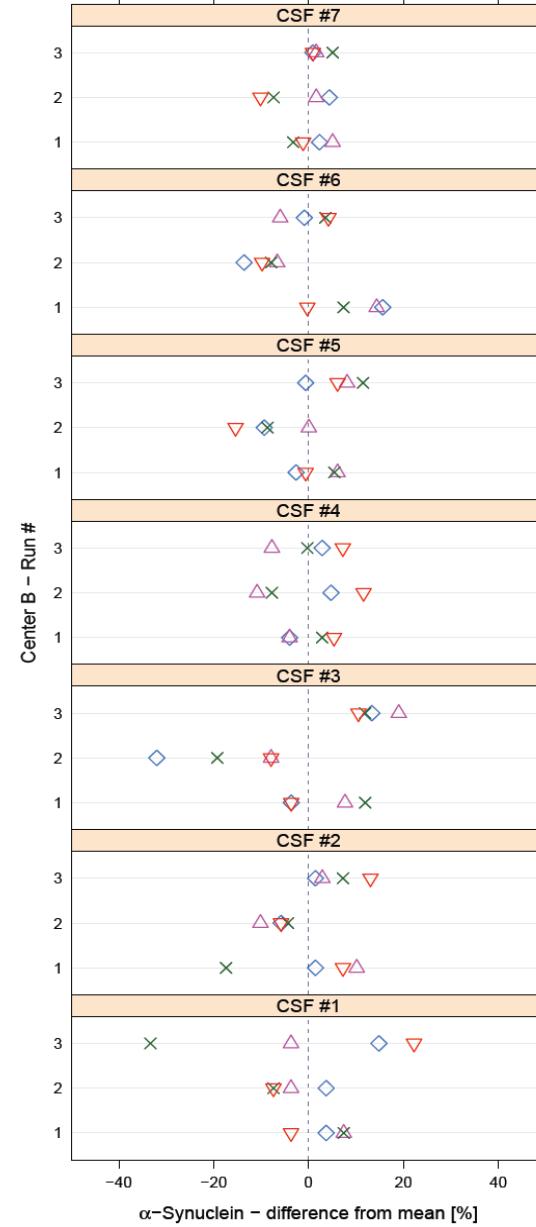


# Percent difference from the mean value for 7 CSFs within each center

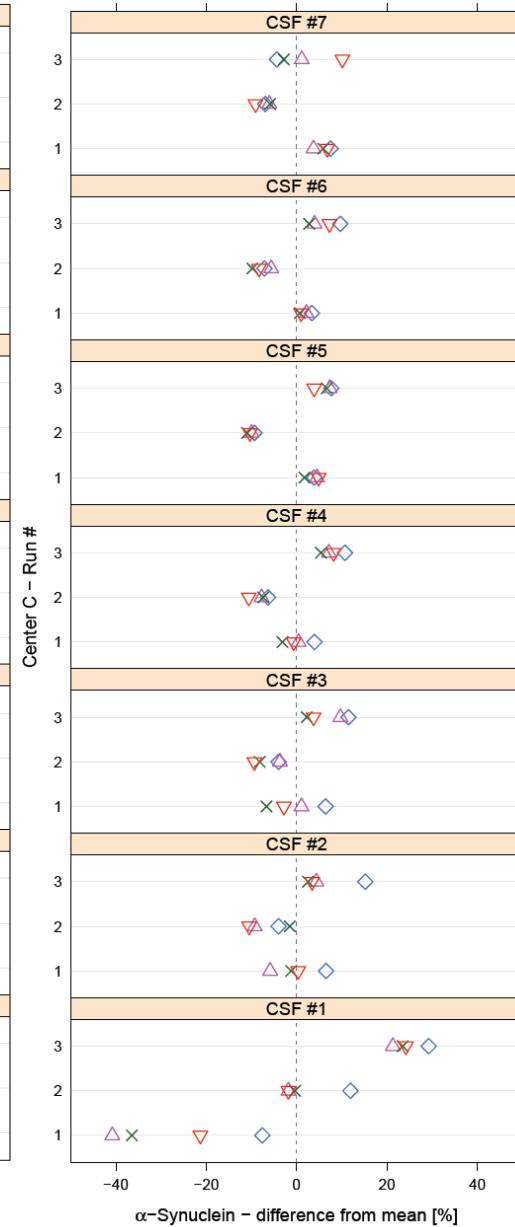
**A**



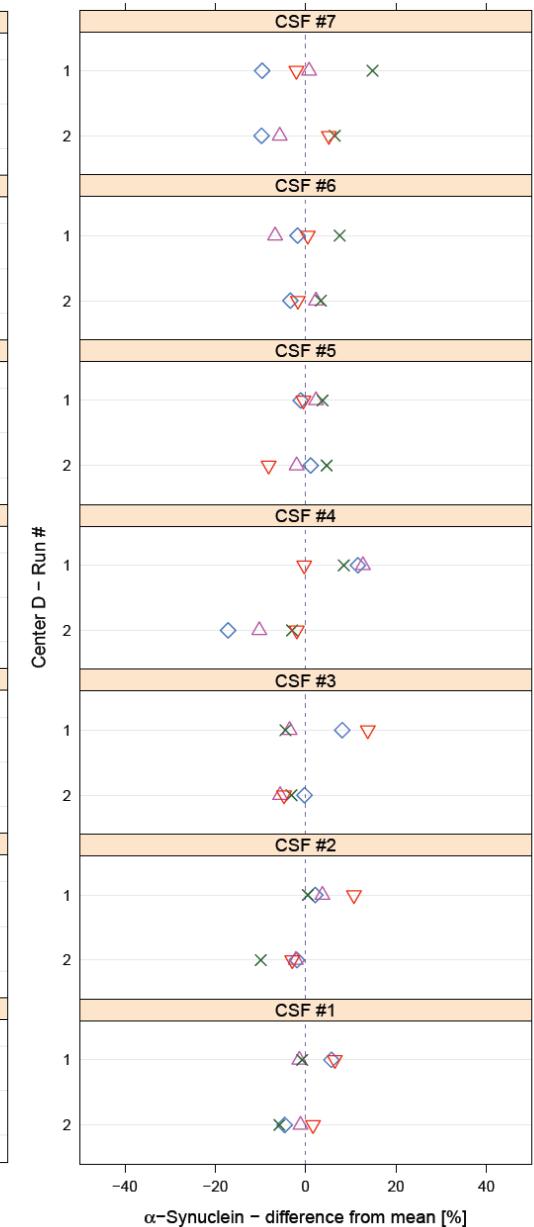
**B**



**C**

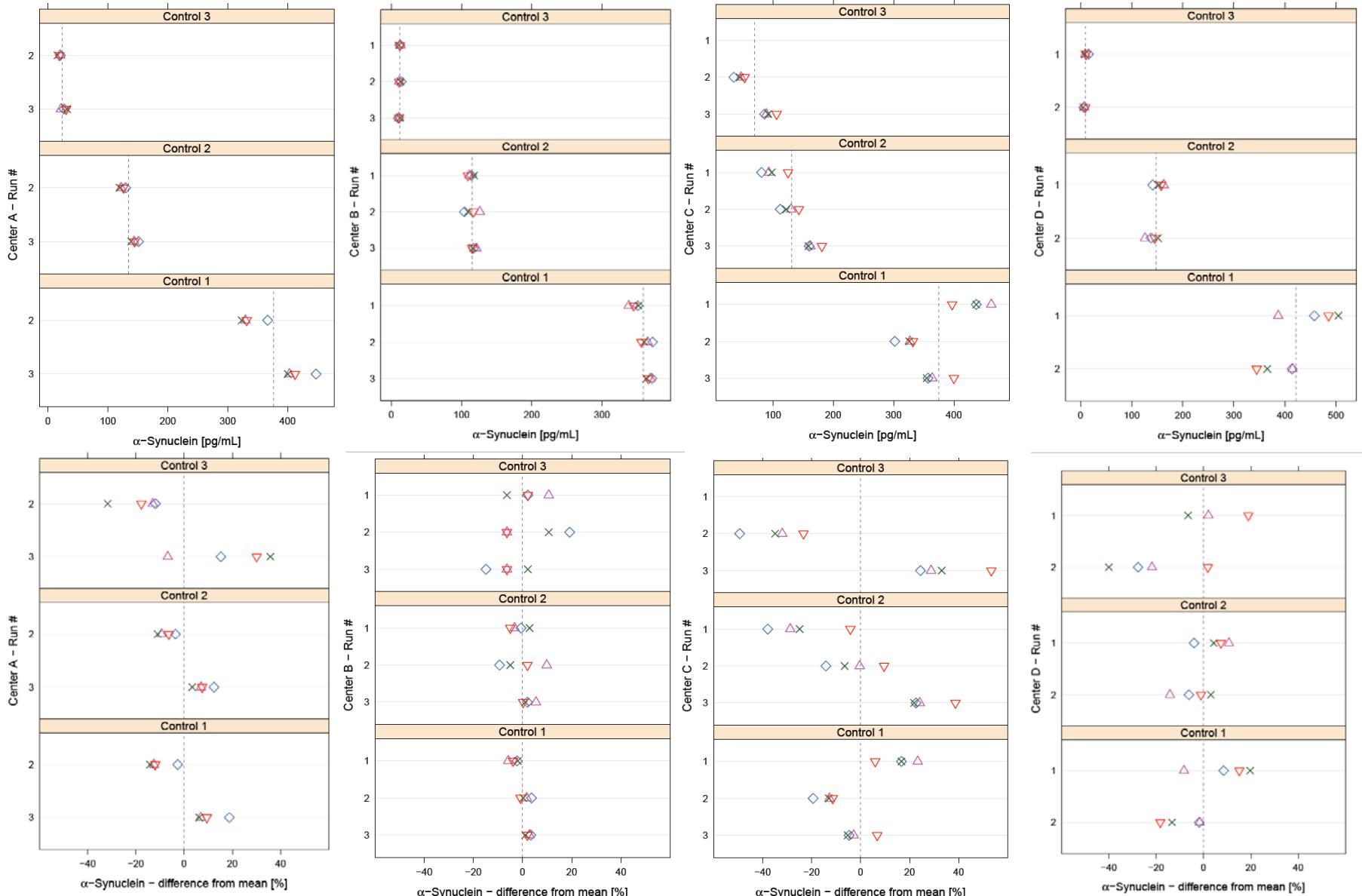


**D**



$\alpha$ -Synuclein - difference from mean [%]

# Precision performance for 3 $\alpha$ -SYN quality control samples



# Summary

- Databank with 848 analytical results has been prepared at UPenn and, independently, at Ulowa
- Analyses of data is underway with plans for review of the data by teleconference within the next month
- The results of the study whose primary purpose is to assess the precision performance of 4 immunoassays using patient CSF samples and  $\alpha$ -SYN quality control samples will be summarized and a report generated for upload on the PPMI web site

# PPMI

# Recruitment, Enrollment and Retention

Update to the PPMI Annual Meeting  
May 5, 2011

*Danna Jennings, R&R Working Group Chair*



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# PPMI

## Recruitment, Enrollment and Retention

*Danna Jennings*

*Claire Meunier*

*Sohini Chowdhury*

*Alexandra Gaenslen*

*Carie Christensen*

*Carlie Tanner*

*Daniela Berg*

*Emily Flagg*

*Christine Hunter*

*Cathi Thomas*

*Tanya Simuni*



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# Study Status and Recruitment Challenges

- 17 sites are actively recruiting
  - Most sites online Fall of 2010 with the remainder being activated winter/spring 2011
  - A couple sites are expected to come online this summer/fall
- Challenges in start-up and recruitment
  - Significant start-up delays as a result of regulatory approvals, organizational requirements, etc
  - Developing new recruitment strategies for observational study design
  - Learning curve for arranging logistics for study visits
  - Limited and lack of availability of DaTSCAN



# Revisiting our Recruitment and Retention Goals

- Recruitment: Enroll 1 PD subject a month and 1 control every other month
- Retention: Keep subjects engaged in the study so that they continue to participate in study visits over time

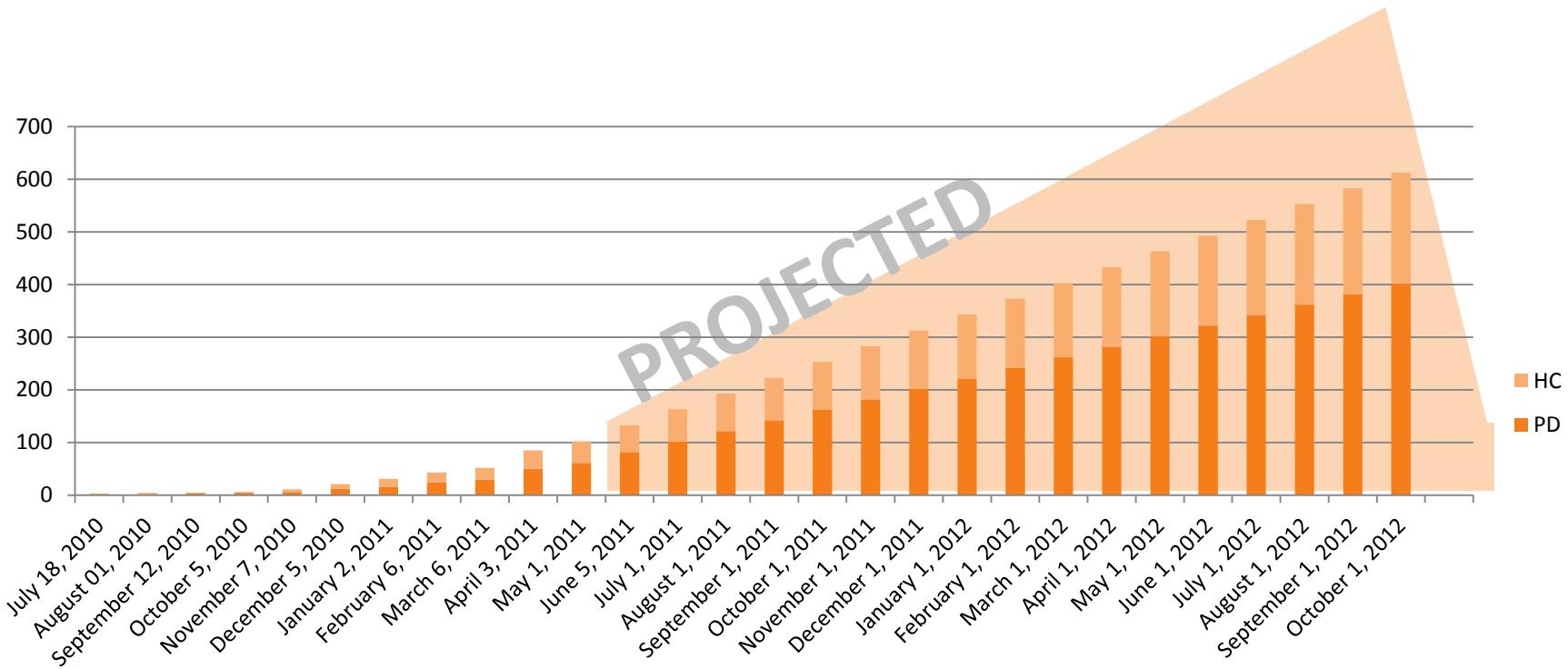


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# Recruitment and Enrollment in the next 17 months



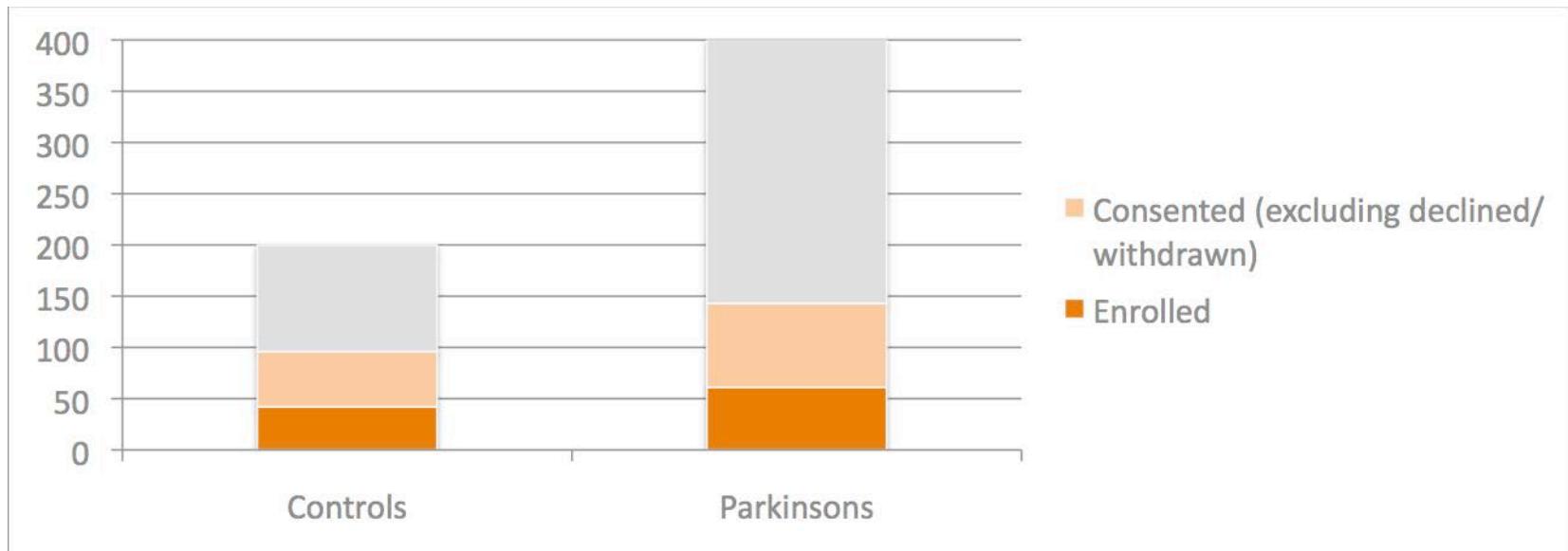
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# Recruitment Progress to Date

(as of May 1, 2011)



- 21% of 42/200 controls are enrolled (48% consented\*)
- 15% of 61/400 Parkinson subjects are enrolled (36% consented\*)



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



# Site Performance to Date - US

US Sites	Activation Status	Consented <u>(excluding declined/ withdrawn)</u>	Enrolled	
			PD	Controls
Baylor (Houston)	✓ Active	9	4	4
BU (Boston)	✓ Active	9	4	4
Cleveland Clinic (Cleveland)	Pending Activation (est April)	-	-	-
Emory (Atlanta)	✓ Active	11	3	6
IND (New Haven)	✓ Active	15	8	5
Hopkins (Baltimore)	✓ Active	3	0	2
Northwestern (Chicago)	✓ Active	13	5	2
OHSU (Portland)	✓ Active	15	9	3
The PI (Bay Area)	✓ Active	11	2	4
Sun Health (Phoenix)	✓ Active	4	3	1
UAB (Birmingham)	✓ Active	10	9	1
UCSD (San Diego)	Pending Activation (est April/May)	-	-	-
U Penn (Philadelphia)	✓ Active	7	2	3
U Rochester (Rochester)	✓ Active	6	3	2
U South FL (Tampa)	✓ Active	8	5	1
U Washington (Seattle)	✓ Active	10	3	1



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# Site Performance to Date - Europe

<u>EU Sites</u>	<u>Activation Status</u>	<u>Consented (excluding declined/ withdrawn)</u>	<u>Enrolled</u>	
			<u>PD</u>	<u>Controls</u>
Innsbruck U (Austria)	✓ Active	4	0	3
Paracelsus Klinik (Kassel/ Marburg Germany)	✓ Active	1	1	0
U Naples (Naples)	Pending Activation (est Summer)	-	-	-
U Tuebingen (Tuebingen)	✓ Active	1	0	0
Imperial College (London)	Pending Activation (est Fall)	-	-	-



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# Recruitment Strategies and Activities

- Site Efforts
  - Many good leads from clinic practices
  - Community outreach (support groups, symposia, physician networks, etc)
- MJFF strategies
  - Produced complete suite of recruitment materials
  - Salons hosted in 15 US cities
  - Physician mailings sent in 5 markets
  - Support group mailings planned for summer/fall
- Media
  - Over 75 major media hits on PPMI– including
    - CNN
    - The New York Times
    - The Chicago Tribune
    - Fox News (National and several local affiliates)
    - The LA Times, Lancet Neurology
    - USA Today, etc



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# Successful Recruitment Strategies

- A multi-pronged approach
- PI actively involved in recruitment
- Physician referral network development – this is a long-term game that requires multiple contacts
- Leverage internal resources at your site- Remind colleagues to refer, leverage affiliations with your University, etc.
- Make media happen- you identify a subject to represent your site to the media; we will do the rest

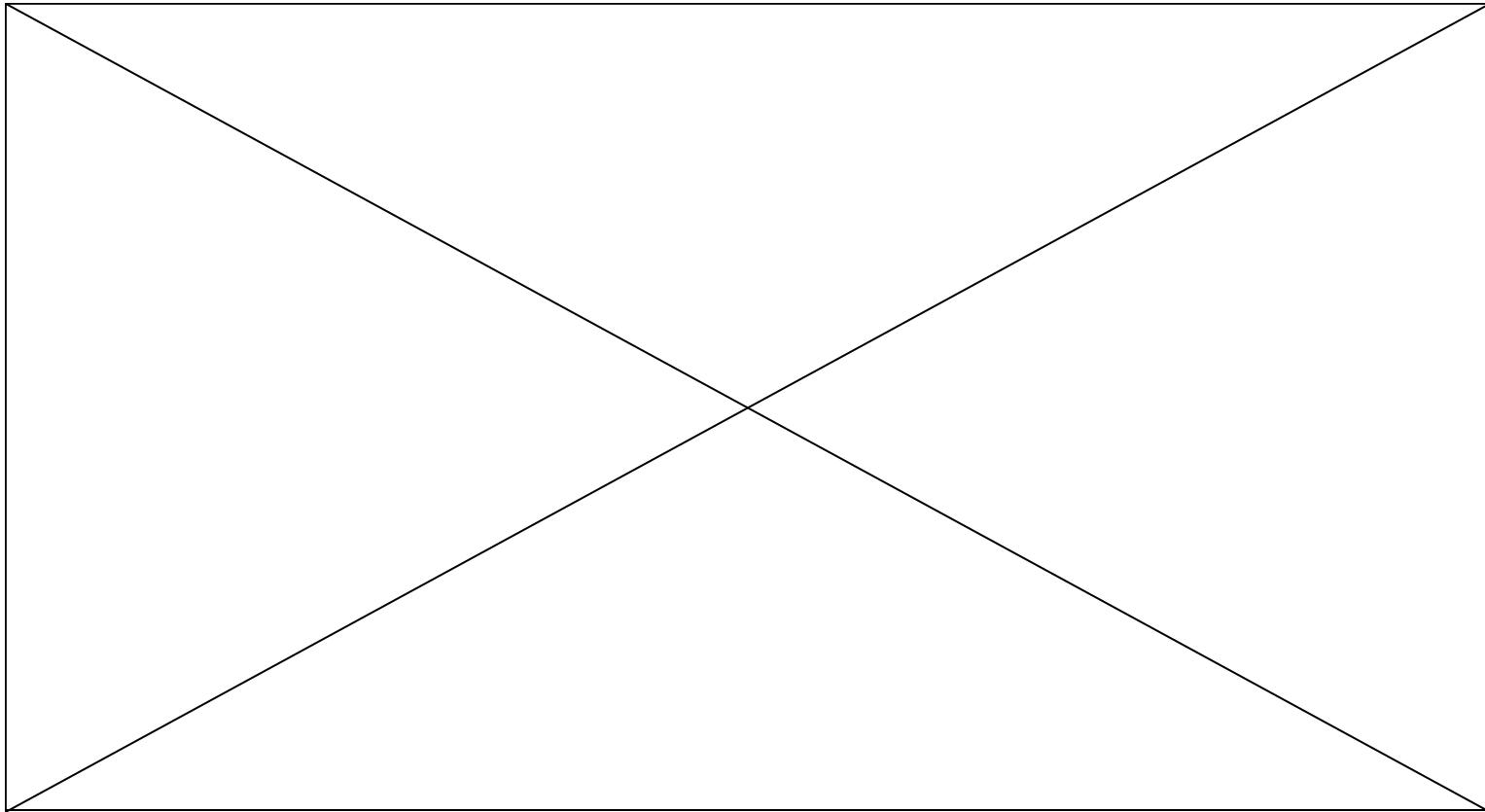


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# PPMI Media Highlights Reel



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# Interest in PPMI through central recruitment channels

19,244 unique visitors to michaeljfox.org/PPMI

5,564 unique visits to PPMI-info.org



3.2%

110 direct inquiries into the call center  
683 people from MJF.org/PPMI complete  
web form to learn more



3%

237 people referred to site



+ an additional 615  
calls directly to site

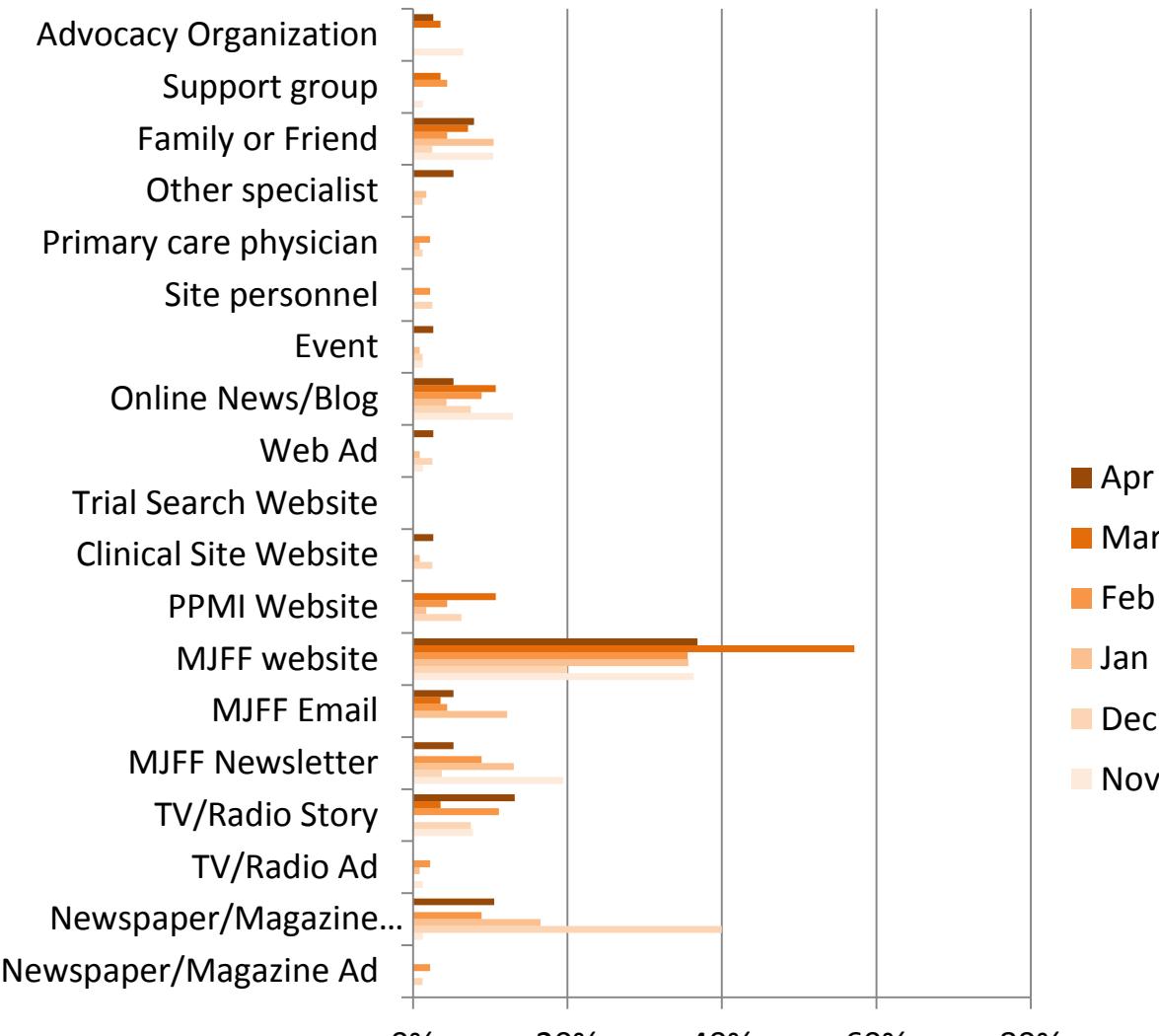
115 faxes have been returned  
19 people (17%) have been screened  
96 individuals not eligible or declined participation



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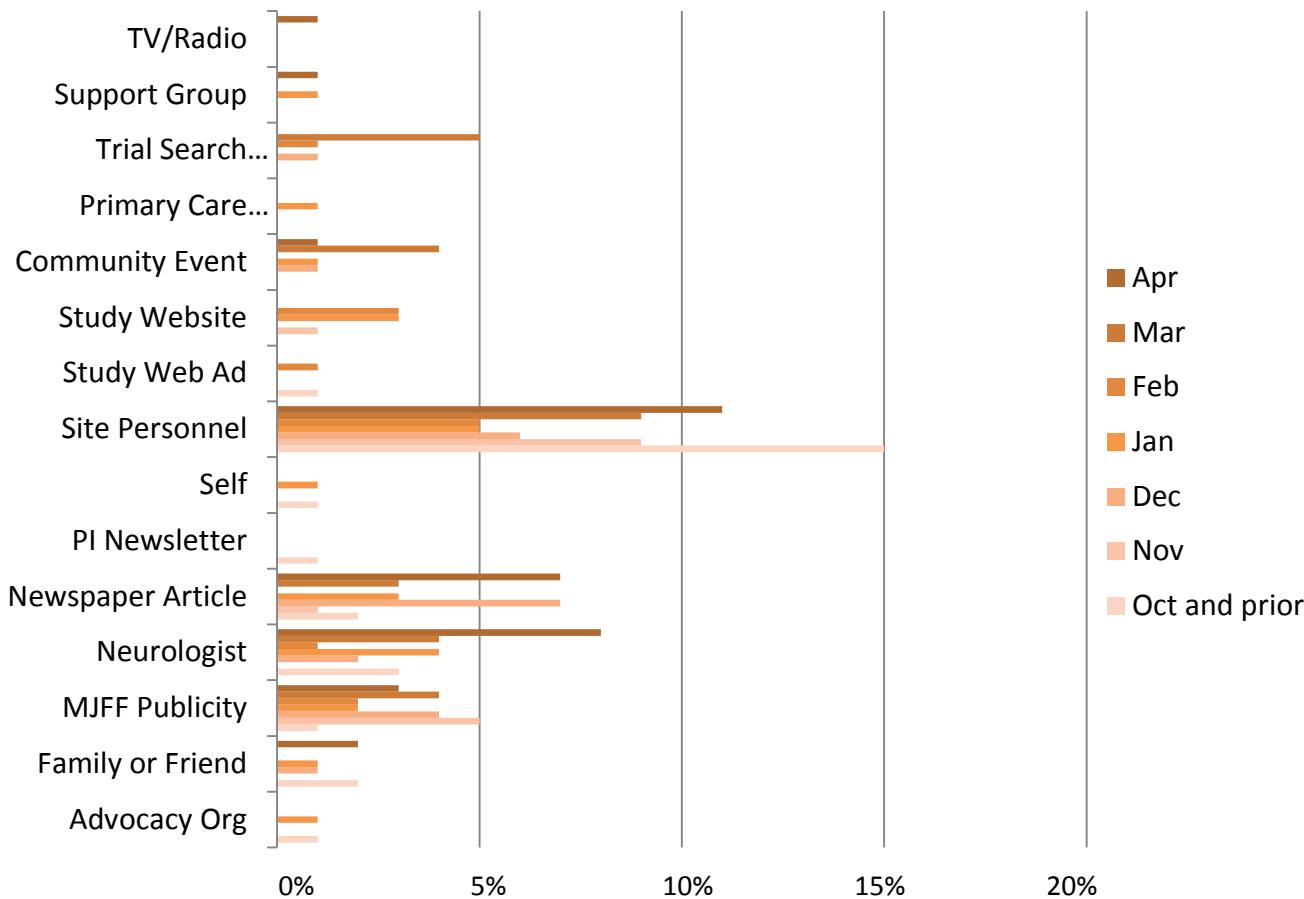
# Sources for Web and Call Center Inquiries



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# Recruitment Sources for Consented Participants



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# Awards for Site Performance

- Most subjects consented per month
- Most PD subjects enrolled
- Most Controls enrolled
- Best recruitment start in Europe
- Most creative and effective outreach to referring practitioners
- Most subjects consented
- Best (multi-pronged) community outreach plan



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# Most Subjects Consented per Month

- This site has consented an average of 2.3 subjects per month since being activated in September 2010
- They also have the second most actively enrolled subjects in the study



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# Most Subjects Consented per Month

- And the winner is....



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# Most PD Subjects Enrolled

- There was a tie between two sites for this award, but since OHSU already won...
- This site has a whopping 9 PD subjects enrolled in the study!



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# Most PD Subjects Enrolled

- And the winner is....



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# Most Controls Enrolled

- This site has enrolled 6 control subjects!
- They also take the cake for the most enrollments in a month with 9 enrollments happening within one 4-week period!



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# Most Controls Enrolled

- And the winner is....



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# Best Recruitment Start in Europe

- This site got started with a bang— one media story generated 55 inquiries about the study in the first 2 weeks
- 3 controls have been consented as a result



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# Best Recruitment Start in Europe

- And the winner is....



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# Most Creative and Effective Outreach to Referring Practitioners

- This site has conducted outreach to their internal referral network and been successful in building a referral network outside of their organization
- They have also had an influx of inquiries as a result of media



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# Most Creative and Effective Outreach to Referring Practitioners

- And the winner is....



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# Most Subjects Consented

- This site has consented 21 subjects for the study and enrolled a whopping 13 to date
- Even though they were the first site activated, their average number of subjects consented per month has ranked within the top 5 consistently throughout the study



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# Most Subjects Consented

- And the winner is....



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# Best (multi-pronged) Community Outreach Plan

- This site is getting out there—speaking at support groups, placing newsletter articles, presenting at events, and getting some well-targeted media



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# Best (multi-pronged) Community Outreach Plan

- And the winner is....



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# The Road Ahead: Two key challenges for sites

- Recruitment: Keeping the pipeline full
  - The study is 1/6 of the way there, but the excitement around the launch is waning.
  - Sites must continue to evolve their recruitment planning and revisit key strategies
- Retention: Maintaining the stamina and loyalty of enrolled subjects
  - Update from Retention Pre-Session yesterday



# Questions?



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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



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# 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. The header includes the PPMI logo, navigation links for 'Study Design', 'Research Documents & SOPs', 'Stats Forum', and 'Ancillary Studies', and a search bar. The main content area is titled 'ANCILLARY STUDIES' and describes the submission process for sub-studies. It includes sections for 'Ancillary Studies Proposal Form' and 'Additional Information'. To the right, there are five orange call-to-action boxes: 'DOWNLOAD DATA', 'REQUEST SPECIMENS', 'for PROSPECTIVE PARTICIPANTS' (with a group of people icon), 'for PRACTITIONERS' (with a brain icon), 'for INDUSTRY PARTNERS' (with a dollar sign icon), and 'for RESEARCHERS' (with a neuron icon). The form itself contains fields for Principal Investigator First Name, Last Name, Suffix, Position Title, Institution, Department, Sector (dropdown menu), Street Address, City, Country, and State.



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# 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](http://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 Chowdhury

Chris Coffey

Danna Jennings

Shirley Lasch

Ken Marek

Todd Sherer

Andrew Siderowf

Tanya Simuni

Carlie Tanner (Chair)

Eduardo Tolosa



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# Current Ancillary Studies

- 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



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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 as PD patients for PPMI who are excluded based on a normal DaTSCAN at screening

## Assessments

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

Clinical (motor, non-motor, neuropsychological)

Biomarker blood draw

DaTSCAN at baseline and 24 months



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# 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

- 15 PPMI PD subjects at 3 sites (OHSU, INDD, UPenn) total of 45 subjects

## 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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# 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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