

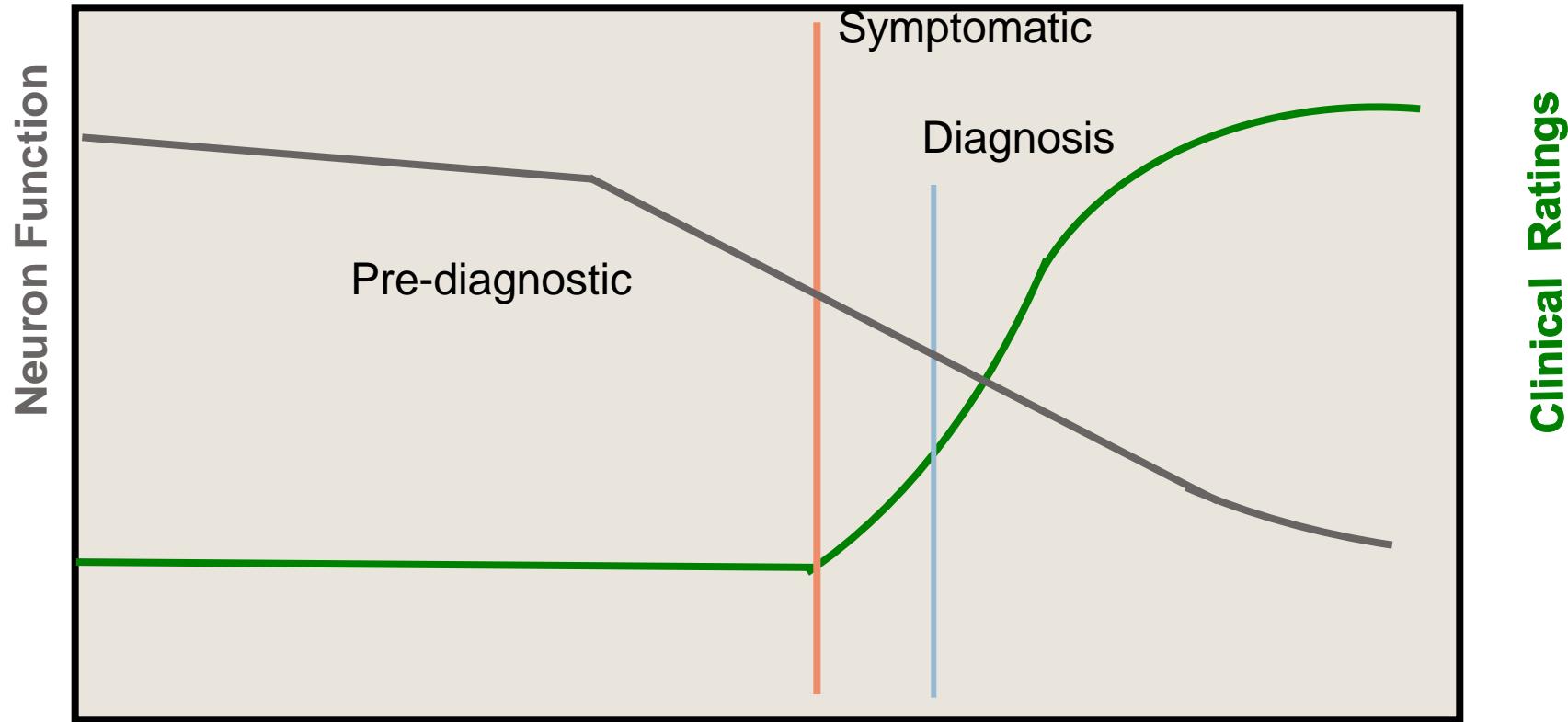
# *Parkinson's Progression Markers Initiative*



*Investigator's Meeting  
March 18-19, 2010*

*New York City*

# Natural History of Parkinson disease



# Neuroprotection studies

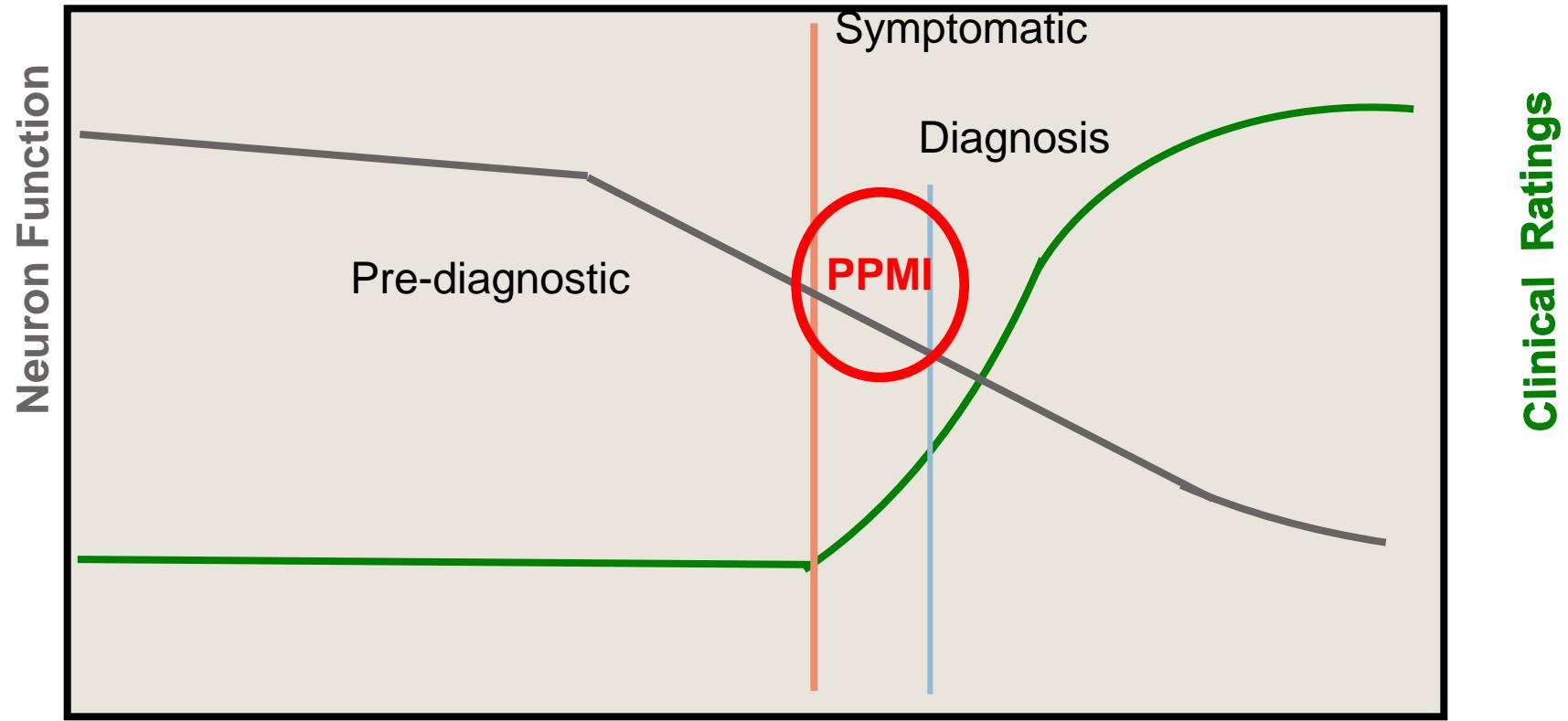
## FAILED

- DATATOP – SELEGILINE/VIT E
  - LAZABEMIDE
  - RULIZOLE
  - TCH-346
  - NEURO-IMMUNOPHILIN
  - GPI 1485
  - CALM-PD
  - MINOCYCLINE
  - CAFFEINE
  - REAL-PET – ROPINIROLE
- ELLDOPA
  - ASA/NSAID
  - SR57667B
  - PRECEPT – CEP1347
  - GREEN TEA
  - PROUD - PRAMIPEXOLE

## UNCERTAIN

- *QE-2/CO-Q10/QE3*
- *ADAGIO – TEVA*
- *NET PS LS1 – CREATINE*
- *ISRADIPINE*
- *SURE-PD*

# Natural History of Parkinson disease



# Clinical markers

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Cognition

Behavioral

Depression  
Apathy  
Anxiety  
ICD

Autonomic

Constipation  
Bladder  
Sexual  
Cardiac

Olfaction

Sleep - RBD

Skin

Motor analysis

Speech

PPMI

PARKINSON'S PROGRESSION  
MARKERS INITIATIVE

# Biomarkers for PD

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Imaging –Phenomics

SPECT/PET-Dopamine -  
DAT, F-Dopa, VMAT2

SPECT/PET-non-dopamine

FDG, MIBG, NE, 5HT, Nicotine,  
Ach, PBR, Amyloid,  $\alpha$ -synuclein

MRI –DTI, volumetrics,  
Nigral Ultrasound

Biologics – Blood/CSF/Urine

Alpha-synuclein, DJ1, Urate, Tau,  
 $\beta$ -Amyloid

'Omics' –

RNA profiling

Genetics

Synuclein, LRRK2  
Parkin DJ-1, Pink1

# Developing the Parkinson's Progression Markers Initiative

- Beginning in March 2007, MJFF staff and SAB has worked with industry, government and academic biomarker researchers to further promote biomarker discovery efforts, accelerate and improve biomarker verification studies, and establish strategies for developing progression biomarkers for PD trials.

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

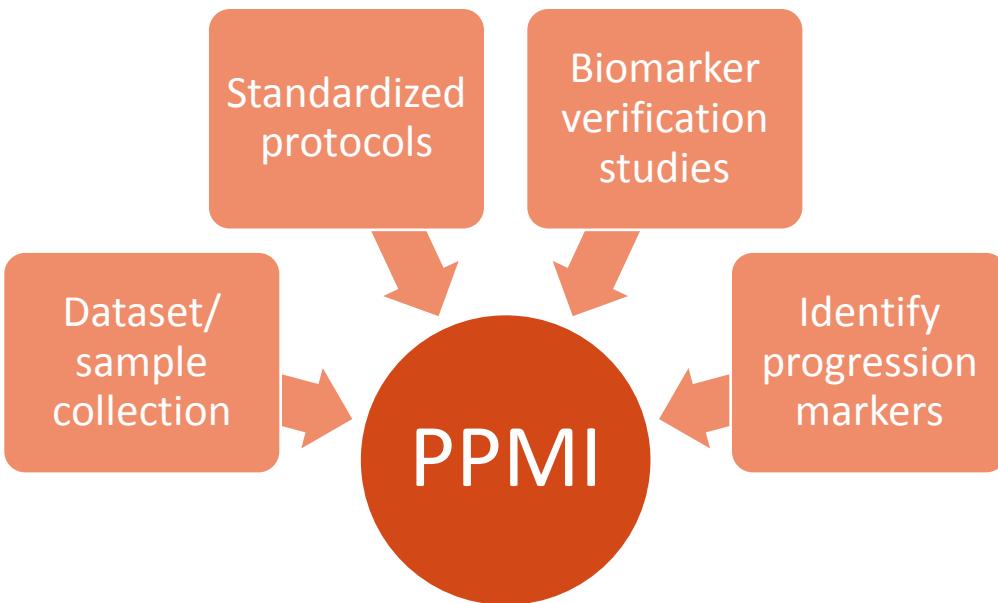
- Uniform collection of data and samples
- Uniform storage of data and samples
- Strict quality control/quality assurance

## Access/Sharing

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

# PPMI: Identify a tool or combinations of tools to inform PD clinical trial design and decisions

*PPMI comprises four core objectives*



- 1. Develop/collect comprehensive clinical/imaging dataset and biological samples, which is made available**
- 2. Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biologic data**
- 3. Conduct preliminary verification and validation studies on imaging and biologic markers**
- 4. Identify and correlate clinical, imaging and biologic markers for use in future trials.**

# PPMI SC and Study Cores

<b>Steering Committee</b>	PI-K Marek, A Siderowf, C Scherzer, D Jennings, K Kieburtz, W Poewe, B Mollenhauer, C Tanner, B Ravina (core leaders, MJFF, ISAB)
<b>Clinical Coordination Core</b>	<ul style="list-style-type: none"><li>▪ University of Rochester's Clinical Trials Coordination Center</li><li>• PI: Bernard Ravina</li></ul>
<b>Imaging Core</b>	<ul style="list-style-type: none"><li>▪ Institute for Neurodegenerative Disorders</li><li>• PI: John Seibyl</li></ul>
<b>Statistics Core</b>	<ul style="list-style-type: none"><li>▪ University of Iowa</li><li>• PI: Chris Coffey</li></ul>
<b>Bioinformatics Core</b>	<ul style="list-style-type: none"><li>▪ Laboratory of Neuroimaging (LONI) at UCLA</li><li>• PI: Arthur Toga</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 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 CLINICAL SITES



# Clinical Sites

- Arizona Parkinson's Disease Consortium (Phoenix, AZ)
- Baylor College of Medicine (Houston, TX)
- Boston University (Boston, MA)
- Emory University (Atlanta, GA)
- Innsbruck University (Innsbruck, Austria)
- Institute of Neurodegenerative Disorders (New Haven, CT)
- Johns Hopkins University (Baltimore, MD)
- Northwestern University (Chicago, IL)
- Oregon Health and Science University (Portland, OR)
- Paracelsus-Elena Clinic Kassel/University of Marburg (Marburg, Kassel, Germany)
- The Parkinson's Institute (Sunnyvale, CA)
- University of Alabama at Birmingham (Birmingham, AL)
- University of Florida – Gainesville (Gainesville, FL)
- University of Napoli (Naples, Italy)
- University of Pennsylvania (Philadelphia, PA)
- University of Rochester (Rochester, NY)
- University of South Florida (Tampa, FL)
- University of Tübingen (Tübingen, Germany)
- University of Washington (Seattle, WA)

# PPMI Taskforces/Committees

- **Biologics Taskforce**

- John Trojanowski, MD, PhD (Chair)
- Un Kang, MD, PhD
- Doug Galasko, MD
- Kalpana Merchant, PhD
- Clemens Scherzer, MD, PhD
- Michael Schlossmacher, MD, PhD
- Howard Schulman, PhD
- Leslie Shaw, PhD
- Jing Zhang, MD, PhD

- **Imaging Taskforce**

- David Brooks, MD
- William Jagust, MD
- Ken Marek, MD
- Norbert Schuff, PhD
- John Seibyl, MD

- **Neuropsych / Behavioral Assessment Taskforce**

- David Burn, MD (Chair)
- Andrew Siderowf, MD
- Keith Hawkins, PhD
- Murat Emre, MD
- Daniel Weintraub, MD

- **Advisory Committee** (*in formation*)

- Gary Cutter, PhD, UAB School of Public Health
- Russell Katz, MD, FDA
- Cristina Sampaio, MD, PhD, EMEA

- **Clinical study oversight committee** (*in formation*)

- **Industry Advisory Board** (*in formation*)

# PPMI Overview

- PPMI is a study to establish PD progression biomarkers – not a treatment trial
- Intensive, comprehensive project for subjects, sites, investigators
- Established study instruments complemented by novel technologies. Flexibility in incorporating new technologies and new studies
- Openness to provide data to community
- Set standards for biomarker collections and image acquisition

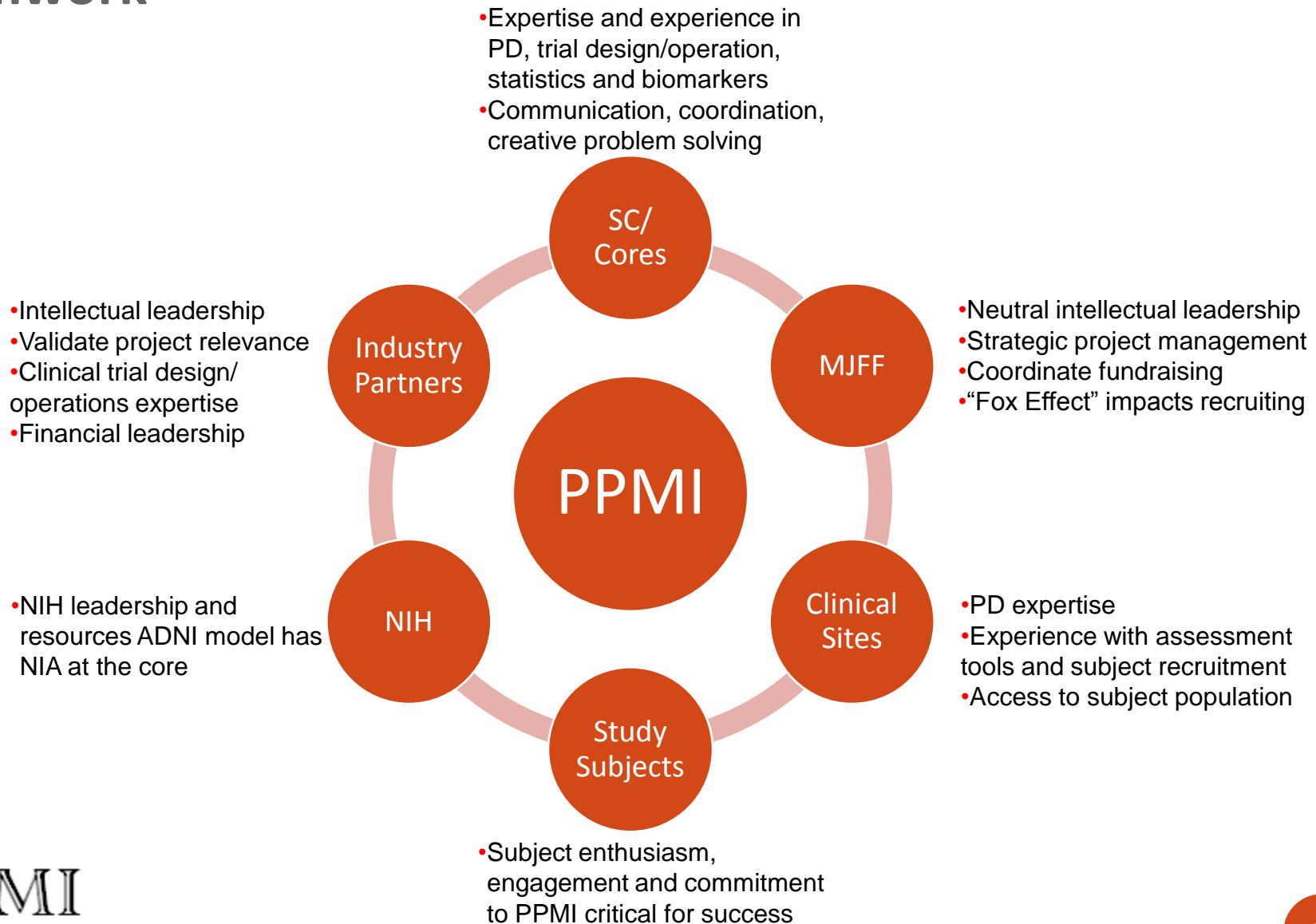
# PPMI - Standardization/Training

- **Biologics - Collection/Aliquoting/Shipping/Storage**
- **Imaging - Acquisition/QC/analysis/backup**
- **UPDRS - MDS UPDRS certification**
- **Neuropsych/Neurobehavioral**
- **CSF collection**
- **Data entry**

# PPMI - Novel features/Critical Challenges

- Subject recruitment and retention
- Early PD/Use of imaging as eligibility
- CSF acquisition
- Data management and coordination of study cores
- Availability of biomarker and imaging candidates
- Study funding

# PPMI requires coordination/creativity/ perseverance/ teamwork



# Schedule of Activities

Bernard Ravina, MD, MS

# Principles

- **Comprehensive and uniformly collected set of clinical data, imaging, and biological samples**
- **Focus on early (and untreated) PD**
- **Lay foundation for future efforts to measure and modify progression**

# Challenges

- Recruitment and Retention
- Diagnostic accuracy (cases and controls)
- Frequency of assessments
- Intensity of assessments
- Training and consistency
- Meticulous sample collection/processing
- Data and sample quality/completeness

# Opportunity

- **Wealth of clinical and biological data and samples that is widely accessible to researchers**

# PPMI

# Schedule of Activities

# Assessments

## Who performs what?

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

# Assessments

## Who performs what?

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

# Screening Visit (SC) Procedures

The following procedures and assessments will be conducted within 30 days before the Baseline visit:

- Acquire informed consent
- Assign subject ID number (list provided from CTCC)
- Assess inclusion/exclusion criteria
- Collect medical history and demographic information
- Assign CTCC unique ID number
- Determine prior and current medications
- Measure vital signs
- A complete physical and neurological exam
- Administer MoCA

# SC Visit (continued)

- Administer MDS-UPDRS and classify according to Hoehn & Yahr (PD subjects only)
- Assess activities of daily living according to Modified Schwab & England scale (PD subjects only)
- Collect blood sample for clinical lab assessments, including for females of child-bearing potential, a urine pregnancy test
- Collect blood sample for DNA
- Conduct DAT imaging scan
  - Females of childbearing potential; urine preg test results prior to scan
  - May be done up to 7 days prior to BL visit
  - Must receive confirmation of eligibility from Imaging core prior to BL visit

# Baseline Visit (BL) – Day 0

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

# BL Visit (continued)

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

# Follow Up In-Person Visits

- Return every 3 months in first year and every 6 months thereafter
- Full set of cognitive/neuropsychological assessments completed annually
- Research blood samples collected each visit up to month 24 (urine collected every other visit) and annually thereafter
- DAT imaging conducted annually (PD subjects)
- LP conducted at month 6 and annually
- MRI with DTI at selected sites at month 12 for all and annually thereafter for PD

# Follow Up Telephone Visits

- Telephone contacts made approx. 7 days after a DAT scan or LP conducted to assess AE's
- Telephone contacts conducted at months 15, 21, 27, 33, 39, 45, 51 and 57 to discuss study questions, verify if any PD meds have been started (for PD subj.), confirm next visit

# Symptomatic Therapy (ST) Visit

- PD subjects only
- Purpose: to obtain assessments and biomarker samples at furthest point into study before starting meds
- Established if meds started before the 12 month visit (Visit 03)
- Follow protocol and operations manual guidelines to determine activities that should be conducted
- After year one less intensive, unscheduled visit

# PD Subjects Only

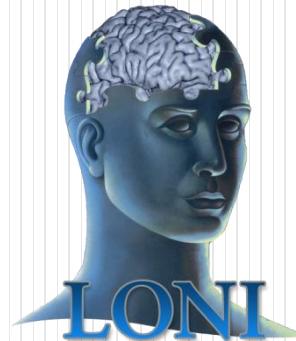
- Month 12 or thereafter, if levodopa or dopamine agonist is being taken:
  - MDS-UPDRS Part III and Hoehn & Yahr conducted in practically defined off
  - Repeated 1 hour after medication dosing in clinic
  - Subjects will need to be reminded to hold meds on day of visit (if applicable)

# Order of Activities

- Will suggest order
- Certain assessments, samples should be collected at similar times over course of study

# Data Flow

Arthur Toga  
Laboratory of Neuro Imaging



# Bioinformatics Core

- PD@LONI
  - Website
  - Data repository
  - Investigator access requests
  - Data downloads
  - Biological sample requests

# Data Flow Overview



Acquisition  
Sites



First Level  
Staging

Bioanalytics Core  
Bioinformatics Core  
Biorepository Core  
Clinical Core

Genetics Core  
Imaging Core  
Statistics Core



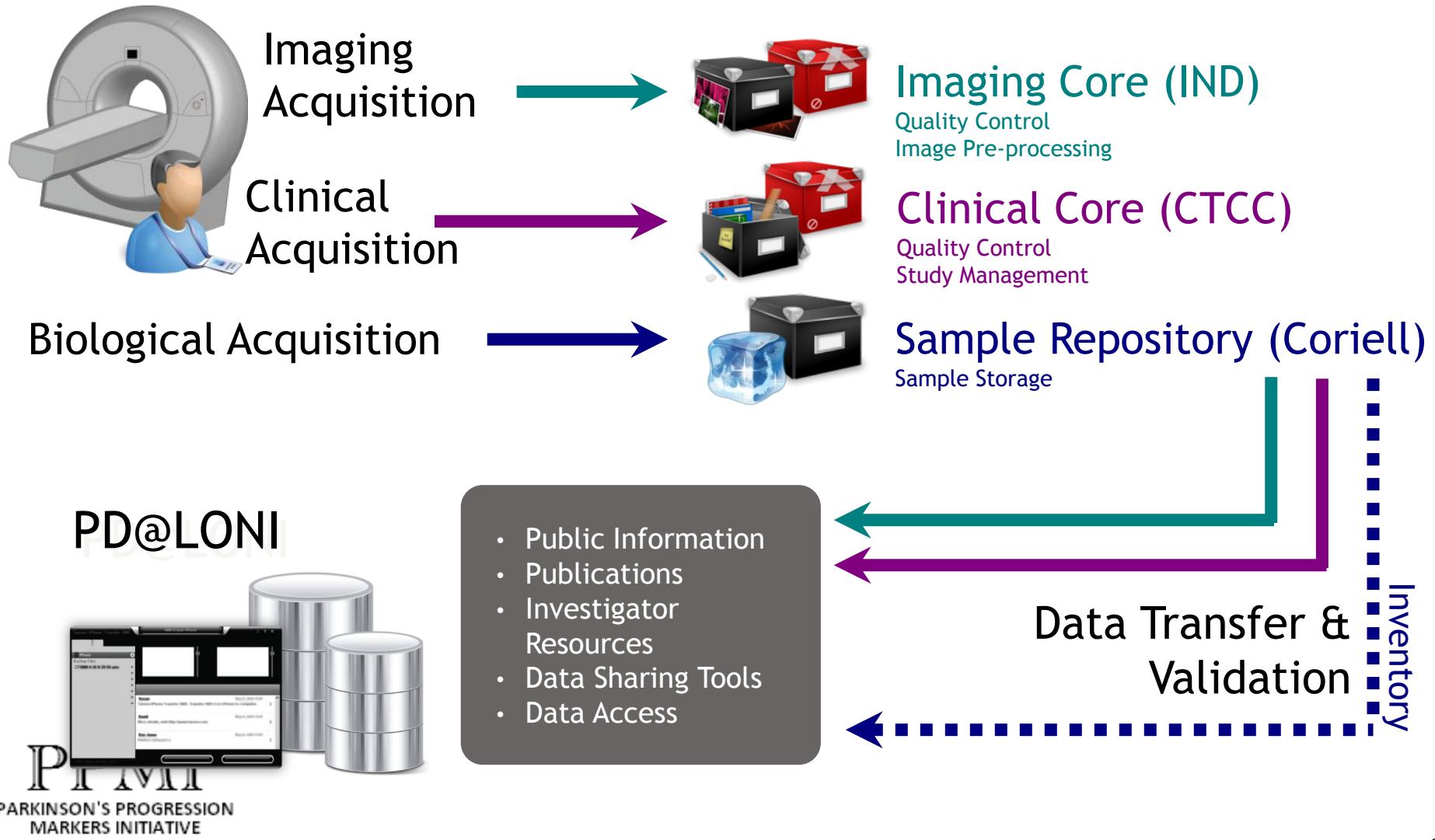
PD@LONI



Scientific  
Investigators

# Data Input

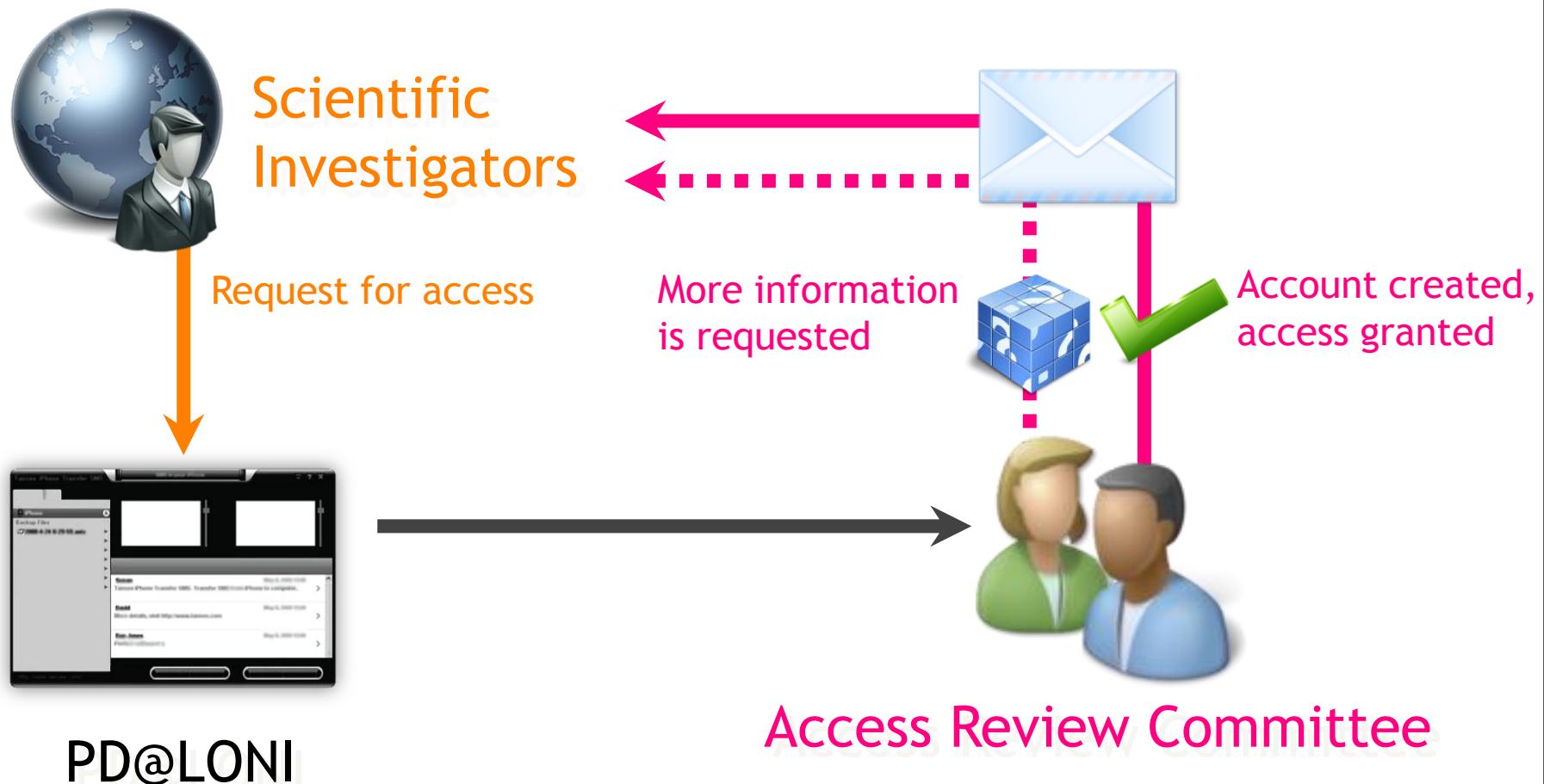
Acquisition → Repository



# Data Transfer to the Cores

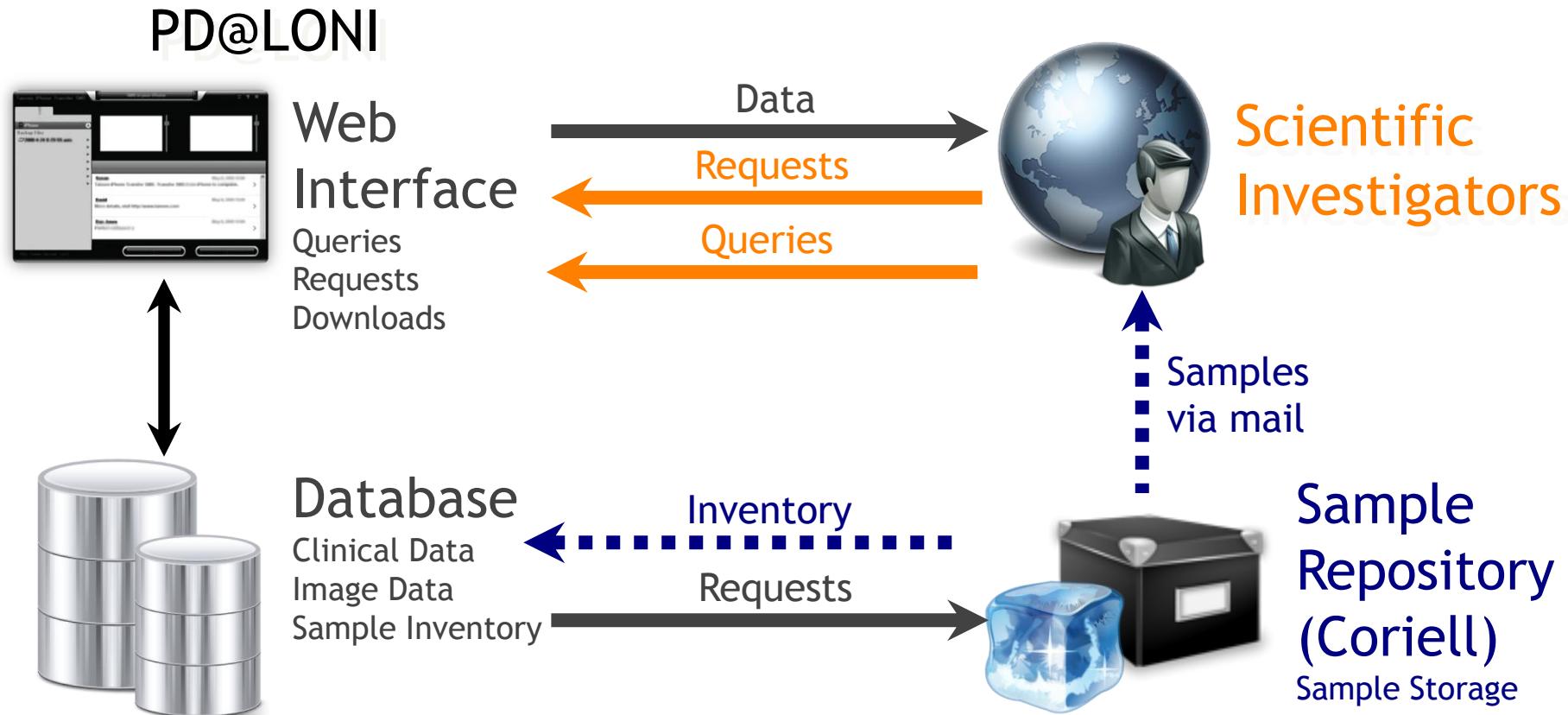
- Specific information for investigators about how to transfer data to the IND, CTCC and Coriell is covered in the following sessions:
  - Thursday, 11:15 – 2:45pm
    - Breakout Session #1: Imaging Overview
    - Breakout Session #2: Biologics Overview
  - Friday, 11:45 – 2:00pm
    - eClinical Training Introduction

# Data Use Application Process



# Data Output

Repository → Investigators



# Database Search

Flexible, Interactive, Customized, Reusable Searches

Search Advanced Search Data Collections

**Search Options**

**SEARCH SECTION**

- Project
- Subject
- Project Specific Information
- Assessments
- Study/Visit
- Image Modality
- Imaging Protocol
- Image Quality
- Image Status
- Image Processing

**IMAGE TYPES**

- Original
- Pre-processed
- Post-processed

**Display Options**

Order by: Subject ID  
and  
and  
Show 500 results

**Search Criteria**

Specify selection criteria using the checkboxes on the left.

**PROJECT**

Projects	<input checked="" type="checkbox"/> ADNI	<input type="checkbox"/> AIBL
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**SUBJECT**

Subject ID	<input type="text"/>	Separate multiple Subject ID's by commas	<input checked="" type="checkbox"/>
Age (years)	Equals <input type="button" value="▼"/>	<input type="text"/>	<input checked="" type="checkbox"/>
Sex	Both <input type="button" value="▼"/>		<input checked="" type="checkbox"/>
Weight (kgs)	Equals <input type="button" value="▼"/>	<input type="text"/>	<input type="checkbox"/>

**RESEARCH GROUP**

Research Group	<input type="checkbox"/> Patient	<input type="checkbox"/> Volunteer	<input type="checkbox"/> Phantom
----------------	----------------------------------	------------------------------------	----------------------------------

**STUDY/VISIT**

Study Date Equals

**(ADNI)**

<input type="checkbox"/> Screening	<input type="checkbox"/> Baseline	<input type="checkbox"/> Month 6
<input type="checkbox"/> Month 12	<input type="checkbox"/> Month 18	<input type="checkbox"/> Month 24
<input type="checkbox"/> Month 30	<input type="checkbox"/> Month 36	<input type="checkbox"/> Month 42
<input type="checkbox"/> Month 48	<input type="checkbox"/> Unscheduled	<input type="checkbox"/> Screen Fail
<input type="checkbox"/> No Visit Defined	<input type="checkbox"/> No Visit	

**OR    AND**  
Subject has at least one

**IMAGE MODALITY**

<input type="checkbox"/> MRA	<input checked="" type="checkbox"/> MRI	<input type="checkbox"/> PET
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**IMAGING PROTOCOL**

**(MRI)**

Series Description	<input type="text"/>	<input type="checkbox"/>			
Acquisition Plane	<input type="checkbox"/> AXIAL	<input type="checkbox"/> CORONAL	<input type="checkbox"/> SAGITTAL	<input type="checkbox"/>	
Acquisition Type	<input type="checkbox"/> 2D	<input type="checkbox"/> 3D		<input type="checkbox"/>	
Field Strength (tesla)	Equals <input type="button" value="▼"/>	<input type="text"/>		<input type="checkbox"/>	
Slice Thickness (mm)	Equals <input type="button" value="▼"/>	<input type="text"/>		<input type="checkbox"/>	
TE (ms)	Equals <input type="button" value="▼"/>	<input type="text"/>		<input type="checkbox"/>	
TR (ms)	Equals <input type="button" value="▼"/>	<input type="text"/>		<input type="checkbox"/>	
Weighting	<input type="checkbox"/> Active S	<input type="checkbox"/> PD	<input type="checkbox"/> T1	<input type="checkbox"/> T2	<input type="checkbox"/>

**RESET ALL** **SEARCH**

Choose data elements

Set search criteria

# Data Access & User Management

- Features

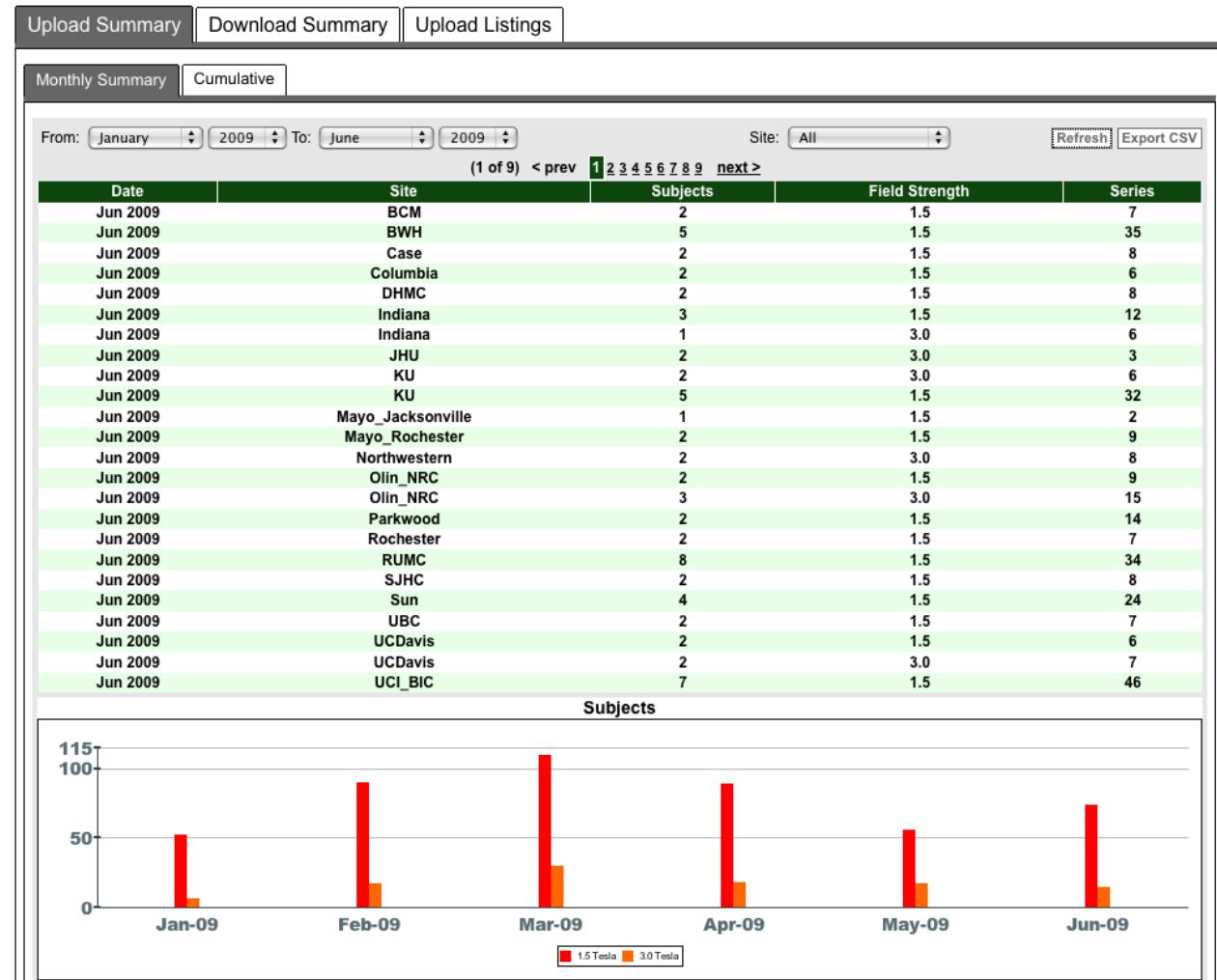
- Applicant listing
- Application details
- Approve/disapprove access
- Review submitted manuscripts
- Send annual notifications
- Expire accounts

The screenshot shows a web-based application interface for managing investigator accounts. At the top, there are five navigation tabs: "Investigator Listing", "Manage Investigator Account", "Manuscript Listing", "Add New Manuscript", and "Update Notification". Below the tabs, there is a search bar with fields for "Search:" and "Date Applied:", and options to "Show:" "Applied", "Approved", "Disapproved", "Closed", or "All". There are also "RESET" and "SEARCH" buttons. The main content area displays a table titled "Displaying APPROVED investigators." The table has columns for "PI", "Investigator", "Email Address", "Institution", "Date Applied", and "Edit". The data is sorted by "PI" and lists 21 rows of investigator information. Each row includes the PI's name, email address, institution, date applied, and an "Edit" link.

PI	Investigator	Email Address	Institution	Date Applied	Edit
Y	Fritz, Jutta, M.D.	JuttaF@med.uni-saarland.de	University of Navarra Clinic	2009-12-01	<a href="#">Edit</a>
Y	Ali, Tipu, M.D.	tipu.ali@pug.csiro.au	Oxford University	2009-12-22	<a href="#">Edit</a>
Y	Barnea, David, Ph.D.	dbarnea@csail.mit.edu	Univ Tennessee	2010-03-02	<a href="#">Edit</a>
Y	bedat, laurent, Ph.D.	Laurent.bedat@inria-rennes.fr	INSA rennes	2009-10-30	<a href="#">Edit</a>
Y	Ben Messoudi, Mohamed, M.D.	M.BenMessoudi@uoguelph.ca	National Eng. School	2009-12-29	<a href="#">Edit</a>
Y	Bhat, SUDRAMANIAM, Ph.D.	sbbhat22@yahoo.com	Canara Engineering College	2010-02-06	<a href="#">Edit</a>
Y	Bhattacharya, Mahua, Ph.D.	MahuaB@hotmail.com	indian institute of information technology and management, gwalior	2009-12-26	<a href="#">Edit</a>
Y	Bruder, Johannes, M.A.	Johannes.Bruder@unilabs.ch	University of Basel	2009-11-30	<a href="#">Edit</a>
Y	Cao, Jia, Ph.D.	jia2497@alumni.princeton.edu	Columbia University	2010-01-20	<a href="#">Edit</a>
N	Catalan, Gisela, Ph.D.	GiselaC@minnmg.umn.edu	Harvard Medical School	2009-12-08	<a href="#">Edit</a>
Y	Chen, Loo, M.D.	LooChen@mednet.ucla.edu	UCLA/WLA VA	2010-01-31	<a href="#">Edit</a>
Y	Chitnis, Komal, M.S.	KomalChitnis@yahoo.com	USC	2010-02-08	<a href="#">Edit</a>
Y	Commissaris, Oliver, Ph.D.	Olivier.Commissaris@inria.fr	INRIA Rennes - Bretagne Atlantique	2010-01-07	<a href="#">Edit</a>
Y	Demirci, Umut, Ph.D.	umut.demirci@deu.edu.tr	Dokuz Eylul University	2009-11-25	<a href="#">Edit</a>
N	Deng, Kai, M.A.	277327884@qq.com	UESTC	2009-12-29	<a href="#">Edit</a>
Y	Diringer, Alex, M.D.	adrimergo@nmr.mgh.harvard.edu	Harvard Medical School	2009-12-08	<a href="#">Edit</a>
Y	Elliis, Rob, Ph.D.	RobJelli@Gmail.com	BIDMC	2009-12-15	<a href="#">Edit</a>
Y	Fang, Junjie, Ph.D.	fangjunjie120@163.com	China Academy of Science	2009-11-18	<a href="#">Edit</a>

# Project Status

- Features
  - Interactive
  - Exportable data



# 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 Healthy 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 the 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 result in 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

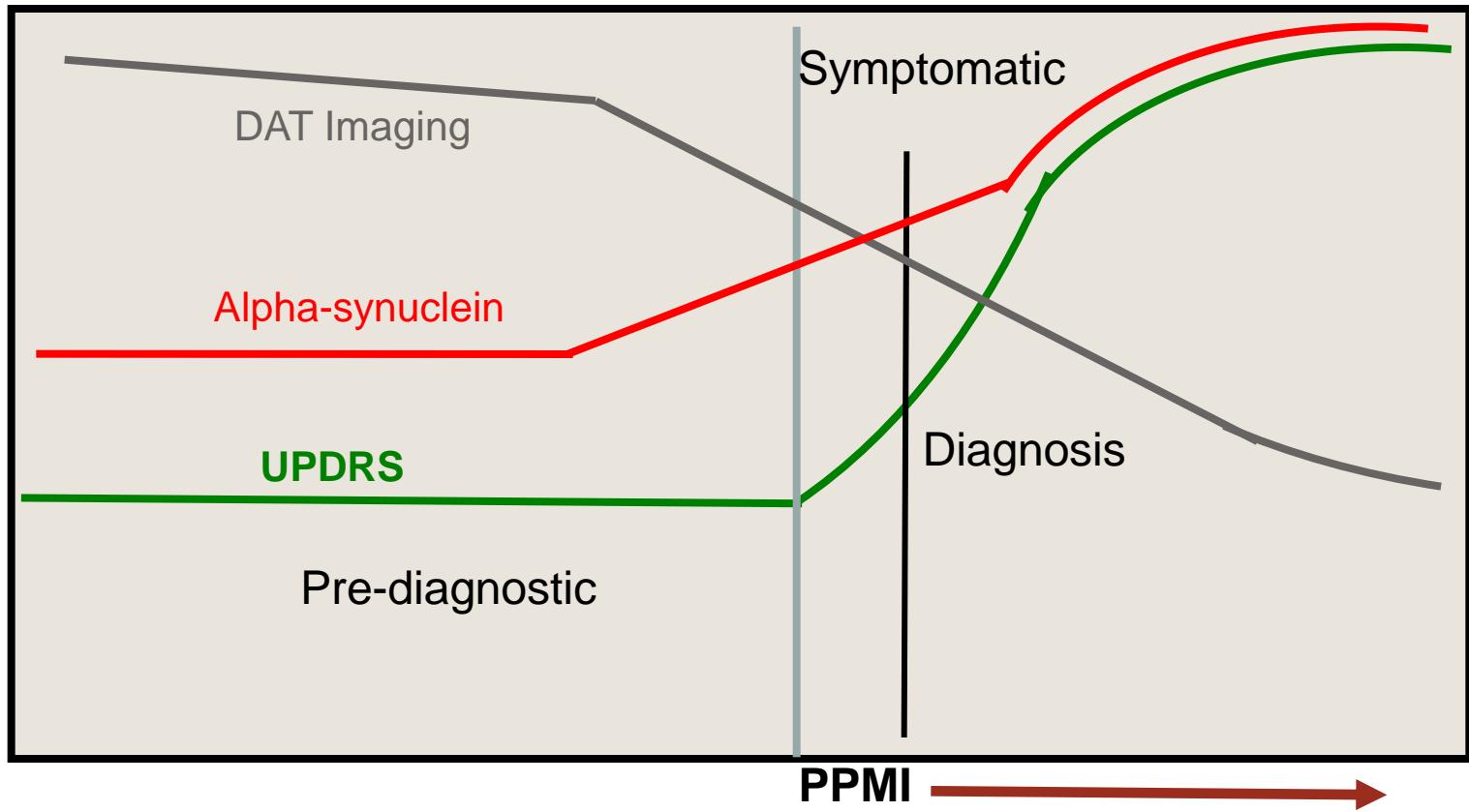
**There are two scenarios for future analyses:**

- 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.**

# PPMI – Imaging Overview

# Natural History of PD

Neuron Function



# Clinical markers

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## Cognition

## Behavioral

Depression  
Apathy  
Anxiety  
ICD

## Autonomic

Constipation  
Bladder  
Sexual  
Cardiac

## Olfaction

## Sleep - RBD

## Skin

## Motor analysis

## Speech

# Biomarkers for PD

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## Imaging –Phenomics

SPECT/PET-Dopamine -  
DAT, F-Dopa, VMAT2

SPECT/PET-non-dopamine

FDG, MIBG, NE, 5HT, Nicotine,  
Ach, PBR, Amyloid,  $\alpha$ -synuclein

**MRI –DTI, volumetrics,**  
**Nigral Ultrasound**

## Biologics – Blood/CSF/Urine

**Alpha-synuclein, DJ1, Urate, Tau,**  
 **$\beta$ -Amyloid**

‘Omics’ –

**RNA profiling**

## Genetics

**Synuclein, LRRK2**  
**Parkin DJ-1, Pink1**

# DAT/F-Dopa imaging

## State and Trait Biomarker for PD

### *Nigral Dopamine loss - Face validity*

Reduction in early PD	50% Put
Reduction Put>Caud	Yes
Reduction asymmetric	Yes
Correlation with severity (UPDRS)	Yes
Reduction in Pre-diagnostic Yes (Hemi-PD)	
Monitor PD progression	Yes

# DAT imaging of PD Progression

- CALM - CIT
- REAL PET-FDopa
- Pelmopet - FDopa
- ELLDOPA - CIT
- Riluzole-FDopa
- GPI 1485 - CIT
- Precept – CIT
- Proud - DaTSCAN

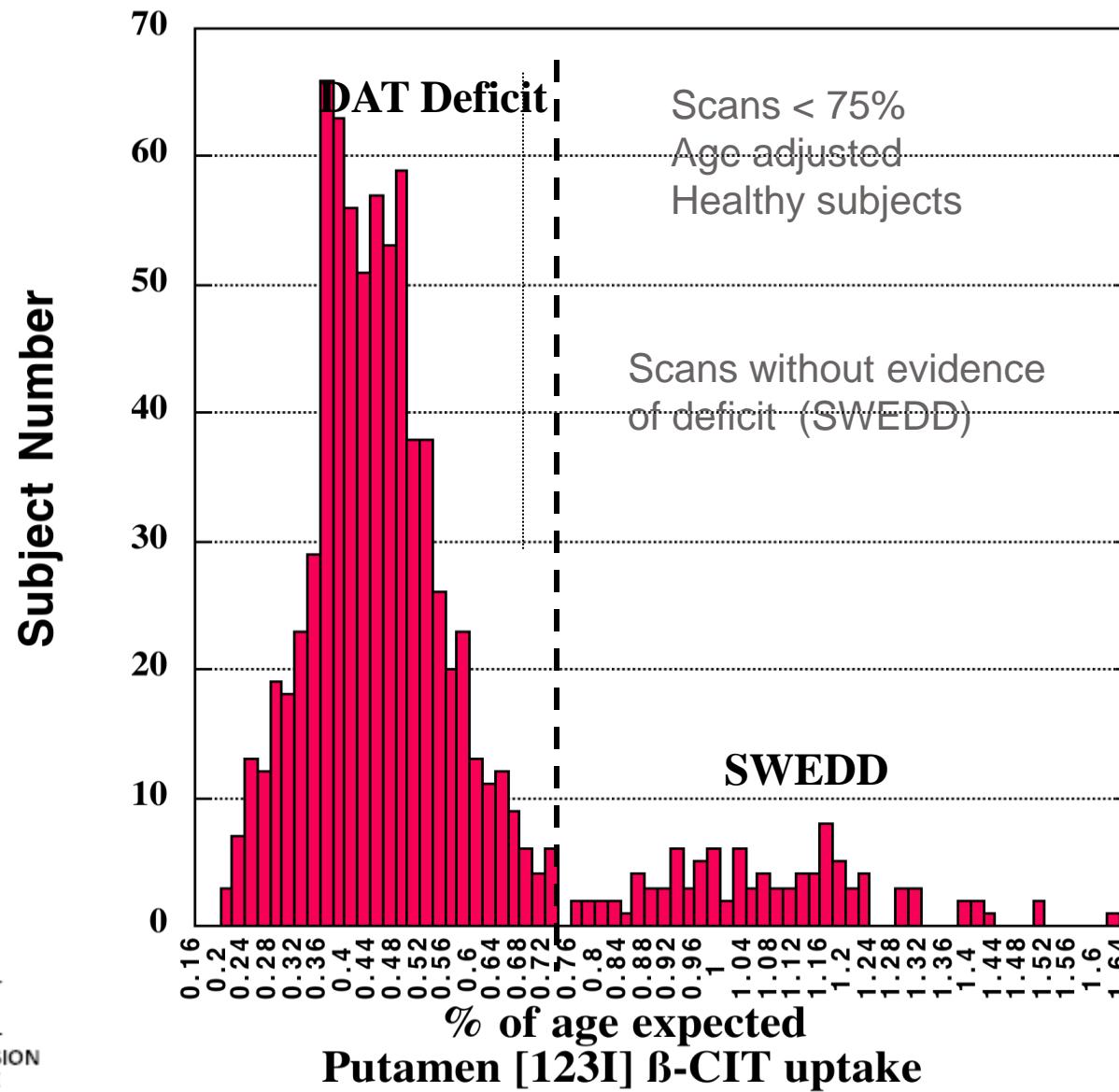
# Percent Striatal Change in CIT uptake - Placebo

Study Baseline	Dur DX	<u>Interval</u>	% change
PRECEPT (n=155)	8 mo	<u>22 mo</u>	-7.2 <u>+11.2</u>
GPI (n=99)	23 mo	<u>24 mo</u>	-7.8 <u>+10.2</u>

# SWEDD (Scans Without Evidence of Dopaminergic Deficit) in PD Trials

Study	Stage –PD	Dur DX at <u>Baseline (mo)</u>	% SWEDD
Elldopa-CIT	Denovo	6	<b>21/142 (14%)</b>
PRECEPT	Denovo	8	<b>91/799 (12%)</b>
REAL-PET	Denovo	9	<b>21/186 (11%)</b>
Calm-CIT	Start of DA Rx	18	<b>3/82 (5%)</b>
GPI1485 Treated		23	<b>3/212 (1.4%)</b>
	<b>Stable responder</b>		

# Baseline PRECEPT - % Age expected Putamen [123I] $\beta$ -CIT uptake



# PRECEPT study - FOLLOWUP IMAGING AND CLINICAL OUTCOMES BY SWEDD STATUS AT BASELINE

	<b>SWEDD &gt;80%</b>	<b>DAT Deficit &lt;=80%</b>	
<b>% Change [<sup>123</sup>I] β-CIT</b>	N = 72	N = 629	
<b>Striatum:</b>	-0.2 (12.2)	-8.5 (11.9)	*
<b>Caudate:</b>	1.0 (13.1)	-6.1 (12.5)	*
<b>Putamen:</b>	-1.9 (12.2)	-13.1 (15.1)	*
<b>CLINICAL</b>	N = 91	N = 708	
<b>Change in Total UPDRS</b>	0.5 (6.9)	10.5 (8.9)	*
<b>Change in Motor UPDRS</b>	-0.4 (5.0)	7.0 (6.9)	*
<b>Need for DA treatment at 12 mo</b>	16.7% (CI 10.2, 26.6)	50.9% (CI 47.2, 54.8)	*

Mean (SD) for Change in [<sup>123</sup>I] β-CIT and UPDRS,  
 Percent (CI) for need for DA treatment. \* indicates p < 0.01

# PreCEPT DAT imaging as Predictor of PostCEPT Endpoints

	Abnor mal MMS E	Abnor mal MoCA	Demen tia/ MCI	Hallucin ation	ICD	Fallin g	Postur al Instabi lity	QOL Decli ne	S/E ADL Decli ne	Low S/E ADL
Outco me Definit ion	MMS E <24	MoCA <26	CBQ1 or 1.1 =1	UPDRS 2≥2	CBQ1 2(1-5) or 13=yes	UPD RS 13 ≥1	UPDR S 30 ≥ 2	PDQ 39 in highe st quart ile	Decli ne ≥15	S/E ADL <80
# Subjec ts, N	489	489	437	491	437	475	487	489	490	487
Outco me Freque ncy	19 (3.9%)	137 (28.0 %)	61 (14.0 %)	34 (6.9%)	37 (8.5%)	60 (12.6 %)	37 (7.6%)	128 (26.2 %)	67 (13.7 %)	43 (8.8%)
BL Mean Striatu m	0.5* (0.2, 1.0)	0.5* (0.4, 0.7)	0.4* (0.2, 0.6)	0.3* (0.2, 0.5)	1.1 (0.6, 1.8)	0.6* (0.4,0 .9)	0.4* (0.2, 0.7)	0.8 (0.6, 1.1)	0.6* (0.4,0 .9)	0.5* (0.3, 0.8)
Chang e: Mean Striatu m	0.9* (0.8, 1.0)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	0.9* (0.8, 0.9)	1.0 (0.9, 1.0)	0.9* (0.9,1 .0)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	0.9* (0.9,1 .0)	0.9* (0.9, 1.0)
Striatu m Decline >4.5	1.7* (0.6, 4.5)	1.5 (1.0, 2.4)	1.5 (0.8, 2.8)	2.7* (1.2, 5.9)	0.7 (0.4, 1.5)	2.0* (1.1,3 .5)	1.2 (0.6, 2.5)	1.2 (0.8,1 .9)	3.6* (1.9,6 .6)	2.2* (1.1, 4.4)

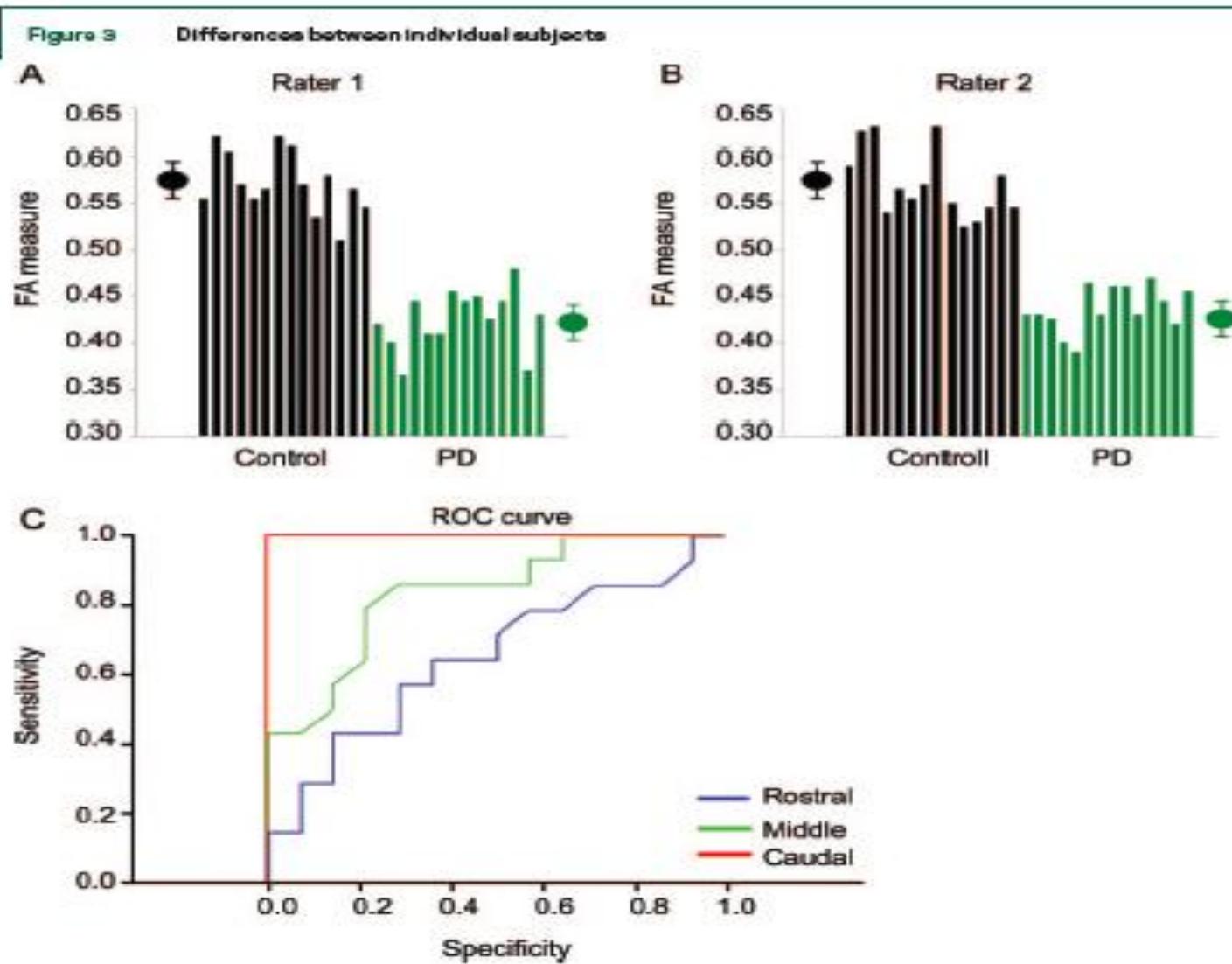
## Odds Ratios, PRECEPT Imaging Predictors of POSTCEPT Outcomes

Odds Ratios (95% confidence intervals) associated with a unit change in each predictor were calculated from separate logistic regressions adjusted for baseline age, gender, duration of disease, and PreCEPT treatment. Asterisks indicate those that were significant at p<0.05. Significance levels for dichotomized striatum decline are those from the continuous model.

# DAT Imaging in PPMI

- DaTSCAN – 123 FP-CIT
- >180,000 doses in EU
- Recent use in PROUD study in 20 EU sites
- Use of DaTSCAN in the US – investigational drug
- Challenges of Multi-site imaging

# DTI – Diagnostic tool for PD



# Imaging Biomarkers

## Modality      Ligand      Target      PPMI Plans

SPECT	DATSCAN	Dopamine Transporter	Use at all sites – eligibility criteria and progression marker
MRI	DTI	Fractional anisotropy (FA)	Sub-study defined by camera – exploratory data for disease progression
<b>DATA IN PD, POSSIBLE VALUE IN PPMI</b>			
PET	DTZB, AV133	VMAT2	Monoamine marker -not available for multi-site
PET	FDG	Glucose Metabolism	Possible progressive changes in cognitive and motor patterns
Ultrasound	Substantia Nigra		Likely not progression marker
PET	AV45, BAY94, PIB	Amyloid	Possible progressive changes in cognitive
SPECT	MIBG	Cardiac sympathetic function	Likely not sensitive progression marker
Pilot data/Limited data in PD			
PET/SPECT	PBR06, PBR111, PK11195	PBR	Inflammatory changes
PET/SPECT	FPEB, MK9640, FCPyPB	MGLuR5, CB1, A2a, GlyT1	Striatal function
PET/SPECT	DASB, MZIENT, INER, MPPF	SERT, NET, 5HT1a, 5HT2a	Monoamine function
Optical coherence tomography (OCT)	Retinal morphology		Limited data for PD, none of progression
Early development			
PET/SPECT		alpha-synuclein	Early development
PET/SPECT		Tau	Early development

# Rationale for Selecting PD Biomarkers

Mark Frasier, PhD

The Michael J. Fox Foundation

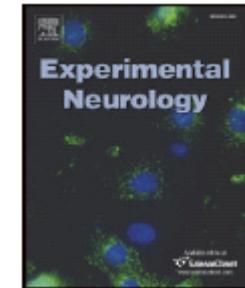


THE MICHAEL J. FOX FOUNDATION FOR  
PARKINSON'S RESEARCH

# Preliminary discoveries of promising PD biomarkers

Direct quantification of CSF  $\alpha$ -synuclein by ELISA and first cross-sectional study in patients with neurodegeneration

Brit Mollenhauer <sup>a,1</sup>, Valerie Cullen <sup>a,1</sup>, Ilana Kahn <sup>a</sup>, Bryan Krastins <sup>b</sup>, Tiago F. Outeiro <sup>c</sup>, Imelda Pepivani <sup>a</sup>, Juliana Ng <sup>d</sup>, Walter Schulz-Schaeffer <sup>e</sup>, Hans A. Kretzschmar <sup>f</sup>, Pamela J. McLean <sup>c</sup>, Claudia Trenkwalder <sup>g</sup>, David A. Sarracino <sup>b</sup>, Jean-Paul VonSattel <sup>h</sup>, Joseph J. Locascio <sup>c</sup>, Omar M.A. El-Agnaf <sup>i</sup>, Michael G. Schlossmacher <sup>a,d,\*</sup>



2008

## Plasma levels of DJ-1 as a possible marker for progression of sporadic Parkinson's disease

Masaaki Waragai <sup>a,b,\*</sup>, Masaaki Nakai <sup>a</sup>, Jianshe Wei <sup>a</sup>, Masayo Fujita <sup>a</sup>, Hideya Mizuno <sup>c</sup>, Gilbert Ho <sup>c</sup>, Eliezer Masliah <sup>c</sup>, Hiroyasu Akatsu <sup>d</sup>, Fusako Yokochi <sup>e</sup>, Makoto Hashimoto <sup>a,\*</sup>

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Neuroscience  
Letters    2007

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## Increased level of DJ-1 in the cerebrospinal fluids of sporadic Parkinson's disease

Masaaki Waragai <sup>a,b,\*</sup>, Jianshe Wei <sup>a</sup>, Masayo Fujita <sup>a</sup>, Masaaki Nakai <sup>a</sup>, Gilbert J. Ho <sup>c</sup>, Eliezer Masliah <sup>c</sup>, Hiroyasu Akatsu <sup>d</sup>, Tatsuo Yamada <sup>e</sup>, Makoto Hashimoto <sup>a,\*</sup>

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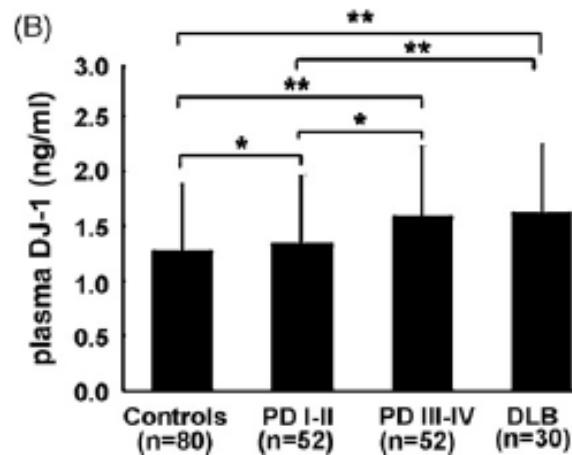
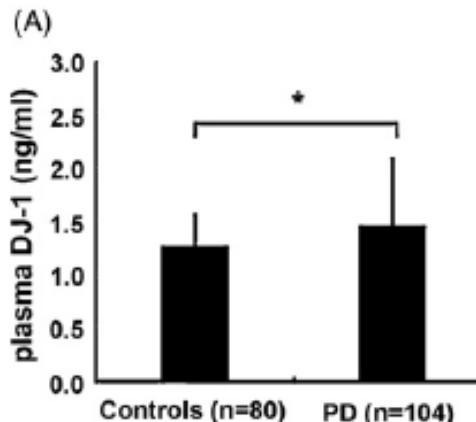
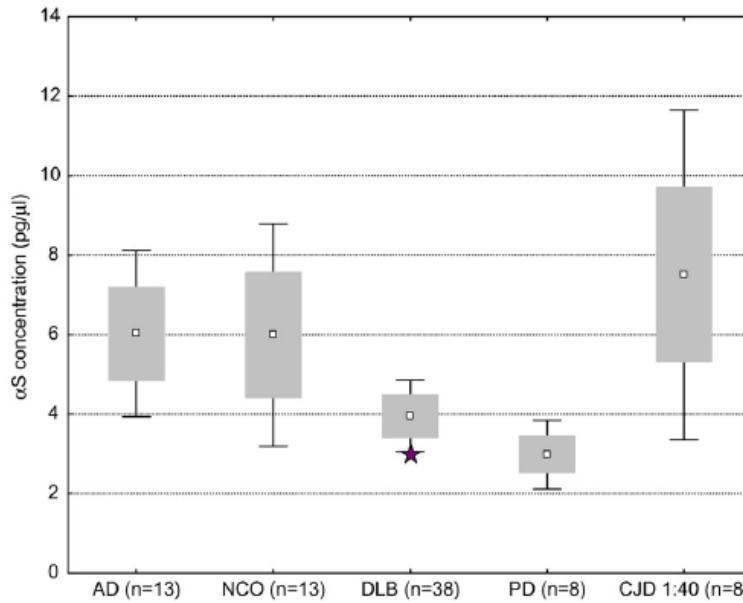
**BBRC**  
2006

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# Preliminary Discoveries of Promising PD Biomarkers

**CSF Alpha-synuclein is reduced in PD subjects**

(Mollenhauer et. al, 2008)



**Plasma DJ-1 is elevated in PD subjects and increases with the progression**

(Waragai et. al, 2007)

# Identification of biomarker candidates for inclusion is critical to PPMI

*The Biomarkers Taskforce identifies/prepares promising candidates for verification*

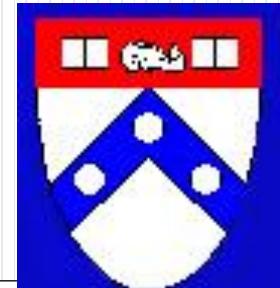
	Tier 1	Tier 2	Tier 3
<b>Criteria</b>	<ul style="list-style-type: none"><li>• Markers for which there is some evidence for a disease association</li><li>• Preliminary data around the detection of the marker in a biochemical assay exist</li></ul>	<ul style="list-style-type: none"><li>• Putative markers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

# **PPMI And The Importance Of Biomarkers For Parkinson's Disease: Lessons From ADNI**

**(ADNI Biomarker Core Co-Leaders are J.Q. Trojanowski and L.M. Shaw)**

**John Q. Trojanowski, M.D., Ph.D.**

PENN Udall Center of Excellence For Parkinson's Disease Research,  
Institute on Aging, Alzheimer's Disease Center,  
Center for Neurodegenerative Disease Research,  
Department of Pathology and Laboratory Medicine,  
University of Pennsylvania  
Philadelphia, PA



Since there is significant variation in CSF biomarker levels between studies, there is an urgent need to standardize and validate AD biomarkers

Study design:

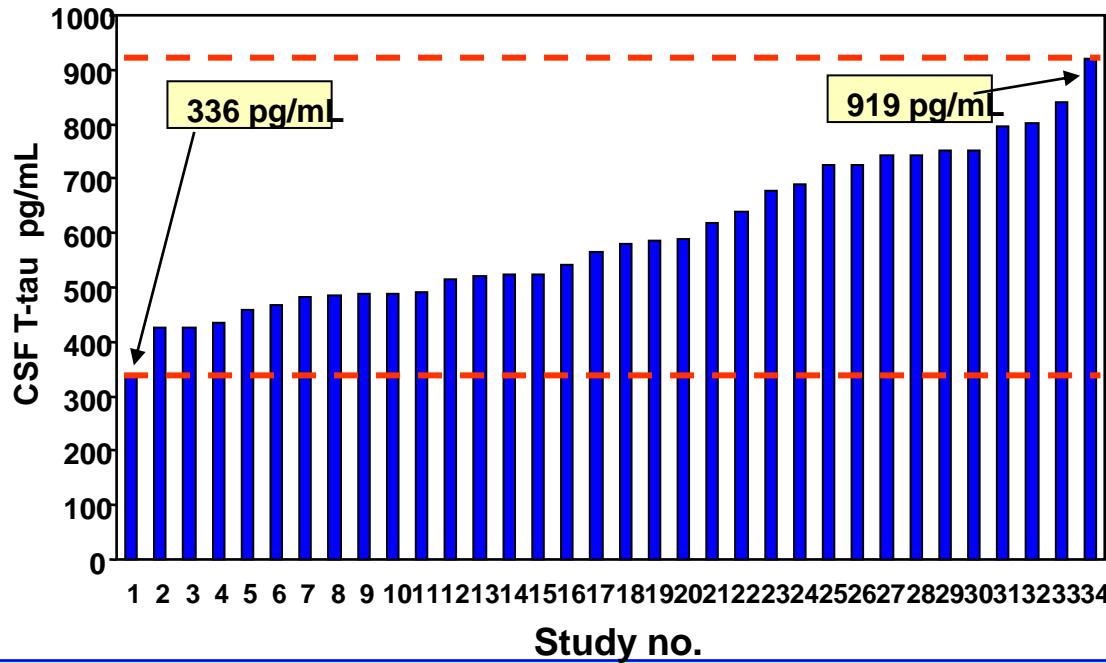
All studies on CSF T-tau with >25 AD cases

Innogenetics T-tau ELISA

→ 34 studies, 2600 AD cases

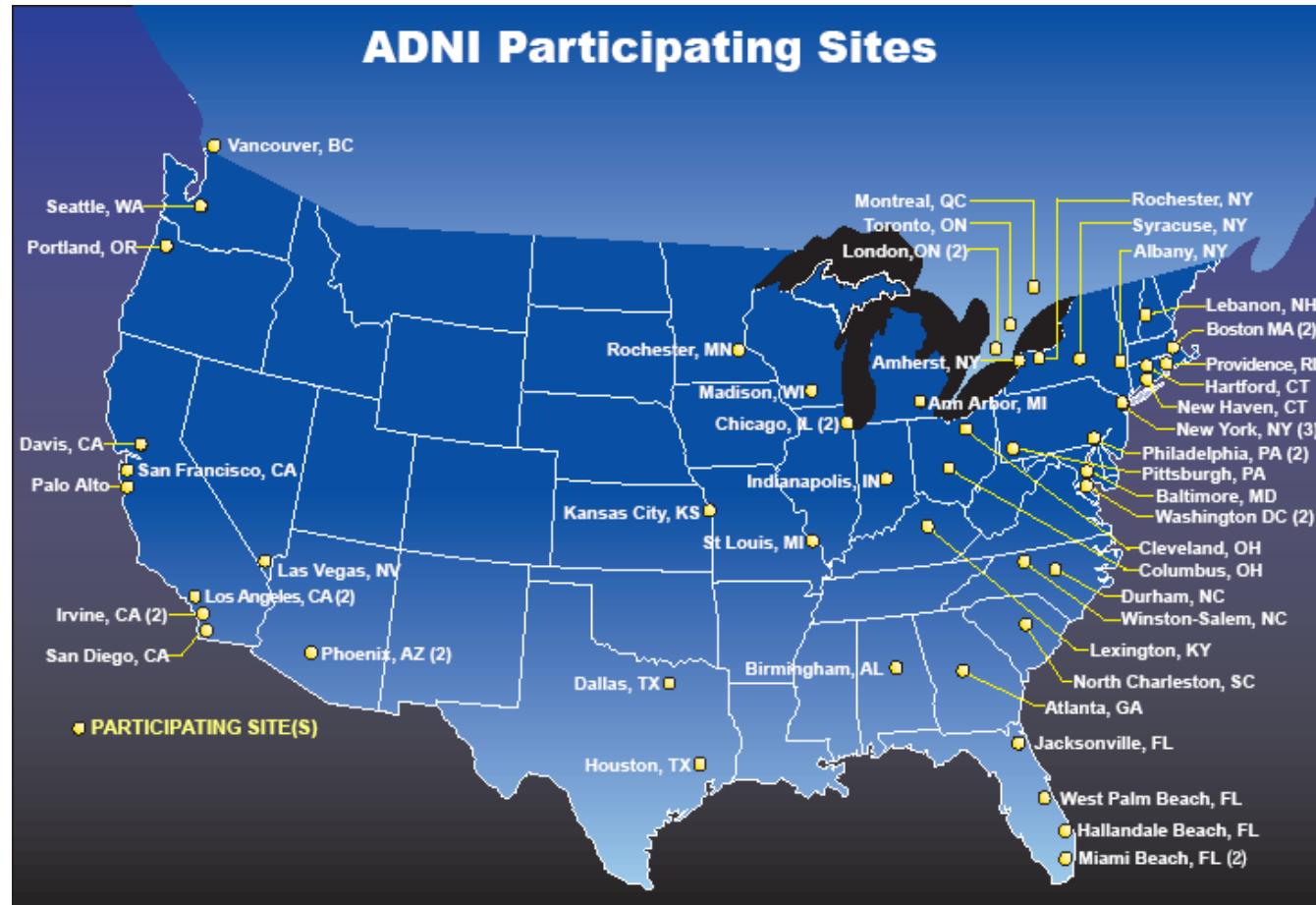
Comparison of:

mean level of CSF T-tau

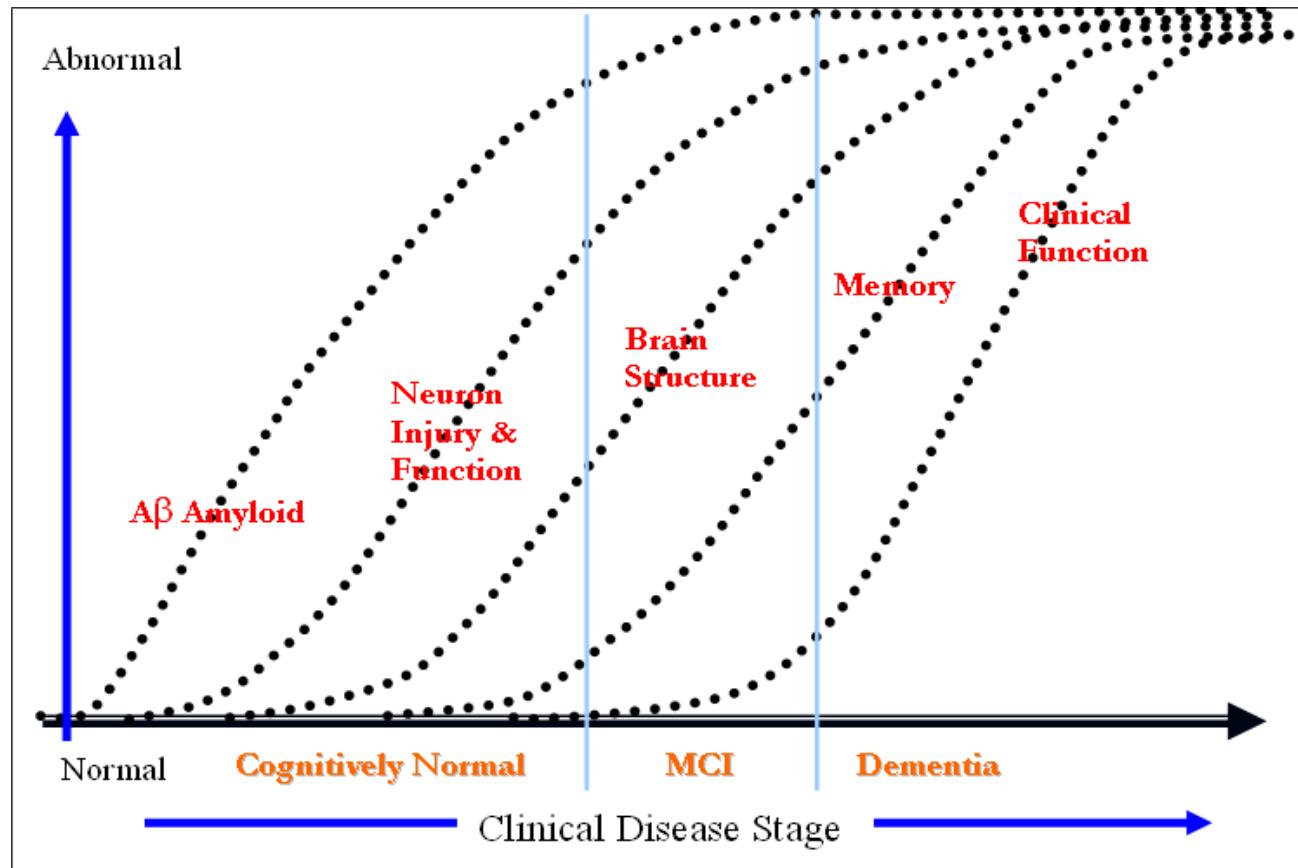


→ Need for standardization: CSF sampling / handling procedures  
Laboratory procedures  
External control program

**Biofluids - They can be boxed and sent safely and reliably from near and far - Les and I have been there and done that thousands of times with 58 sites in North America in ADNI.**



# Hypothetical Temporal Ordering Of AD Biomarkers – An ADNI Breakthrough



**Proposed model illustrating the ordering of biomarkers of AD pathology relative to stages in the clinical onset and progression of AD.** Clinical disease, on the horizontal axis, is divided into three stages; cognitively normal, MCI (including eMCI), and dementia. The vertical axis indicates the range from normal to abnormal for each of the biomarkers as well as memory and functional impairments. Amyloid imaging and CSF A $\beta$  are biomarkers of brain A $\beta$  amyloidosis. CSF tau and FDG PET are biomarkers of neuron injury and degeneration while structural MRI is a biomarker of abnormal brain morphology. Jack et al Lancet Neurol 2010; 9: 119-28

# Genetics in PPMI

Andrew Singleton, PhD  
Laboratory of Neurogenetics

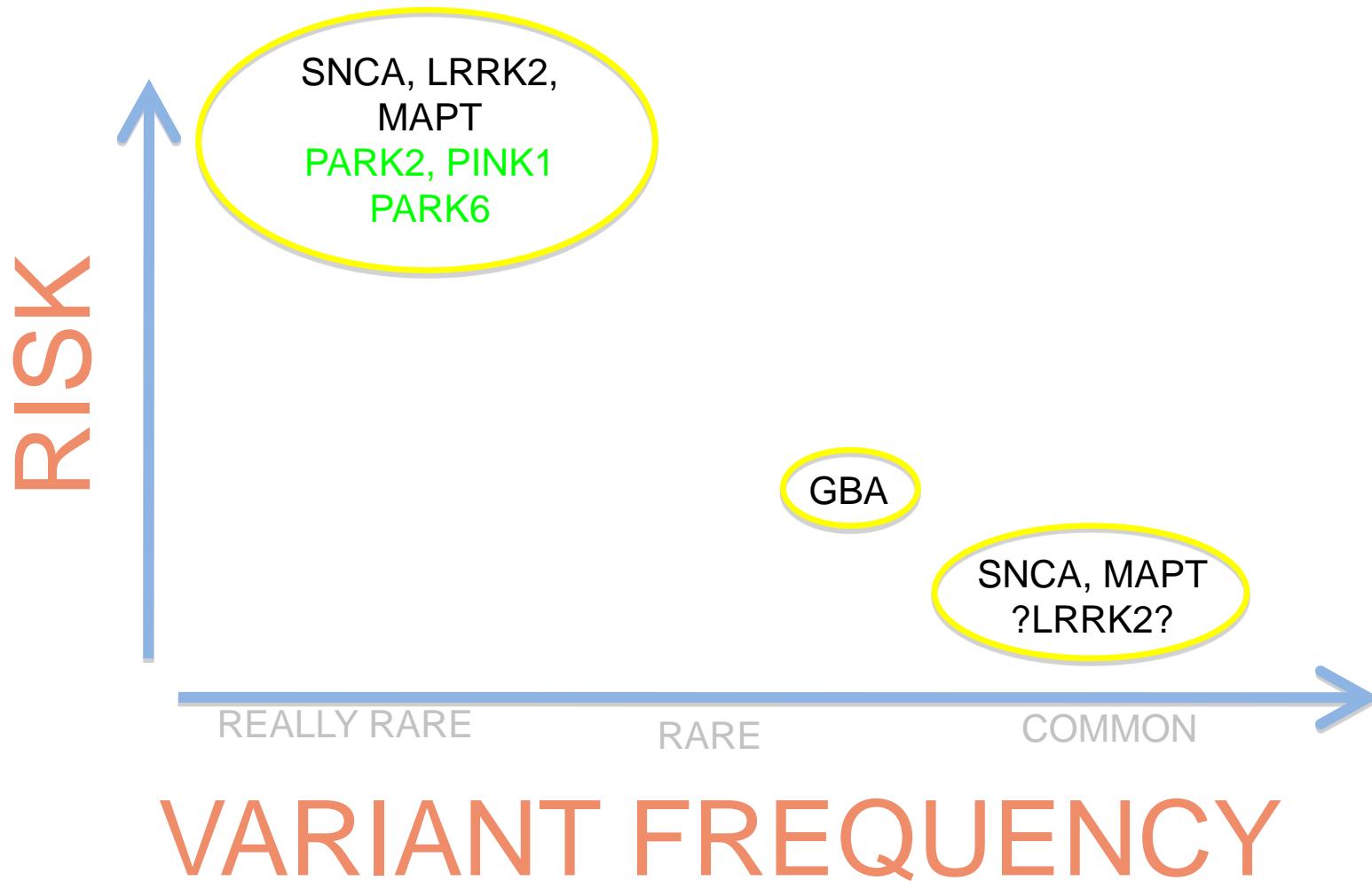
# Why Genetics?

- To provide a view into the initiation of a disease process – and to help us guess the route the process takes
- To allow modeling of disease
- To facilitate early detection
  - Presymptomatic genetic diagnosis
  - Finding pre-clinical measures

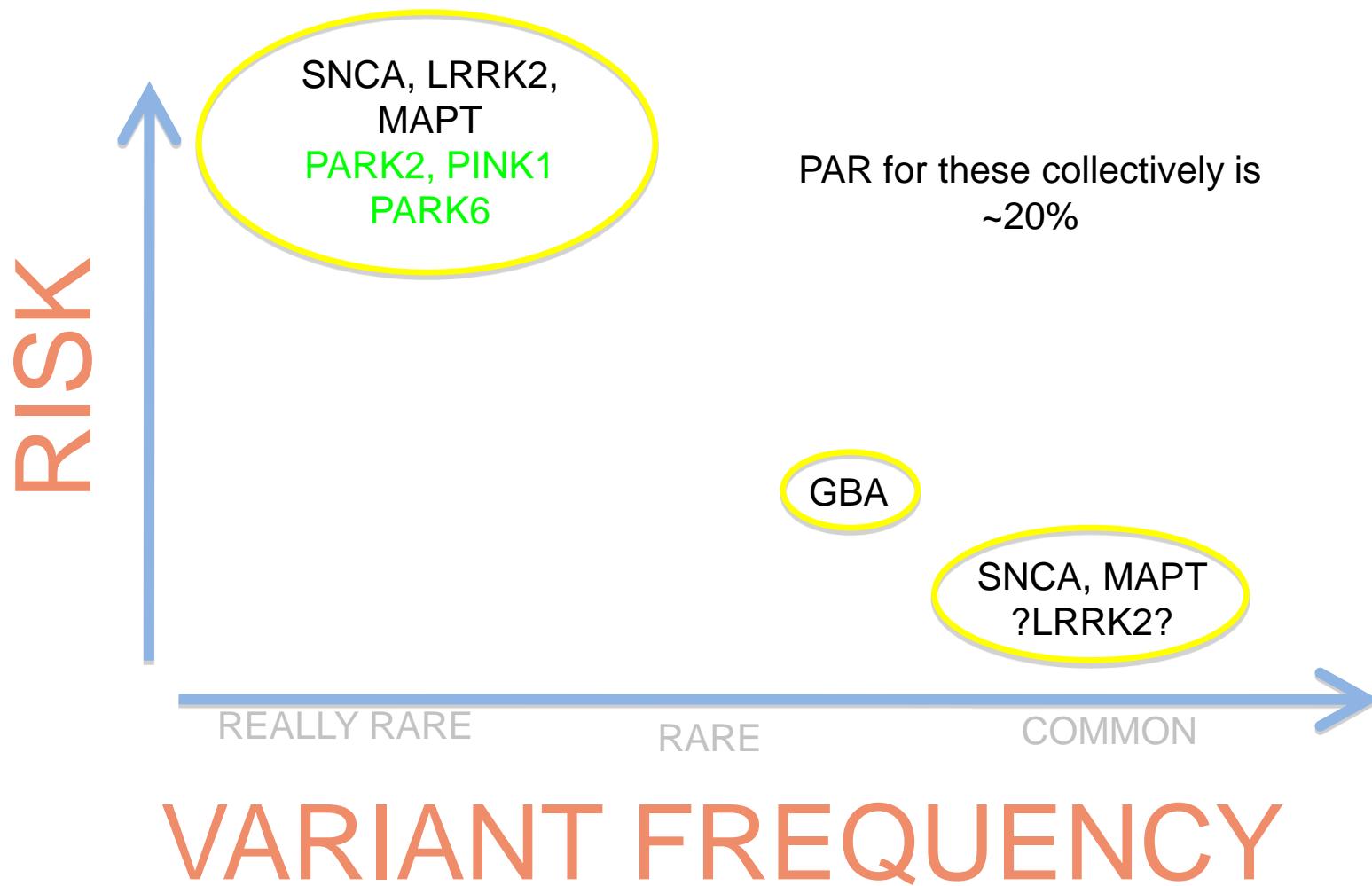
# Why Genetics in PPMI?

- Primary:
  - Are genetic forms the same disease
  - Can genetic risk profiling help diagnosis and prognosis
- Secondary:
  - Gene discovery, adding and refining loci

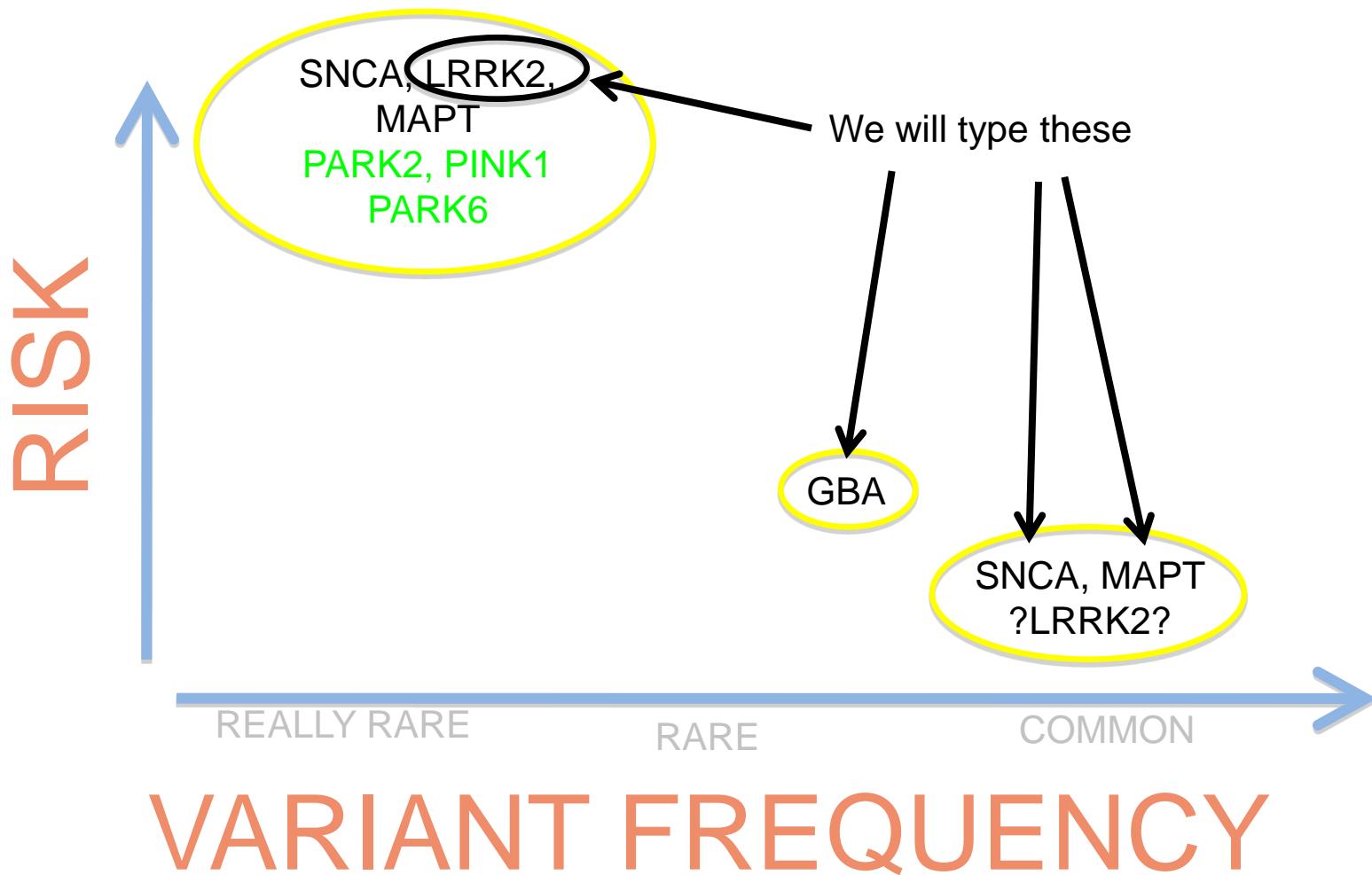
# Landscape of Genetics in PD



# Landscape of Genetics in PD



# Landscape of Genetics in PD



# What will we initially find

- About 3-10 LRRK2 mutation positive cases
- About 16 GBA mutation positive cases (and about 4 controls)
- Low risk variants in ~15% of the cases and ~10% of the controls

# Can ask several research questions

- Is the disease process qualitatively different in mutation positive cases?
- Can low risk variants be combined with any other measure to more accurately predict progression?
- Are genetic risk factors more prevalent in any sub-type of disease?

# Secondarily

- This will be an extremely well phenotyped cohort that will be a powerful addition to gene discovery efforts
- Particularly important as (if) we begin to subtype disease

# Summary

- We will type common high risk and low risk variants
- Will capture the majority of known genetic risk for PD
- Affords the opportunity to look at genetics and progression
- Cohort will be invaluable for future gene identification efforts

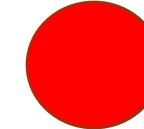
# **BREAK**

**Presentations will resume  
at 11:15 am**

# BREAKOUT SESSIONS

- **Breakout Session #1**

- Imaging Overview
  - DAT Scan Imaging
  - MRI



- **Breakout Session #2**

- Biologics Overview
  - Kits and Supplies
  - Specimen collection, processing, storage, and shipment



- **Breakout Session #3**

- Lumbar Puncture
  - Purpose of LP
  - Process and Procedures
  - Helpful Hints



# LUNCH

**Break-out sessions will  
resume at 1:05 pm**

# *PPMI Recruitment and Retention*

*Engaging the PD community*



# Robust recruitment and retention strategies are critical to PPMI success

- Challenges in subject recruitment persist across most disease indications ... PD is no exception!
  - 30% of all trials fail to enroll a single subject
  - 85% of all trials finish late because of enrollment troubles
  - Less than 1% of PD patients are participating in a clinical trials
- Demand for *de novo* patients for interventional trials and significant numbers of controls may present additional hurdles
- MJFF sponsorship role provides unique opportunity for publicity and outreach
  - PPMI publicity will be nested within broader MJFF-driven community call-to-action
  - Activation of MJFF networks and Michael J. Fox will elevate visibility of PPMI and other trials
- Recent site assessments have informed our PPMI communications plan
  - “Core” materials are in development and will be available to sites this spring
  - Additional “Plus” strategies are under consideration—your feedback will help prioritize selection

# MJFF gained valuable insights from coordinators at each site

- Sites have a wealth of experience recruiting *de novo* patients
- A subset of sites have actively recruited controls and successfully enrolled subjects in trials that require LP procedures
- Some effective recruitment strategies to be shared within the network include:
  - The Parkinson's Institute, Carlie Tanner, MD, PhD -- *Recruiting Healthy Controls for Clinical Trials*
  - OHSU, Penelope Hogarth, MD -- *Opportunities to Engage De Novo Subjects*
  - University of Washington, James Leverenz, MD -- *Leveraging an Alternative Medicine Physician Network for Observational Trials and Addressing the LP with Patients Considering Enrolling in a Study*
  - University of South Florida, Robert Hauser, MD -- *Developing a Physician Referral Network*
  - Baylor College of Medicine, Christine Hunter, RN -- *Using Current and Previous Trial Subjects as Recruiters for New Trials*

# The PPMI communications plan pairs core pieces with key pluses

- Core materials include:
  - Subject marketing materials:
    - Study folder with one-page inserts that include descriptions of study details
    - Study Video that features LP procedure
    - Postcards and posters for office display and leave-behinds
    - Translations to German, Spanish and other requested languages is anticipated
  - Physician/coordinator outreach tools:
    - Letter from PI to referring network
    - Slides introducing PPMI (for patient and physician audiences)
    - Physician pocket card
- Local community efforts to boost awareness
  - MJFF sponsored PD community events in your area
  - GYMR assisted local media placements
- National messaging to reinforce engagement, volunteerism, and partnership
  - MJFF outreach / tools ... PPMI plus broader call-to-action for clinical trial participation
  - Michael J. Fox featured in print ads, PSA's and select media

# **RECRUITING HEALTHY CONTROLS & RETENTION**

**Caroline M Tanner MD, PhD  
Parkinson's Institute  
Sunnyvale, CA**

# RECRUITING HEALTHY CONTROLS - CONSIDERATIONS

- **Big commitment:**
  - Time away from work, other activities
  - Personal discomfort
- **PPMI – Specific Considerations:**
  - Long term commitment
  - Invasive procedures

# RECRUITING HEALTHY CONTROLS

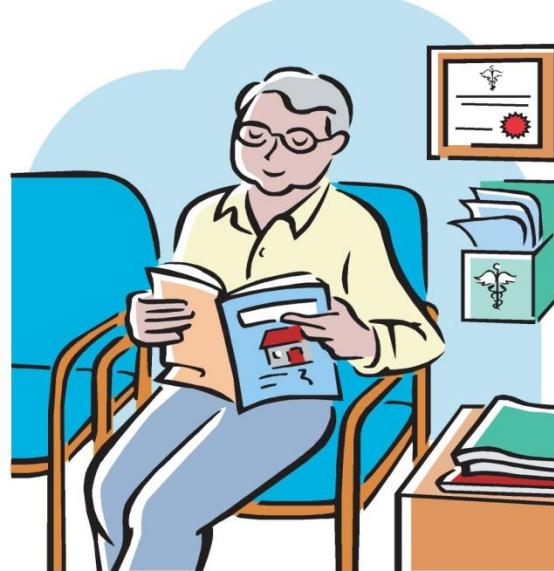
- **Where to focus efforts?**
- Most volunteers have a motivation:
  - Friend, family member with PD
  - Concerned about own health
  - Source of income
  - Pure altruism
- **Target high yield groups**

# RECRUITING HEALTHY CONTROLS – FINDING VOLUNTEERS

**Examples of strategies for recruiting controls:**

- **Persons identified through a PD patient:**
  - Relatives of PD cases (must meet inclusion criteria)
  - Friends of PD cases: Give a brief talk, answer questions
    - Clubs, teams, other groups
    - Professional colleagues
  - Friends/relatives of other clinic patients
- **ASK PPMI PARTICIPANTS FOR IDEAS & ASSISTANCE**
- **Persons identified through PD support groups:**
  - PPMI team gives talk, attends meetings with brochures
  - PPMI participant recruits
  - Articles/ads in newsletters, websites
- **Be Creative! Many strategies needed**

# I Don't Have Parkinson's, But How Can I Help?



## Volunteers Needed for Research Studies

Must be

\*Spouse of a PD Patient,

OR

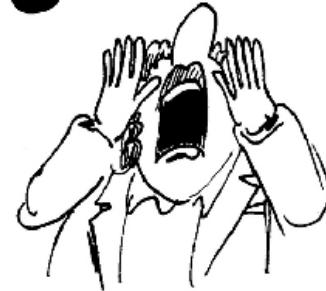
\*In-law of a PD Patient,

OR

\*Step- or Adopted Family Member of a PD Patient

Details are available at the Research Study Information Desk

# **Volunteers!**



**The Parkinson's Institute  
is currently recruiting**

## **Family & Friends**

**not diagnosed with Parkinson's Disease  
nor other neurological conditions  
for Clinical Trials**

**For More Information:**

**Liza or Kathie  
408-734-2800  
[trials@thepi.org](mailto:trials@thepi.org)**

**PPMI**

PARKINSON'S PROGRESSION  
MARKERS INITIATIVE

# RECRUITING HEALTHY CONTROLS – FINDING VOLUNTEERS

Examples of successful strategies for recruiting controls:

- **Members of Service or Religious Groups:** Give a brief talk, answer questions
  - Church/synagogue, etc
  - Community-service clubs (e.g., Lions)
- **Participants in volunteer rosters?**
- **Respondants to ads, media campaigns?**

*Be Creative! Share Ideas! Each site  
different! Many strategies needed!*

# **RETENTION – How to Keep Research Volunteers Involved Over Years**

- **Each study participant is precious**
- **Our goal is to keep each person involved throughout the length of the study**

# RETENTION – How to Keep Research Volunteers Involved Over Years

- **Gratitude:**
  - An attitude toward participants
  - Remember to say “Thank you” : in person, thank you notes, in public (anonymously)
- **Shared mission / teamwork:** “We are working together to solve PD” ; Share information about study progress at visits, by newsletter, on website
- **Individual recognition:** “Your contribution is critical”
- **Build relationships:** Continuity of staff members, introduce new staff, keep in touch, remember personal information, preferences

# RETENTION – How to Keep Research Volunteers Involved Over Years

- **Make it easy:** Facilitate participation – schedules, special requests
- **Make it fun:**
  - Personal touches – make notes, share info w/in team
    - Birthdays, holidays
    - Small niceties at study visits: favorite beverage, music, movie
  - Special things
    - Get togethers for study volunteers – informal groups, lunch, etc. , research update
    - Small gifts with study logo// Team Fox logo
    - Feature volunteers in newsletter, waiting room, website, etc., if they are willing – personal profile, what motivates them , etc.
    - “Treats” at study visits: car service, special meal, hotel stay (if affordable!!)
    - Online community//study blog?
  - **Ask for Suggestions**

# Time to Brainstorm!

## What Works at Your Site?

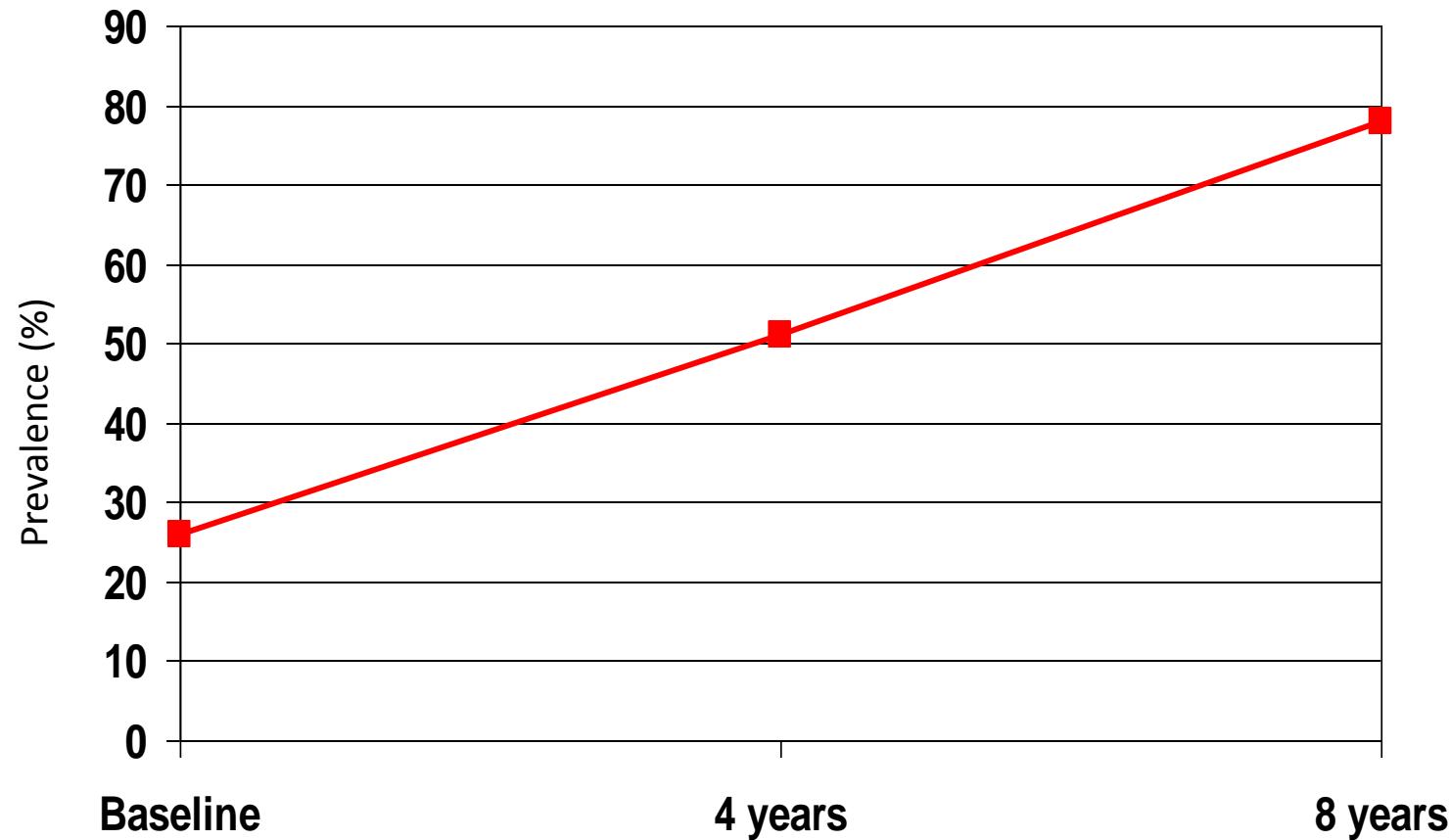
# **BREAK**

**Presentations will resume  
at 4:15 pm**

# **Review of Behavioral Assessments**

**Andrew Siderowf, MD**  
**University of Pennsylvania**

# Prevalence of dementia over 8 years



From Aarsland et al., Archives of Neurology, Volume 60(3), March 2003, p 387–392

# Consequences of cognitive impairment

- Disability
- Institutionalization
- Caregiver burden
- Increased costs
- Death

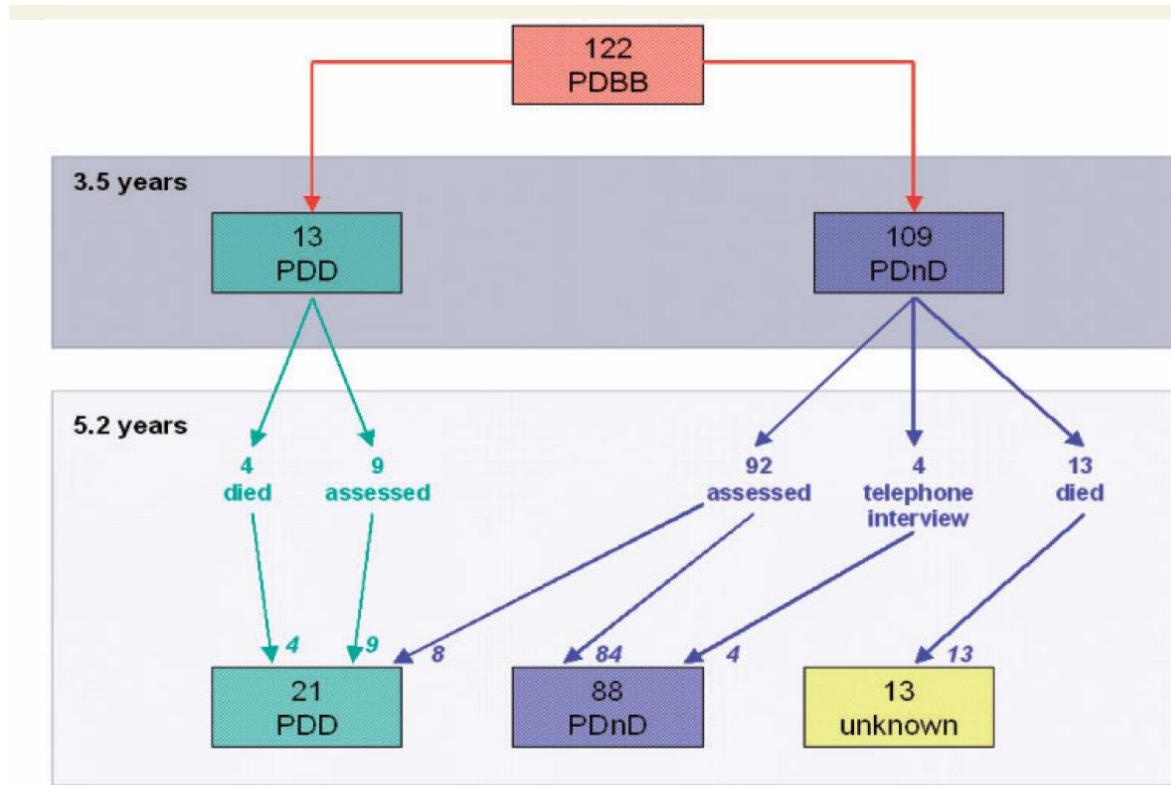
# Cognitive profile in early PD

	MMSE<25	Pattern recognition task (<16)	Tower of London (<8)	Normal on all
Normal	146 (92%)	115 (82%)	104 (76%)	92 (66%)
Impaired	13	35	33	50

From Foltynie et al, Brain, 2004

# Risk factors and frequency of cognitive decline in PD

- Age
- PIGD sub-type
- Greater cognitive impairment
- MAPT H1/H1 genotype

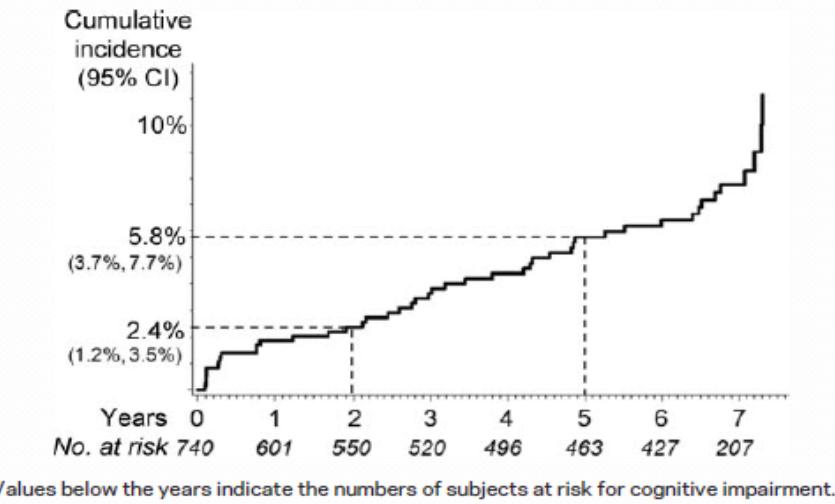


13/122 at 3.5 yrs; 21/109 at 5.2 years

# Cognitive decline in early PD: Frequency and risk factors

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

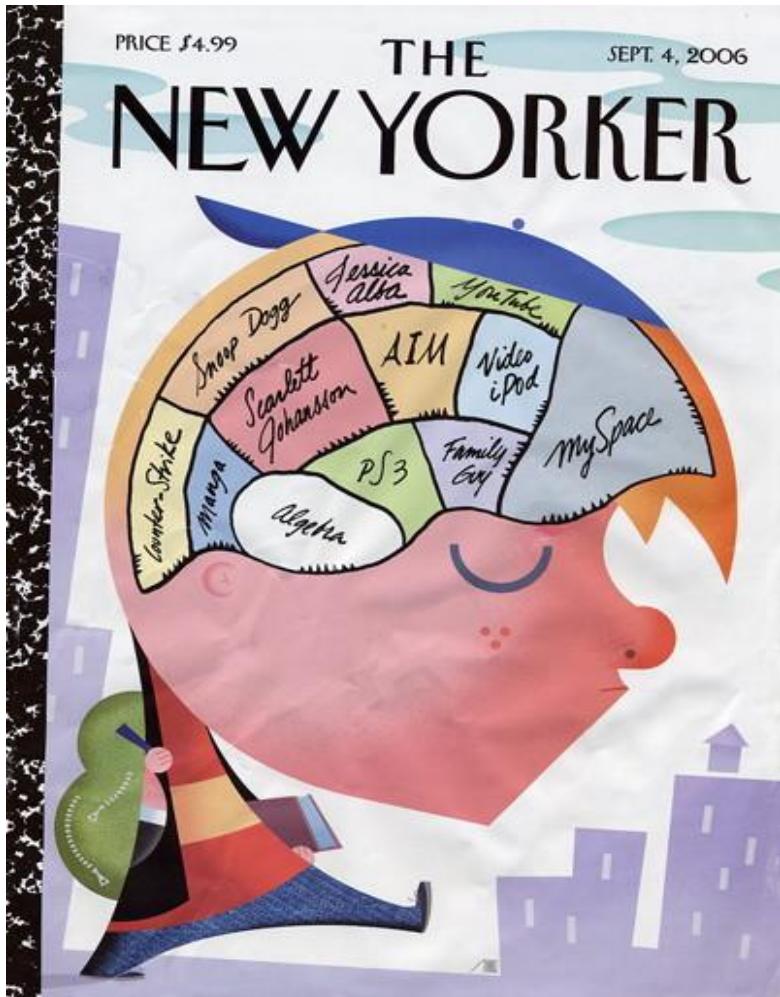
Figure 1 Kaplan-Meier curve showing the cumulative incidence of cognitive impairment in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism cohort



# History of cognitive behavioral battery

- Expert committee formed by steering committee (Burn, Emre, Weintraub)
- Steering committee review and modification
- Operationalization and refinement

# Background and rationale for the PPMI Cognitive/Behavioral Assessment



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

**PPMI is a biomarker study!!**

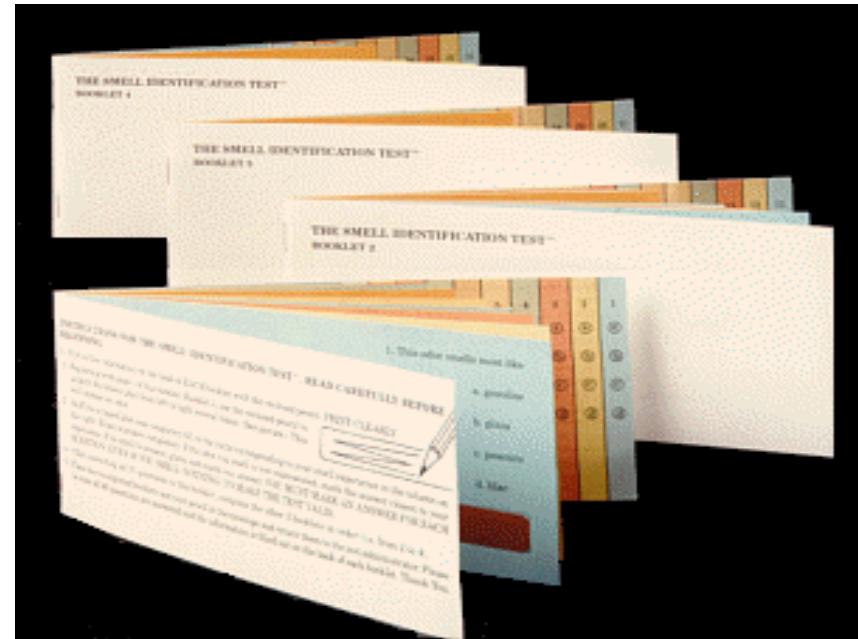
# Review of behavioral and psychophysical tests

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



# University of Pennsylvania Smell Identification Test (UPSIT)

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



# Sleep Scales

- Sleep disturbances are common in PD
  - Insomnia
  - Daytime drowsiness
  - Restless leg syndrome
- Only REM sleep behavior disorder (RBD) occurs prior to the onset of motor symptoms of PD



# Epworth Sleepiness Scale

- **8 items, very brief**
- **Score of 8-10 indicate significant daytime drowsiness**
- **Up to 25% of PD patients have daytime drowsiness**
- **Greater motor and cognitive severity and medications are risk factors**

## Epworth Sleepiness Scale

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

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

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

# REM Sleep Disorder Questionnaire

- 10 items, 5 minutes
- Self-report questionnaire
- Validated in RBD patients vs controls
- Maximum score is 13
- RBD patient score =9, control score= 4

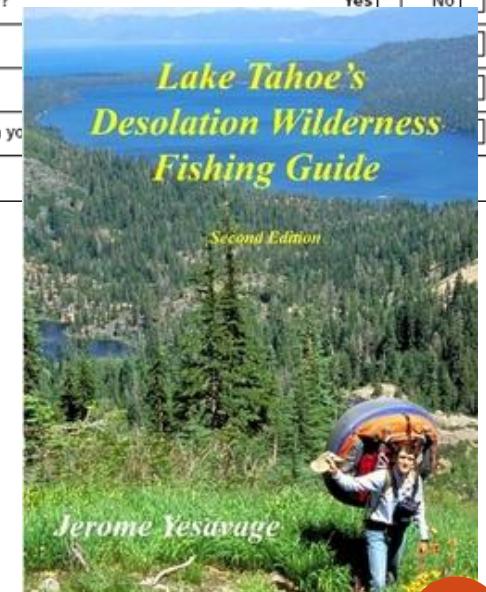
I sometimes have vivid dreams

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

# Geriatric Depression Scale (GDS-15)

- 15 items, 5-10 minutes
- Self-administered
- Developed for geriatrics, but works well for PD
- Score of 5 or higher indicates depression (Weintraub)
- Free (optional donation) and widely translated
- [www.stanford.edu/~esavage/GDS.html](http://www.stanford.edu/~esavage/GDS.html)

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



# State-Trait Anxiety

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



Charles D. Spielberger, Ph.D

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

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

# Impulse Control Disorders

- 8 item QUIP screening questionnaire (2 questions each for eating, buying, sex and gambling)
- 5 minutes to complete
- Score of 1 or higher on any item indicates presence of an ICD



# SCOPA-AUT

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

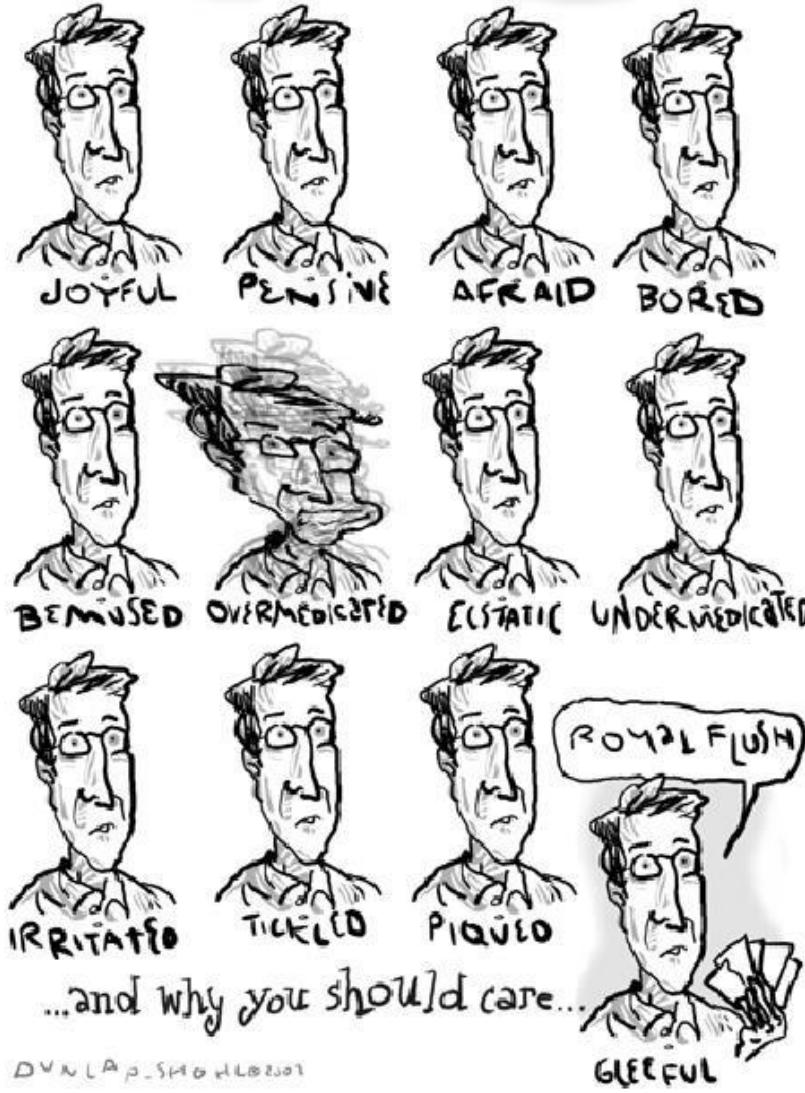


## SCOPA-AUT

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

1. In the past month have you had difficulty swallowing or have you choked?  
 never       sometimes       regularly       often
2. In the past month, has saliva dribbled out of your mouth?  
 never       sometimes       regularly       often
3. In the past month, has food ever become stuck in your throat?  
 never       sometimes       regularly       often
4. In the past month, did you ever have the feeling during a meal that you were full very quickly?  
 never       sometimes       regularly       often

## POCKET GUIDE to DECODING THE PARKINSONIAN FACE...



DAN LIPSHIZON

# Neuropsychological Battery & Cognitive Data Validity

Keith Hawkins, PhD

Yale University

# Cognitive Battery Purpose

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

# Neuropsychological Test Selection Rationale

Attempt to balance competing criteria:

- **Sensitivity to PD relevant cognitive domains**
- **Provide some data in a common/known metric**
  - i. e. a clinically interpretable global score
- **Brevity**
- **Relatively easy to administer & score**
  - Maximize reliability across examiners, sites, & time.
  - Minimize examiner judgment. (WAIS-III Block D. runs 18 pages).
- **Test selection by Expert Committee**
  - Guided by the recommendations of the Movement Disorders Task Force:  
Dubois, B.; Burn, D. et al. (2007) Movement Disorders, 22 pp. 2314-2324

# Neuropsychological Battery

**MoCA - at screening (use as baseline), year 3.**

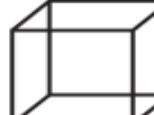
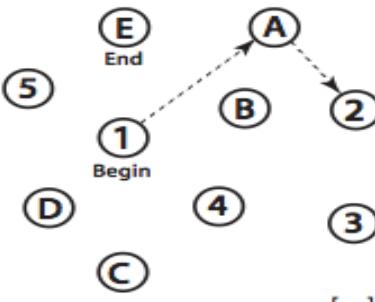
**Baseline and annual re-assessments:**

- **Dementia Rating Scale-2**
- **Symbol-Digit**
- **Hopkins Verbal Learning Test**
- **Semantic Fluency**
- **Benton Line Orientation**
- **WAIS-III Letter-Number working memory test**

**MONTREAL COGNITIVE ASSESSMENT (MOCA)**

 NAME :  
 Education :  
 Sex :

 Date of birth :  
 DATE :

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

# Dementia Rating Scale-2

- Provides a global score
  - Ranks subjects on impairment
  - A commonly understood metric
- Provides subscale data for separate domains
  - Attention
  - Initiation/Perseveration
  - Construction
  - Conceptualization
  - Memory

# Symbol Digit Modalities Test

- Assesses information processing speed
- Rapid (trial is 90 seconds)
- Easily administered and scored
  - no (or minimal) variance across examiners
    - WAIS examiner interference a problem
- Well established, long track history

# Hopkins Verbal Learning Test - Revised

- 12 word list
- 3 learning trials
- delayed recall trial
- recognition trial
- Increasingly used in multi-site, longitudinal trials (MATRICS)
- Examiner challenge: subject abdication

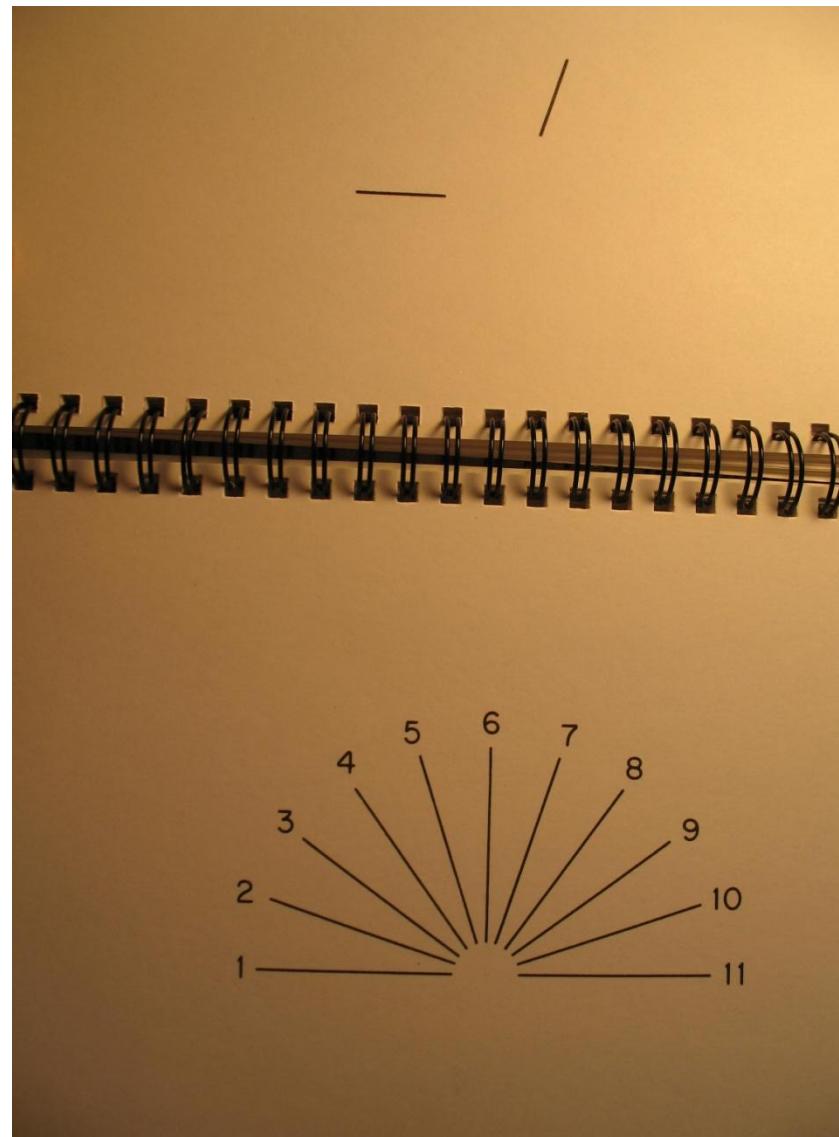
# Semantic Fluency

- Animals
- Vegetables
- Consistency with ADNI directions & scoring
  - In turn based on CERAD

# WAIS-III Letter Number Sequencing

- Examiner reads mixed numbers & letters:
  - f 8 a 4
  - Subject recites in numerical & alphabetical order:
  - 4 8 a f
- Task increases in difficulty (like digit span)
- Challenge is helping older subjects understand task requirements (what they need to do)
  - Distinction between:  
teaching the subject what the test requires them to do,  
versus  
• helping them do better on the test

# Benton Line Orientation



# Maximizing Data Validity

- **Minimizing Error Variance:**
  - **Setting risk factors for error variance**
  - **Testing materials risk factors**
  - **Examiner risk factors**
  - **Subject risk factors**

# Error Risk Factors: Setting

- **Noisy testing settings**
- **Pulling tests together case by case**
  - **organized materials and dedicated space are best**
- **Interruptions during testing**

# Error Risk Factors: Tests

- Tests that are difficult to administer & score
  - the more judgment involved, the lower the reliability
- Incomplete test administration instructions
- Incomplete scoring instructions
- Need to strike a balance between:
  - Adequate instruction detail
  - Too much detail:
    - Unnecessarily complicated, cluttered, or contradictory administration & scoring instructions

# Error Risk Factors: Tests

- **Ineffective or incomplete training of examiners**
- **Insufficient monitoring of examiners**
  - monitor for examiner drift
    - It is important that examiners know they will be monitored
- **Failure to follow data checking procedures:**
  - double scoring, arithmetic checking
  - double data entry

# Positive Examiner Attributes

- **Understands the rationale for the testing**
- **Accepts the rationale, and is fully committed to gathering valid data**
  - not going through the motions
- **Understands the intent behind specific tests**
  - facilitates sound decision making in the face of subject variability, unexpected events

# Positive Examiner Attributes

- Able to establish good rapport
  - Can walk the line between putting subjects at ease, and
  - Maintaining a business-like demeanor
    - Respect for the subject, & respect for the process
    - Maintain the professional expectation that subjects will do their best.
    - Keeps things moving along and the subject focused on the testing

# Examiner Error Risk Factors

- Use of different examiners for the same subject over time
- Frequent examiner turn-over
- Use of examiners who test infrequently
- Having new examiners certified by departing examiners (rather than via a core process)
  - charge of the light brigade.....

# Examiner Error Risk Factors ...

- Examiners who don't communicate about novel situations or scoring dilemmas.
  - Each such circumstance allows for refinement of the rules and improves standardization.
- Examiners who know better than the manual.
- Examiners who think an administration or scoring rule is unfair.
  - bend the rules ("I know she can do this")
  - lean on the side of lenient scoring in misplaced kindness

# Subject risk factors (for error variance)

- Flip-side of examiner risk factors.
- Failure to put forth good effort.

Mitigate by:

- Help them understand of the purpose of the testing.
- Help them understand the costs of invalid data:
  - cozy little chats
  - redux: rapport/professional attitude balancing act
- Examiners should record any concerns at time of testing

# Preparations for PPMI Study

- Forms, administration & scoring manual in preparation
- Regional “hands on” workshop for examiners
- Annual brief quiz on administration, scoring
- Sample protocols & audio tapes for scoring trials
- Reliability checks:
  - Site audio taping of HVLT memory and fluency tests?
    - Facilitates scoring
    - Periodic central reliability review

# **END OF DAY ONE**

**Reception and Dinner begin at 6:30 pm**

# *Parkinson's Progression Markers Initiative*

**PPMI**

PARKINSON'S PROGRESSION  
MARKERS INITIATIVE

*Investigator's Meeting  
March 18-19, 2010*

*New York City*

*DAY TWO*

# **MDS-UPDRS**

**Movement Disorder Society Unified  
Parkinson's Disease Rating Scale**

**Christopher G. Goetz, MD**

Rush University Medical Center  
Chicago, IL USA

# Introduction

- 1987: Original development of UPDRS
- 1998: Most widely used scale
- 2001: MDS Task Force on Rating Scales
- 2003: Published UPDRS critique
- 2004: Initiation of MDS-UPDRS revision

# Conclusions of UPDRS critique

## Strengths

- Single scale for research and practice
- Generally comprehensive for motor issues
- Good clinimetric standards: Parts II and III

## Weaknesses

- Ambiguities in instructions
- Poor inter-rater reliability on some items
- Not all aspects (non-motor) covered

# **Recommendation:**

## ***“Develop a new UPDRS”***

- **Retain basic 4-part structure**
- **Retain 0-4 ratings**
- **Resolve ambiguities**
- **Provide detailed instructions**
- **Expand non-motor section**
- **Provide Appendix for other scales focusing on non-motor in detail**
- **Attend to mild disease where change anticipated**
- **Define clinically pertinent groups of patients (slight, mild, moderate and severe)**

# Steering Committee: Identified

- **Chairperson:** CG Goetz
- **Part I:** W Poewe
- **Part II:** MB Stern
- **Part III:** S Fahn
- **Part IV:** P Martinez-Martin
- **Appendix** C Sampaio
- **Scale development:** GT Stebbins
- **Statistical issues:** B Tilley

# Membership:

- **Part I:** A Schrag, B Dubois
- **Part II:** P LeWitt, AE Lang
- **Part III:** J Jankovic, CW Olanow
- **Part IV:** O Rascol, A Lees,  
B van Hilten
- **Appendix:** J Kulisevsky, R Dodel
- **Scale development:** D Nuyenhuis, R Holloway
- **Statistical issues:** J Teresi, S Leurgans

# **Major Changes - 1**

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

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

**13 items: Interview (6) Questionnaire (7)**

**II: Motor Experiences of Daily Living**

**13 items all patient questionnaire**

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

**IV: Motor Complications**

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

# Major Changes - 2

- Detailed instructions
- All scores are anchored to clinical statement:
  - 0 = normal
  - 1 = slight-present but without functional consequence
  - 2 = mild-present with modest functional consequence
  - 3 = moderate-present and affecting several aspects of function
  - 4 = severe-present and prevent the activity or function
- More emphasis on early/mild disease: slight vs mild
- Direct involvement of patient in Questionnaire (Part I and Part II)
- Official Appendix

# MDS-UPDRS

## I. NON-MOTOR ASPECTS OF EXPERIENCES OF DAILY LIVING (nM-EDL)

### INTERVIEW

1. COGNITIVE IMPAIRMENT
2. HALLUCINATIONS
3. DEPRESSED MOOD  
ABNORMAL  
SENSATIONS
4. ANXIOUS MOOD
5. APATHY
6. DOPAMINE  
DYSREGULATION

### QUESTIONNAIRES

1. SLEEP
2. STAYING AWAKE
3. PAIN AND  
SENSORY
4. URINARY FUNCTION
5. CONSTIPATION
6. LIGHTHEADEDNESS  
ON STANDING
7. FATIGUE

# MDS UPDRS

## II. MOTOR ASPECTS OF EXPERIENCES OF DAILY LIVING (M-EDL)

- 1. Speech
- 2. Handling saliva
- 3. Swallowing & chewing
- 4. Feeding
- 5. Dressing
- 6. Hygiene
- 7. Handwriting
- 8. Other fine motor tasks
- 9. Tremor impact on activities
- 10. Turning in bed and adjusting bed clothes
- 11. Getting in and out of bed, car, or deep chair
- 12. Balance and walking
- 13. Gait Freezing

# MDS UPDRS

## III. MOTOR EXAMINATION:

- 1. Speech
- 2. Facial Expression
- 3. Rigidity
- 4. Finger Tapping
- 5. Hand Movements
- 6. Pronation-supination
- 7. Toe Tapping
- 8. Leg Agility
- 9. Arising from chair
- 10. Gait
- 11. Freezing of Gait
- 12. Postural Stability
- 13. Posture
- 14. Body Bradykinesia
- 15. Postural Tremor of Hands
- 16. Kinetic Tremor of Hands
- 17. Rest Tremor Amplitude
- 18. Rest Tremor Consistency

# MDS UPDRS

## IV. MOTOR COMPLICATIONS:

### A . DYSKINESIAS [exclusive of OFF-state dystonia]

1. Time spent with dyskinesias
2. Functional impact of dyskinesias
3. Painful off-state dystonia

### B . MOTOR FLUCTUATIONS

3. Time spent in the off state
4. Functional impact of fluctuations
5. Complexity of motor fluctuations

# Appendix: Recommended and Suggested Scales

- For each item in Part I and II, available scales reviewed
- Review integrated with MDS Task Force on PD Rating Scales
- Scales to examine symptoms in greater depth rated
- Recommended: Used in PD, clinimetric data established and published by multiple groups

# Time Required: 40 minutes

- Original UPDRS → 40 minutes

## New UPDRS

- Parts Ia → 10 minutes to conduct
- Parts Ib, II → To be self administered  
10 minutes to review
- Parts III, IV → 20 minutes

# Testing Timeline

**2008: Demonstrated concurrent validity with UPDRS**

**2008: Conducted Factor Analysis of MDS-UPDRS**

**2008: Established guidelines for numeric relationship to UPDRS**

**2009: Teaching tape and certificate program**

**2010: Demonstrate ability to detect change**

**2010: Establish score ranges that fit clinically pertinent categories**

**2010-2012: Official non-English translations**

# On-going Translations

- Spanish
- Italian
- Estonian
- Korean
- Japanese
- French
- German
- Interest stated: Danish, Chinese, Russian, Hungarian

# Disclosure

**This project was supported by unrestricted grants to the Movement Disorder Society by:**

- Boehringer-Ingelheim USA,
- GlaxoSmithKline,
- Pfizer, Inc.

**Other sponsors are welcome in this ongoing program**

# Certificate Exercise

# Instructions for Certificate Program

- Put your name and email address at top clearly written (typed for future submissions)
- Only use full numbers (no 0.5, 1.5, etc)
- Every item must be rated
- Add the numbers for each patient up at the bottom and enter Total Score

# Certificate Process

- Certificate acquisition occurs when all total scores fall into the range established by the expert panel.
- This exercise does not judge your ability to rate patients as good or bad.
- The aim is to have everyone rate similarly in this.
- For this reason, it is essential that each rater rate the cases INDEPENDENTLY

# **BREAK**

**Presentations will resume at  
10:45 am**

# Safety Reporting and Monitoring

Presented by:

Emily Flagg

Project Manager - CTCC

# Overview

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Incidents
- Notifications
- Clinical Study Oversight Committee (CSOC)

# Adverse Events

- An AE is any untoward medical occurrence in a subject enrolled in a study after informed consent has been obtained
- Will be captured once a DAT scan or lumbar puncture is completed through the time of the 7 day follow up phone call

# Adverse Events

- Examples of AEs include:
  - Any reaction from injection of imaging tracer or lumbar puncture (e.g., pain, headache, dizziness)
  - Injury or accident during 7-day reporting period following DAT scan or LP
  - Development of intercurrent illness during 7- day reporting period following DAT scan or LP

# Adverse Events

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

# Recording Adverse Events

- All AEs captured on the Adverse Event Log data form
- Data form includes:
  - Description of AE
  - Severity
  - Relationship to the study
  - Seriousness (AE vs. SAE)

# AE Severity

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

# AE Relationship to Study

- As determined by the Investigator
- Indicating whether there is a reasonable possibility of a relationship between the AE and a study procedure or the DaTSCAN™
  - Possible
  - Probable
  - Definite
  - Unlikely
- No reasonable possibility of such a relationship
  - Unrelated

## ADVERSE EVENT LOG

1 3 2

5 8

SUBJECT ID

--	--	--	--

INITIALS

--	--	--

SITE NO

--	--	--

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

AE # (e.g., 1, 2, etc.)	Adverse Event (Record diagnosis if known)	START DATE (MM/DD/YYYY)	STOP DATE (MM/DD/YYYY)	Severity	SAE	Relationship to Study	Complete when resolved or at Final Visit		If unresolved, is follow-up required? 0 = No 1 = Yes
							Primary Outcome	AE Status at Final Visit	

--	--	--

--	--	--

--	--	--

INVESTIGATOR'S SIGNATURE

DATE

STAFF CODE

# AE Follow Up

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

# Serious Adverse Events

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

# Reporting Serious Adverse Events

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

# Clinical Study Oversight Committee

- **Assess safety by review of:**
  - AEs and SAEs
  - Premature Withdrawals
  - Protocol Violations
- **Meet about twice a year**
- **Prepare written reports to Steering Committee of recommendations for the study**

# Questions?



# Good Clinical Practices and Study Monitoring

Emily Flagg, Project Manager - CTCC

# Definitions

- **Good Clinical Practices (GCP)**
  - Standards for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and the rights, integrity, and confidentiality of trial subjects are protected
- **Compliance (in clinical trials):**
  - Adherence to all the trial-related requirements, GCP requirements, and the applicable regulatory requirements

# GCP: Shared Responsibility

- The PPMI study will adhere to ICH and FDA regulations
- Investigator Responsibilities
  - International Conference on Harmonization (ICH) Guidelines (E6 – Good Clinical Practice)
  - 21CFR312 Subpart D

# Importance of Compliance

- Protection of human subjects
- Legal and ethical requirements
- Protect the integrity of the trial outcome
- Avoid any compromise of professional integrity

# Formula for Compliance Success

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

# How to Handle Non-Compliance

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

# Investigator Qualifications & Agreements

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the study
- Be thoroughly familiar with the appropriate use of the (investigational) product (DaTSCAN™) as described in the protocol and current IB
- Be aware of and comply with GCP/ICH and other applicable regulatory requirements
- Permit monitoring
- Maintain a list of qualified persons to whom significant trial-related duties are delegated

# Investigator Responsibilities

- **Maintain adequate records of receipt and use of the DaTSCAN™**
- **Prepare and maintain adequate and accurate source information**
- **Complete all required reports**
- **Oversee the conduct of the study at your site**

# Informed Consent is not a form... it's a process

- An exchange of essential information about the research study
- Allows the participant to ask questions & have them answered
- Is evidenced by the signing of the informed consent document and giving a copy to the subject
- Is documented in source documents
- Continues at each interaction and by providing the participant new information as applicable

# Study Monitoring

# Monitoring Overview

- Clinical Study Oversight Committee (CSOC)
- Steering Committee (SC)
- Site Monitoring Team

# Site Monitoring

- Monitors will conduct an on-site monitoring visit after first 2 subjects are enrolled.
- Subsequent visits will be annually.
- Monitoring responsibilities for the study include:
  - reviewing regulatory documentation filed at site,
  - ensuring protocol compliance on site,
  - comparing source-documents to entries in the eDE system
  - reviewing records for receipt and use of DaTSCAN™

# Coordination of Visits/Contacts

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

# Monitoring Expectations

- At each Periodic Monitoring Visit, the monitor will:
  - Review screening/enrollment procedures
  - Review Informed Consents
  - Complete source document verification
  - Review Regulatory Binder documentation, including study-related training records for staff involved
  - Review accountability and management of the DaTSCAN™

# Questions?

# Sample Access



Alison Ansbach, MS  
Senior Project Manager

# What happens to samples once they arrive at Coriell?



# Samples arrive at Coriell and are logged in by a Project Manager



- Each sample is assigned a unique Coriell ID
- Computerized barcode labels are applied to each tube and the submission form

# Samples are delivered to labs for processing & QC



- Yellow top tubes → DNA extraction
- PAXgene tubes → RNA extraction
- Plasma, serum, CSF & Urine → sub aliquots & storage
- Appropriate QC is performed for each type of sample

# Sample distribution

- Sample inventory is tracked in Queue
- Inventory information is reported to LONI
- Sample requests will be made through LONI
- Samples are distributed to researchers based on criteria set by the PPMI steering committee



# Coriell Contact Info:

Alison Ansbach

Senior Project Manager

(856) 757-9756

[aansbach@coriell.org](mailto:aansbach@coriell.org)

[www.coriell.org](http://www.coriell.org)

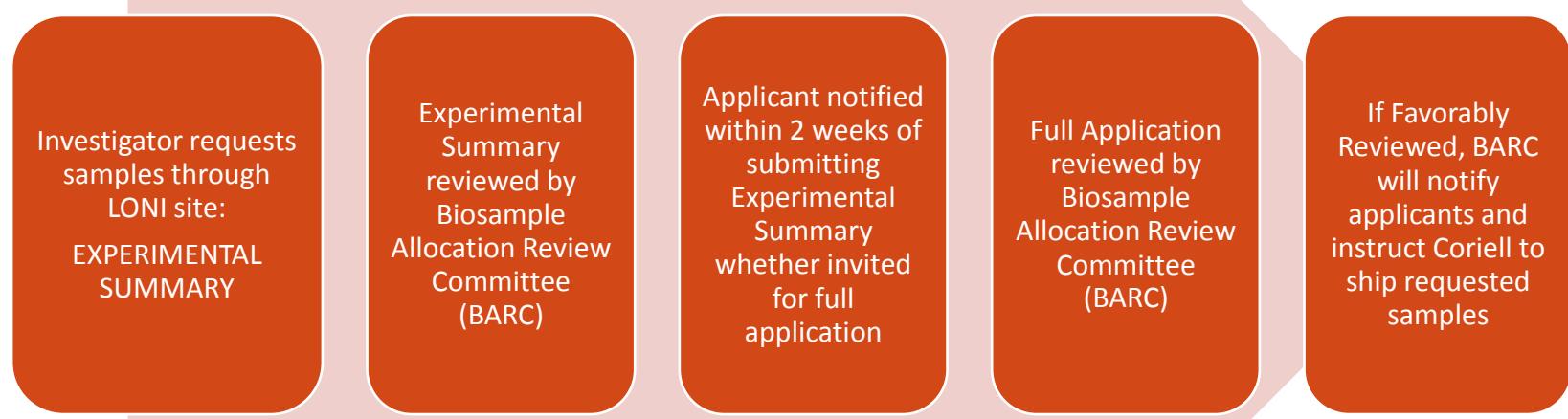
# Thank you!

# Sample Access and Biospecimen Allocation Review Committee

Mark Frasier, PhD

The Michael J. Fox Foundation

# Process for Accessing Biosamples

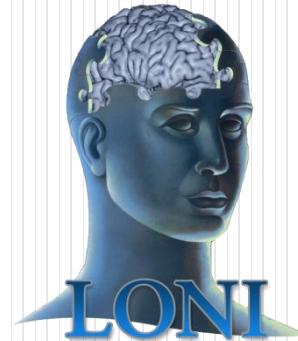


# Considerations for Accessing Biologic Samples

- **Biomarker Assay and Rationale**
  - Stability in PPMI storage considerations
  - Reproducibility of assay
  - Volume of sample required
  - Test-retest reliability
  - Previous use in human samples
- **Experimental Plan and Feasibility**
  - Justified sample size
  - Incorporating relevant PPMI datasets (clinical/imaging)
- **Collaborative Team and Environment**
  - Appropriate expertise
  - Agreement to PPMI sharing policies and IP guidelines

# PPMI Website

Arthur Toga



# PPMI Website Audience

- PPMI Website will provide resources for PPMI Participants:
  - Acquisition Sites
  - Funded Researchers
  - Non-Funded Researchers

# Website Hierarchy

Main Pages	Sub Pages	Description
Home		Main home page
About Parkinson's		General information about Parkinson's Disease
Our Research		Main research page and study information
	About PPMI	Information about PPMI
	Our Team	People involved in PPMI
	Research Groups	Sub-groups and their research
	Research Guidelines	Guideline documents for publications, authorship, committees, data use, etc
	Publications	Publications by PPMI researchers
	Presentations	Powerpoint presentation archive on Parkinson's Disease topics
	Funding	Information about PPMI funding

*Cont'd on next slide*

# Website Hierarchy

Main Pages	Sub Pages	Description
Data		Main data page
	Data Archive*	Information about types of data and link to the data archive section.  *This will link to the repository which is not represented in this hierarchy.
	Data FAQ	Frequently asked questions about the data archive
	Data Use	Data use agreement for current or potential users
	Acquisitions Sites	Information about where the data is collected
	Patient Security	Information on patient data rights and HIPAA rules
	Data Contact	A redundant link to the contact page which serves to funnel people into the right place to ask questions about the data
News		General news page
	Blog	Blog page or Twitter page link to announce PPMI news
	Media	Any media coverage of the PPMI work, ie online articles about PPMI, tv coverage, journal articles, etc
Contact		Contact page for interested parties, website contact info and data archive contact info.

# Website Hierarchy

Main Pages	Sub Pages
Home	
About Parkinson's	
Our Research	<ul style="list-style-type: none"><li>&gt;About PPMI</li><li>Our Team</li><li>Research Groups</li><li>Research Guidelines</li><li>Publications</li><li>Presentations</li><li>Funding</li></ul>
Data	<ul style="list-style-type: none"><li>Data Archive*</li><li>Data FAQ</li><li>Data Use</li><li>Acquisitions Sites</li><li>Patient Security</li><li>Data Contact</li></ul>
For Patients	
News	<ul style="list-style-type: none"><li>Blog</li><li>Media</li></ul>
Contact	



# PPMI Website Mockup 1

*logo pending*

The screenshot shows a website for "The Michael J. Fox Foundation for Parkinson's Research". The header features the foundation's logo with a stylized orange fox head and the text "THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH". The top navigation bar includes links for Home, About Parkinson's, Our Research, Data, News, and Contact. Below the header, there are two main content columns. The left column is titled "OUR MISSION" and contains text about MJFF's mission to find a cure for Parkinson's disease through research and improved therapies. It also features a section titled "JOIN TEAMFOX" with a call to action to learn more. The right column is titled "NEWS & EVENTS" and lists several news items with dates and brief descriptions. To the right of the news column is a vertical sidebar with four icons: "DATA LOGIN" (arrow), "FAQs" (question mark), "REQUEST DATA ACCESS" (key), and "UPDATE ACCOUNT" (person). The footer contains copyright information for LONI and a link to contact the webmaster.

Parkinson's Progression Markers Initiative

Subscribe | News | Email

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Home About Parkinson's Our Research Data News Contact

**OUR MISSION:**

MJFF is dedicated to finding a cure for Parkinson's disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson's today.

**JOIN TEAMFOX**

Whether you flip pancakes, sell lemons or run a marathon, you can be part of a team that has found countless ways to raise over five million dollars for The Michael J. Fox Foundation.

[LEARN MORE](#)

**NEWS & EVENTS**

**Eisai Discontinues Phase 3 Trial of E2007 (Perampanel)**  
02/22/2010 - PipelineReview.com via Gerson Lehrman Group - Experimental evidence and early clinical trials supported AMPA receptor blockade as a therapeutic option, but later studies failed to show a significant reduction in clinical "off" time compared to placebo.

**MJFF Awards \$1.1 Million for Clinical Trial of Transdermal Nicotine as Disease-modifying Treatment for Parkinson's**  
02/10/2010 - Researchers will evaluate the disease-modifying potential of transdermal nicotine using standard skin patches of the type used by millions of smokers as a quitting aid.

**Ex-NBAer Grant, Actor Fox Join Forces to Battle Parkinson's**  
02/17/2010 - NBA.com - Ex-NBAer Brian Grant's friendship with Michael J. Fox – perhaps one of the most famous people living with Parkinson's – has provided Grant with a compass, some sense of direction of what to do with his new life.

**MJFF Awards \$3.5 Million to Advance LRRK2 Therapeutic Development Efforts**  
02/17/2010 - Using a multipronged approach that includes collaboration between the research teams, the funded projects will help advance understanding of the LRRK2 gene.

**Research Roundtable in Charlotte: Tuesday, February 23**  
02/10/2010 - Join MJFF CEO Katie Hood, VP of Research Programs Todd Sherer, PhD, and three leading PD researchers for a presentation on current Parkinson's research and expert Q&A in Charlotte on Tuesday evening, February 23.

[LEARN MORE](#)

© 2010 LONI

For more information, please contact the [LONI Webmaster](#)

DATA LOGIN

FAQs

REQUEST DATA ACCESS

UPDATE ACCOUNT

# PPMI Website Mockup 2

*logo pending*

Parkinson's Progression Markers Initiative

Subscribe: News | Email



THE MICHAEL J.  
**FOX**

FOUNDATION FOR  
PARKINSON'S  
RESEARCH

Home About Parkinson's Our Research Data News Contact

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 DATA LOGIN

 FAQS

 REQUEST DATA ACCESS

 UPDATE ACCOUNT

# Admin Features

- Content Management System
  - Document Management
  - Multi-level Roles
  - Revision Control
  - Search Engine Optimization
  - Easy editing of pages and news items

# Admin Features *in detail...*

- Content Management System
  - Document Management: documents are archived by date and user
  - Multi-level Roles: any user can be assigned to edit and add content to the website, such as news for a specific core
  - Revision Control: revert to previous page edits
  - Search Engine Optimization: techniques employed for getting high page rankings and reaching a larger audience
  - Easy editing of pages and news items: Microsoft Word-like interface for quickly updating content and keeping the site “fresh”

# Admin Dashboard

The screenshot shows the WordPress Admin Dashboard for the PPMI website. The top navigation bar includes a logo, the site name "PPMI", a "Visit Site" link, a "New Post" button, and a greeting "Howdy, aham". The left sidebar contains a navigation menu with links to Dashboard, Akismet Stats, Pages, Media, Links, Posts, Appearance, Plugins (14), Users, Tools, and Settings. The main content area features a "Dashboard" header and a "Right Now" summary box showing statistics: 23 Posts, 34 Pages, 2 Categories, 24 Tags, 5 Comments, 4 Approved, 1 Pending, and 0 Spam. It also displays the theme "Fresh News" with 1 Widget, the WordPress version "2.8.4", and a note from Akismet. Below this is a "Recent Comments" section with two entries. The first entry is from Ron on "Request Features #", stating: "I would like to have an option to open workflows in different windows. Currently, the tab system does not ...". The second entry is from Hans Johnson on "Request Features # [Pending]", stating: "It would be nice if there was an easy way to map tools that are compliant with the slicer execution ...". At the bottom of the dashboard, there is a "Pingback on 3. Interface Overview" section mentioning "Provenance in Version 4.2.1 | LONI Pipeline" and a note about enabling provenance.

PPMI

PARKINSON'S PROGRESSION  
MARKERS INITIATIVE

69

# Admin Page Editing

 [Edit Page](#)

**Module Definitions**

Permalink: <http://pipeline.loni.ucla.edu/module-definitions/> [Edit](#)

Upload/Insert 

Visual [HTML](#)

**B** **I** **A<sub>BC</sub>**        

The module definitions for some popular packages have been provided here for your convenience so that you will not have to create the definitions yourself. In order run these modules locally, change the executable path within the module definition to point to the appropriate location.

**All Packages**

[All Module Definitions](#)

**Individual Packages**

Path:

Word count: 108 Last edited by ahammond on September 3, 2009 at 11:42 am

**Custom Fields**

**Discussion**

**Page Author**

**Page Revisions**

[9 February, 2009 @ 12:08](#) by zliu  
[23 September, 2008 @ 15:58](#) by zliu  
[23 September, 2008 @ 15:57](#) [Autosave] by kaliprando  
[25 August, 2008 @ 13:54](#) by crmena

**Publish**

[Save Draft](#) [Preview](#)

Status: **Draft** [Edit](#)

Visibility: **Public** [Edit](#)

 Publish on: Aug 19, 2008 @ 15:45 [Edit](#)

[Delete](#) [Publish](#)

**Attributes**

Parent: **Main Page (no parent)**

You can arrange your pages in hierarchies, for example you could have an "About" page that has "Life Story" and "My Dog" pages under it. There are no limits to how deeply nested you can make pages.

Template: **Default Template**

Some themes have custom templates you can use for certain pages that might have additional features or custom layouts. If so, you'll see them above.

Order: **1**

Pages are usually ordered alphabetically, but you can put a number above to change the order pages appear in. (We know this is a little

# Admin User Roles

 *Users*

All (10) | Administrator (4) | Editor (6)

Bulk Actions ▾  Change role to... ▾

<input type="checkbox"/> Username	Name	E-mail	Role
<input type="checkbox"/>  admin			Administrator
<input type="checkbox"/>  ahammond	Amanda Hammond		Administrator
<input type="checkbox"/>  cmena	Carlos Mena		Editor
<input type="checkbox"/>  dhasson	David Hasson		Administrator
<input type="checkbox"/>  kaliprando	Katie Aliprando		Editor
<input type="checkbox"/>  klozev	Kamen Lozev		Editor
<input type="checkbox"/>  ppetrosyan	Petros Petrosyan		Editor
<input type="checkbox"/>  rdelacruz	Robert De La Cruz		Administrator
<input type="checkbox"/>  vgreer	Vaughan Greer		Editor
<input type="checkbox"/>  zliu	Zhizhong Liu		Editor

Username Name E-mail Role

Bulk Actions ▾

# User Features

- Data access
- Powerful search capabilities
- Protocols
- Research guidelines
- Data sharing policies and procedures
- Technical manuals
- Authorship list and citation information
- General news updates
- Specific core or data news
- Subscriptions
- FAQs
- Contact information
- Meeting PowerPoints and minutes

# User Features *in detail...*

■ Visitors can access ■ Needs approval to view/submit ■ Can be edited by user if given role

- Data access ■
- Powerful search capabilities ■
- Protocols ■■
- Research guidelines ■■
- Data sharing policies and procedures ■■
- Technical manuals ■■
- Authorship list and citation information ■■
- General news updates ■■
- Specific core or data news ■■■
- Subscriptions ■
- FAQs ■■
- Contact information ■■
- Meeting PowerPoints and minutes ■■

# LUNCH

**Presentations will resume at  
1:00 pm**

# Publication Policy

Kenneth Marek, MD

# Publication Policy

- PPMI SC/Investigators/Sponsors are committed to open and timely publication of PPMI data
- Data is our only product – this study is IP free
- Data will be generally available through the PPMI website

# Publication Policy

- PPMI primary reports will be authored by the PPMI study with SC, investigators and other contributors as authors
- The PPMI SC working with appropriate PPMI committee and task forces will guide secondary reports - goal is to have opportunities for many
- Secondary reports will be authored by study investigators and will site the PPMI study as final author.

# Data Access

- De-identified data available publically to all investigators
  - agree to PPMI Data access and Publication policy
- Required to provide yearly feedback to PPMI data and publication committee
- Encourage collaboration among investigators

# Data and Publication Committee

- **Administrative review for compliance with user agreement– not content review**
- Add PPMI group authorship as permitted by journal
- Include recommended language describing PPMI methods and data gathering
- Cite PPMI sponsors (see User Agreement)
- Provide manuscript to PPMI DPC for review 2 weeks prior to planned submission (see User Agreement)
- Provide manuscript or abstract citation to PPMI upon acceptance
- Provide URL to published work, if possible.

# Data and Publication Committee

- Formed by the PPMI SC
- 5-7 members
- Adjudicate disputes
- Appeal to the SC

# Publication Policy

- PPMI SC/Investigators/Sponsors are committed to open and timely publication of PPMI data

# REMARKS

# PPMI

# Communications & Reports

Emily Flagg, Project Manager - CTCC



**Coordination  
Center (CTCC)**



**Central Lab**



**Site Monitors**



**Steering Committee**



**Michael J. Fox  
Foundation (MJFF)**



**Sites**



**CSOC**



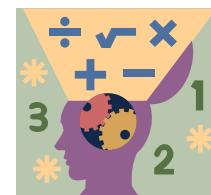
**Biorepository  
(Coriell)**



**Imaging Core (IND)**



**Bioinformatics  
Core (LONI)**



**Statistics Core**



**Bioanalytics  
Core**



**Genetics Core**

# Study Contacts

## CTCC Team

- **Emily Flagg**  
Lead Project Manager  
Phone: (585) 275-8869  
Fax: (585) 461-3554  
Email: [emily.flagg@ctcc.rochester.edu](mailto:emily.flagg@ctcc.rochester.edu)



- **Protocol Questions**
  - Eligibility, General questions
- **Reportable Events (Incidents, including SAEs)**
- **Regulatory Documents and Staff Changes**

# Study Contacts

## CTCC Team

- Alice Rudolph

Project Manager

Phone: (585) 275-0556

Fax: (585) 461-3554

Email: [alice.rudolph@ctcc.rochester.edu](mailto:alice.rudolph@ctcc.rochester.edu)

- Back up to Lead PM

# Study Contacts

## Imaging Team

- **Susan Mendick**

**Director, Clinical Imaging Programs Management**

**Phone: (203) 401-4337**

**Fax: (203) 401-4303**

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

- **Imaging Questions**

- **Imaging Acquisition Protocol**

- **Imaging Queries**

- **DaTSCAN Injection**

# Site Personnel

- **One Primary Investigator**
  - Sub-investigators accepted as approved by sponsor and study team
  - Subjects screened/enrolled by a sub-I should be followed by same individual throughout for consistency of assessments and evaluations
- **One Primary Coordinator**
  - Co-coordinators accepted as approved by sponsor and study team
- **Investigator is responsible for seeing *all* subjects at *all* visits and conducting Investigator required assessments**
- **Any change in Investigator must be preapproved by the PPMI Steering Committee**

# Site Personnel

- Report staff changes to the CTCC as soon as possible (complete the new/change staff form)
- Update Log of Investigators, Study Staff and Staff Related Duties (fax copy to CTCC)
- Update 1572 (if applicable)

# Confirmation to Enroll

- Requirements include:
  - IRB approval
  - Subcontract in place
  - Regulatory documents completed
  - PI and Coordinator protocol training completed
  - eDE training (if not previously done)
- Approval memo to begin recruitment and enrollment received from the CTCC
- Additional study team members notified

# Reports

# Enrollment Confirmation

## Enrollment Verification Report Generated

- Report appears on RANDOM page once page is completed after eligibility confirmed and subject completes Baseline visit
- Visit Window Schedule with Target Visit Dates
- Check for accuracy; notify CTCC Project Manager if any corrections are required
- Print and file in study binder

# Activity Report

- Site included on report once actively enrolling
- Includes summary study information (listed by site) about total enrollment, withdrawals, SAEs, etc.

# Reportable Events (Incidents)

- The following events are considered reportable events (incidents) and must be reported to the CTCC project manager as soon as possible and within 24 hours of site awareness:
  - Initiation of any PD medication
  - Change of diagnosis (PD and HC subjects)
  - Participation in any other clinical trial or study
  - Premature withdrawal (e.g., withdrawal of consent)
  - Serious adverse event (SAE)
  - Pregnancy
  - Death

# Incident Report

- **Summary of the event as reported to CTCC**
- **Sites to review and verify information upon receipt**
- **Print copy for study file**

# Notifications

- Purpose: to report noteworthy and relevant clinical or data management information that might influence the interpretation of the study data
- May be a general site issue as well as subject specific
- Notifications should be communicated by telephone or email to the CTCC within 3 days of site awareness

# Notifications

- Examples of issues requiring notification:
  - Protocol violation
  - Blood sample not processed correctly
- Include with the report to CTCC:
  - Site number
  - Staff code of Investigator or Coordinator reporting
  - Subject ID number
  - Date of event or observation

# Notification Report

- Generated as a summary of the event as reported to the CTCC
- Sites to review and verify information upon receipt
- Print copy for study file

# General Communications

- Periodic phone calls and teleconferences
- Additional protocol training as needed
- General email communications
- Questions?
  - Call Emily Flagg  
(585) 275-8869

Questions?



# eClinical Training

## Introduction

**Joe Weber**  
**University of Rochester**  
**Clinical Trials Coordination Center**

# OmniComm eClinical

- Web-based trial management system
- Accessible with a Windows PC and Internet Explorer
  - Not accessible with a Macintosh
  - Not accessible with other browsers such as FireFox, Chrome or Safari

# System Availability

- System available 24x7
  - Maintenance window of 8am-Noon ET on Sundays
  - Daily restart at 6am ET

# ePortal

- Main screen for the application
- Access to study documents
  - Protocol
  - Operations Manual
  - Source Document Worksheets



Welcome, Training Coordinator 1!

[Home](#) - [My Account](#) - [Sign Out](#) - [Help](#)  
[Add Content](#) - [Page Settings](#)[My Places](#) » Training Coordinator 1  
(Private)

## EXPeRT Data Capture

## Study Map

- Home
- LEARNECLIN
  - ... 999

## Announcements

Welcome to the Clinical Trials Coordination Center's eClinical Training Session!

## Folders

Folder Name	New Items
Administrative	0
Amendment(s)	0
Consent	0
Investigator Brochure	0
Laboratory and ECG	0
Newsletters	0
Operations Manual	0
Operations Manual - Forms	0
Protocol (Final)	0
Reports	0
Source Document Worksheets	0
Training	0

## EDC Functions List

Data Review/Capture

## FAQ

# Electronic Data Capture

- Allows you to:
  - Create patients
  - Enter clinical data
  - Apply electronic signatures
  - Address data queries

**EXPeRT®**  
Data Capture

All Protocols | LEARNECLINUS | 999

User ID: TRIICRD1

Select Action

Help

Exit

**Filter Panel**

None

**Navigation Panel**

- All Protocols
- LEARNECLINUS
  - 999
    - +1001
    - +1234
    - +9876
    - +9998

**Entry Status Legend**

- No Pages Entered
- Some Pages Entered
- All Pages Entered

**Patient ID Filter :**  Search

	Patient ID	Initials	Baseline Visit Date	Country	Entry Status	Batch Status	
	1001	AAA	01252010			S	
	1234	AAA				S	
	9876	ZZZ	10232009			S	
	9998	TST	03012010			S	

**Filter Panel**

None

**Navigation Panel**

- All Protocols
- LEARNECLINUS
- 999
  - 1001
    - CONSENT
    - SC
    - LOG
    - RANDOM
    - BL
    - T01
    - V01
    - V02
    - FNL
    - U01
  - 1234
  - 9876
  - 9998

**Entry Status Legend**

	Event ID	Description	Visit Date	Entry Status	Event Order	Batch Status	
	CONSENT	Consent			1	S	
	SC	Screen			2	S	
	LOG	Log			3	S	
	RANDOM	Random			4	S	
	BL	Baseline			5	S	
	T01	Telephone 1 (Week 1)			6	S	
	V01	Visit 1 (Month 1)			7	S	
	V02	Visit 2 (Month 2)			8	S	
	FNL	Final			9	S	
	U01	Unscheduled			10	S	X

[1/1]

## SCREEN (Screening / Demographics )



Utilities



Complete one form for each subject who is potentially eligible to participate in the study.



A. Check box if subject has signed consent

02102010



B. Date informed consent was signed

1



C. Indicate the type of subject: 1 = Parkinson disease, 2 = Healthy control

05241965



1. Date of birth

2



2. Gender (0 = Female of child bearing potential, 1 = Female of non-child bearing potential, 2 = Male)

Women who are surgically sterile (hysterectomy or tubal ligation) or post-menopausal (last menstruation was 1 year or more prior to Screening Visit) are considered to be of non-childbearing potential.

AE (Adverse Event Log)	?	S	...	Show...	▼		<	<	>	>	!!	!!	<input checked="" type="checkbox"/> Save Page
------------------------	---	---	-----	---------	---	--	---	---	---	---	----	----	---

[1/1]	LOGHEAD	?	Utilities	▼	+ -
-------	---------	---	-----------	---	-----

Subject Initials **JOE**

Investigator's staff code **1324**

[1/1]	AE (Adverse Event)	?	Utilities	▼		<	<	<	>	>	!!	!!	+ -
-------	--------------------	---	-----------	---	--	---	---	---	---	---	----	----	-----

AE#	Adverse Event (Record diagnosis if known)	Start Date MMDDYYYY	Start Date Estimated? (ACT,DAY MD,MON)	Stop Date MMDDYYYY
1	HEADACHE	07012009	ACT	

# Training

- Training will be provided via webinar
- After successful completion of certification exam, you will be given a username and password to access the system

# User Account Details

- Your user account will be the same for any other studies you do with the CTCC
- If you have received training previously and already have an account, you do not need to attend a training session again

# Support

- System support website available at:  
<http://support.ctcc.rochester.edu/>
  - User Guide reference materials
  - Frequently Asked Questions
  - Training Videos will be posted soon
- Telephone help desk support available from 8:30am – 9:00pm ET Monday-Friday. (585) 275-3893

# Financial Overview

Sohini Chowdhury, Associate Director, Team  
Leader  
The Michael J. Fox Foundation

# Subcontracts

- MJFF will contract with all sites/cores involved in PPMI
- Agreements have been sent out to all sites/cores in early March – discussions are in progress
- Goal: Successfully finalise and execute agreements by April 15<sup>th</sup>

# Site Payment Process & Schedule

- Site budget comprised of three factors:
  - Pay per subject per assessment/biospecimen collected
  - \$20,000 to cover site personnel/costs
    - Year 1 - \$3K of the \$20K will be paid upon execution of award agreement to cover upfront costs
  - \$7,500 to cover subject accommodation/travel reimbursement
- Payments will be issued on a quarterly basis
  - Sites: CTCC will generate reports on subjects enrolled/assessments collections completed → will form the basis for payments

# Meeting Reimbursement

- Logistic email sent by Kathy Vestuto included Expense Reimbursement Form
- Please fill it out and attach original receipts and send to Kathy by April 23<sup>rd</sup>
- MJFF can only reimburse items accompanied with a receipt

# WRAP UP AND QUESTIONS

# PPMI Timeline

Activity	Timing
<b>PPMI Investigators Meeting</b>	<b>March 18-19 2010</b>
<b>Site contracting</b>	<b>April/May 2010</b>
<b>IRB submission</b>	<b>April/May 2010</b>
<b>DaTSCAN IND submission</b>	<b>March 30, 2010</b>
<b>DaTSCAN available US</b>	<b>May 2010</b>
<b>First subjects enrolled</b>	<b>May 2010</b>
<b>Subject recruitment/media program launched</b>	<b>May 2010</b>
<b>Site training – Imaging, SOPs, UPDRS, Neuropsych</b>	<b>May-July, 2010</b>
<b>All sites recruiting</b>	<b>July/Aug 2010</b>

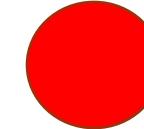
# THANK YOU!

We appreciate you taking the time to join us at this meeting, and look forward to beginning this very exciting study!

# BREAKOUT SESSIONS

- **Breakout Session #1**

- Imaging Overview
  - DAT Scan Imaging
  - MRI



- **Breakout Session #2**

- Biologics Overview
  - Kits and Supplies
  - Specimen collection, processing, storage, and shipment



- **Breakout Session #3**

- Lumbar Puncture
  - Purpose of LP
  - Process and Procedures
  - Helpful Hints



# PPMI Investigators Meeting

## Biofluids Overview

Leslie M Shaw

University of Pennsylvania Medical Center

# Qualification of the analytical and clinical performance of CSF A $\beta$ <sub>1-42</sub>, tau and p-tau<sub>181p</sub> in the ADNI study

1. Selection of CSF Ab<sub>1-42</sub>, tau, p-tau<sub>181p</sub> based on prior studies that showed their promise for AD detection & a consensus among experts in this field

2. Pre-analytical factors for the **Ip & CSF handling**

Identify and control for pre-analytical variables

- Time of day for **Ip** *-morning following overnight fast*
- Collection tube type *-avoid PS and glass tubes & use PP tubes*
- Transport temperature *-avoid storage at refrigerator temp*
- # of freeze-thaw cycles *-minimize*
- Time from collection to freezing *-minimize*

3. Analytical performance

Assure stability of reproducibility of test performance

- Within each run
- Day to day
- Among expert laboratories
- From batch to batch of immunoassay reagents
- AA-sponsored international CSF external blinded quality control program

4. Clinical diagnostic performance

Establish diagnostic and predictive performance using the qualified test method

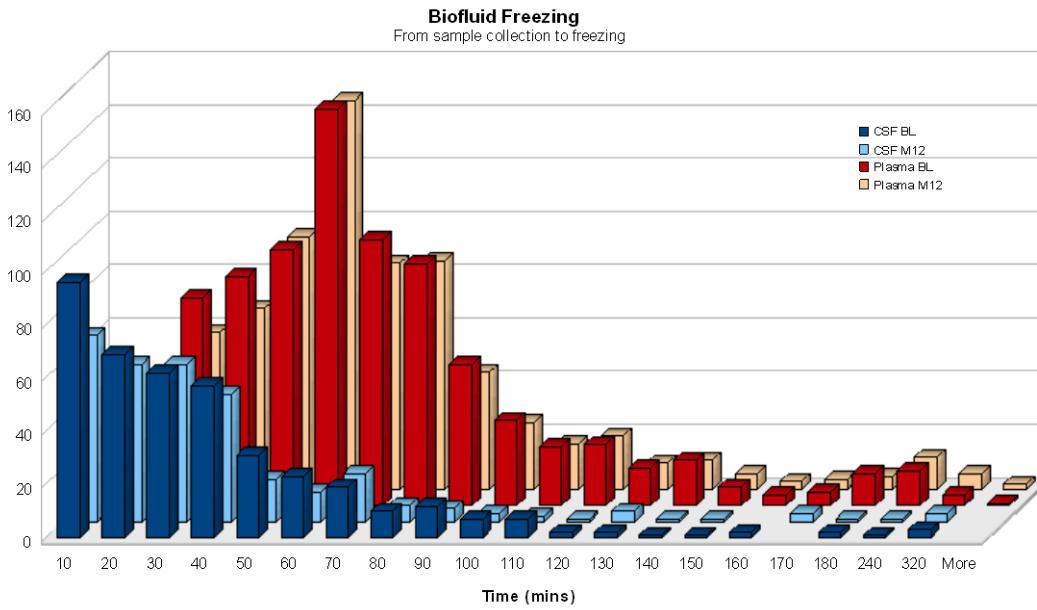
- Establish sensitivity & specificity in ADNI-independent CSF samples from autopsy-confirmed AD subjects
- Use these diagnostic cutpoints to characterize AD CSF pathologic biomarker signatures in ADNI subjects
- Evaluate predictive performance for MCI→AD converters
- Characterize the longitudinal changes in CSF biomarker changes in a subset of ADNI CSF donors
- Study multiple biomarker types in combination for optimal disease detection and progression

# Documentation of biofluid sample “history”

- Time/date
- Time to process
- Time to freeze
- Assess sample quality
- Accurate de-identified labeling
- 24/7 tracking of storage temp
- ***A critical part of the value of biofluids is documentation of pertinent pre-analytical factors that can affect biomarker measurements***

# ADNI biofluid collections

## *Time from sample collection to freezing*

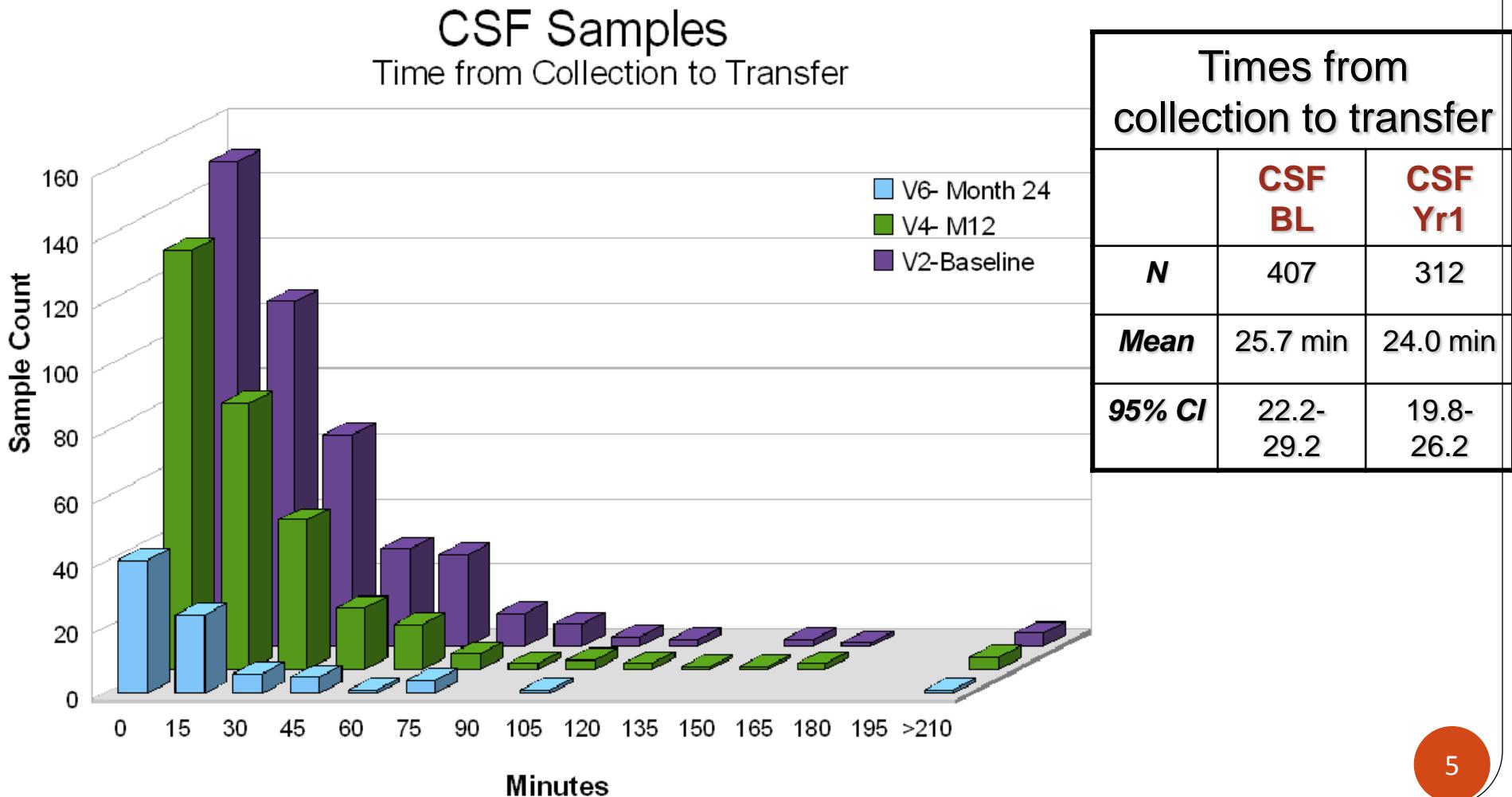


### CSF sample collection for ADNI:

- After overnight fast
- Collect into polypropylene tube
- Transfer to polypropylene transfer tube
- No centrifugation
- Freeze at site, ship on dry ice
- Thaw & aliquot at UPenn, storage at -80°C

# ADNI CSF samples

## *Time from collection to transfer*



# The Future of Biomarker Research: Critical Goals

- Standardize CSF sampling / handling procedures
- Laboratory procedures
- Manufacture lot to lot consistency
- External control program
- Prospective studies:
  - Interrelationships between imaging and biochemical biomarkers in longitudinal studies
  - Longitudinal trajectories for transitions from cognitively normal → early MCI → late MCI → AD
  - Effect(s) of various treatment strategies on disease progression and biomarker measures
  - More biomarker study data on natural history of AD in the cognitively normal elderly population
- Approval for use in clinical practice

# Breakout Session: Biologics Overview

## March 18th & 19th, 2010

Alison Ansbach, MS  
Senior Project Manager



# Coriell Supports Scientists, Clinicians, and the Community

- Genotyping and Microarray Center
- Research
  - Coriell Personalized Medicine Collaborative (CPMC)
  - Stem Cells
- Coriell Cell Repositories
  - NINDS, NIGMS, GENNID, NEI-AREDS, COHORT



# Submitting samples to Coriell: 3 types of visits, 3 types of kits

Sample	SCREENING VISIT	Baseline/V02/V04/V06/V08/V10/V12	V01/V03/V05/V07/V09/V11
Blood for Plasma		x	x
Blood for Serum		x	x
Blood for RNA extraction		x	x
Blood for DNA extraction	x		
Urine		x	
CSF		x	

# Ordering Kits

- Coriell provides materials to collect and ship samples
- Each site will place kit orders through Coriell's online database
- Please allow turnaround time of at least one week

The screenshot shows the 'QUEUE AT CORIELL' web application interface. At the top right, it displays the date 'The current date is: 3-16-2010', the user 'ninds ninds', visit count 'Visits: 758 (Last Login: 03/08/2010)', and links for 'Logout' and '@ TEST Prod'. The main navigation bar includes 'Contracts' and 'Resources'. Below this, the current location is 'Home > Contracts > NINDS Project Management > Kit Request'. On the left, a sidebar titled 'Project Management' lists 'Kit Request', 'Submitter Information' (with sub-links: CDE Management, Gender Data, Microsatellite Data, Project Overview, Search, and Shipping History), and 'Q Memory Links (?)'.

The central area is titled 'New Kit Order Request Page'. It contains a section titled 'Important Information:' with the following instructions:

- Please allow one week lead time when requesting kit supplies
- If this is the first time you will be receiving kits, please indicate this when entering your request
- Verify shipping information by clicking on the 'Verify Contact' button. If your current shipping address is different than what is on file, please contact the NINDS Project Manager to update.

Below this is a 'Kit Request Required Data:' section. It includes fields for 'Contact Name' (set to 'ninds ninds') and a 'Verify Contact' button. A dropdown menu labeled 'Select where supplies need to be shipped:' is set to 'Select One:'. A large text area labeled 'Request:' is present. At the bottom is a 'Submit' button.

# Screening Visit: Blood for DNA Extraction

- Fill one 8.5ml yellow-top tube with blood
- Keep blood at room temp- do NOT refrigerate or freeze
- Ship to Coriell same day as blood is drawn



# Baseline, 6 month, and Annual Visits: Plasma, Serum, RNA, Urine & CSF

- Fill one each of the following blood tubes:

- Purple top (plasma)
- Red top (serum)
- PAXgene (RNA)

- Collect urine and CSF
- Process each specimen per protocol and freeze
- Ship to Coriell on dry ice



# 3, 9, 18, 30, 42, and 54 month visits: Plasma, Serum & RNA

- Fill one each of the following blood tubes:

- Purple top (plasma)
- Red top (serum)
- PAXgene (RNA)



- Process each specimen per protocol and freeze
- Ship to Coriell on dry ice

# What happens to samples once they arrive at Coriell?



Coriell Contact Info:  
Alison Ansbach  
Senior Project Manager  
(856) 757-9756  
[aansbach@coriell.org](mailto:aansbach@coriell.org)  
[www.coriell.org](http://www.coriell.org)

Thank you!