

# **The Parkinson's Progression Markers Initiative (PPMI)**

**Oct 6, 2010**

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# PD patient vignette

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



# 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***



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# Rationale for PPMI:

## Challenges of disease-modifying trials

- **Disease modifying PD therapeutics remain a major unmet need**
- **A major obstacle to current phase 2/3 neuroprotection studies is the lack of biomarkers for**
  - **Disease mechanism**
  - **Drug mechanism**
  - **Dosage determination**
  - **Study eligibility**
  - **Stratification into PD sub-types**
  - **Correlation with clinical signals**
- **Biomarkers would potentially shorten study duration, reduce study sample size, limit study costs.**



# Developing the Parkinson's Progression Markers Initiative

**Academic, industry, government, foundation, patient constituencies worked to develop the PPMI study - process driven by the MJFF through its SAB and its unique ability to convene the interested groups**

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

## Access/Sharing

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



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# PPMI Overview

- **PPMI is an observational multi-center study to assess progression of clinical features, imaging and biologic biomarkers in Parkinson's patients and healthy controls**
- **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**
- **Biological samples will be used for verification of promising biomarkers**
- **Sponsor – MJFF// Support from Pfizer, GE healthcare**



# PPMI Study Details: Synopsis

<b>Study population</b>	<ul style="list-style-type: none"><li>▪ 400 <i>de novo</i> PD subjects (newly diagnosed and unmedicated)</li><li>▪ 200 age- and gender-matched healthy controls</li><li>▪ Subjects will be followed for a minimum of 3 years and a maximum of 5 years</li></ul>
<b>Assessments/ Clinical data collection</b>	<ul style="list-style-type: none"><li>▪ Motor assessments</li><li>▪ Neuropsychiatric/cognitive testing</li><li>▪ Olfaction</li><li>▪ DaTSCAN imaging, MRI</li></ul>
<b>Biologic collection/</b>	<ul style="list-style-type: none"><li>▪ DNA collected at screening</li><li>▪ Serum and plasma collected at each visit; urine collected annually</li><li>▪ CSF collected at baseline, 6mo 12 mo and then annually</li><li>▪ Samples aliquotted and stored in central biorepository</li></ul>
<b>Initial Verification studies</b>	<ul style="list-style-type: none"><li>▪ Lead biologic candidates to be tested:<ul style="list-style-type: none"><li>• Alpha-synuclein (CSF)</li><li>• DJ-1 (CSF and blood)</li><li>• Urate (blood)</li><li>• Abeta 1-42 (CSF)</li><li>• Total tau, Phospho-tau (p-181) (CSF)</li></ul></li></ul>
<b>PD treatment</b>	<ul style="list-style-type: none"><li>▪ <i>De novo</i> for ~6 months</li><li>▪ Can participate in other clinical trials (including interventional trials) after 12 months</li></ul>



# PPMI SC and Study Cores

<b>Steering Committee</b>	<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>
<b>Clinical Coordination Core</b>	<ul style="list-style-type: none"><li>▪ <b>University of Rochester's Clinical Trials Coordination Center</b></li><li>• <b>PI: Karl Kieburtz</b></li></ul>
<b>Imaging Core</b>	<ul style="list-style-type: none"><li>▪ <b>Institute for Neurodegenerative Disorders</b></li><li>• <b>PI: John Seibyl</b></li></ul>
<b>Statistics Core</b>	<ul style="list-style-type: none"><li>▪ <b>University of Iowa</b></li><li>• <b>PI: Chris Coffey</b></li></ul>
<b>Bioinformatics Core</b>	<ul style="list-style-type: none"><li>▪ <b>Laboratory of Neuroimaging (LONI) at UCLA</b></li><li>• <b>PI: Arthur Toga</b></li></ul>
<b>BioRepository</b>	<ul style="list-style-type: none"><li>▪ <b>Coriell/BioRep</b></li><li>• <b>PI: Alison Ansbach,</b></li><li>• <b>Pasquale De Blasio, Michele Piovella</b></li></ul>
<b>Bioanalytics Core</b>	<ul style="list-style-type: none"><li>▪ <b>University of Pennsylvania</b></li><li>• <b>PI: John Trojanowski, Les Shaw</b></li></ul>
<b>Genetics Core</b>	<ul style="list-style-type: none"><li>▪ <b>National Institute on Aging/NIH</b></li><li>• <b>PI: Andy Singleton</b></li></ul>
<b>ISAB</b>	<ul style="list-style-type: none"><li>▪ <b>Kim Gallagher/GE Healthcare</b></li><li>• <b>Thomas Comery/Pfizer</b></li></ul>
<b>MJ FOX PPMI</b>	<ul style="list-style-type: none"><li>• <b>Sohini Chowdhury, Mark Frasier, Claire Meunier, Jamie Eberling, Todd Sherer</b></li></ul>



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# PPMI Clinical Sites

## US sites

- **AZ PD Consortium (Phoenix, AZ)**
- **Baylor College of Medicine (Houston, TX)**
- **Boston University (Boston, MA)**
- **Emory University (Atlanta, GA)**
- **Institute of Neurodegenerative Disorders (New Haven, CT)**
- **Johns Hopkins University (Baltimore, MD)**
- **Northwestern University (Chicago, IL)**
- **Oregon Health and Science University (Portland, OR)**
- **The Parkinson's Institute (Sunnyvale, CA)**
- **University of Alabama at Birmingham (Birmingham, AL)**
- **University of Pennsylvania (Philadelphia, PA)**
- **University of Rochester (Rochester, NY)**
- **University of South Florida (Tampa, FL)**
- **University of Washington (Seattle, WA)**

## European sites

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



# PPMI Schedule of Events

	S C	B L	V0 1	V 0 2	V 0 3	V0 4 <sup>b</sup>	V0 5 <sup>b</sup>	V0 6 <sup>b</sup>	V0 7 <sup>b</sup>	V0 8 <sup>b</sup>	V0 9 <sup>b</sup>	V1 0 <sup>b</sup>	V1 1 <sup>b</sup>	V1 2/ P W	S T	Unsch Visit
Visit Description	Mo 1	0	3	6	9	12	18	24	30	36	42	48	54	60	- - -	---
Written Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Medical and Family History/Demographics	X															
Physical Examination	X															
Neurological Examination/Diagnosis	X					X		X		X		X		X		X <sup>g</sup>
Vital Signs	X	X <sup>c</sup>	X	X	X	X <sup>c</sup>	X	X <sup>c</sup>	X	X <sup>c</sup>	X	X <sup>c</sup>	X	X <sup>c</sup>	X	X
Blood Sample for DNA	X															
Clinical Laboratory Assessments	X					X		X		X		X		X		X <sup>g</sup>
Biomic blood sample		X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>
MDS-UPDRS (including Hoehn & Yahr)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>g</sup>
Modified Schwab & England ADL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>g</sup>
MDS-UPDRS Part III / Hoehn & Yahr <sup>b</sup>						X		X		X		X		X		
Olfactory Testing (UPSIT)		X														
Hopkins Verbal Learning Test – Revised		X				X		X		X		X		X		
Benton Judgment of Line Orientation		X				X		X		X		X		X		
Semantic Fluency		X				X		X		X		X		X		
Letter Number Sequencing		X				X		X		X		X		X		
Symbol Digit Modalities Test		X				X		X		X		X		X		
Montreal Cognitive Assessment (MoCA)	X					X		X		X		X		X		
Epworth Sleepiness Scale		X		X		X		X		X		X		X		X
REM Sleep Behavior Questionnaire		X		X		X		X		X		X		X		X
Geriatric Depression Scale (GDS-15)		X		X		X		X		X		X		X		X
State-Trait Anxiety Inventory for Adults		X		X		X		X		X		X		X		X
QUIP		X		X		X		X		X		X		X		X
SCOPA-AUT		X		X		X		X		X		X		X		X
MRI (structural)		X														
MRI (DTI) <sup>c</sup>		X				X		X				X		X		
DAT imaging		X <sup>d</sup>				X		X				X		X		
Lumbar puncture (CSF collection)		X		X <sup>i</sup>		X		X		X		X		X		X
Adverse Events	X	X		X		X <sup>a</sup>		X <sup>a</sup>		X <sup>a</sup>		X <sup>a</sup>		X <sup>a</sup>		X



# Clinical markers

**Cognition**

**Behavioral**

**Depression**

**Apathy**

**Anxiety**

**ICD**

**Autonomic**

**Constipation**

**Bladder**

**Sexual**

**Cardiac**

**Olfaction**

**Sleep - RBD**

**Skin**

**Motor analysis**

**Speech**

# Biomarkers for PD

Imaging –Phenotomics

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

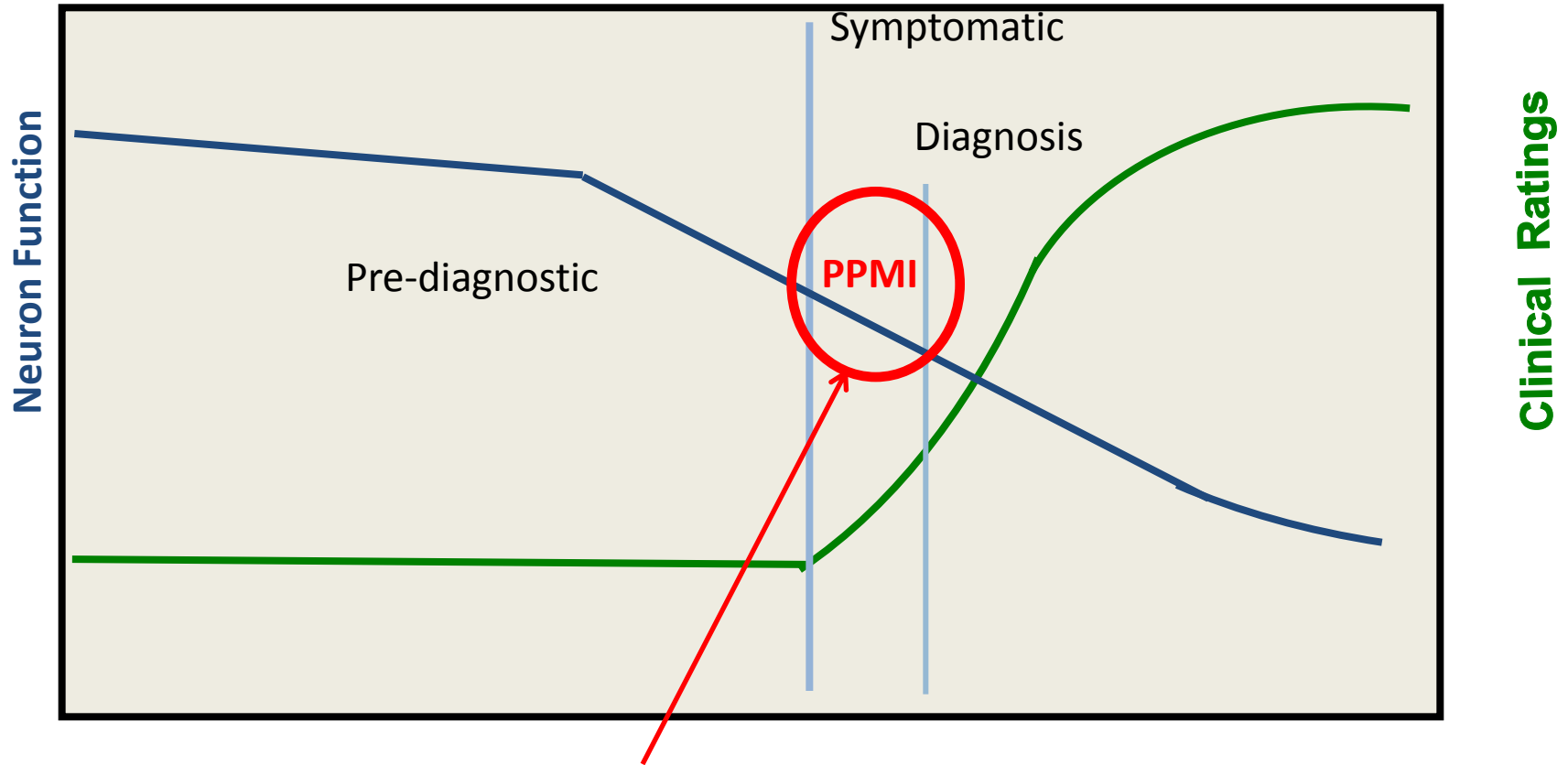
**Synuclein, LRRK2**

**Parkin DJ-1, Pink1**



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# PPMI – Pushing back Diagnosis



**Eligibility for PD - Possible PD + DAT deficit**



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# 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
Criteria	<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>
Candidates	<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>



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# Data Input

Acquisition → Repository



Imaging Acquisition

Clinical Acquisition

Biological Acquisition



Imaging Core (IND)

Quality Control  
Image Pre-processing

Clinical Core (CTCC)

Quality Control  
Study Management

Sample Repository (Coriell)

Sample Storage

PD@LONI



- Public Information
- Publications
- Investigator Resources
- Data Sharing Tools
- Data Access

Data Transfer & Validation

Inventory

# Data Output

Repository → Investigators

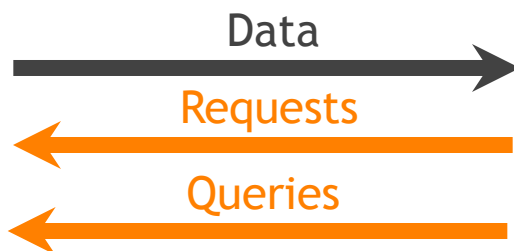
## PD@LONI



Web Interface  
Queries  
Requests  
Downloads



Database  
Clinical Data  
Image Data  
Sample Inventory



Scientific Investigators



Sample Repository (Coriell)  
Sample Storage



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

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- **Portal for PPMI data**
- **Portal for PPMI samples through the biologic resource committee**
- **PPMI – study documents and SOPs available**
- **PPMI study progress**
- **Recruitment and retention tool**



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# **PPMI - Standardization/Training**

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



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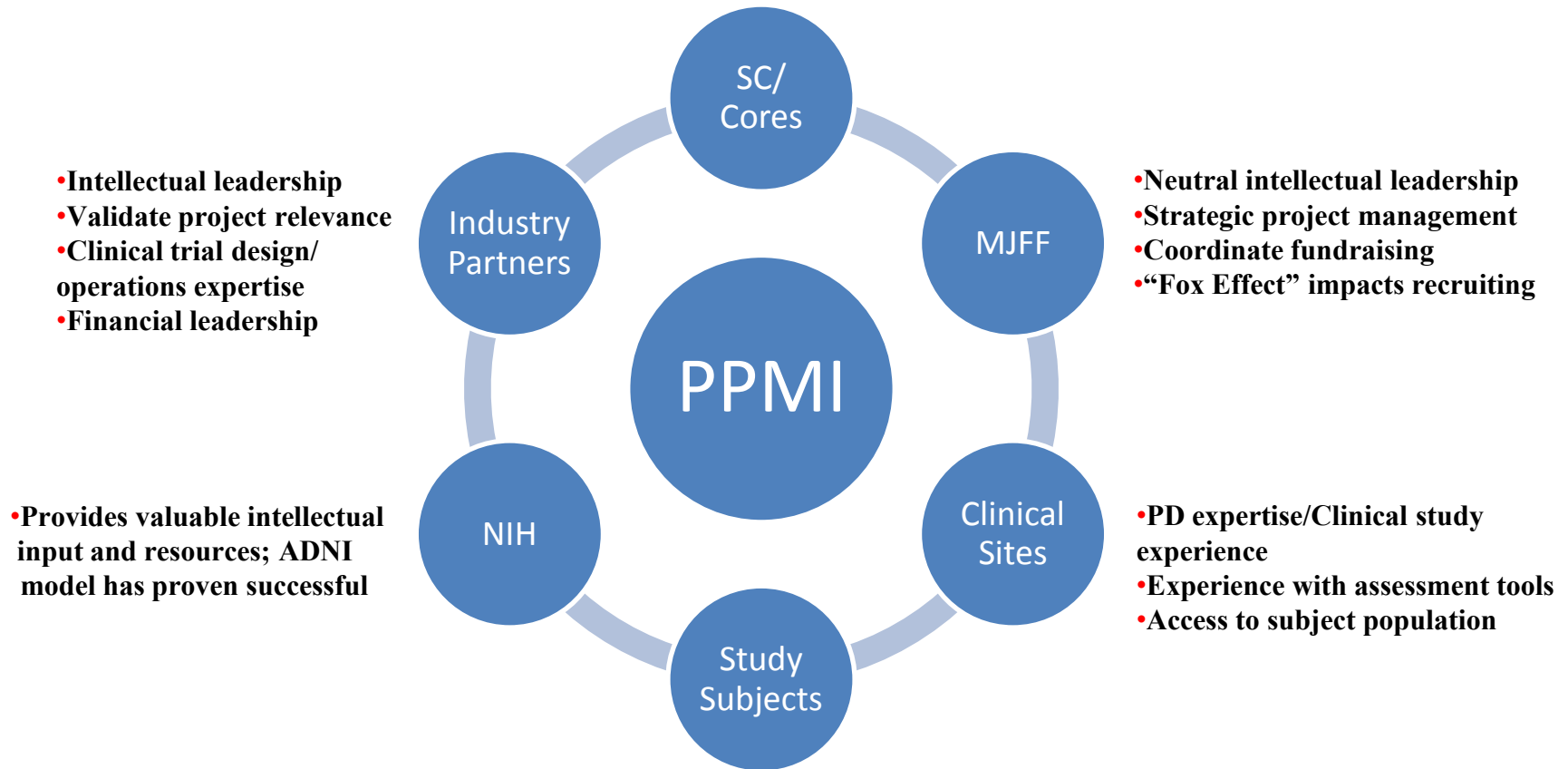
# PPMI Key Features

- **Subject recruitment eligibility includes DAT imaging status**
- **Comprehensive longitudinal biomarker and imaging assessments**
- **Longitudinal CSF acquisition in all study subjects**
- **Standardization of all data acquisition**
- **All data merged into PPMI database and data and biologic samples rapidly available to scientific community**  
  
via PPMI website *www. PPMI-info.org*
- **Flexibility to incorporate novel biomarker candidates – ongoing biologic and imaging task forces to seek new candidates**
- **Public private partnership in pre-competitive space.**



# PPMI requires a Partnership

- Expertise and experience in PD, trial design/operation, statistics and biomarkers
- Communication and coordination



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# **PPMI - Current Status/Timeline**

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- **Study launched June 2010**
- **All US sites recruiting by mid Nov.**
- **All EU sites recruiting by mid Feb**
- **All SOPs complete**
- **Database operational**
- **Web site live**
- **11 subjects consented**





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