PPMI Paving the Way for Defining Prodromal PD

Ken Marek
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Disclosure

- Co-founder on Molecular Neuroimaging LLC – PET and SPECT imaging services
- Consultant – BMS, GEHC, Lilly, Merck, Navidea, Piramal, Pfizer, Sanofi, Roche, LTI
Natural History of Neurodegenerative Disorders

Biomarker outcome

Preclinical

Prodromal

Symptomatic

Time

Clinical Ratings

Diagnosis
Why – Prodromal/Preclinical

• Prevent Disease onset and/or progression

• Elucidate/Test therapeutic targets
  – Inflammation
  – Synuclein/GBA/LRRK2

• Enable Precision/Personalized medicine
  – Genetics/biomarkers to establish disease subsets and targeted therapies

• Reduce long-term care costs
Parkinson Progression Marker Initiative

Specific Data Set
- Appropriate population (early stage PD and controls, prodromal, genetic PD subjects)
- 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
- www/ppmi-info.org
## PPMI Study Details: Synopsis

| Study population | 423 de novo PD subjects (newly diagnosed and unmedicated)  
|                  | 96 age- and gender-matched healthy controls  
|                  | 64 SWEDD  
|                  | 67 Prodromal - Olfactory/RBD  
|                  | 250 LRRK2 - PD manifest and non-manifesting family members  
|                  | 250 GBA- PD manifest and non-manifesting family members  
|                  | 100 SNCA - PD manifest and non-manifesting family members  
|                  | Subjects will be followed through 2018  

| Assessments/ Clinical data collection | Motor assessments  
|                                      | Neurobehavioral/cognitive testing  
|                                      | Autonomic, Olfaction, Sleep  
|                                      | DaTSCAN, AV133, Amyloid, DTI/RS MRI  

| Biologic collection/ | DNA, RNA, IPSC  
|                      | Serum and plasma collected at each visit; urine collected annually  
|                      | CSF collected at baseline, 6mo 12 mo and then annually  
|                      | Samples aliquotted and stored in central biorepository  

| Data and Biosamples shared on website - www.ppmi-info.org | > 420,000 Data downloads  
|                                                            | > 100 Sample requests via BRC  
|                                                            | Ancillary study development |
Natural History of Parkinson disease

Prodromal

Symptomatic

Diagnosis

Time

Neuron Function

Clinical Ratings

PPMI
Rate of SWEDD is higher in earlier Stages of PD
Natural History of Parkinson disease

Neuron Function

Prodromal PPMI P-PPMI

Symptomatic Diagnosis

Time
Comprehensive Data and Biomarker candidates being collected and evaluated

<table>
<thead>
<tr>
<th>CLINICAL MARKERS</th>
<th>IMAGING - PHENOTOMICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cognition</td>
<td>• SPECT/PET- Dopamine- DAT, VMAT2</td>
</tr>
<tr>
<td>• Behavioral</td>
<td>• Amyloid,</td>
</tr>
<tr>
<td>– Depression</td>
<td>• MRI –DTI/RS, volumetrics</td>
</tr>
<tr>
<td>– Anxiety</td>
<td></td>
</tr>
<tr>
<td>– ICD</td>
<td></td>
</tr>
<tr>
<td>• Autonomic</td>
<td><strong>BIOLOGICS</strong></td>
</tr>
<tr>
<td>– Constipation</td>
<td>• Blood, CSF, Urine</td>
</tr>
<tr>
<td>– Bladder</td>
<td>• Alpha-synuclein, Urate, Tau, Beta-Amyloid, EGF1, ApoA</td>
</tr>
<tr>
<td>– Sexual</td>
<td>• RNA Profiling</td>
</tr>
<tr>
<td>– Cardiac</td>
<td>• IPS cells</td>
</tr>
<tr>
<td>• Olfaction</td>
<td><strong>GENETICS</strong></td>
</tr>
<tr>
<td>• Sleep- RBD</td>
<td>• Synuclein, LRRK2, Parkin, DJ-1, Pink 1, GBA, Tau</td>
</tr>
<tr>
<td>• Skin</td>
<td>• Exome Sequencing</td>
</tr>
<tr>
<td>• Motor Analysis</td>
<td></td>
</tr>
</tbody>
</table>
Eligibility for P-PPMI

- **Hyposmic Subjects**: 80% Mild to moderate DAT, 20% Min to No-DAT
- **RBD Subjects**: Min to No-DAT

Eligible for PPMI

Not eligible for PPMI
Ascertainment of PARS Cohort

N = 10,139 Returned screening and background

N = 741 Not eligible
N = 9398 Eligible

N = 4999 Completed UPSIT
N = 4330 Normosmic
N = 669 Hyposmic

N = 4399 Did not complete UPSIT

N = 669 Hyposmic

Hyposmic N= 203 DAT
N = 23 <65% age expected
N = 178 >65% age expected
### PARS 4 yr follow-up

**Baseline**

<table>
<thead>
<tr>
<th>Age expected uptake in lowest putamen</th>
<th>Normosmics</th>
<th>Hyposmics</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DAT deficit ≥80%</td>
<td>N = 100</td>
<td>N = 203</td>
<td></td>
</tr>
<tr>
<td></td>
<td>92 (92%)</td>
<td>146 (72%)</td>
<td></td>
</tr>
<tr>
<td>65 – 80%</td>
<td>7 (7%)</td>
<td>34 (17%)</td>
<td></td>
</tr>
<tr>
<td>&lt;65%</td>
<td>1 (1%)</td>
<td>23 (11%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;80%</td>
<td>8 (8%)</td>
<td>57 (28%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**4 yr follow-up**

![Graph showing percentage uptake](chart.png)

- **<65% expected uptake**
- **65-80% expected uptake**
- **≥80% expected uptake**

- **61% (14/23)**
Ascertainment of PPMI Olfactory Cohort

N = 8699 Returned screening

N = 1074 Not eligible

N = 7592 Eligible

N = 4611 Completed UPSIT
N = 721 Hyposmic
N = 3890 Normosmic

N = 2991 Did not complete UPSIT
N = 721 Hyposmic

N = 1074 Not complete UPSIT
N = 721 Hyposmic

N = 477 Referred to sites

N = 106 DATscan
N = 81 Not eligible

N = 301 No DATscan
RBD and Risk of PD

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

A. Iranzo,, for the Sleep Innsbruck Barcelona (SINBAR) group
Lancet, 2010

17 of 43 RBD subjects demonstrate reduced DAT uptake

Putamen > caudate reduction

6/17 developed PD or DLB within 2.5 years

115 RBD consented

N = 18 Not eligible

97 Eligible PSG

82 -Completed DAT

41 PPMI ELIGIBLE

41 NOT ELIGIBLE

15 No DAT

Not eligible

PSG
PPMI-LRRK2/GBA/SNCA cohort

• Leverage existing PPMI infrastructure and add sites with existing expertise and experience with LRRK2 patients and families.

• Enroll 300 LRRK/GBA/SNCA + PD and 300 LRRK/GBA/SNCA + unaffected family members with an intensive longitudinal clinical assessment protocol.

• Follow PD and unaffected family members for four years
  – Establish pre-motor biomarker signature
  – Define phenoconversion

• Maintain PPMI database structure and commitment to rapid access to data
## LRRK2/GBA/SNCA Enrollment (Aug 2015)

**PD Subjects enrolled cohort**
- LRRK2 83
- SNCA 10

**Unaffected Subjects enrolled cohort**
- LRRK2 63
- SNCA 3

**PD Subjects tested/pos at sites**
- LRRK2 708/220
- SNCA 23/15
- GBA 106/8

**Unaffected Subjects tested/pos at sites**
- LRRK2 359/162
- SNCA 11/8
- GBA 22/6

<table>
<thead>
<tr>
<th>WRI</th>
<th>N</th>
<th>%</th>
<th>% M</th>
<th>% F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consented through WRI site, no previous testing</td>
<td>2471</td>
<td>100%</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>Qualified and confirmed through WRI</td>
<td>1664</td>
<td>67%</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Did not qualify through WRI</td>
<td>561</td>
<td>23%</td>
<td>28%</td>
<td>72%</td>
</tr>
<tr>
<td>Testing for LRRK2 G2019S</td>
<td>1087</td>
<td>100%</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>LRRK2-</td>
<td>973</td>
<td>90%</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td>LRRK2+</td>
<td>114</td>
<td>101%</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>Tested with PD</td>
<td>480</td>
<td>100%</td>
<td>59%</td>
<td>41%</td>
</tr>
<tr>
<td>LRRK2-</td>
<td>426</td>
<td>89%</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>LRRK2+</td>
<td>54</td>
<td>11%</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td>Tested without PD</td>
<td>607</td>
<td>100%</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>LRRK2-</td>
<td>547</td>
<td>90%</td>
<td>34%</td>
<td>66%</td>
</tr>
<tr>
<td>LRRK2+</td>
<td>60</td>
<td>10%</td>
<td>30%</td>
<td>70%</td>
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</table>
### PPMI Prodromal/Genetic Baseline Characteristics

#### Table 3a. PPMI Demographic Characteristics by Group: Genetic and Prodromal Cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Genetic Cohort</th>
<th>Prodromal Cohort</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PD Subjects</td>
<td>Unaffected Subjects</td>
</tr>
<tr>
<td></td>
<td>(N = 75)</td>
<td>(N = 82)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (35%)</td>
<td>21 (40%)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (65%)</td>
<td>31 (60%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 Years</td>
<td>27 (30%)</td>
<td>14 (27%)</td>
</tr>
<tr>
<td>50-65 Years</td>
<td>20 (27%)</td>
<td>21 (40%)</td>
</tr>
<tr>
<td>&gt;65 Years</td>
<td>28 (37%)</td>
<td>17 (33%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>66.6 (11.1)</td>
<td>61.2 (8.1)</td>
</tr>
<tr>
<td><strong>(Min, Max)</strong></td>
<td>(32, 85)</td>
<td>(44, 81)</td>
</tr>
<tr>
<td><strong>RBD Subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;13 Years</td>
<td>28 (37%)</td>
<td>21 (40%)</td>
</tr>
<tr>
<td>13-23 Years</td>
<td>45 (60%)</td>
<td>29 (56%)</td>
</tr>
<tr>
<td>&gt;23 Years</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
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</tr>
<tr>
<td>Hispanic/Latino</td>
<td>27 (33%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>45 (64%)</td>
<td>47 (80%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>82 (63%)</td>
<td>49 (44%)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (16%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>MDS-UPDRS Part III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22.8 (12.9)</td>
<td>26.4 (3.6)</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(4, 71)</td>
<td>(0, 13)</td>
</tr>
<tr>
<td>Missing</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><strong>MOCA Total Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>25.8 (5.5)</td>
<td>26.3 (2.7)</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(17, 30)</td>
<td>(19, 30)</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>GDS Total Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.8 (3.3)</td>
<td>1.9 (2.2)</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(0, 13)</td>
<td>(0, 8)</td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><strong>SCOPA-AUT Total Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.2 (6.2)</td>
<td>9.0 (6.8)</td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(0, 40)</td>
<td>(1, 28)</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Report Generated on Data Submitted as of: 01Apr2015.
Risk Profiling- PPMI

- Risk profiling
  - 28 loci
  - p.G2019S
  - p.N370S
  - Age
  - Sex
  - Family Hx
  - hyposmia

Nalls et al., Lancet Neurol. 2015
Risk Profiling –
Case probability from 5 cohorts
Risk Profiling –
Case probability from 5 cohorts

SWEDDS WITH ABNORMAL SCAN AT FU
>450,000 Data downloads worldwide
PPMI DATA SHARING

• Papers (>50) and Presentations

• Processes and Procedures

• Data to support sample size estimates for clinical trials

• Data to establish clinical trial cohorts for prodromal/genetic studies
PPMI Sites

**PPMI SITES IN THE UNITED STATES:**
- Arizona PD Consortium (Sun City, AZ)
- Beth Israel Medical Center (NY, NY)
- Baylor College of Medicine (Houston, TX)
- Boston University (Boston, MA)
- Cleveland Clinic (Cleveland, OH)
- Columbia University (NY, NY)
- Emory University (Atlanta, GA)
- Institute of Neurodegenerative Disorders (New Haven, CT)
- Johns Hopkins University (Baltimore, MD)
- Northwestern University (Chicago, IL)
- Oregon Health and Science University (Portland, OR)
- The Parkinson’s Institute (Sunnyvale, CA)
- PD & Movement Disorders Center at Boca Raton (Boca Raton, FL)
- University of Alabama at Birmingham (Birmingham, AL)
- University of California at San Diego (San Diego, CA)
- University of California at San Francisco (San Francisco, CA)
- University of Cincinnati (Cincinnati, OH)
- University of Pennsylvania (Philadelphia, PA)
- University of Rochester (Rochester, NY)
- University of South Florida (Tampa, FL)
- University of Washington (Seattle, WA)

**PPMI SITES IN EUROPE:**
- Foundation for Biomedical Research of the Academy of Athens (Athens, Greece)
- Imperial College (London, UK)
- Innsbruck University (Innsbruck, Austria)
- Norwegian University of Science and Technology (Trondheim, Norway)
- Paracelsus-Elena Clinic Kassel/University of Marburg (Kassel and Marburg, Germany)
- Pitié-Salpêtrière Hospital (Paris, France)
- University of Barcelona (Barcelona, Spain)
- University of Donostia (San Sebastien, Spain)
- University of Salerno (Salerno, Italy)
- University of Tübingen (Tübingen, Germany)

**PPMI SITES IN AUSTRALIA:**
- Macquarie University (Sydney, Australia)

**PPMI SITES IN Israel:**
- Tel Aviv Sourasky Medical Center (Tel Aviv, Israel)
PPMI funding partners

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