Agenda

1. Final touches on lit review
2. Review of available PPMI data
3. Profile bits and bobs – reclaiming a claim
4. AOB
ADDED LIT REVIEW TO REFERENCES

REORGANIZED CATEGORIES TO REFLECT TOPIC HEADINGS IN THE PROFILE

ADEQUATE FOR PRESENT

STILL NEEDS SOME ORGANIZATION

WILL REQUIRE CHANGES WITH FURTHER REVISIONS OF PROFILE
Are PPMI Data of Use to QIBA SPECT Committee?

Background: Rationale and Study Synopsis

Recruitment and State of the Data

Data Accessibility and Acquisition Logistics
# Parkinson’s Progression Marker Initiative (PPMI)

## Study synopsis

| Study population | 423 *de novo* PD subjects (newly diagnosed and unmedicated)  
|                  | 196 age- and gender-matched healthy controls  
|                  | 64 SWEDDs  
|                  | + Prodromal & Genetic cohorts  
|                  | Subjects are followed for a minimum of 3 years and a maximum of 5 years |
| Assessments/ Clinical data collection | • Motor assessments  
|                                            | • Neuropsychiatric/cognitive testing  
|                                            | • Olfaction  
|                                            | • DaTSCAN imaging- eligibility/serial monitoring  
|                                            | • DTI, resting state MRI  
|                                            | • AV-133, florbetaben PET substudies |
| Biologic collection/ Verification studies | • DNA collected at baseline  
|                                             | • Blood collected at each visit; CSF collected at 6mo and then annually  
|                                             | • Samples aliquoted and stored in central biorepository  
|                                             | • Lead biologic candidates potential to be tested: alpha-synuclein, DJ-1, urate |
| Data biosamples sharing | • > 586,000 data downloads  
|                            | • > 70 biosamples shared  
|                            | • www.ppmi-info.org |
Goals for PPMI – to inform clinical trials

- Improve diagnostic accuracy (enrich a study population)
- Develop tools to assess disease progression
- Establish outcomes prior to onset of motor symptoms
- Identify PD progression subsets -
  - Develop clinical outcomes (cognition, gait, autonomic)
  - Progression at different rates (fast vs slow)
  - Respond to specific therapy
  - Characterization of Genetic cohorts, Prodromal cohorts

- Phase 2 - provide an efficacy signal to increase confidence for subsequent Phase 3

- Phase 3 studies - enrich the study sample and provide objective outcomes of that reflect clinical benefit
<table>
<thead>
<tr>
<th>GROUP</th>
<th>Consented</th>
<th>Enrolled (n)</th>
<th>Withdrawn</th>
<th>Active</th>
<th>Complete</th>
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<tbody>
<tr>
<td>PD Subjects</td>
<td>488</td>
<td>423</td>
<td>45</td>
<td>371</td>
<td>7</td>
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<td>Healthy Controls</td>
<td>241</td>
<td>196</td>
<td>20</td>
<td>170</td>
<td>6</td>
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<td>SWEDD Subjects</td>
<td>82</td>
<td>64</td>
<td>9</td>
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<td>50</td>
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<td>Prodromal -Hyposmic</td>
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<td>26</td>
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<td>Prodromal-RBD</td>
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<td>LRRK2 PD Cohort</td>
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<td>92</td>
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<td>12</td>
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<td>GBA UA Cohort</td>
<td>26</td>
<td>21</td>
<td>0</td>
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<td>PD Registry</td>
<td>120</td>
<td>114</td>
<td>3</td>
<td>111</td>
<td>0</td>
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<td>UA Registry</td>
<td>127</td>
<td>120</td>
<td>0</td>
<td>120</td>
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<td><strong>TOTAL</strong></td>
<td><strong>1531</strong></td>
<td><strong>1213</strong></td>
<td><strong>83</strong></td>
<td><strong>1067</strong></td>
<td><strong>63</strong></td>
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Research Questions

• In an ongoing multi-center trial, do PD participants demonstrate serial reduction in Ioflupane DAT SPECT with appropriate signal:noise to be used as a progression biomarker?

• Which striatal subregions provide the best signal characteristics for longitudinal assessment of DAT density?
DAT SPECT LONGITUDINAL STUDY

- In an ongoing study, serial 123-I ioflupane SPECT were acquired at baseline, Year 1 and Year 2 post enrollment of 241 de novo Parkinson’s volunteers in the PPMI Trial

- Standardized reconstruction and image processing performed at the PPMI Core Imaging Lab in New Haven

- Regional specific binding ratios (SBR) were measured in ipsilateral and contralateral caudate, anterior putamen, and posterior putamen for each timepoint; baseline, Year 1, and Year 2

- Percent change from baseline reported for Year 1 and Year 2 as composite SBR and for separate striatal subregions and sides

In Addition.....

- Regional specific binding ratios (SBR) were measured in ipsilateral and contralateral caudate, anterior putamen, and posterior putamen for each timepoint; baseline and Year 4 (N=82)

- Percent change from baseline reported for Year 4 as composite SBR and for separate striatal subregions and sides
DAT Volumes of Interest

Caudate
Ant putamen
Post putamen

SBR = striatal region - 1 occipital
Characteristics of PPMI subjects

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Gender %M</th>
<th>Age (yrs)</th>
<th>Dz duration (months)</th>
<th>Part III MDS UPDRS baseline</th>
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<tbody>
<tr>
<td>Two Yr PD n=241</td>
<td>64.3%</td>
<td>60.8 ± 6.6</td>
<td>6.7 ± 6.8</td>
<td>21.5 ± 8.5</td>
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</table>

All had an Ioflupane SPECT scan demonstrating presynaptic striatal dopaminergic loss consistent with Parkinsonism prior to enrollment
Baseline DAT SBR, Age-corrected

Mean Striatal SBR

Contralateral Putamen SBR

PD n= 423
HC n= 196
SWEDD = 64
Results: Composite Striatal SBRs

Mean Striatum

<table>
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<tr>
<th>SBR</th>
<th>Contralateral</th>
<th>Ipsilateral</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>Y1</td>
<td>Y2</td>
</tr>
<tr>
<td>Mean</td>
<td>1.20</td>
<td>1.08</td>
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<tr>
<td>Std. Deviation</td>
<td>0.35</td>
<td>0.31</td>
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</table>

N= 241
Mean±SD
* p<0.0001 v Baseline
Results: Striatal SBR Rate of Change

Percent change Striatal Binding from baseline at Year 1 and Year 2 in 241 PD Subjects

% change SBR

<table>
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<tr>
<th>Year</th>
<th>Contra</th>
<th>Ipsilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yr 1</td>
<td>-7.4%</td>
<td>-11.8%</td>
</tr>
<tr>
<td>Yr 2</td>
<td>-15.0%</td>
<td>-17.1%</td>
</tr>
</tbody>
</table>

% Subj w/ change SBR <0:

- 80.0%
- 88.1%
*Results- SBR Striatal Subregions*

**Regional Striatal SBRs**

- **Ipsilateral**
  - CD
  - AP
  - PUT

- **Contralateral**
  - CD
  - AP
  - PUT

- N = 241
- Mean ± SD
- Pink = baseline
- Green = year 2
- *p < 0.0001
- Baseline vs Yr2

CD = caudate
AP = ant putamen
PUT = post putamen
Results - Rate of Change in Striatal Subregions

Percent Rate of Change of Striatal SBR Depends on Side and Subregion Measured

* p < .05 ipsi v contra
# p < .05 put v caud

Ipsi = ipsilateral, contra = contralateral, caud = caudate
Put = putamen, PutAnt = anterior putamen
Ipsilateral and Contralateral Mean % Change Striatal SBR over Four Years

Each timepoint is change from original baseline.
Baseline to Y4 Mean % Change SBR are Similar Across all Striatal Subregions
## Mean % change SBR in Striatal Subregions over 4 years

<table>
<thead>
<tr>
<th></th>
<th>ipsi caud</th>
<th>contra caud</th>
<th>ipsi ant put</th>
<th>contra ant put</th>
<th>ipsi put</th>
<th>contra put</th>
<th>ipsi stria</th>
<th>contra stria</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>-25.8</td>
<td>-27.5</td>
<td>-29.0</td>
<td>-28.7</td>
<td>-29.4</td>
<td>-21.8</td>
<td><strong>-28.2</strong></td>
<td><strong>-27.8</strong></td>
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<tr>
<td><strong>Std. Deviation</strong></td>
<td>16.6</td>
<td>18.1</td>
<td>18.9</td>
<td>22.4</td>
<td>22.3</td>
<td>31.8</td>
<td>16.1</td>
<td>18.5</td>
</tr>
<tr>
<td><strong>% COV</strong></td>
<td><strong>64.2</strong></td>
<td><strong>65.8</strong></td>
<td><strong>65.3</strong></td>
<td><strong>78.0</strong></td>
<td><strong>75.8</strong></td>
<td><strong>146.2</strong></td>
<td>57.0</td>
<td>66.6</td>
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<tr>
<td><strong>Mean baseline SBR</strong></td>
<td>2.23</td>
<td>1.86</td>
<td>1.53</td>
<td>1.16</td>
<td>0.98</td>
<td>0.65</td>
<td>1.58</td>
<td>1.22</td>
</tr>
</tbody>
</table>

N= 82

%COV variability between regions may be inversely related to baseline SBR
Are PPMI Data of Use to QIBA SPECT Committee?

Data Accessibility and Acquisition Logistics
- Web-based provision of DAT images; PD and age-matched controls
- Create normative templates
- Support claims (longitudinal, discriminatory)
- Standardize test datasets for processing validation
Reclaiming the discriminatory claim?

Claim 1: Cross sectional discrimination. During the initial presentation of newly symptomatic patients, a diagnosis of Parkinson’s disease (PD) is consistent with a finding of a SBR in the posterior putamen that is 50% or less than the value in aged-matched controls, or 80% or less than the value in the whole striatum.
Wrap-up

Review action Items

Any other business