PPMI in the Medical Literature
PPMI DATA SHARING

Downloads by Country:
- >10,000
- 1,000-10,000
- 501-1,000
- 101-500
- 1-100

Number of Downloads: 1,538,914
Number of Specimen Requests: 102

Downloads by Sector:
- 2% Biotech
- 1% Government
- 4% Other
- 5% Pharmaceutical
- 0% Scanner Mfg
- 88% University/Research
PUBLICATIONS USING PPMI DATA BY YEAR

YEAR
Number Of Publications
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
HOW IS PPMI DATA BEING USED?

» Advanced analytics
» Clinical-biomarker correlations
» Novel biomarkers and genetic associations
» Non-motor features
» Clinical trial methods development
LARGE-SCALE IDENTIFICATION OF CLINICAL AND GENETIC PREDICTORS OF MOTOR PROGRESSION

• Machine learning approach using PPMI and LABS-PD data
• Reverse Engineering and Forward Simulation (REFS) platform: constructed a predictive ensemble, consisting of 128 generalized linear models using Markov Chain Monte Carlo sampling of the full Bayesian posterior distribution
  • Protects against overfitting in the case when the potential number of predictors exceeds the number of observation
  • Allows incorporation of previous knowledge regarding the different types of data

Latourelle et al. Lancet Neurology, November 2017
LATTOURELLE: RESULTS

**Figure 1:** Variable importance of model predictors in motor progression
The relative contribution to the overall explanatory power for individual or sets of features is shown. The variable importance of the features is expressed as a percentage increase in the mean squared error in leave-one-out cross-validation, with each feature plotted in descending order of importance. Diamonds denote the mean and error bars the 95% CI. The dashed red line represents the full model (reference) without excluding any features. SNP = single nucleotide polymorphism.

R² for PPMI: 41%
R² for LABS-PD: 9%
LATTOURELLE: RESULTS

Figure 3: LABS-PD cohort motor scores by predicted progression group. Datapoints denote the median MDS-UPDRS (parts II and III) motor scores and error bars the 95% CI. The first follow-up examination was at either 3 or 4 years after baseline and scores are shown for patients predicted to have slow, moderate, or fast disease progression at study baseline. LABS-PD = Longitudinal and Biomarker Study in Parkinson's disease. MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

Latourelle et al. Lancet Neurology, November 2017

PARKINSON'S PROGRESSION MARKERS INITIATIVE
A MULTILEVEL-ROI-FEATURES-BASED MACHINE LEARNING METHOD FOR DETECTION OF MORPHOMETRIC BIOMARKERS IN PARKINSON’S DISEASE


\[ c(i, j) = \exp \left\{ -\frac{(t(i) - t(j))^2}{2(\sigma_i^2 + \sigma_j^2)} \right\} \]

\[ F(x) = \text{sign} \left( \sum_{n=1}^{N} \alpha_n y_n \sum_{m=1}^{M} \beta_m \left( x_n^{(m)}, x^{(m)} \right) \right) \]

\[ \sum_{n=1}^{N} \alpha_n y_n = 0 \text{ with } 0 \leq \alpha_n \leq c, \ n = 1, \ldots \]
Overall model predicts cognitive impairment with 88% sensitivity and 88% specificity.

Strongest predictors are clustered in frontal lobes.
NUCLEUS BASALIS OF MYNERT DEGENERATION PRECEDES AND PREDICTS COGNITIVE IMPAIRMENT IN PARKINSON’S DISEASE

Schultz and Pagano et al. Brain 2018

- Cross sectional and longitudinal analysis using PPMI data
- Hypothesis: structural alterations in NBM are related to cognitive impairment in PD
- Examined gray matter volume and mean diffusivity
Results

- Mean diffusivity and volume loss in the NBM were both associated with cognitive decline.
- Changes in other brainstem and deep gray matter structures were not associated with cognitive decline.
- Findings may be used to stratify patients at higher risk.
AGING MODIFIES THE EFFECT OF GCH1 RS11158026 ON DAT UPTAKE AND PD CLINICAL SEVERITY

» GCH1 is an essential enzyme for dopamine production in nigrostriatal cells

» Goals of study
  – To determine if GCH1 mutation carriers are at higher risk for PD
  – Compare age at onset in carriers vs. non-carriers

Webb and Willette, Neurobiology of Aging, 2017
RESULTS

Webb and Willette, Neurobiology of Aging, 2017
RESULTS

Webb and Willette, Neurobiology of Aging, 2017
LONGITUDINAL CSF BIOMARKERS IN PATIENTS WITH EARLY PD AND CONTROLS

» Analyzed tau, p-tau and abeta in CSF
» Time points included baseline, 6 months and 12 months follow up
» Correlated with changes in clinical and/or DATscan indices of disease progression

Mollenhauer et al. Neurology. November 2017
RESULTS

» Evaluated samples from 173 PD patients and 112 healthy controls
» CSF biomarker levels were stable over one year
» CSF biomarkers did not correlate with change in motor function assessed by MDS-UPDRS

Mollenhauer et al. Neurology. November 2017
SEEDING ASSAYS

PMCA Assay

JAMA Neurology, 2017

88% sensitivity
97% specificity

RT-QuIC Assay

Ann Clin Transl Neurol, 2016

95% sensitivity
100% specificity

<table>
<thead>
<tr>
<th>Number of Positive ASN-RT-QuIC (%)</th>
<th>Pure DLB (12)</th>
<th>PD (2)</th>
<th>DLB with AD pathology (17)</th>
<th>AD with incidental LB (13)</th>
<th>Pure AD (30)</th>
<th>Progressive supranuclear palsy (PSP) (2)</th>
<th>Corticobasal degeneration (CBD) (3)</th>
<th>Controls (20)</th>
<th>Parkinson’s disease (20)</th>
<th>At-risk RBD patients (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (92%)</td>
<td>2 (100%)</td>
<td>11 (65%)</td>
<td>4 (31%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>19 (95%)</td>
<td>3 (100%)</td>
</tr>
</tbody>
</table>
PREDICTORS OF ANXIETY IN EARLY-STAGE PARKINSON'S DISEASE: RESULTS FROM THE FIRST TWO YEARS OF A PROSPECTIVE COHORT STUDY

Rutten et al. Parkinsonism and Related Disorders 2017

Goals and Methods

» Goal: To assess which sociodemographic and clinical characteristics predict the course of anxiety in early PD

» Methods:
  – Two year prospective study
  – Included 306 PPMI participants
  – Mixed model analysis
Factors associated with increased anxiety over time

» Older age
» Lower baseline MoCA
» Probable RBD at baseline

Factors associated with decreased anxiety over time

» Higher baseline depression
» Compulsive behavior at baseline
» Family history of PD
Goal: Develop a screen for dementia risk score based on simple clinical measures for use in normal and MCI subjects

Used data from Montreal (n = 80), Tottori, Japan (n = 134) and PPMI (n = 393)

Items chosen based on literature review

Scoring system based on split sample validation approach
MONTREAL PARKINSON RISK OF DEMENTIA SCALE: ITEMS AND WEIGHTS

<table>
<thead>
<tr>
<th>Predictors</th>
<th>MoPaRDS</th>
<th>Weighted MoPaRDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bilateral disease onset</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Falls or freezing</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Age greater than 70 years</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Orthostatic BP drop &gt; 10 mmHg</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>REM Sleep Behavior Disorder (RBD)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Positive MCI status</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Maximum score</td>
<td>8</td>
<td>33</td>
</tr>
</tbody>
</table>

From Dawson, JAMA Neurology 2018
DAWSON ET AL. RESULTS

ROC = 0.88

Figure 1. Progression to Dementia by Risk Group

The hazard ratios for Montreal Parkinson Risk of Dementia Scale (MoPaRDS) scores of 0 to 3, 4 and 5, and 6 to 8 are 1 (Reference), 10.4 (95% CI, 5.1-19.8), and 20.8 (95% CI, 10.4-41.6), respectively. Log rank test, P < .001.
ARTICLE

Dopamine Transporter Neuroimaging as an Enrichment Biomarker in Early Parkinson’s Disease Clinical Trials: A Disease Progression Modeling Analysis

Daniela J. Conrado¹,* , Timothy Nicholas², Kuenhi Tsai³, Sreeraj Macha³, Vikram Sinha³, Julie Stone³, Brian Corrigan², Massimo Bani⁴, Pierandrea Muglia¹, Ian A. Watson⁵, Volker D. Kern¹, Elena Sheveleva¹,⁶, Kenneth Marek⁷, Diane T. Stephenson¹ and Klaus Romero¹ on behalf of the Critical Path for Parkinson’s (CPP) Parkinson’s Disease Modeling and Simulation Working Group

Given the recognition that disease-modifying therapies should focus on earlier Parkinson’s disease stages, trial enrollment based purely on clinical criteria poses significant challenges. The goal herein was to determine the utility of dopamine transporter neuroimaging as an enrichment biomarker in early motor Parkinson’s disease clinical trials. Patient-level longitudinal data of 672 subjects with early-stage Parkinson’s disease in the Parkinson’s Progression Markers Initiative (PPMI) observational study and the Parkinson Research Examination of CEP-1347 Trial (PRECEPT) clinical trial were utilized in a linear mixed-effects model analysis. The rate of worsening in the motor scores between subjects with or without a scan without evidence of dopamine transporter deficit was different both statistically and clinically. The average difference in the change from baseline of motor scores at 24 months between biomarker statuses was −3.16 (90% confidence interval [CI] = −0.96 to −5.42) points. Dopamine transporter imaging could identify subjects with a steeper worsening of the motor scores, allowing trial enrichment and 24% reduction of sample size.

CONRADO ET AL: RESULTS
SUMMARY

» PPMI data is being used widely
» Expect to see more big-data approaches, hopefully with replication in other cohorts
» Will results from studies with 1-2 year of follow up hold up when more data becomes available?