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RESEARCH ARTICLE

The Parkinson's progression markers initiative (PPMI) – establishing a PD biomarker cohort

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Abstract

Objective: The Parkinson's Progression Markers Initiative (PPMI) is an observational, international study designed to establish biomarker-defined cohorts and identify clinical, imaging, genetic, and biospecimen Parkinson's disease (PD) progression markers to accelerate disease-modifying therapeutic trials. **Methods**: A total of 423 untreated PD, 196 Healthy Control (HC) and 64 SWEDD (scans without evidence of dopaminergic deficit) subjects were enrolled at 24 sites. To enroll PD subjects as early as possible following diagnosis, subjects were eligible with only asymmetric bradykinesia or tremor plus a dopamine transporter (DAT) binding deficit on SPECT imaging. Acquisition of data was standardized as detailed at www.ppmi-info.org. **Results**: Approximately 9% of enrolled subjects had a single PD sign at baseline. DAT imaging excluded 16% of potential PD subjects with SWEDD. The total MDS-UPDRS for PD was 32.4 compared to 4.6 for HC and 28.2 for SWEDD. On average, PD subjects demonstrated 45% and 68% reduction in mean striatal and contralateral putamen Specific Binding Ratios (SBR), respectively. Cerebrospinal fluid (CSF) was acquired from >97% of all subjects. CSF (PD/HC/SWEDD pg/mL) α-synuclein (1845/2204/2141) was reduced in PD vs HC or SWEDD ($P < 0.03$). Similarly, *t*-tau (45/53) and *p*-tau (16/18) were reduced in PD versus HC ($P < 0.01$), **Interpretation**: PPMI has detailed the biomarker signature for an early PD cohort defined by clinical features and imaging biomarkers. This strategy provides the framework to establish biomarker cohorts and to define longitudinal progression biomarkers to support future PD treatment trials.

Introduction

Utilizing biomarkers to define optimal study cohorts and identifying reliable and well-validated biomarkers for Parkinson's disease (PD) progression are crucial to advance research to develop therapeutics that may slow or prevent PD symptoms and pathology.[1,2] The Parkinson's Progression Markers Initiative (PPMI) is an observational, international, multicenter study designed to establish biomarker-defined cohorts, identify PD progression biomarkers to improve understanding of disease etiology and course, and to provide the necessary tools to enhance the likelihood of success of PD disease-modifying therapeutic trials (ClinicalTrials.gov Identifier: NCT01141023). PPMI is a collaborative effort of PD researchers with expertise in biomarker development, PD clinical study design and implementation, bioinformatics, statistics, and data management.[3] The study is a public-private partnership of academic researchers, The Michael J. Fox Foundation for Parkinson's Research (MJFF), and pharmaceutical and biotech industry partners. The overall goal of PPMI is to investigate novel methods to establish longitudinal PD cohorts to examine clinical, imaging, genetic, and biospecimen PD progression markers that individually or in combination will rapidly demonstrate interval change in PD patients in comparison to Healthy Controls (HC) or in sub-sets of PD patients defined by baseline assessments, genetic mutations, progression milestones, and/or rate of clinical, imaging, or biospecimen change.

PPMI has established standardized protocols for acquisition, transfer, and analysis of clinical, imaging, genetic, and biospecimen data that can be used by the PD research community. Importantly, PPMI is committed to data and biospecimen sharing. PPMI data are available to the research community on the PPMI website as it is collected. As of December 2017, there are more than 1.5 million downloads of data, and more than 100 request applications for PPMI biospecimens reviewed by the PPMI Biospecimen Review Committee. All PPMI standardized protocols and data are available atwww.ppmi-info.org.

A major initial goal of PPMI was to establish a biomarker-defined early PD cohort to be followed longitudinally to identify progression biomarkers. Early and accurate diagnosis of PD subjects enabling enrollment as soon as possible following diagnosis would potentially allow assessment of subjects in clinical trials for as long as possible prior to initiating PD medications. This strategy is crucial to the early investigation of novel disease-modifying PD therapies. We recognize that some of these data have been part of other publications that have utilized PPMI open access data. In this paper from the PPMI steering committee, we comprehensively detail the methods utilized to establish the biomarker-defined PD cohort and the baseline clinical, imaging, and CSF characteristics of the cohort.

Methods

Study organization and governance

The PPMI steering committee is responsible for all aspects of study conduct and directs the study through the clinical, imaging, genetics, bioanalytic, biorepository, statistics, and bioinformatics cores. The steering committee includes PD clinical and biomarker experts, study core leaders, MJFF, and industry scientists.

Study participants

PD and HC subjects of similar age and gender from 24 study sites in the US (18), Europe (5) and Australia (1) were enrolled after obtaining informed consent. We acknowledge that the early PD cohort likely includes a small number of subjects with other DAT deficit parkinsonian syndromes such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and cortical basal syndrome (CBS), which may be indistinguishable from PD at the earliest stages of disease. At each study visit, the investigators reassess the subject diagnosis to identify any non-PD subjects.

This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines after approval of the local ethics committees of the participating sites. At enrollment, PD subjects were required to be age 30 years or older, untreated with PD medications (levodopa, dopamine agonists, MAO-B inhibitors, or amantadine), within 2 years of diagnosis, Hoehn and Yahr <3, and to have either at least two of resting tremor, bradykinesia, or rigidity (must have either resting tremor or bradykinesia) or a single asymmetric resting tremor or asymmetric bradykinesia. All PD subjects underwent dopamine transporter (DAT) imaging with 123I Ioflupane or vesicular monoamine transporter (VMAT-2) imaging with 18F AV133 (Australia only) and were only eligible if DAT or VMAT-2 imaging demonstrated dopaminergic deficit consistent with PD in addition to clinical features of the disease. Study investigators evaluated enrolled PD subjects to assess absence of current or imminent (6 months) disability requiring PD medications, though subjects could

initiate PD medications at any time after enrollment if the subject or investigator deemed it clinically necessary. Those subjects screened as potential PD subjects who were ineligible due to DAT or VMAT-2 scans without evidence of dopaminergic deficit (SWEDD) were eligible to be enrolled in a SWEDD cohort.[4] HC subjects were required to be age 30 years or older without an active, clinically significant neurological disorder or a first-degree relative with PD. All enrolled subjects agreed to complete all study evaluations, including lumbar puncture.

PD and SWEDD subjects were excluded if they had a clinical diagnosis of dementia or had taken PD medications within 60 days of baseline or for longer than 60 days in total. HC subjects were excluded if they had a Montreal Cognitive Assessment (MoCA) total score $\leq$26. All subjects were excluded if they were treated with neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative within 6 months or were currently treated with anticoagulants that might preclude safe completion of the lumbar puncture.

Study assessments

All subjects underwent a comprehensive battery of clinical testing, imaging assessments, blood, urine, and cerebrospinal fluid (CSF) biospecimen collection at baseline. Planned follow-up for all subjects included clinical motor assessments at 3-month intervals during year one followed by 6-month intervals. Cognitive and behavioral assessments were conducted at 12-month intervals for all subjects. DAT or VMAT-2 (Australia only) imaging was conducted at 12, 24, and 48-month visits for PD subjects, 24-month visits for SWEDD subjects, and only at baseline for HC subjects. All subjects underwent MRI at baseline, and approximately 50% of the subjects (based on the potential to standardize their MRI acquisition) underwent more extensive MRI with diffusion tensor imaging (DTI) at baseline and at similar longitudinal intervals to DAT imaging. All subjects had planned follow-up with blood collection at 3-month intervals during year one followed by 6-month intervals, CSF collection at six, and 12-month visits, followed by 12-month intervals. All subjects underwent urine collection at 12-month intervals.

Clinical assessments included Movement Disorders Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) and Hoehn and Yahr scales.[5] Global cognition was assessed with the MoCA.[6,7] Cognitive testing included the Hopkins Verbal Learning Test-Revised (HLVT-R) to assess memory; Benton Judgment of Line Orientation (JOLO) 15-item version to assess visuospatial function; Symbol-Digit Modalities Test (SDMT) to assess processing speed-attention; and Letter-Number Sequencing (LNS) and semantic (animal) fluency to assess executive abilities-working memory.[8–12] Published norms were applied. Neurobehavioral testing included the Geriatric Depression Scale (GDS), State – Trait Anxiety Inventory (STAI), and Questionnaire for Impulsive-Compulsive Disorders (QUIP).[13–15] Additional assessments included Epworth Sleepiness Scale and a REM sleep behavior disorder (RBD) questionnaire to assess sleep behavior, Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) to assess autonomic function, and the 40-item University of Pennsylvania Smell Identification Test (UPSIT) to assess olfactory function..[16–19]

All subjects had dopaminergic imaging with either 123I Ioflupane targeting the dopamine transporter (DAT-SPECT) or 18F AV133 (Australian site only) targeting the vesicular monoamine transporter (VMAT-PET) at screening according to the imaging technical operations manual (www.ppmi-info.org).[20–24] To ensure technical standardization across multiple sites and cameras employed in this study, a central core imaging laboratory developed a program for technical qualification, quality assurance, and ongoing camera quality control. An anthropomorphic striatal phantom was filled with 123-I and acquired with the same protocol used for PPMI subjects. This phantom was used to check for the accuracy and resolution of the reconstructed image volume, as well as to develop a site-specific attenuation correction factor (μ) to be applied to the data at the imaging core lab.

All imaging data were visually read and analyzed quantitatively at the central core imaging laboratory at the Institute for Neurodegenerative Disorders (IND) in New Haven, CT. For DAT studies, subjects were injected with 185 MBq of 123I Ioflupane then imaged 4 ± 0.5 h postinjection for 30–45 min. Sites transferred raw projection data to the central core imaging laboratory for quality control, including assessment for motion, standardized reconstruction, attenuation correction, and quantification. SPECT raw projection data were imported to a HERMES (Hermes Medical Solutions, Stockholm, Sweden) system for iterative (HOSEM) reconstruction. This was performed for all imaging data to ensure consistency of the reconstructions. Iterative reconstruction was performed without any filtering applied. The HOSEM reconstructed files were then transferred to PMOD (PMOD Technologies, Zurich, Switzerland) analysis software for subsequent processing. Attenuation correction ellipses were drawn on the images and a Chang 0 attenuation correction were applied to images utilizing a site-specific mu that was empirically derived from phantom data acquired during site initiation for the study., A standard Gaussian 3D 6.0 mm filter was applied after attenuation correction was completed. These files were then normalized to a SPECT ioflupane reference template in standard Montreal

Neurologic Institute (MNI) space to ensure standard anatomical alignment across scans. Intramodality spatial normalization using the standard template provided the most robust normalizations for the ioflupane DAT-SPECT image volumes. Subsequently, the transaxial slice with the highest striatal uptake was identified and the eighth hottest striatal slices around it were averaged to generate a single slice image. For VMAT-PET studies, subjects were injected with 222 MBq of 18F AV133 then imaged for 10 min at 50 min postinjection and for 10 min at 80 min postinjection, for a total of 20 min of imaging. PET data were imported to a PMOD system for processing and analysis following technical and scientific quality control, including assessment for motion performed at the central core imaging laboratory. The PET volume was co-registered to the subject's MRI. The MRI was normalized to standard MNI space and the transformations from that normalization applied to the co-registered PET volume to ensure standard anatomical alignment across scans. A standardized striatal template created at the central core imaging laboratory was then placed on the normalized MRI volume. Volume of interest (VOI) placement was adjusted on images with atrophy, or if the VOI template did not exactly align.

All images were visually interpreted as either positive or negative for DAT or VMAT-2 deficit[25] by two experienced, independent nuclear medicine readers blinded to clinical diagnosis. Visual interpretation for both DAT and VMAT-2 images required the reader to interrogate the intensity and symmetry of radiotracer uptake in left and right putamen to determine whether the pattern was consistent with a dopaminergic deficit. Criteria for abnormality for DAT were as indicated on the product label. Similar criteria were also used for VMAT-2. In the event of disagreement between the readers' visual interpretation, a consensus review process was implemented for the final scan interpretation. Subjects were enrolled in the PD, SWEDD, or HC cohorts based on a combination of visual interpretation of DAT or VMAT-2 imaging and the clinical eligibility criteria (above).

Quantitative outcomes were acquired for all images. For DAT VOI were placed on the left and right caudate, left and right putamen, and the occipital cortex (reference tissue) (Fig. S1). Count densities for each region were extracted and used to calculate SBRs for each of the four striatal regions. SBR was calculated as (target region/reference region)-1. For VMAT-2 quantitative measurements (count densities or average standard uptake value (SUV) per voxel) were extracted and used to calculate SBRs for all of the striatal areas (left and right caudate, anterior putamen, and posterior putamen). SBR was calculated as (target region/reference region)-1. The reference region was the occipital lobe. Note that the posterior putamen for VMAT-2 was equivalent to the putamen reported for DAT. DAT and VMAT-2 striatal regional SBR were characterized as either ipsilateral or contralateral to the motor symptoms as defined by the MDS-UPDRS. If there was no motor asymmetry (<5%), the right side was called ipsilateral by convention.

All subjects underwent MRI imaging at baseline to identify significant non-PD pathology. Subjects from 10 study sites had a standardized MRI acquisition protocol including a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence for imaging anatomical details and a cardiac-gated 2D single-shot echo-planar DTI sequence for mapping brain water diffusion requiring a 3 Tesla Siemens Trio (these data have been reported elsewhere).[26]

Baseline blood (plasma, whole blood, RNA) and CSF were collected as detailed in the PPMI biologics manual (www.ppmi-info.org). Blood samples were collected in the morning after fasting (all times of collection and fasting status were recorded). CSF (15–20 mL) was collected into siliconized polypropylene tubes and centrifuged at 2000*g* for 10 min at room temperature, then transferred into 1.5 mL precooled siliconized polypropylene aliquot tubes followed by immediate freezing on dry ice. All frozen blood, plasma, and CSF were shipped overnight to the PPMI Biorepository Core laboratories (Coriell, Camden NJ, US; Indiana University, IN, US; BioRep, Milan, Italy).

Measurements of Aβ1–42, *T*-tau, and *P*-tau$_{181}$ were obtained for CSF samples at the University of Pennsylvania using the multiplex Luminex xMAP platform (Luminex Corp: Austin, Texas, USA) with research-use-only Fujirebio-Innogenetics INNO-BIA AlzBio3 immunoassay kit-based reagents (Innogenetics Inc: Harvard, MA, USA) from a single lot as described previously.[27,28] All standards, aqueous controls, and CSF samples (including 2 CSF pools for quality control, 75 μL each) were analyzed in duplicate in each run.[27,28] The reported values were calculated as the arithmetic mean of the concentration of the duplicates. CSF α-syn was analyzed at a central laboratory (Covance, MA, US) using a commercially available enzyme-linked immunosorbent assay kit. This kit was developed and optimized for PPMI.[29,30] Briefly, 200 μL/well of diluted α-syn standards (range, 6.1–1500 pg/mL) using reconstituted stock and diluted duplicate CSF samples (200 μL/well) were added to the capture antibody–coated plate after washing the plate four times. After overnight incubation of the plate at 2–8°C with shaking, 50 μL/well of biotinylated detector antibody was added followed by incubation for 2 h at room temperature. Diluted streptavidin horseradish peroxidase was added, and the plate was incubated at room temperature for an additional 1 h. After washing the plate four times, a mixture of two different chemiluminescent

substrates was added and end-point luminescence was read with a luminometer (Synergy 2; BioTek). The concentration of α-syn was measured using standard curves with four-parameter curve fitting. Cross-reactivity with β-syn or γ-syn has not been observed with the antibodies used in this assay.[29,30] CSF hemoglobin was measured at Covance using an enyzme-linked immunosorbent assay method with reagents obtained from Bethyl Laboratories according to the manufacturer's instruction. Hemoglobin was measured to assess the extent of blood contamination of CSF samples, and to control for the possible effect of α-syn coming from red blood cells on observed CSF levels.[31]

Blood DNA was extracted, and subjects were genotyped using ImmunoChip and NeuroX genotyping arrays. Briefly, the ImmunoChip is an Illumina Infinium based array that interrogates 196,524 variants. The ImmunoChip was designed in 2009 by investigators interested in inflammatory and autoimmune disorders. However, this content also included ~2000 variants prioritized for follow-up by PD genome-wide association study (GWAS). The content of the ImmunoChip is available (https://ida.loni.usc.edu/pages/access/geneticData.jsp) and this platform has been previously described.[32] NeuroX was designed in conjunction with Illumina Inc. and includes over 240,000 exonic variants, as well as over 24,000 variants relevant to the study of neurodegenerative disease. Subsequently, whole-genome sequencing has been completed on the entire cohort.

Standardization

Prior to activation of sites for subject enrollment, all site personnel received extensive training related to acquisition of study data and biospecimen collections to ensure standardization. This included training for MDS-UPDRS (all examiners required to complete MDS-UPDRS training), cognitive and behavioral assessments, electronic data entry, biospecimen collection and handling, and imaging acquisition.[33] Training was provided either by web-based instruction and/or in-person by PPMI study core personnel. Specific study data and biospecimen acquisition manuals (available on www.ppmi-info.org) were developed to augment site training and ensure ongoing standardization. All data were routinely subjected to quality control processes by study cores. Documentation of standardized analysis processes are made available at www.ppmi-info.org.

Data flow and access

All data collected at sites were transferred to the clinical core (Clinical Trials Coordination Center (CTCC), Rochester, NY), imaging core (Institute for Neurodegenerative Disorders (IND), New Haven, CT), and biorepositories (Coriell Institute, NJ, US and subsequently Indiana University, IN, US; BioRep, Milan, Italy). Data for each subject visit were reconciled and then transferred to the bioinformatics core (Laboratory of Neuroimaging (LONI), Los Angeles, CA). All data are made available to the PD research community as these data are collected. Data can be downloaded from the website (www.ppmi-info.org) after completion of the data access application.

Statistical analysis

All analyses were performed by the biostatistics core (University of Iowa, IA, US). For the findings reported here, the overall goal of the statistical plan was to compare baseline clinical and biomarker results between PD, HC, and SWEDD groups and to evaluate associations between clinical and biomarker data. *T*-tests or Chi-square were used for pairwise comparisons of demographic, clinical, and imaging data in PD, HC, and SWEDD subjects. Due to skewed distributions of biospecimen data, nonparametric Mann–Whitney U tests were used for pairwise group comparisons of these variables. The total MDS-UPDRS and DAT contralateral putamen were identified prior to the study as two candidate biomarkers with face validity for PD progression. Thus, we sought to assess the associations between clinical, imaging, and biospecimen variables and baseline total MDS-UPDRS and DAT SBR (contralateral putamen) in PD subjects using multivariable linear regression models with a backwards selection approach. All models adjusted for age, gender, and duration of disease. For model fitting, a covariate was included if it was associated with an outcome at a significance level of 0.20 or less after adjustment for age, gender, and duration of disease. To avoid collinearity issues in the multivariable models, the following hierarchical rules were used: for CSF biomarkers, if the individual markers were significant in the screening models, they were considered in the multivariable model; the CSF ratios were only considered if neither of the individual markers were significant. Similarly, for the DAT SBR variables, if the contralateral putamen or caudate scores were significant, they were considered; if not, but the ipsilateral putamen or caudate were significant, they were considered. This screening process revealed a set of potential predictor variables for both outcomes under consideration. This set of predictor variables made up an initial "full model." Subsequently, a backwards selection process was used to remove variables one at a time until all variables remaining in the model were significant at the 0.10 level. Due to the

exploratory nature of these analyses and a desire to cast a wide net to suggest areas for further exploration of any findings, we chose not to adjust for multiple comparisons.

Results

A total of 811 subjects (570 PD and 241 HC) were screened for participation in PPMI. Of the 570 screened as PD subjects, 423 subjects were enrolled, 30 were excluded, 36 declined participation following screening, and 81 (16%) were found to have SWEDD. Subjects with SWEDD were eligible to participate in the SWEDD cohort. Of the 81 subjects with a SWEDD, 64 (79%) agreed to enroll in PPMI, and 16 declined participation following screening. Of those screened as HC subjects, 196 were enrolled, 31 were excluded, and 14 declined participation following screening. Subjects were enrolled in PPMI at 24 sites (553 at 18 US sites, 124 at 5 European sites and 6 subjects at 1 Australian site). Enrollment began June 1, 2010. The duration of the enrollment period was approximately 32 months (Fig. 1). The average enrollment rate was 1 subject/month/site for PD subjects and 0.5 subjects/month for HC subjects. The enrollment curve for HC subjects (Fig. 1B) reflects that HC subject enrollment was deliberately slowed for 6 months to ensure that the PD and HC subject enrollment would be completed concurrently, and to ensure a reasonable age and gender balance among the PD and HC cohorts. Enrollment of SWEDD subjects occurred at a similar rate to PD subjects throughout the enrollment period. Subjects with SWEDD were enrolled in 22 of 24 sites ranging from 1 to 6 subjects/site.

The subject demographics (Table 1) confirm that we were successful in obtaining groups of PD, HC, and SWEDD subjects who were similar with regard to age and gender. The entire cohort was overwhelmingly white and non-Hispanic. The PD and HC subjects were generally highly educated. By design, HC subjects could not be first-degree relatives of PD patients. First-degree family members with PD were slightly more prevalent, and education levels were significantly lower, among SWEDD compared to PD subjects.

The number of PD features (signs and symptoms) at enrollment for PD and SWEDD subjects is indicated in Table 2. Initial symptom categories were resting tremor, bradykinesia, rigidity, postural instability, and other (i.e., micrographia, hypophonia, sialorhea, dystonia, reduced arm swing). Study investigators were asked to enroll subjects as early in their disease as possible. Approximately 9% of both PD and SWEDD subjects were enrolled into the study with a single asymmetric PD feature, and in those subjects asymmetric resting tremor was the single feature in more than 80% of these single feature subjects. The duration of diagnosis at baseline was approximately 7 months and did not differ between PD and SWEDD subjects. The focus on enrollment of subjects early in disease raises the possibility that some of the PD subjects may have other DAT deficit parkinsonian syndromes that will emerge with follow-up.

The baseline clinical motor, cognitive, and behavioral characteristics of the PD, HC, and SWEDD cohort are shown in Table 2. PD subjects had increased total MDS-UPDRS compared to both HC and SWEDD subjects. As expected, PD subjects had significantly higher values than HC subjects on all MDS-UPDRS components. The SWEDD subjects have increased MDS-UPDRS part 1, decreased MDS-UPDRS part 3, and similar MDS-UPDRS part 2 compared to PD subjects. PD subjects demonstrated modest but clear impairment in tests of cognition, depression, autonomic function, anxiety, and sleep compared to HC subjects. SWEDD subjects showed modestly increased depression, anxiety, and abnormalities in autonomic testing compared to PD subjects. The UPSIT was markedly abnormal in PD subjects, but within the normal range in both HC and SWEDD subjects. Approximately 40% of PD and SWEDD subjects endorsed questions consistent with RBD compared to 20% of HC subjects. Baseline cognitive and behavioral status of the PD and HC cohorts is detailed further in another report.[34]

DAT imaging data demonstrated a marked reduction in approximately 45% in SBR in PD compared to HC subjects (Table 3). All striatal regions were substantially reduced in PD subjects compared to HC or SWEDD subjects. The greatest reduction in PD at baseline of 67.8% was found in the contralateral putamen. Regional quantitative imaging values did not differ between SWEDD subjects and HC subjects.

Figure S2 demonstrates the SBR scatterplots for PD and HC subjects for the mean striatum, ipsilateral and contralateral putamen, and ipsilateral and contralateral caudate. To further compare the visual and quantitative eligibility strategies, a linear discriminant analysis (LDA) model that included variables representing SBRs for different regions as well as indices of asymmetry (Table S1). From the model, the region providing the best discrimination between HC and PD subjects was the contralateral putamen. Using leave-one-out cross-validation, the function returned an overall accuracy of 97.4% (Table S1) and indicates the sensitivity, specificity, and positive and negative predictive value of the discriminant function compared to the enrollment eligibility using the visual read standard. Sensitivity analyses inspecting the consequences of violating the assumptions of equal variability across cohorts and nonexcessive multicollinearity returned very similar results (data not shown).

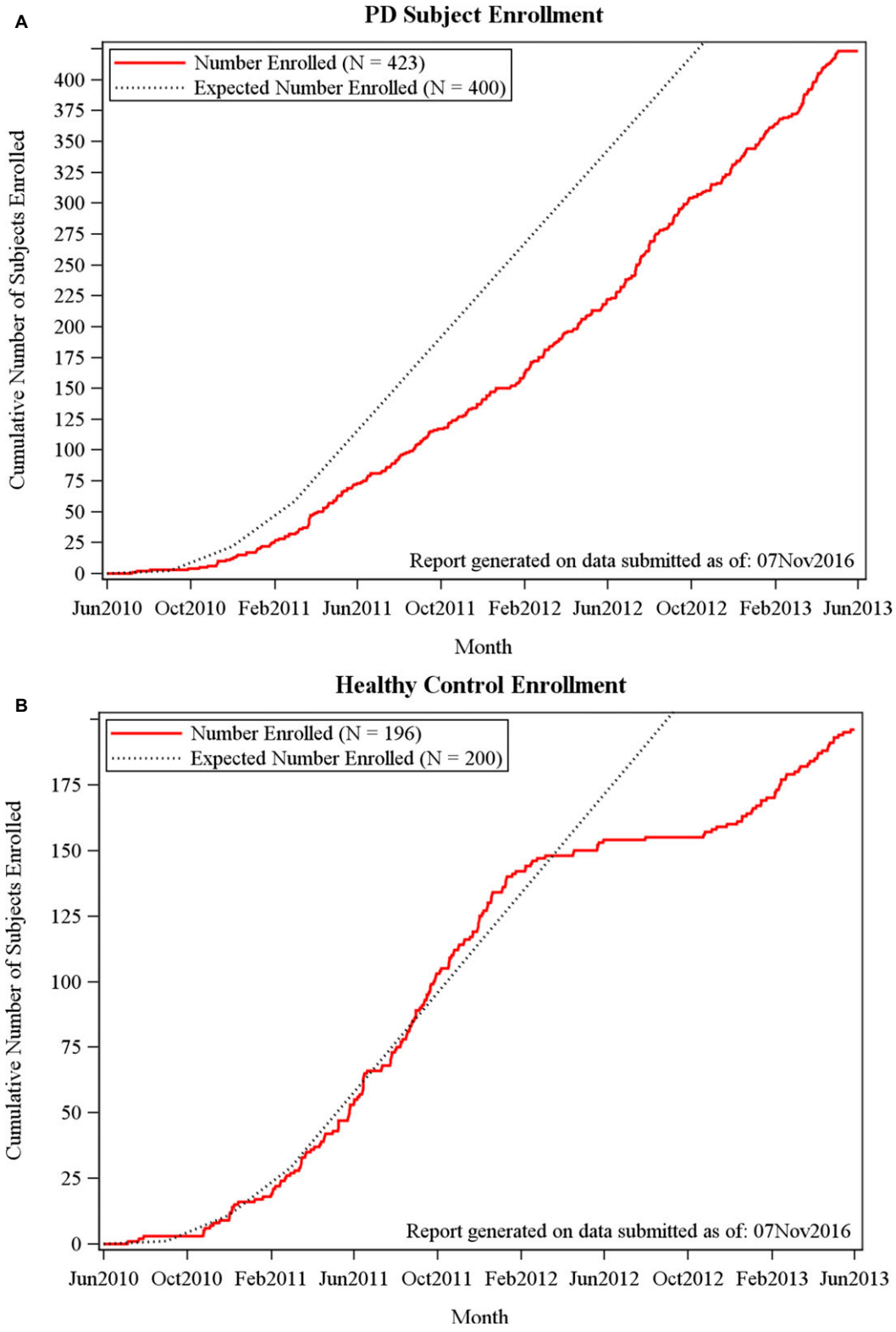

Figure 1. Parkinson's disease and Healthy control subject enrollment. Enrollment of PD (A) and Healthy Control Subject (B) compared to predicted enrollment at study start. Note that healthy control subject enrollment was stopped to allow PD and healthy control enrollment to end simultaneously.

Table 1. Subject demographics.

Variable	Enrolled subjects				
	PD subjects (N = 423)	Healthy controls (N = 196)	SWEDD subjects (N = 64)	P-value (PD vs. HC)	P-value (PD vs. SWEDD)
Gender				0.77	0.64
Male	277 (65%)	126 (64%)	40 (63%)		
Female	146 (35%)	70 (36%)	24 (38%)		
Age				0.33	0.58
Mean (Min, Max)	61.7 (33, 85)	60.8 (31, 84)	60.9 (38, 79)		
Education				0.59	<0.01
<13 years	76 (18%)	29 (15%)	18 (28%)		
≥13 years	347 (82%)	167 (85%)	46 (72%)		
Ethnicity (self-report)				0.62	0.62
Hispanic/latino	9 (2%)	3 (2%)	2 (3%)		
Not hispanic/latino	414 (98%)	193 (98%)	62 (97%)		
Race				0.85	0.41
White	391 (92%)	182 (93%)	61 (95%)		
Black/African-American	6 (1%)	9 (5%)	1 (2%)		
Asian	8 (2%)	1 (1%)	1 (2%)		
Other	18 (4%)	4 (2%)	1 (2%)		
Family history				<0.01	0.14
1st degree family members w/PD	55 (13%)	0 (0%)	15 (23%)		
Other family members w/PD	47 (11%)	10 (5%)	6 (9%)		
No family members w/PD	320 (76%)	186 (95%)	43 (67%)		

PD subject is missing family history.

Biospecimen data for CSF analyzed for $A\beta_{1\text{-}42}$, *t*-tau, *p*-tau, and α-syn showed a reduction in *t*-tau, *p*-tau, and α-syn in the PD compared to HC subjects (Table 4). A similar reduction in α-syn for PD compared to SWEDD subjects was also apparent, as was a trend for reduction in *t*-tau and *p*-tau for PD compared to SWEDD subjects. There was also a significant increase in A-Beta in SWEDD compared to PD subjects. There was a strong correlation between α-syn and *t*-tau in both PD and HC subjects ($P < 0.001$). Given ongoing optimization of these research assays as indicated at www.ppmi-info.org, the absolute values of these CSF analytes may be assay-dependent when baseline samples are re-assayed, but the relationship between the PD, HC, and SWEDD subjects remains stable.

Analysis of subject DNA for common PD mutations revealed six carriers of the *LRRK2* p.G2019S variant, all PD subjects, nine subjects who carried the *GBA* p.N370S risk variant (also called p.N409S) including 7 PD, 1 SWEDD, and 1 HC subjects. There were no subjects with SNCA duplication or point mutations.

The MDS-UPDRS and DAT contralateral putamen SBR were identified prior to the study as two candidate biomarkers with face validity for PD progression. At baseline, the performance of the clinical, imaging, and biospecimen markers tested in PPMI were compared to both MDS-UPDRS and DAT SBR using univariate and multivariate correlation analysis. Results of the model fitting process for total MDS-UPDRS and DAT contralateral putamen SBR are provided in Tables 5, 6, respectively. After adjustment for age, gender, and disease duration, the final model for total MDS-UPDRS included three predictors with positive associations (GDS, SCOPA-AUT, STAI) and three predictors with negative associations (MoCA, QUIP, contralateral putamen). Similarly, after adjustment for age, gender, and disease duration, the final model for DAT contralateral putamen SBR included three predictors with positive associations (STAI, QUIP, UPSIT) and a negative association with MDS-UPDRS total score. In summary, both models demonstrated a significant negative correlation between DAT contralateral putamen SBR and total MDS-UPDRS. There was no correlation between baseline total MDS-UPDRS or DAT contralateral putamen SBR with any of the baseline CSF biomarkers.

Discussion

PPMI is an international, observational study to establish biomarker-defined cohorts and to identify PD progression biomarkers. The primary goal of PPMI is to provide the necessary tools to support and accelerate PD disease-

Table 2. Comparison of clinical baseline motor and nonmotor data.

	Enrolled subjects				
Variable	PD Subjects (*N* = 423)	Healthy controls (*N* = 196)	SWEDD subjects (*N* = 64)	*P*-value (PD vs. HC)	*P*-value (PD vs. SWEDD)
MDS-UPDRS mean scores					
MDS-UPDRS total	32.4	4.6	28.2	<0.01	0.03
MDS-UPDRS part I	5.6	2.9	8.3	<0.01	<0.01
MDS-UPDRS part II	5.9	0.5	5.7	<0.01	0.67
MDS-UPDRS part III	20.9	1.2	14.3	<0.01	<0.01
Hoehn & Yahr N (%)				<0.01	0.11
Stage 0	0 (0%)	193 (98%)	0 (0%)		
Stage 1	186 (44%)	2 (1%)	37 (58%)		
Stage 2	235 (56%)	0 (0%)	27 (42%)		
Stage 3–5	2 (0%)	0 (0%)	0 (0%)		
Modified SE ADLs scale				N/A	0.03
Mean	93.2	N/A	94.8		
(Min, Max)	(70, 100)		(75, 100)		
Duration of disease (months from diagnosis)				N/A	0.39
Mean	6.7	N/A	7.4		
(Min, Max)	(0, 36)		(1, 37)		
MOCA total score				<0.01	0.95
Mean	27.1	28.2	27.1		
(Min, Max)	(17, 30)	(26, 30)	(17, 30)		
GDS total score				<0.01	<0.01
Mean	2.3	1.3	3.3		
(Min, Max)	(0, 14)	(0, 15)	(0, 14)		
SCOPA-AUT total score				<0.01	<0.01
Mean	9.5	5.9	13.8		
(Min, Max)	(0, 39)	(0, 20)	(2, 44)		
State trait anxiety score				<0.01	0.07
Mean	65.3	57.1	69.8		
(Min, Max)	(40, 137)	(40, 105)	(40, 113)		
QUIP				0.77	<0.01
Mean	0.3	0.3	0.6		
(Min, Max)	(0, 4)	(0, 5)	(0, 4)		
UPSIT raw score				<0.01	<0.01
Mean	22.4	34.0	31.4		
(Min, Max)	(1, 40)	(11, 40)	(12, 39)		
Epworth sleepiness scale				0.28	<0.01
Not sleepy (<10)	357 (84%)	171 (87%)	43 (67%)		
Sleepy (10 or above)	66 (16%)	24 (12%)	21 (33%)		
RBD questionnaire				<0.01	0.67
Negative (less than 5)	263 (62%)	157 (80%)	38 (59%)		
Positive (5 or above)	160 (38%)	39 (20%)	26 (41%)		
Number of initial PD symptoms				N/A	0.04
0	0 (0%)	N/A	1 (2%)		
1	37 (9%)		6 (9%)		
2	138 (33%)		28 (44%)		
3	209 (49%)		20 (31%)		
4	26 (9%)		9 (14%)		
5	3 (1%)		0 (0%)		

1 PD subject is missing MDS-UPDRS Total Score, STAI Score, and QUIP.

1 Healthy Control is missing MDS-UPDRS Total Score, Hoehn & Yahr, SCOPA-AUT Score, and Epworth Sleepiness Scale.

Initial symptom categories were resting tremor, bradykinesia, rigidity, postural instability, and other (i.e., micrographia, hypophonia, sialorhea, dystonia, reduced arm swing).

The Initial PD Symptoms *P*-value is from a test comparing 0–2 versus 3–5 symptoms.

Table 3. Comparison of ioflupane striatal binding ratios (SBR).

	Enrolled subjects				
Variable	PD subjects (N = 419)	Healthy controls (N = 193)	SWEDD subjects (N = 62)	P-value (PD vs. HC)	P-value (PD vs. SWEDD)
Contralateral caudate				<0.01	<0.01
Mean (SD)	1.838 (0.558)	2.982 (0.625)	2.849 (0.596)		
(Min, Max)	(0.35, 3.70)	(1.32, 5.20)	(1.40, 4.18)		
Ipsilateral caudate				<0.01	<0.01
Mean (SD)	2.154 (0.595)	2.982 (0.625)	2.828 (0.569)		
(Min, Max)	(0.42, 3.98)	(1.32, 5.20)	(1.36, 3.83)		
Contralateral putamen				<0.01	<0.01
Mean (SD)	0.693 (0.270)	2.147 (0.555)	2.068 (0.522)		
(Min, Max)	(0.12, 2.16)	(0.64, 3.89)	(0.80, 3.24)		
Ipsilateral putamen				<0.01	<0.01
Mean (SD)	0.961 (0.382)	2.147 (0.555)	2.066 (0.493)		
(Min, Max)	(0.22, 2.60)	(0.64, 3.89)	(0.76, 3.08)		

For PD subjects with symmetrical presentation and Healthy Controls, Ipsilateral and Contralateral sides are defined as the mean of the left and right values.

The six study participants enrolled in Australia did not have DAT obtained. An additional one PD subject and two healthy controls are missing DAT imaging values at baseline.

modifying therapeutic trials. In this report, we have detailed the methods used to develop a cohort of 423 early untreated PD, 196 HC and 64 SWEDD subjects and the comprehensive baseline data from these research subjects. A major goal of PPMI is to establish a PD cohort accurately and as early in the disease as possible. There are both scientific and practical reasons why an early PD cohort would likely have the best chance of success in demonstrating the effects of potential disease-modifying therapeutics. First, there is increasing evidence that ongoing progression may lessen any potential therapeutic effect, as pathologic studies indicate significant dopaminergic degeneration present already at 4 years postdiagnosis.[35] Second, studies designed to evaluate disease-modifying therapeutics are limited by the slow change in MDS-UPDRS following treatment with dopaminergic PD medications, as even subjects early in disease may require treatment. Therefore, the earlier in disease that subjects are enrolled, the potentially longer duration these subjects can be maintained in a therapeutic study while untreated with PD medications.

In our study, we enrolled subjects using two novel strategies. All subjects were evaluated with DAT imaging at baseline to improve accuracy of diagnosis and to allow subjects to be enrolled earlier in disease with greater confidence in diagnosis. In PPMI, we have predominantly utilized 123I Ioflupane imaging to determine eligibility, whereas prior studies that have identified subjects with SWEDD have utilized 123I ß-CIT or 18F FDopa.[36–38] Approximately 16% of subjects with clinical features of PD who would otherwise have been enrolled as PD subjects in PPMI were enrolled as SWEDD subjects. We will acquire longitudinal data on the SWEDD subjects to further assess diagnostic accuracy. Additionally, we encouraged all investigators to enroll subjects with single asymmetric tremor or bradykinesia (understanding that a single PD feature does not generally meet standard clinical diagnostic criteria)[39] in an attempt to encourage early stage PD enrollment. Approximately 9% of PD subjects were enrolled with a single PD feature, and over 80% of those subjects had asymmetric tremor. The PD and SWEDD subjects were within 7 months of diagnosis, which is comparable or slightly earlier than other studies in which SWEDD subjects were included (Elldopa 7 month, Precept 9.5 months).[36,37] Importantly, even with our focus on enrollment of early subjects, the overwhelming majority of subjects had more than one PD feature suggesting subjects may develop more than one feature very soon after disease onset and/or that additional biomarker strategies may be necessary to accurately identify subjects even earlier with a single feature. We recognize that there are potential pitfalls to our early diagnosis strategy including errors in diagnosis, especially with parkinsonian disorders with a DAT imaging deficit such as PSP, MSA, and CBS.

PPMI enrollment was completed at 24 sites in 32 months despite requirements for very extensive study assessments for both newly diagnosed PD, HC, and SWEDD subjects, including frequent and comprehensive clinical assessments, DAT imaging, and biospecimen collection including CSF. Enrollment was aided by a targeted recruitment program directed by MJFF that provided

Table 4. Comparison of CSF biomarkers.

Variable	Enrolled subjects				
	PD subjects (*N* = 423)	Healthy controls (*N* = 196)	SWEDD subjects (*N* = 64)	*P*-value[1] (PD vs. HC)	*P*-value[1] (PD vs. SWEDD)
A-Beta				0.39	0.01
Mean (SD)	370.6 (100.39)	377.8 (113.56)	404.3 (106.86)		
(Min, Max)	(129, 797)	(89, 880)	(156, 628)		
Missing	11	7	5		
T-Tau				<0.01	0.38
Mean (SD)	44.7 (18.28)	52.5 (27.16)	48.4 (22.98)		
(Min, Max)	(14, 121)	(18, 223)	(23, 141)		
Missing	15	9	5		
P-Tau				<0.01	0.34
Mean (SD)	15.6 (10.05)	18.3 (11.69)	17.2 (11.84)		
(Min, Max)	(4.7, 94)	(5.1, 73)	(6.1, 71)		
Missing	13	7	5		
T-Tau/A-Beta				0.02	0.44
Mean (SD)	0.13 (0.06)	0.16 (0.19)	0.13 (0.08)		
(Min, Max)	(0.04, 0.52)	(0.05, 2.12)	(0.05, 0.50)		
Missing	15	9	5		
P-Tau/A-Beta				0.01	0.60
Mean (SD)	0.04 (0.03)	0.06 (0.06)	0.05 (0.03)		
(Min, Max)	(0.01, 0.51)	(0.02, 0.66)	(0.02, 0.18)		
Missing	13	7	5		
P-Tau/T-Tau				0.52	0.97
Mean (SD)	0.37 (0.22)	0.37 (0.19)	0.38 (0.24)		
(Min, Max)	(0.08, 2.14)	(0.13, 1.40)	(0.13, 1.23)		
Missing	17	9	5		
Alpha-Synuclein				<0.01	0.03
Mean (SD)	1844.7 (786.13)	2204.3 (1089.11)	2140.8 (1026.70)		
(Min, Max)	(333, 6695)	(593, 8609)	(743, 7201)		
Missing	11	7	5		

β-amyloid (A-Beta), total tau protein (*T*-Tau), phosphorylated tau protein at Serine 181 (P-Tau_{181}) and alpha-synuclein–assays for CSF analytes run between September and December 2013.
[1]*P*-values from Mann–Whitney *U* tests.

study sites with customized recruitment strategies and materials. This recruitment strategy is another tool that could be deployed in future disease-modifying trials. Importantly, neither the requirement for longitudinal CSF collection nor DAT imaging was a major deterrent for enrollment. Subject retention has also been outstanding with subject dropout <5% when fully enrolled.

A major strength of the PPMI study was the robust and comprehensive acquisition of within subject clinical, imaging, genetic, and biospecimen data, and the utilization of detailed, standardized protocols for data and biospecimen acquisition. The study demographics are consistent with age, gender, education, and ethnicity typical of large PD clinical trials.[35–37] There was no difference in demographics between US and European participants. Baseline clinical data demonstrate the expected increase in the MDS-UPDRS in PD compared to HC subjects. Comparison of MoCA scores between PD and HC subjects is limited since HC subjects were not eligible if MoCA was <27, but approximately 20% of PD subjects had a baseline MoCA <26 consistent with early cognitive impairment.[40–42] Furthermore, testing for depression, anxiety, and autonomic function demonstrate impairment in PD compared to HC subjects. These findings are consistent with the notion that PD results in widespread nervous system dysfunction even early in the disease course and potentially prior to motor dysfunction.[43–46]

DAT imaging for all subjects was analyzed to provide a quantitative outcome to compare the SBR in PD, HC, and SWEDD subjects and to characterize the range of DAT deficit among PD subjects even at the earliest stage of disease. The eligibility assessment for DAT was based on visual assessment (the regulatory approved strategy for 123I Ioflupane) and comparison of the visual and quantitative outcomes shows outstanding agreement (Table S1). The imaging characteristics of the SWEDD subjects confirm prior reports that quantitative dopamine transporter

Table 5. Relationship of baseline MDS-UPDRS total score with nonmotor, imaging, and biospecimen variables for PD subjects.

	Screening			Multivariable	
Variable	Estimate (SE)	*P*-value	*N* missing	Estimate (SE)	*P*-value
MOCA total score	−0.49 (0.279)	0.08	1	−0.58 (0.252)	0.022
GDS total score	1.60 (0.246)	<0.001	1	0.62 (0.323)	0.055
SCOPA-AUT total score	0.81 (0.097)	<0.001	1	0.70 (0.103)	<0.001
STAI score	0.22 (0.033)	<0.001	1	0.12 (0.042)	0.003
QUIP	1.35 (0.996)	0.18	1	−1.85 (0.975)	0.059
UPSIT raw score	−0.13 (0.081)	0.11	1	-	N.S.
Epworth sleepiness scale	0.67 (0.180)	<0.001	1	-	N.S.
Mean striatum	−6.65 (1.572)	<.001	5	Not Included	
Mean putamen	−9.81 (2.097)	<.001	5	Not Included	
Mean caudate	−4.10 (1.143)	<0.001	5	Not Included	
Ipsilateral caudate	−3.53 (1.081)	0.001	5	Not Included	
Contralateral caudate	−4.11 (1.126)	<0.001	5	-	N.S.
Ipsilateral putamen	−7.89 (1.649)	<.001	5	Not Included	
Contralateral putamen	−8.31 (2.328)	<0.001	5	-8.69 (2.119)	<.001
A-Beta	−0.008 (0.005)	0.14	12	-	N.S.
T-Tau	−0.003 (0.006)	0.65	16	Not Included	
P-Tau	−0.009 (0.005)	0.12	14	-	N.S.
T-Tau/A-Beta	0.003 (0.006)	0.59	16	Not Included	
P-Tau/A-Beta	−0.005 (0.005)	0.36	14	Not Included	
P-Tau/T-Tau	−0.008 (0.006)	0.17	18	Not Included	
Alpha-Synuclein	−0.002 (0.005)	0.69	12	Not Included	
Urate	0.006 (0.010)	0.52	7	Not Included	

Estimates shown are change in 1 unit increase in MDS-UPDRS total score per 1 unit change in predictor variable.
All screening analyses adjust for age, gender, and duration of disease. The multivariable analysis forces age, gender, and duration of disease into the model.

Table 6. Relationship of baseline DAT imaging contralateral putman SBR with nonmotor, imaging, and biospecimen variables for PD subjects.

	Univariate			Multivariable	
Variable	Estimate (SE)	*P*-value	*N* missing	Estimate (SE)	*P*-value
MDS-UPDRS total score	−0.004 (0.001)	<0.001	5	−0.004 (0.001)	<0.001
MOCA total score	−0.002 (0.006)	0.68	4	Not Included	
GDS total score	0.007 (0.005)	0.22	4	Not Included	
SCOPA-AUT total score	0.0004 (0.002)	0.84	4	Not Included	
STAI score	0.001 (0.001)	0.15	5	0.002 (0.001)	0.033
QUIP	0.071 (0.021)	<0.001	5	0.066 (0.021)	0.002
UPSIT raw score	0.004 (0.002)	0.014	4	0.004 (0.002)	0.010
Epworth sleepiness scale	−0.0002 (0.004)	0.96	4	Not Included	
A-Beta	0.0002 (<0.001)	0.067	15	-	N.S.
T-Tau	0.0001 (<0.001)	0.24	19	Not Included	
P-Tau	0.0001 (<0.001)	0.27	17	Not Included	
T-Tau/A-Beta	−0.00001 (<0.001)	0.94	19	Not Included	
P-Tau/A-Beta	<0.0001 (<0.001)	0.68	17	Not Included	
P-Tau/T-Tau	<0.0001 (<0.001)	0.68	21	Not Included	
Alpha-synuclein	<0.0001 (<0.001)	0.77	15	Not Included	
Urate	<0.0001 (<0.001)	0.79	10	Not Included	

Estimates shown are change in 1 unit increase in contralateral putamen SBR score per 1 unit increase in predictor variable.
All screening analyses adjust for age, gender, and duration of disease. The multivariable analysis forces age, gender, and duration of disease into the model.

assessments in this population are comparable to HC subjects.[4] The wide range of DAT deficit among PD subjects (30–80% loss at baseline) suggest that additional characteristics may define subsets of PD that manifest PD symptoms after modest DAT loss compared to those requiring more severe DAT deficit.[36,37,47] Further to the

point, longitudinal follow-up would be expected to elucidate the biomarker signature of these PD sub-sets.

More than 97% of all PPMI subjects had baseline lumbar puncture for CSF acquisition. Lumbar punctures were generally very well tolerated, with headache occurring in 7% of subjects. The procedure was done with atraumatic needles in 82% of subjects, and that may have contributed to its safety and tolerability.[48] PPMI's success in acquiring these samples both provides a model for collection of CSF in future PD studies, as well as a unique resource for PPMI and the PD research community. Baseline data demonstrated a reduction in tau, *p*-tau, and α-syn in PD compared to HC subjects of about 15%. There was no difference in A-Beta levels between PD and HC subjects. Prior studies have shown similar changes in α-syn and tau in PD subjects,[29,49–52] but the PPMI cohort is unique as a large, prospectively enrolled, previously untreated PD cohort with well-characterized clinical, imaging, biospecimen, and genetic biomarkers.

PPMI offers the opportunity to combine and correlate clinical, imaging, biospecimen, and genetic biomarker data to establish data-driven PD subtypes. We have examined the correlation of the baseline biomarkers to MDS-UPDRS and DAT imaging, the two data anchors to the PPMI study. There is limited correlation of the clinical features or biomarkers to baseline MDS-UPDRS or DAT. Baseline MDS-UPDRS and putamen DAT SBR demonstrated a modest correlation, as in other clinical studies. The lack of correlation may reflect the heterogeneity of presentation, course, and response to therapy, a hallmark of PD.[53–55] The PPMI longitudinal data will examine whether baseline biomarkers and/or short-term change in baseline biomarkers are predictive of longitudinal PD progression outcomes. Developing biomarker-defined subsets of PD subjects with more consistent disease progression and ultimately response to therapy is a major goal of the PPMI study.

This report also provides baseline data comparing the PD and SWEDD subjects. While recent data from clinical trials have demonstrated that subjects enrolled with SWEDD are unlikely to have PD,[4] the clinical and biomarker characteristics of subjects with SWEDD have not been reported. The baseline PPMI data suggest that subjects with SWEDD have increased MDS-UPDRS part 1 scores and greater degrees of depression, anxiety, and autonomic dysfunction compared to PD subjects. These nonmotor symptoms may contribute to the early suspicion of PD in SWEDD subjects. There was no difference in cognitive scores between PD and SWEDD subjects and no difference in UPSIT between HC and SWEDD subjects. Importantly, imaging and CSF biomarker assessments demonstrated that SWEDD subjects were similar to HC and different from PD subjects. SWEDD subject longitudinal data will be reported separately.

A major contribution of PPMI was to establish standardized strategies to acquire and analyze biomarker data that could be utilized for PPMI and for future clinical trials. Standardized protocols for the collection and analysis of blood, CSF, imaging, and other study data were deployed at all sites in PPMI. The acquisition of DAT data from multiple sites is an example of the technical challenges in acquiring multicenter quantitative data. PPMI sought to mitigate the variance in DAT SBR associated with varied camera, software, and imaging experience by performing on-site technical visits, including acquisition of striatal anthropomorphic phantoms to establish consistent acquisition protocols. Standardized analysis included central reconstructions of raw projection data, attenuation correction, and objective quantitative analysis at a central imaging core laboratory. These methods produced a high-quality baseline dataset with roughly similar variance to Ioflupane imaging acquired in single-center trials.[56] The present study suggests it is feasible (as previously shown in smaller studies) to acquire poolable, multicenter quantitative data with Ioflupane SPECT.[22]

All PPMI standardized techniques are available at www.ppmi-info.org and can be utilized in future clinical studies.

During the past two decades, numerous studies have tested putative neuroprotective drugs for PD, but none have clearly demonstrated slowing of disease progression. A critical lesson learned from these studies is that the lack of PD biomarkers severely limits the success and interpretation of these trials. Biomarkers of PD progression that could provide an objective signal indicating study therapeutic response within a short treatment interval (and without the confound of existing PD medications) would enable more rational and sub-type selective therapeutic development. The primary goal of PPMI is to establish biomarker-defined cohorts and PD progression biomarkers that could inform clinical studies of PD therapeutics. Combining comprehensive clinical, imaging, biospecimen, and genetic data enhance the value of each biomarker and provides the opportunity to combine biomarker data to establish data-driven PD sub-sets that may ultimately identify specific PD pathology and/or response to specific PD therapeutics. Ongoing longitudinal follow-up of the PPMI subjects will further address whether singly or in combination the change in biomarker signature can be used to monitor disease progression and/or can predict the course of disease progression. Finally, the ongoing major expansion of the PPMI study to include prodromal PD cohorts defined by olfactory loss or RBD with DAT deficit, or common mutations including variants in LRRK2, GBA, and SNCA will further establish the PD biomarker signature prior to

diagnosis, fully illuminating the progression of biomarkers across the entire spectrum of PD.

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Search Terms: Parkinson's disease, excessive daytime sleepiness, case–control study, biomarkers. Dr. Kenneth Marek had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis."

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Conflict of Interest

None declared.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Axial ioflupane SPECT image in PD and HV with volume of interest template placed on striata and occipital reference region.
Figure S2. SBR data PD, HV, and SWEDDs for mean striatum, ipsilateral and contralateral putamen, and ipsilateral and contralateral caudate.
Table S1. Linear discriminant function.

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