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Research Report

Predicting Progression in Parkinson's Disease Using Baseline and 1-Year Change Measures

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Abstract.
Background: Improved prediction of Parkinson's disease (PD) progression is needed to support clinical decision-making and to accelerate research trials.
Objectives: To examine whether baseline measures and their 1-year change predict longer-term progression in early PD.
Methods: Parkinson's Progression Markers Initiative study data were used. Participants had disease duration $\leq$2 years, abnormal dopamine transporter (DAT) imaging, and were untreated with PD medications. Baseline and 1-year change in clinical, cerebrospinal fluid (CSF), and imaging measures were evaluated as candidate predictors of longer-term (up to 5 years) change in Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) score and DAT specific binding ratios (SBR) using linear mixed-effects models.

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Results: Among 413 PD participants, median follow-up was 5 years. Change in MDS-UPDRS from year-2 to last follow-up was associated with disease duration (β = 0.351; 95%CI = 0.146, 0.555), male gender (β = 3.090; 95%CI = 0.310, 5.869), and baseline (β = –0.199; 95%CI = –0.315, –0.082) and 1-year change (β = 0.540; 95%CI = 0.423, 0.658) in MDS-UPDRS; predictors in the model accounted for 17.6% of the variance in outcome. Predictors of percent change in mean SBR from year-2 to last follow-up included baseline rapid eye movement sleep behavior disorder score (β = –0.6229; 95%CI = –1.2910, 0.0452), baseline (β = 7.232; 95%CI = 2.268, 12.195) and 1-year change (β = 45.918; 95%CI = 35.994,55.843) in mean striatum SBR, and 1-year change in autonomic symptom score (β = –0.325;95%CI = –0.695, 0.045); predictors in the model accounted for 44.1% of the variance.

Conclusions: Baseline clinical, CSF, and imaging measures in early PD predicted change in MDS-UPDRS and dopamine-transporter binding, but the predictive value of the models was low. Adding the short-term change of possible predictors improved the predictive value, especially for modeling change in dopamine-transporter binding.

Keywords: Parkinson's disease, biomarkers, disease progression, surrogate endpoint

INTRODUCTION

Understanding the progression of Parkinson's disease (PD) is crucial to improve clinical management and to enhance therapeutic research. Offering patients accurate prognostic information at the time of diagnosis would inform patient decision making and physician management. Accurate baseline or early disease measures of longer-term outcomes in PD could improve trial efficiency by optimizing accuracy of sample size estimates, reducing required trial duration, and, when desired, informing selection criteria to allow for enrichment of the sample with participants who are at known risk of a given outcome.

An increasing array of possible predictors of PD progression can be explored. Several clinical predictors of motor progression in PD have been identified and replicated with high level of evidence, including age of onset [1] and greater degree of postural instability and gait disorder (PIGD) manifestations [1]. Other measures of motor and neuropsychiatric manifestations may be predictive of motor progression as well [1–3]. However, clinical measures of PD are subjective and fluctuate especially early-on in the disease course [4]. Thus, more objective measures of PD progression are needed, and multimodal models that incorporate both clinical measures and objective biomarkers are being pursued. The Parkinson Progression Markers Initiative (PPMI) study was established with the aim of identifying biomarkers of PD progression. PPMI is a multi-center longitudinal observational study of PD participants that were newly diagnosed and untreated at baseline, and a non-PD comparator group, as previously described [5]. Many groups have applied machine-learning techniques to PPMI data to explore multimodal models for PD diagnosis, subtyping, and modeling of progression [6–8]. While yielding interesting insights and promising results, replication and reproducibility of the models remain to be demonstrated. In addition, machine learning techniques have not yet provided clinically relevant predictive models, despite the integration of massive amounts of multimodal data. For example, in one study, machine learning was applied to 17,499 data points derived from clinical, genetic, imaging, and biofluid biomarker data from PPMI [7]. The best model accounted for 27% of the variation in motor progression, as measured by the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), a validated rating scale comprised of patient- and physician-assessed symptoms and examination findings. Thus, models that account for a greater proportion of the variance in outcome are needed. Much of the literature on predicting PD progression has focused on single measures at a baseline timepoint in longitudinal studies. Given the variability of PD across and within subjects, even early on in the disease, it would be of value to examine whether the short-term change of possible predictors improves the predictive utility of models of progression over the longer-term.

While many tools now exist to measure and define PD progression, change in MDS-UPDRS (or its predecessor UPDRS) remains the most commonly used clinical trial outcome. Among current potential objective measures of disease progression, dopamine transporter (DAT) ligand binding has emerged as a key outcome of interest. DAT binding and MDS-UPDRS motor scores have significant but weak correlation longitudinally [9], and they likely measure different processes and effects on functional outcome. The objectives of this analysis were to examine baseline predictors of change in total and motor MDS-UPDRS and DAT imaging over the first

5 years of PD diagnosis, and to assess the utility of adding the 1-year change of predictors into the predictive models.

METHODS

Sample

PPMI is a multicenter international prospective cohort study. Study aims and methodology have been published elsewhere [5] and are available on the PPMI website (http://www.ppmi-info.org/study-design). Briefly, PD participant enrollment criteria included (i) presence of 2 or more of the following: bradykinesia, rigidity, and resting tremor OR presence of either an asymmetric resting tremor or asymmetric bradykinesia (ii) disease duration from diagnosis of $\leq$2 years, (iii) dopamine transporter deficit on SPECT imaging. Participants could not be treated for PD or expected to need treatment within 6 months of enrollment. A comparator group of generally healthy individuals without PD (healthy controls, HC) were also enrolled. Enrollment criteria for the HC group were: (i) no significant neurologic dysfunction (ii) no 1st-degree relative with PD (iii) and a Montreal Cognitive Assessment (MOCA) score >26. At enrollment both PD and HC groups could not have contraindications to lumbar puncture or a diagnosis of dementia as determined by the investigator.

Only PD and HC participants with at least 1 post-baseline assessment for at least one outcome were included in this analysis. Data downloaded from www.ppmi-info.org/data on November 6, 2017 were used for this analysis.

Assessments

The following assessments were administered:

- Demographics: age at baseline, gender, education
- Body mass index: weight/height^2 (kg/m^2)
- Motor severity: Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [10] scores from the baseline and annual assessments during years 1–5 were considered for this analysis. A tremor score and postural instability gait disorder (PIGD) score were generated (see Supplementary Methods) [11]. Once participants started levodopa and/or dopamine agonists (dopaminergic therapy, DT), the MDS-UPDRS total/part III in the relative OFF and ON medication states were considered separately. The "relative OFF" MDS-UPDRS part III score was obtained after subjects withheld levodopa or dopamine agonist for at least 6 hours. Other PD medications were not held for OFF testing. Previously published work has demonstrated that the duration of OFF did not appreciably influence the change in MDS-UPDRS score over time [9]; also see the Supplementary Materials). The ON MDS-UPDRS part III score was obtained 1 hour after administration of prescribed medications. For a given visit, when OFF testing was not obtained, the MDS-UPDRS OFF score was considered missing and only ON scores were considered.
- Functional abilities: Modified Schwab and England Activities of Daily Living Scale (S&E) was administered at baseline in PD and HC groups and annually in the PD group.
- Cognition: Montreal Cognitive Assessment [12]. Baseline and annual assessments during years 1–5 in the PD and HC were considered for this analysis.
- Psychiatric symptoms: 15-item Geriatric Depression Scale [13] and State and Trait Anxiety Scale [14] were administered. Baseline and annual assessments during years 1–5 were considered for this analysis.
- Autonomic: Scales for Outcomes in PD-Autonomic (SCOPA-AUT) [15] was administered. Blood pressure and heart rate were measured in supine position and standing position. Baseline and annual assessments during years 1–5 were considered for this analysis.
- Sleep/Sleepiness: Epworth Sleepiness Scale (ESS) and REM Sleep Behavior Disorder Questionnaire (RBDSQ) were administered. Baseline and annual assessments during years 1–5 were considered for this analysis.
- Imaging: DAT SPECT scan was performed using the radionuclide ligand DatScan™ as previously described [5] at baseline in the PD and HC group and subsequently at years 1, 2, and 4 only in the PD group. Mean striatal specific binding ratio (SBR; average of putamen and caudate SBR on right and left) and mean putamen SBR were the DAT measures of interest in this analysis.
- PD therapy: PD medication intake was captured in logs. Time to PD medication was ascertained as previously described [16]. Levodopa

equivalent daily dose (LEDD) were calculated as previously described [17].
– Biofluid biomarkers: cerebrospinal fluid (CSF) was collected via lumbar puncture at baseline, 6 months, annually thereafter. β-amyloid 1–42 [Aβ1–42], total tau [T-tau], tau phosphorylated at threonine 181 [P-tau181], and unphosphorylated α-synuclein [α-Syn]) were measured as previously described [18].

Analysis

Outcome measures of progression

Three main outcome measures of progression were selected for examination:

(1) Absolute change in total MDS-UPDRS score (sum of parts I–III)
(2) Absolute change in the MDS-UPDRS part III motor subscore and
(3) Percent change from baseline in DAT measures (mean striatal SBR and mean putamen SBR).

Once participants began DT, the MDS-UPDRS part III score was measured in the ON and OFF state, as defined above, and OFF and ON total and part III subscores were considered as outcome measures in separate statistical models (see below).

Selection of predictors

The primary objective of this analysis was to identify variables for which the baseline and 1-year change predict longer-term change in PD. All putative clinical, imaging, and biofluid measures collected in PPMI that could be baseline predictors of change and had the possibility to change over time were included (thus, we did not examine genetic predictors). The exceptions were age, gender, and disease duration at baseline, all of which were included in all models to mitigate any potential confounding between identified predictors and the outcome.

Variables were selected as candidate short-term change predictors (STP) if they met the following criteria:

(i) Significant difference in change from baseline to 1 year in the PD group vs. the HC group (for variables measured in both groups at these time points; this step was necessary in order to focus on STP specific to PD and not those that change in the course of "normal aging") and
(ii) Significant change in the PD group from baseline to 1 year

An exception to these criteria was made for S&E and DATscan SPECT since these were only performed longitudinally in the PD group. These measures were selected as STP if they changed significantly in the PD group over 1 year.

For selection of the STP, significant change was defined statistically as $p < 0.05$, using two-sample t-test, Wilcoxon signed rank sum, or McNemar's test as appropriate.

Model building

As mentioned, data were limited to PD subjects with at least 1 annual follow-up ($n = 413$). Baseline characteristics were summarized using descriptive statistics. The analysis was conducted in 4 steps.

Step 1: Each outcome was modeled from baseline to last follow-up (up to year 5) with linear and non-linear time models and a variety of covariance structures (see Supplementary Material; Supplementary Table 1). The optimal model fit for the MDS-UPDRS and mean striatum outcomes was a linear time model with a random intercept and slope and an unstructured covariance structure. The optimal model for mean putamen was a linear time model with a random intercept and an unstructured covariance structure.

Step 2: Next, associations between the outcomes and baseline predictors were examined by fitting pseudo-univariate models including the predictors of interest with a model adjusted for the baseline value of the respective outcome. The term pseudo-univariate (as opposed to univariate) is used to denote that baseline age, gender, and baseline disease duration were forced into the backwards selection model along with the baseline outcome value (regardless of their p-value). All baseline predictors that had a p-value <0.20 were next included in a multivariate model. The multivariate linear mixed-effects model was reduced to a final model using backwards selection where predictors with p-values >0.10 were eliminated.

Step 3: After the best-fit models were constructed with the baseline predictors, we next incorporated the STP variables. To examine whether the STP add any additional predictive ability to the model, above that of only baseline predictors, we adjusted all STP models for the significant baseline predictors identified in step 2, along with baseline age, gender, baseline disease duration, and the baseline outcome value. For the models examining STP, change in the key outcomes was measured from year-2 to last follow-up (up to year 5). Thereby, associations between the key

outcomes (starting at year 2 to last follow-up) and STP were tested. All STP with a p-value <0.20 were included in a multivariate model. Backwards selection was performed on the multivariate model using a 0.10 significance level.

Step 4: In order to compare the amount of variation explained by the addition of the STP, a method by Seyla et al. [19] was used to compute a coefficient of variation, R^2, for each of the final multivariate models. The R^2 was calculated by computing the proportion of the variance accounted for by the predictors:

$$R^2 = \frac{V_{null} - V_{full}}{V_{null}}, \quad (1)$$

where V_{null} is the residual variance of a model with only random effects and V_{full} is the residual variance of a model with predictors and random effects. To ensure the reduction in variance was only due to the predictors, the variance explained by the random effects was held constant at that of the final STP models. For comparison, it was also necessary to model the outcomes over the same time points and with equal sample sizes to the final STP models.

To evaluate the replication stability of selected predictors in our models we performed cross-validation. The data were randomly split in to two folds without replacement to form a training and a test data set. The training data set was fit with pseudo-univariate models and backwards selection was performed with the test data set. The same model building was performed in each step as described above. The number and percent of times the predictor was in the final backwards selection model was reported out of 1000 iterations [20, 21]. Higher selection percentage (SP) indicates more validity of the predictor. The fold assignment was varied at each iteration so that the pseudo-univariate and multivariate models were fit on a different subset of the data each iteration. Within each iteration, the same grouping was used when fitting each pseudo-univariate model for the various predictors. Selection frequencies are not reported for variables forced into the multivariate models since they are not considered in the backwards selection algorithm.

RESULTS

413 PD and 185 HC participants were included in this analysis (Table 1). Mean age was 61.69 (SD 9.77) years and 61.01 (SD 11.16) in the PD and HC groups respectively. 339 (82.08%) were enrolled at US sites and 74 (17.92%) at non-US. Other baseline and year 1 characteristics of this cohort are shown in Table 1. Summary statistics for each of the outcome measures are shown in Table 2.

Median follow up time for the PD group was 60 months. 375 participants (91%) of the sample had at least 3 years of follow-up.

Pseudo-univariate relationships between each baseline predictor and the outcome measures are shown in Supplementary Table 2, as are the relationships for these variables with the outcome measures examined in the final models (after backwards selection was applied as per step 2 of the model building, as described above). The selection frequencies from the cross-validation are also shown in Supplementary Table 2.

Multivariate models of baseline predictors of long-term change in MDS-UPRDS

Table 3 (Supplementary Table 2) shows significant ($p \leq 0.10$) baseline predictors of change from baseline of total MDS-UPRDS score in the OFF state. These were baseline disease duration, MDS-UPDRS total score in the OFF state, male gender, CSF amyloid-β_{1-42} (SP = 28.6%), mean striatum SBR (SP = 16.1%), orthostatic SBP (SP = 0.1%), and SCOPA-AUT (SP = 1.2%).

Baseline MDS-UPDRS total score in the ON state, male gender, CSF amyloid-β_{1-42} (SP = 7.5%), MoCA score (SP = 1.4%), and SCOPA-AUT score (SP = 0.70%) were significant predictors for the model examining total MDS-UPRDS score in the ON state.

When the change from baseline in the part III subscore of MDS-UPRDS in the OFF state was examined as the outcome, significant predictors were baseline disease duration, baseline MDS-UPDRS part III subscore in the OFF state, US site (SP = 25.4%), baseline CSF amyloid-β1–42 (SP = 10.9%), and baseline mean striatum SBR (SP = 7.2%).

When the change from baseline in the ON state part III subscore was the outcome, baseline disease duration, baseline MDS-UPDRS part III subscore in the ON state CSF amyloid-β1–42 (SP = 0.8%), and US site (SP = 20.9%) continued to be significant. Baseline mean striatum SBR was no longer significant and baseline Epworth sleepiness scale score became significant (SP = 0.5%) (in comparison to the model for which the OFF state part III subscore was the outcome).

Table 1

Baseline and 1-year values of clinical, biofluid biomarker, and imaging variables in the PD group and HC groups. NC, not collected as per study protocol; BMI, body mass index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; GDS-15, 15-item Geriatric Depression Scale; PIGD, postural instability gait disorder; MoCA, Montreal Cognitive Assessment; RBDSQ, REM Sleep Behavior Disorder Questionnaire; SBR, specific binding ratio; SCOPA-AUT, Scales for Outcomes in Parkinsons—Autonomic; SBP, systolic blood pressure

Variable	PD group ($N=413$)		HC group ($N=185$)		p-value for significance of difference:	
	BL*	1 year*	BL*	1 year*	from BL to 1 year, PD vs HC	from BL to 1 year in PD group
H&Y score (N)	H&Y 0:0 H&Y 1:181 H&Y ≥2:232 Missing: 0	H&Y 0:1 H&Y 1:99 H&Y ≥2:233 Missing: 80	H&Y 0:182 H&Y 1:2 H&Y ≥2:0 Missing: 1	H&Y 0:178 H&Y 1:3 H&Y ≥2:4 Missing: 0	n/a**	<0.0001**
BMI (kg/m^2)	27.1 (4.6; 16.9–43.8; 3)	26.8 (4.6; 16.7–44.2; 40)	26.9 (4.4; 17.5–42.3; 1)	27.18 (4.9; 18.0–45.4; 1)	0.0002	0.0003
Schwab and England total score (S&E)	93.2 (5.9; 70–100; 0)	90.5 (6.7; 70–100; 20)	NC	NC	NC	<0.0001
Tremor score	0.5 (0.3; 0–1.8; 19)	0.6 (0.4; 0–2;79)	0.0 (0.1; 0–0.6; 1)	0.1 (0.1; 0–0.6; 1)	0.0006	<0.0001
PIGD score	0.2 (0.2; 0–14; 1)	0.3 (0.3; 0–1.8; 79)	0.0 (0.1; 0–0.8; 1)	0.0 (0.1; 0–0.6; 1)	0.0001	<0.0001
GDS-15 Total Score	2.3 (2.4; 0–14; 0)	2.6 (2.9; 0–15; 18)	1.3 (2.1; 0–15; 0)	1.4 (2.4; 0–15; 0)	0.6046	0.0828
SCOPA-AUT Total Score	9.4 (6.2; 0–39; 8)	10.9 (6.4; 0–45, 23)	5.8 (3.7; 0–20; 2)	5.8 (4.4; 0–22; 2)	0.0001	<0.0001
STAI Score	65.2 (18.2; 40–137; 1)	65.2 (18.7; 40–142; 18)	57.0 (14.1; 40–105; 0)	56.2 (16.7; 40–128; 0)	0.5840	0.7460
ESS total score	5.7 (3.4; 0–20; 0)	6.1 (4.0; 0–21; 18)	5.6 (3.4; 0–19; 1)	5.4 (3.2; 0–16; 1)	0.0409	0.0240
RBDSQ total score	4.1 (2.7; 0–12; 3)	4.1 (2.8; 0–13; 20)	2.8 (2.2; 0–11; 0)	2.8 (2.3; 0–11; 0)	0.9704	0.9154
Orthostatic SBP change	4.7 (12.7; –31–72; 1)	3.9 (13.1; –32–58; 20)	1.9 (12.3; –47–41; 0)	1.6 (10.5; –26–30; 0)	0.6911	0.1679
Mean striatum SBR	1.41 (0.39; 0.31–2.64; 3)	1.24 (0.4; 0.2–2.7; 45)	2.6 (0.6; 0.98–4.2; 1)	NC	NC	<0.0001
Mean putamen SBR SBR	0.8 (0.3; 0.2–2.1; 3)	0.7 (0.3; 0.05–2.3; 45)	2.14 (0.5; 0.6–3.9; 1)	NC	NC	<0.0001
MoCA	27.1 (2.3; 17–30; 3)	26.3 (2.8; 15–30; 21)	28.2 (1.1; 26–30; 0)	27.3 (2.2; 20–30; 0)	0.5736	<0.0001
CSF amyloid-β_{1-42}	849.10 (320.8; 238.8–1664.0; 68)	818.20 (310.3; 249.5–1645.0; 116)	899.54 (333.2; 239.1–1632.0; 36)	930.9 (318.9; 312–1611; 52)	0.0080	0.1194
CSF Total-Tau	168.9 (57.0; 80.9–467.0; 55)	169.1 (58.4; 82.2–388.7; 99)	192.3 (79.2; 82.0–580.8; 23)	200.4 (83.1; 82.4–600.1; 37)	0.0851	0.8698
CSF Phoso-Tau$_{181}$	14.9 (5.2; 8.0–40.1; 82)	14.9 (5.3; 8.2–34.3; 127)	17.6 (8.5; 8.2–73.6; 32)	18.2 (9.0; 8.3–80.1; 44)	0.0336	0.7021
CSF α-Synuclein	1494.3 (672.1; 432.4– 5256.9; 45)	1425.5 (619.3; 420.0–3685.3; 88)	1709.3 (761.2; 488.6–4683.1; 19)	1778.9 (788.4; 517.1–4388.6; 32)	0.0016	0.0032

*Values shown are mean (SD; range (min–max); number missing) for all continuous variables. **Hoehn and Yahr was the only variable examined as a categorical variable. The count in each stage followed by the number missing is indicated (H&Y 0:1:≥2; missing). Change is defined as change from 1 or 2 to >2. Comparison between the PD and HC group was not possible due to the small number of HC participants with H&Y >0 at any time points.

Table 2
Summary statistics for change in the values of the outcome measures from baseline to year-5 of follow-up. NC, not collected

Outcome	BL*	Change* from BL to Year 1**	Change* from BL to Year 2**	Change* from BL to Year 3**	Change* from BL to Year 4**	Change* from BL to Year 5**
MDS-UPDRS Total Score Off	32.2 (13.1; 7–70; 1)	7.5 (11.6; –31–60; 79)	10.4 (12.9; –30–60; 131)	14.3 (15.6; –35–78; 158)	19.1(16.5; –20–84; 164)	20.9 (17.7; –11–111; 250)
MDS-UPDRS Total Score On	32.2 (13.1; 7–70; 1)	5.4 (12.7; –38–60; 32)	7.0 (13.4; –33–60; 59)	9.8 (16.6; 40–79; 71)	11.9 (18.0;–35–103; 92)	15.2 (19.4; 24–111; 208)
MDS-UPDRS III Score Off	20.9 (8.9; 4–51; 0)	4.5 (8.2; –22–34; 79)	6.3 (9.3; –28–45; 130)	8.8 (10.9; –28–54; 158)	11.6 (11.3;–20–54; 164)	12.3 (11.8; 3–64; 250)
MDS-UPDRS III Score On	20.6 (8.9; 4–51; 0)	2.5 (9.1; – 25–34; 31)	2.6 (10.1; –31–45; 58)	3.7 (11.8; –31–39; 70)	4.1 (12.6; –27–48; 91)	5.6 (12.3; –27–58; 208)
Putamen SBR	0.82 (0.3; 0.2–2.2; 3)	–13.4 (21.8; –83.1–141.2; 45)	–19.2 (21.5; –86.7–167.7; 67)	NC	–30.9 (21.0; –83.3–123.2; 132)	NC
Striatum SBR	1.4 (0.4; 0.3–2.6; 3)	–11.2 (15.1;–59.6–124.8; 45)	–17.1 (16.6; –87.5–146.2; 67)	NC	–27.7 (16.8; –83.0–104.3; 132)	NC

*% Change from baseline shown for mean putamen SBR and mean striatum SBR. **Values shown are mean (SD; range (min–max); number missing) for all continuous variables.

In all models examining change from baseline in the MDS-UPDRS and its part III subscore as an outcome the proportion of variance in the outcome accounted for by the predictors in the model did not exceed 15% for the OFF scores, and for the ON state scores was <5%.

Multivariate models of baseline predictors of long-term change in DaTscan binding measures

When percent change from baseline in mean putamen SBR was examined as the outcome, baseline CSF amyloid-$\beta_{1–42}$ (SP = 12.70%), mean putamen score (SP = 97.80%) and RBDSQ (SP = 56.00%) were the only predictors (Table 3; Supplementary Table 2). In contrast, when percent change from baseline in mean striatal SBR was the outcome, both baseline RBDSQ (SP = 85.30%) and baseline S&E (SP = 9.50%) were significant clinical predictors, as were baseline CSF amyloid-$\beta_{1–42}$ (SP = 9.80%) and baseline mean striatum SBR (SP = 65.40%). 29% and 36% of the variance in change in putamen and striatal DAT binding respectively was accounted for by these baseline predictors.

Short-term changes in candidate predictors

Table 1 shows the change from baseline to year-1 in all considered variables. Candidate STP that met criteria for consideration in the multivariate models were: BMI, S&E, tremor score, PIGD score, SCOPA-AUT Total Score, ESS, CSF α-synuclein, mean striatal SBR, and mean putamen SBR.

Univariate relationships between STP and the outcome measures are shown in Supplementary Table 3 (1-year-changes (1-yr-Δ)), as are the relationships for these variables with the outcome measures in the final models (after backwards selection was applied as per step 3 of the model building, as described above). The selection frequencies from the cross-validation are also shown in Supplementary Table 3.

Multivariate models of short-term change predictors of longer-term change in MDS-UPRDS

Table 4 (Supplementary Table 3) shows results of the multivariate mixed models examining predictors of change in key outcomes (from year 1 to last annual follow-up), but including the 1-yr-Δ of the STPs, as well as the baseline variables significantly associated with the key outcomes. Importantly, after

Table 3
Final results of mixed models examining baseline predictors of outcomes. Only variables associated with the outcome at a p-value of ≤ 0.10 are listed here. For the full model, see Supplementary Table 2. BMI, body mass index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; PIGD, postural instability gait disorder; MoCA, Montreal Cognitive Assessment; RBDSQ, REM Sleep Behavior Disorder Questionnaire; SBR, specific binding ratio; SCOPA-AUT, Scales for Outcomes in Parkinsons—Autonomic; SBP, systolic blood pressure

Outcome	Predictor (All baseline values)[i]	Multivariate Effect Estimate β (95% CI)	Multivariate p-value	Multivariate Adjusted R^2
MDS-UPDRS Total Score	Disease duration	0.1596 (0.0204, 0.2988)	0.0246	
OFF - Change from Baseline	MDS-UPDRS total score in OFF	–0.1345 (–0.2097, –0.0593)	0.0005	0.1383
N = 373	Gender (Male)	1.9042 (0.0550, 3.7535)	0.0436	
	CSF amyloid-β_{1-42}	–0.0031 (–0.0058, –0.0005)	0.0217	
	Mean striatum SBR	–2.5317 (–4.8456, –0.2179)	0.0320	
	SBP	–0.0779 (–0.1468, –0.0090)	0.0267	
	SCOPA-AUT	0.1413 (–0.0174, 0.3000)	0.0809	
MDS-UPDRS Total Score	MDS-UPDRS total score in ON	–0.1990 (–0.2721, –0.1260)	<0.0001	
ON - Change from Baseline	CSF amyloid-β_{1-42}	–0.0028 (–0.0054, –0.0001)	0.0407	0.0533
N = 374	Gender (Male)	1.6797 (–0.1650, 3.5244)	0.0743	
	MoCA	–0.3482 (–0.7439, 0.0474)	0.0844	
	SCOPA-AUT	0.1487 (–0.0105, 0.3079)	0.0671	
MDS-UPDRS Part III Score	Disease duration	0.1377 (0.0405, 0.2349)	0.0055	
OFF - Change from Baseline	MDS-UPDRS part III score OFF	–0.1849 (–0.2567, –0.1131)	<0.0001	0.1156
N = 382	Clinical Site (US)	1.1952 (0.2462, 3.5841)	0.0246	
	CSF amyloid-β_{1-42}	–0.0021 (–0.0039, –0.0002)	0.0284	
	Mean striatum SBR	–1.6005 (–3.1793, –0.0218)	0.0469	
MDS-UPDRS Part III Score	Disease duration	0.1239 (0.0252, 0.2227)	0.0140	
ON - Change from Baseline	MDS-UPDRS part III score ON	–0.2497 (–0.3199, –0.1795)	<0.0001	0.0345
N = 385	Clinical Site (US)	1.9541 (0.3446, 3.5636)	0.0174	
	ESS	–0.1572 (–0.3351, 0.0207)	0.0833	
	CSF amyloid-β_{1-42}	–0.0019 (–0.0038, –0.0001)	0.0417	
Mean putamen SBR -	CSF amyloid-β_{1-42}	0.0055 (–0.0001, 0.0111)	0.0526	0.2870
% Change from Baseline	Mean putamen SBR	–17.1848 (–23.6240, –10.7457)	<0.0001	
N = 352	RBDSQ	–1.0837 (–1.7730, –0.3945)	0.0021	
Mean striatum SBR -	CSF amyloid-β_{1-42}	0.0039 (–0.0003, 0.0081)	0.0708	
% Change from Baseline	Mean striatum SBR	–6.2020 (–9.7532, –2.6508)	0.0007	0.3563
N = 351	Modified Schwab & England (S&E)	0.2417 (0.0037, 0.4797)	0.0466	
	RBDSQ	–1.0030 (–1.5268, –0.4793)	0.0002	

[i]Age, gender, disease duration, and the baseline value of the outcome were forced into each model.

adjustment for the short-term change in total MDS-UPDRS OFF score, many of the significant baseline predictors noted above (CSF amyloid-β_{1-42}, mean striatum, baseline SBP, baseline SCOPA) become non-significant. In the final model, change from baseline in total MDS-UPDRS score in the OFF state was significantly associated with baseline disease duration, male gender, baseline MDS-UPDRS score in the OFF state, and 1-yr-Δ in total MDS-UPDRS score in the OFF state (SP = 99.90%).

For the model examining change from baseline in total MDS-UPDRS score in the ON state as the outcome, significant predictors included baseline disease duration, baseline total MDS-UPDRS score in ON state, baseline SCOPA-AUT, baseline CSF amyloid-β_{1-42}, male gender, 1-yr-Δ in total MDS-UPDRS score in the ON state (SP = 99.90%), and 1-yr-Δ in SCOPA-AUT (SP = 34.40%). Compared to the model only containing the baseline predictors, MoCA was not a significant predictor.

When the long-term change from baseline in the part III subscore of the MDS-UPDRS in the OFF state was the outcome, baseline disease duration, male gender, baseline part III subscore of the MDS-UPDRS in the OFF state, 1-yr-Δ in part III subscore of the MDS-UPDRS (SP = 100.00%), 1-yr-Δ in BMI (SP = 2.10%), and 1-yr-Δ PIGD score (SP = 20.60%) were significant predictors.

Predictors of long-term change in part III subscore of the MDS-UPDRS in the ON state, on the other hand, included US site, male gender, baseline CSF amyloid-β_{1-42}, baseline part III subscore

Table 4
Final results of mixed models examining baseline and short-term change predictors of outcomes. Only variables associated with the outcome at a p-value of ≤ 0.10 are listed here. For the full model, see Supplementary Table 3. BMI, body mass index; CSF, cerebrospinal fluid; ESS, Epworth Sleepiness Scale; PIGD, postural instability gait disorder; RBDSQ, REM Sleep Behavior Disorder Questionnaire; SBR, specific binding ratio; SCOPA-AUT, Scales for Outcomes in Parkinsons—Autonomic; SBP, systolic blood pressure

Outcome	Predictor[i]	Multivariate Effect Estimate β (95% CI)	Multivariate p-value	Multivariate Adjusted R^2
MDS-UPDRS Total Score Off - Change from Baseline N = 280	Baseline disease duration	0.3506 (0.1457, 0.5554)	0.0009	0.1763
	Baseline MDS-UPDRS Total Score Off	–0.1986 (–0.3149, –0.0822)	0.0009	
	1-yr-Δ MDS-UPDRS Total Score Off	0.5403 (0.4228, 0.6578)	<0.0001	
	Gender (Male)	3.0895 (0.3104, 5.8687)	0.0295	
MDS-UPDRS Total Score On - Change from Baseline N = 329	Baseline disease duration	0.2087 (0.0075, 0.4098)	0.0421	0.0943
	Baseline CSF amyloid-β_{1-42}	–0.0039 (–0.0077, –0.0002)	0.0414	
	Gender (Male)	4.0093 (1.3736, 6.6451)	0.0030	
	Baseline MDS-UPDRS Total Score On	–0.2384 (–0.3492, –0.1276)	<0.0001	
	Baseline SCOPA-AUT	0.3266 (0.0766, 0.5767)	0.0106	
	1-yr-Δ MDS-UPDRS Total Score On	0.4985 (0.3953, 0.6018)	<0.0001	
	1-yr-Δ SCOPA-AUT	0.3629 (0.0623, 0.6636)	0.0181	
MDS-UPDRS Part III Score Off - Change from Baseline N = 264	Baseline disease duration	0.1558 (0.0152, 0.2965)	0.0301	0.1719
	Gender (Male)	1.7635 (–0.1740, 3.7009)	0.0743	
	Baseline MDS-UPDRS Part III Score Off	–0.1690 (–0.2823, –0.0557)	0.0036	
	1-yr-Δ MDS-UPDRS Part III Score Off	0.5155 (0.3875, 0.6436)	<0.0001	
	1-yr-Δ BMI	–0.5612 (–1.1287, 0.0063)	0.0526	
	1-yr-Δ PIGD Score	3.4132 (–0.0565, 6.8829)	0.0538	
MDS-UPDRS Part III Score On - Change from Baseline N = 341	Clinical Site (US)	2.1511 (–0.1819, 4.4841)	0.0706	0.0755
	Gender (Male)	2.1375 (0.3268, 3.9482)	0.0208	
	Baseline CSF amyloid-β_{1-42}	–0.2610 (–0.3659, –0.1562)	<0.0001	
	Baseline MDS-UPDRS Part III Score On	–0.0025 (–0.0051, 0.0001)	0.0633	
	1-yr-Δ MDS-UPDRS Part III Score On	0.5132 (0.4149, 0.6115)	<0.0001	
Mean putamen SBR - % Change from Baseline N = 313	Baseline RBDSQ	–0.8478 (–1.5740, –0.1216)	0.0223	0.3580
	1-yr-Δ Mean putamen SBR	65.3565 (51.7328, 78.9803)	<0.0001	
Mean striatum SBR - % Change from Baseline N = 302	Baseline Mean striatum SBR	7.2315 (2.2679, 12.1951)	0.0088	0.4405
	Baseline RBDSQ	–0.6229 (–1.2910, 0.0452)	0.0645	
	1-yr-Δ Mean striatum SBR	45.9181 (35.9935, 55.8427)	<0.0001	
	1-yr-Δ SCOPA-AUT	–0.3251 (–0.6948, 0.0446)	0.0786	

[i]Age, gender, disease duration, and the baseline value of the outcome were forced into each model.

of the MDS-UPDRS in the ON state, and its 1-yr-Δ (SP = 100.00%).

In all models that incorporated the STP variables, the percentage of variance in the outcome accounted for by the predictors in the model increased a few percentages as compared to the model without STP, though none exceeded 17.2%, and variance in the ON state outcomes continued to be largely unexplained by the models.

Multivariate models of short-term change predictors of long-term change in DaTscan binding measures

As shown in Table 4 (Supplementary Table 3), 1-yr-Δ in mean putamen (SP = 100.00%) and baseline RBDSQ score were predictors of long-term (from 1-year to last follow-up) percent change in mean putamen SBR from baseline. On the other hand, baseline mean striatum SBR, baseline RBDSQ, 1-yr-Δ in mean striatum SBR (SP = 100.00%), and 1-yr-Δ change in SCOPA-AUT (SP = 1.07%) predicted long-term (2-year to last follow-up) percent change in mean striatum SBR. In both models, CSF amyloid-β_{1-42} was no longer significantly associated with the outcome. The predictors in the model accounted for 44.1% of the variance in percent change from baseline in mean striatum SBR.

DISCUSSION

This analysis examined clinical, imaging and biofluid predictors of progression in PD, assessed

clinically with total and motor subscore of the MDS-UPDRS and by imaging with DAT binding, to explore whether baseline and short-term (1-year) change in these measures can improve prediction of longer-term change in PD. There are three key findings. First, while a combination of baseline clinical, imaging, and biofluid biomarker measures consistently predicted change in MDS-UPDRS, the predictive value in the models was low, accounting for <15% of the variance in the outcome. Second, and in contrast, this multimodal model did account for a substantial percentage of the variance in DAT binding change. Third, combining the short-term change with baseline values of possible predictors improved the percentage of the variance in the outcome accounted for by the model especially for DAT binding.

We found that a multimodal model consisting of baseline clinical, CSF, and imaging measures can predict motor progression. The clinical predictors varied somewhat depending on the outcome measure examined, which is not surprising considering that in treated patients, motor measures are impacted by the effect of the underlying treatment [9]. Generally, though, our results suggest that motor progression is greater among men (similar to other studies [2]). While clinical measures of autonomic dysfunction (blood pressure measures and/or questionnaire-based) were statistically associated with greater motor disease progression, the low percentage of selection of these variables in the cross-validation indicates that these results should be interpreted with caution. Lower baseline striatal DAT binding was also a consistent predictor of greater motor progression. Our findings add to the accumulating evidence that DAT binding may be a biomarker for PD disease progression [22–24]. It is of note that the Schwab and England did not predict motor progression, in contrast to more advanced cohorts [1]. Perhaps in earlier PD, DAT measures are a more sensitive correlate of disability, as compared to motor scores. Finally, lower CSF amyloid-β_{1-42} predicted motor progression, though again here the low percentage of selection in the cross-validation raises caution in interpretation of this result. Having said that, in prior studies, CSF amyloid-β_{1-42} has been associated with greater α-synuclein pathology in the cortex in advanced disease [25], suggesting a possible mechanism for this association. It would be of interest to examine the relationship between CSF amyloid-β_{1-42} and subcortical α-synuclein pathology in earlier PD disease stages, but our current data do not permit such an analysis.

When DAT binding measures were examined as the outcome, perhaps not surprisingly, baseline DAT binding measures predicted the change in DAT binding, with a large effect size. Of interest is that higher REM sleep behavior disorder (RBD) questionnaire scores predicted greater decline in DAT binding, and the cross-validation analysis adds strength to this observed effect. This is consistent with the possibility that RBD is a marker of worse disease severity in PD, likely due to more widespread neurodegeneration [26, 27].

In general, adding the short-term changes in the predictors, rather than using just the baseline values of those predictors, improved modeling of the outcome, especially for DAT binding. The short-term change of the outcome of interest was selected >99% of the time in the cross-validation. These findings are in line with the idea that, given the clinical variability of PD, single baseline cross-sectional clinical measures are likely not as useful as longitudinal in predicting longer clinical trajectory. Our results indicate that clinical and DAT binding trajectory may be identifiable early on in the PD diagnosis, and the trajectory exhibited early in disease may reflect longer-term change. The utility of incorporating short-term changes as entry criteria into PD clinical trials has not been examined. However, an example from another neurodegenerative disease, ALS, illustrates its potential utility. In a trial of the agent edaravone as a modifier of disease progression in ALS, short-term change, over a 12-week period, in a functional outcome score was used to identify patients who progressed either too rapidly or not at all. These patients were excluded from the trial as it was felt that evaluation of the effect of edaravone in these subgroups would not be useful [28].

Several limitations of this study warrant mention. The definition of "OFF" in PPMI, requiring holding of only levodopa or dopamine agonists for 6 hours, makes it challenging to extricate the effect of PD medications on the results. In addition, while overall retention in the PPMI cohort has been high, there are some missing data longitudinally, and this many influence the results. Furthermore, there is some diagnostic accuracy in early PD, such that some patients may have had alternate disorders marked by parkinsonism and abnormal DAT imaging, including the more severe neurodegenerative parkinsonian syndromes. The number of cases with a revision of

clinical diagnosis was low. However, additional undetected misdiagnosed cases may have been included in the sample. Future analyses using PPMI brain bank data will help investigate this possibility in the future.

The results of this analysis might be considered in the context of an FDA regulatory guidance on accelerated drug approval for serious conditions [29] suggesting the concept of *intermediate clinical outcomes* as measures that are "considered reasonably likely to predict long-term benefit" (page 18). For example, could baseline plus short-term changes in MDS- UPDRS be considered a candidate intermediate clinical outcome in studies of diseases modifying therapies with the caveat that long term benefit would need to be proven? This approach therefore holds the promise of improving the efficiency and possibly shortening PD clinical trial duration. In terms of the clinical applicability of our results, if future work validates the predictors we have identified in independent cohorts representative of the general PD population, they may translate into clinical tools for prognostication.

Our results show that baseline and short-term change in measures of motor disability (MDS-UPRRS) are the strongest predictors of longer-term change in this clinically relevant metric and that baseline and one-year change in striatal DAT binging are predictors of longer-term change in this imaging measure. These findings if replicated, suggest baseline combined with short-term change in PD predictors may have value as proxies for longer-term change in PD. These data may be considered in study design strategies of PD clinical trials as tools to either gain an early signal of a therapeutic intervention or to develop an outcome for an adaptive design.

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54 Institut de Recherches Internationales Servier, Neuilly-sur-Seine, France
55 Merck and Co., Kenilworth, NJ, USA
56 Meso Scale Diagnostics, Rockville, MD, USA
57 Pfizer Inc, Cambridge, MA, USA
58 Piramal Group, Mumbai, India
59 F. Hoffmann-La Roche Limited, Basel, Switzerland
60 Teva Pharmaceutical Industries, Petah Tikva, Israel
61 UCB Pharma, Brussel Belgium
62 TransThera Consulting, Portland, OR, USA
63 Takeda, Osaka, Japan

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JPD-181518.

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