RESEARCH ARTICLE

Predicting Ambulatory Capacity in Parkinson's Disease to Analyze Progression, Biomarkers, and Trial Design

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ABSTRACT: Background: In Parkinson's disease (PD), gait and balance is impaired, relatively resistant to available treatment and associated with falls and disability. Predictive models of ambulatory progression could enhance understanding of gait/balance disturbances and aid in trial design.

Objectives: To predict trajectories of ambulatory abilities from baseline clinical data in early PD, relate trajectories to clinical milestones, compare biomarkers, and evaluate trajectories for enrichment of clinical trials.

Methods: Data from two multicenter, longitudinal, observational studies were used for model training (Tracking Parkinson's, n = 1598) and external testing (Parkinson's Progression Markers Initiative, n = 407). Models were trained and validated to predict individuals as having a "Progressive" or "Stable" trajectory based on changes of ambulatory capacity scores from the Movement Disorders Society Unified Parkinson's Disease Rating Scale parts II and III. Survival analyses compared time-to-clinical milestones and trial outcomes between predicted trajectories.

Results: On external evaluation, a support vector machine model predicted Progressive trajectories using baseline clinical data with an accuracy, weighted-F1 (proportionally weighted harmonic mean of precision and sensitivity), and sensitivity/specificity of 0.735, 0.799, and 0.688/0.739, respectively. Over 4 years, the predicted Progressive trajectory was more likely to experience impaired balance, loss of independence, impaired function and cognition. Baseline dopamine transporter imaging and select biomarkers of neurodegeneration were significantly different between predicted trajectory groups. For an 18-month, randomized (1:1) clinical trial, sample size savings up to 30% were possible when enrollment was enriched for the Progressive trajectory versus no enrichment.

Conclusions: It is possible to predict ambulatory abilities from clinical data that are associated with meaningful outcomes in people with early PD. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease progression; ambulatory capacity; prediction; progression model; clinical trial enrichment

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Introduction

Parkinson's disease (PD) global prevalence has more than doubled to over 6 million individuals between 1990 and 2016, making it the fastest growing neurological disorder. Over this same time span, deaths and disability-adjusted life years because of PD have also doubled.[1] Impaired gait and balance are major contributors to PD disability, while injuries from falls are a leading cause of PD-related deaths.[2]

Gait and balance disturbances are common features of PD and worsen with progression. Deterioration in the ability to walk independently (ie, ambulatory capacity) negatively impacts quality of life,[3] reduces independence,[4,5] and increases the risk of falls.[6-9] Dopaminergic medications improve some aspects of gait, but many features appear refractory to current pharmacologic interventions or may even be worsened with their introduction.[10-13] Furthermore, fall prevention strategies are currently insufficient as an increasing number of people with PD suffer hip fractures as a result of falls.[14]

It remains challenging to predict impaired mobility because of heterogeneity in the presentation and progression of the impairments in PD, complicating appropriate targeting of gait preservation therapies.[13] Although commonly used subtyping classification of PD incorporates posture and gait to account for symptomatic heterogeneity, the stability and usefulness of these subtypes in predicting progression have been questioned.[15,16] Therefore, it remains a high research priority to develop prognostic models for gait and balance disturbances in PD.[17]

The aims of this investigation were to: (1) develop and validate prognostic models that predict rapid and stable trajectories on the ambulatory capacity scale in early PD; (2) compare rates at which predicted trajectory groups reach key clinical milestones; (3) explore baseline biomarker differences between predicted trajectory groups; and, (4) evaluate the predicted trajectory groups as enrollment enrichment factors to potentially reduce sample sizes in clinical trials that use Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) score changes as the outcome.

Methods

Data

Data from two observational multicenter study cohorts were used to develop progression models of ambulatory capacity in early PD: the original Parkinson's Progression Markers Initiative (PPMI), downloaded October 26, 2022 from the PPMI database (http://www.ppmi-info.org/access–data–specimens/download–data), RRID:SCR_006431 (for up–to–date information on the study, visit www.ppmi–info.org); and, Tracking Parkinson's (Tracking) (https://www.trackingparkinsons.org.uk/). Both studies prospectively follow individuals diagnosed with PD to assess the progression of clinical symptoms. Participants with >1 observed ambulatory capacity score over a follow-up duration of ∼4 years in PPMI (visit 10) and ∼ 4.5 years in Tracking (visit 9) were included in the analysis. Additional key inclusion criteria and study design elements are described elsewhere (Supplementary Methods).[18,19]

Ambulatory Capacity Measure

Ambulatory capacity was measured using a construct of the MDS-UPDRS, calculated as the sum of items 2.12 (walking and balance), 2.13 (freezing), 3.10 (gait), 3.11 (freezing of gait), and 3.12 (postural stability) (Supplementary Table S1). For each item, symptom severity is either self-assessed by the participant (part II questions) or assessed by a rater (part III questions). Increasing scores signify more severe disease symptoms and highly correlate with self-reported measures of ambulatory capacity.[20,21] The majority of scores were measured before initiation of dopaminergic treatment (untreated), or after initiation of dopaminergic treatment while in the *on* state (94% of Tracking scores, and 80% of PPMI scores). Therefore, untreated and *on* scores were used for modeling, whereas *off* scores were not used because of data sparseness.

Latent class linear mixed-models were used to derive distinct trajectories of longitudinal changes in ambulatory capacity scores. Linear trajectory models with up to 10 latent classes were tested on both study cohorts separately. The optimal number of latent classes was defined by minimization of the Bayesian Information Criterion, and that the mean maximum posterior probabilities for assignment to the latent classes are ≥80%. Latent mixed modeling was conducted in R 3.6.2 using the "lcmm" package (Supporting Data).[22]

Classification Models

For prediction modeling, the latent class trajectories were collapsed into two progression categories of either "Progressive" or "Stable" trajectories. The progression categories were determined by the estimated fixed-effect slope parameter estimates (β) of each latent trajectory class: Progressive was defined by those within a trajectory class that had an estimated $\beta \geq 1.0$ point/year; and, Stable as $\beta < 1.0$ point/year. The cutoff of 1.0 represents approximately double the estimated average rate of ambulatory capacity score progression in PPMI, Tracking, and other PD cohorts (Supplementary Fig. S1).[23,24]

Support vector machine (SVM) models ("scikit-learn" Python package with linear kernel, $C = 1$) were

developed to predict Progressive versus Stable trajectories from baseline data. We performed five repetitions of a stratified three-fold cross validation of the SVM model. Because of class imbalance, synthetic oversampling was applied individually to each training split ("SMOTE" Python package with $k = 5$ neighbors).[25] Each oversampled training split was tested on the holdout dataset in Tracking and externally on the full PPMI data. The prediction performance of the models were evaluated according to accuracy, weighted-F1 score (harmonic mean of precision and sensitivity but weighted proportionally to the class sizes), area under the receiving operating characteristic curve (AUROC), sensitivity, specificity, and Matthew's correlation coefficient (MCC) (interpretation is similar to that of a Pearson correlation coefficient, with −1 the worst value and + 1 the best value).[26] Logistic regression and random forest classifier models were also developed, but performances were worse or no better than the SVM (Supplementary Methods; Supplementary Table S2).

Prognostic Features

Data collected at screening or baseline study visits were used for prediction of disease progression. The following baseline features were initially considered in the classification models based on their availability in both datasets, and clinician expert input: age, sex, body mass index, MDS-UPDRS parts I-III individual items, Scales for Outcomes in PD-Autonomic dysfunction, Epworth Sleepiness Scale total score, Rapid Eye Movement Sleep Behavior Disorder Questionnaire total score, Montreal Cognitive Assessment (MoCA) total score, and history of select comorbidities (Supplementary Methods). Features were ranked and selected based on their importance as quantified by Shapley additive explanations (SHAP) values ("shap" Python package), which quantify the average contribution of each feature to the predictions.[27,28] Ultimately, 23 baseline features were included in the model after multiple rounds of backward elimination steps resulting in a combination of features producing an optimal MCC.

Time-To-Clinical Milestones

Predicted Stable and Progressive trajectories were further evaluated by comparing time-to-clinical progression milestones in each cohort. The following time to clinical milestones were assessed out to visit 10 of PPMI and visit nine of Tracking:

- Hoehn and Yahr (HY) score ≥3, indicating at least the presence of balance impairment with mild to moderate disease severity (loss of recovery from a retropulsive stress);
- modified Schwab and England Activities of Daily Living (ADL) score <80%, corresponding to a threshold of not being completely independent in performing daily activities;
- scoring ≥3 (moderate to severe problems) on any one of the following functional items of the MDS-UPDRS questions: (2.3) swallowing and chewing, (2.4) eating tasks, (2.5) dressing, (2.6) hygiene, (2.8) doing hobbies and other activities, and (3.1) speech.
- MoCA score ≤23, corresponding to a cutoff for diagnosis of cognitive impairment.[29]

Similar analyses were performed, but stratifying instead by baseline motor phenotype (postural instability gait disorder [PIGD] vs. tremor dominant [TD]),[30] allowing for comparison of the contribution of previously identified potential baseline subtyping approaches.

The endpoint event rates were based on Kaplan–Meier estimates stratified by predicted progression (Progressive vs. Stable), and comparisons of curves using the log-rank test. Cox proportional hazards regression determined the hazard ratios between predicted progression groups. Analyses were conducted in R using the "survival" and "prodlim" packages.

Exploratory Biomarker Comparison

The PPMI study collected additional imaging, biofluid, and digital sensor (Verily Study Watch) biomarkers (Supplementary Methods) that were not available in Tracking, and therefore, not tested as features in the prediction models. To explore if there were differences in these biomarkers between predicted trajectories, unpaired t tests and χ^2 tests compared baseline values between predicted Progressive and Stable trajectories in PPMI only. Significance levels were not adjusted for multiple comparisons.

Clinical Trial Enrichment

Potential clinical trial outcome measures were evaluated using the model-predicted Progressive and Stable trajectory groups from PPMI. Trial outcomes included time to changes in MDS-UPDRS scores from baseline that are considered the minimal clinically meaningful changes to patients out to visit 5 (∼year 1.5)[31,32]:

- MDS-UPDRS part III ≥5-point increase, or, time to initiation of levodopa/dopamine agonist (part III/treatment outcome);
- part III/treatment outcome, and MDS-UPDRS part II ≥3-point increase;
- part III/treatment outcome, and MDS-UPDRS part II ≥3-point increase, and MDS-UPDRS part I ≥3-point increase.

The required sample sizes for clinical trials to detect various treatment effects using these outcomes were computed for a hypothetical intervention, comparing the enrichment of enrolling only model-predicted Progressive cases versus having no enrichment. The clinical

trial scenario was 1:1 (active:placebo) randomization with 18 months of follow-up. Sample sizes were calculated for detecting 20% to 50% reductions (at 2.5% increments) in outcome events at the significance level of 0.05 and power of 80%. Percent changes in sample sizes between enrichment versus no enrichment were calculated for each treatment difference and averaged.

Results

The modeling dataset included 1598 and 407 participants from Tracking and PPMI, respectively (Supplementary Fig. S2). Individuals from the Tracking cohort were on average older, had a longer disease duration, more severe baseline mean HY and

TABLE 1 *Summary of baseline characteristics of PPMI and Tracking Parkinson's disease study cohorts*

Characteristic	Tracking Parkinson's (n = 1598)	PPMI (n = 407)	*P*-value[a]
Age, years	67.1 ± 9.0	61.6 ± 9.8	**<0.0001**
Sex			
Male	1028 (64.3)	266 (65.4)	0.70
Female	570 (35.7)	141 (34.6)	
Race			
Caucasian	1564 (97.9)	382 (93.9)	**<0.0001**[b]
Asian	10 (0.6)	8 (2.0)	
Black	4 (0.3)	7 (1.7)	
>1 race	4 (0.3)	8 (2.0)	
Other	2 (0.1)	0	
Missing/not specified	14 (0.9)	2 (0.5)	
PD duration at baseline, years	1.3 ± 0.9	0.5 ± 0.5	**<0.0001**
Hoehn and Yahr stage[c]	1.7 ± 0.6	1.6 ± 0.5	**<0.0001**
Hoehn and Yahr by stage[c]			**<0.0001**[d]
1	503 (31.9)	181 (44.5)	
1.5	287 (18.2)	–	
2.0	520 (33.0)	224 (55.0)	
2.5	188 (11.9)	–	
3	76 (4.8)	2 (0.5)	
4	2 (0.13)	0	
5	1 (0.06)	0	
Baseline ambulatory capacity	2.6 ± 2.4	1.1 ± 1.1	**<0.0001**
Diagnostic feature: prominent freezing early in course[e]			
Yes	19 (1.3)	1 (0.3)	0.07
No	1434 (98.7)	392 (99.7)	
Diagnostic feature: likely to fall if not extra careful[e]			**0.0014**
Yes	65 (4.5)	4 (1.0)	
No	1392 (95.5)	389 (99.0)	

Note: Data are mean ± standard deviation, or n (%).
Abbreviations: PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative.
[a]Student *t* test or χ^2 test.
[b]Caucasian versus non-Caucasian.
[c]Hoehn and Yahr stage at baseline missing for 21 participants from Tracking Parkinson's cohort.
[d]Proportion with Hoehn and Yahr stage ≥3.
[e]The Diagnostic Features questionnaire was not part of the PPMI protocol until Amendment 4 (~2 years after the release of the original study protocol).

ambulatory capacity score, and reported more likely to fall than PPMI participants (Table 1). Both cohorts had processes in place to identify potential cases of misdiagnosis as data emerged, using consensus criteria. Identified cases of misdiagnosis were excluded from our analyses.

Ambulatory Capacity Trajectory Modeling

Latent class mixed-modeling of longitudinal ambulatory capacity scores from the Tracking cohort resulted in 88% with a Stable trajectory and 12% with a Progressive trajectory (Supplementary Fig. S3A and Supplementary Tables S3 and S4). In PPMI, 93% and 7% had Stable and Progressive trajectories, respectively (Supplementary Fig. S3B and Supplementary Tables S3 and S5).

Predicting these trajectory labels from baseline data with the SVM model using the Tracking testing dataset resulted in mean (95% CI) accuracy of 0.711 (0.699, 0.722), weighted-F1 of 0.760 (0.751, 0.769), AUROC 0.698 (0.684, 0.713), sensitivity/specificity of 0.682 (0.649, 0.716)/0.714 (0.699, 0.730) and MCC of 0.270 (0.251, 0.289). Performance metrics were similar when externally tested in PPMI (Fig. 1A).

Overall, baseline age as a continuous variable was the most important feature in discriminating between predicted trajectories (Figs. 1B and Supplementary Fig. S4); as age increased, there was a higher likelihood of having a Progressive trajectory. Baseline age was also assessed separately as a feature by itself, but overall performance of this model decreased compared to the model using all baseline features (Supplementary Table S6). At the individual level, the relative contributions of each feature varied in determining an individual's trajectory. For example, problems turning in bed, arising from deep sitting positions, and handwriting were the main factors driving a Progressive trajectory for one individual (Fig. 1C), whereas older age was the dominant factor for another (Fig. 1D) (see Supplementary Fig. S5 for additional examples).

There was little overlap between baseline PIGD and model-predicted Progressive trajectory in PPMI; 21.2%

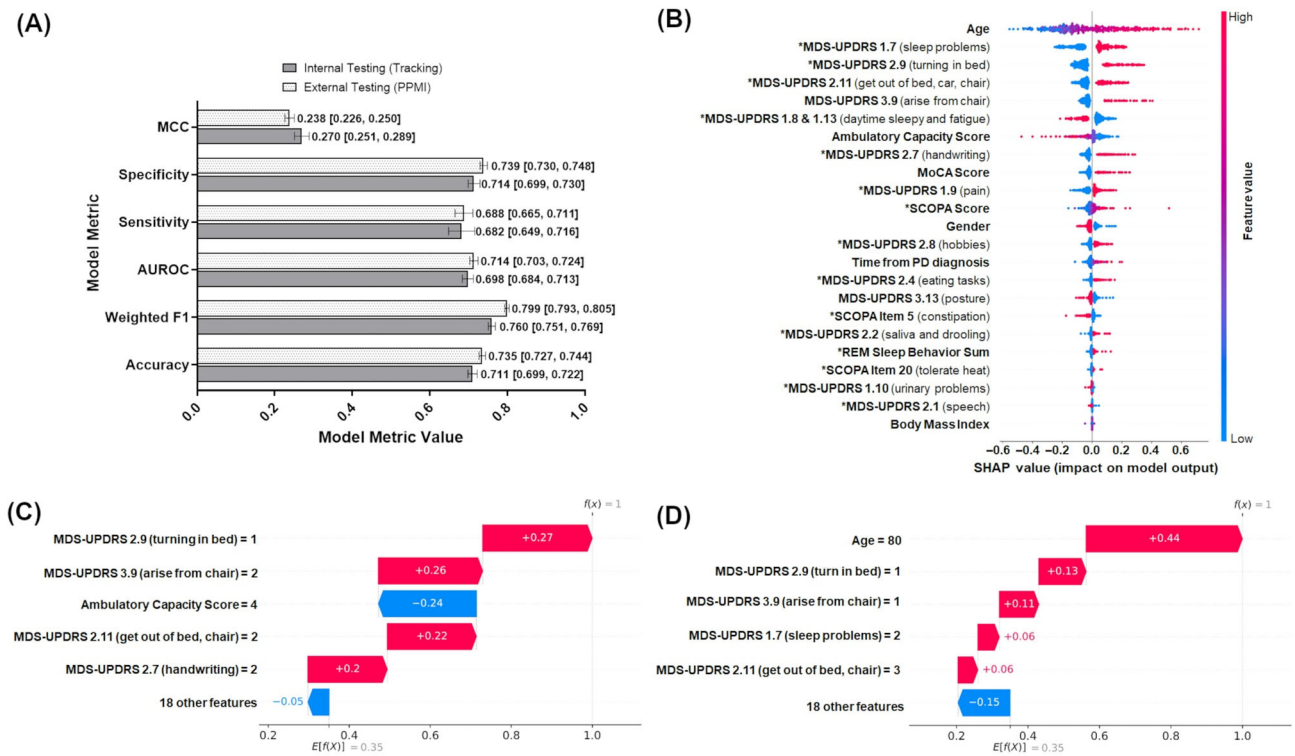

FIG. 1. Model performance metrics and importance of features for predicting "Stable" versus "Progressive" trajectories. (**A**) Overall mean [95% confidence interval] model performance metrics in Tracking Parkinson's and Parkinson's Progression Markers Initiative (PPMI) datasets. (**B**) Beeswarm plot of SHAP values (x-axis) per baseline feature (y-axis) with each point representing a SHAP value for a predictor and an individual PPMI participant. The values of the features are represented by color, with red indicating high values (or having the symptom if a binary predictor) and blue indicating low values (or not having the symptom if a binary predictor). Baseline features with asterisks (*) next to them represent those that are assessed by the patient/caregiver. (**C**,**D**) Waterfall plots generated for two examples of individual participants correctly predicted as having a Progressive trajectory. These plots display the value of the model output probability of a Progressive trajectory (f(x) = 1) or Stable trajectory (f(x) = 0) (x-axis), and the top five features with their individual values contributing to that participant's predicted trajectory (y-axis). The contribution of each feature is represented as either pushing the prediction toward a Stable trajectory (blue pentagon) or toward a Progressive trajectory (red pentagon) relative to the null model (E[f(x)]). AUROC, area under receiving operating curve; MCC, Matthew's correlation coefficient; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; REM, rapid eye movement; SCOPA, Scale For Outcomes in Parkinson's Disease Autonomic. [Color figure can be viewed at wileyonlinelibrary.com]

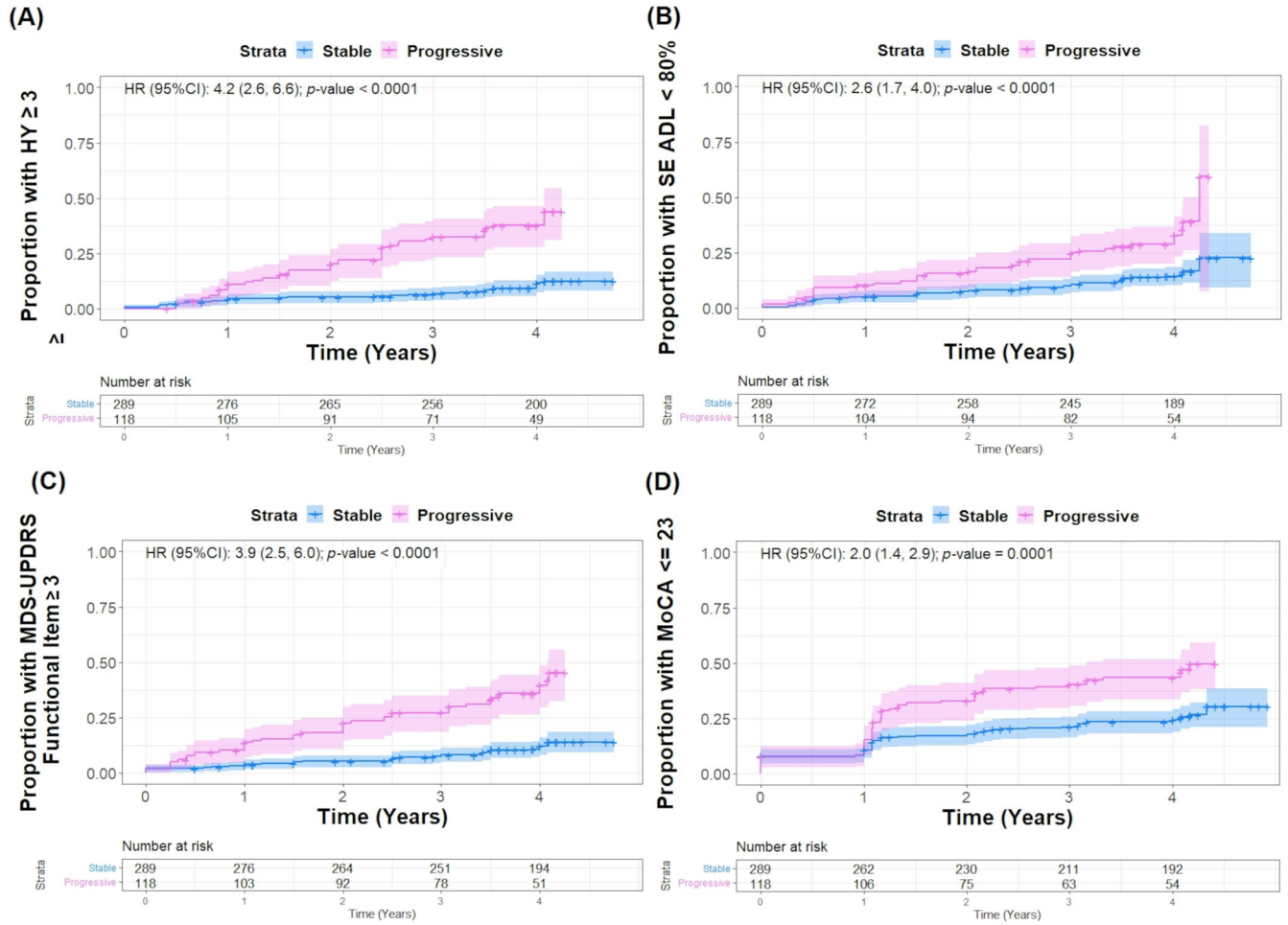

FIG. 2. Kaplan–Meier curves comparing time-to-clinical milestones between predicted "Progressors" and "Stable" groups in the Parkinson's Progression Markers Initiative (PPMI) cohort. HR with 95% CI derived from Cox proportional hazards models and *P*-values from likelihood ratio tests. (**A**) Time to Hoehn and Yahr score ≥ 3. (**B**) Time to Schwab and England Activities of Daily Living score <80%. (**C**) Time to score ≥ 3 on any one of the following MDS-UPDRS items 2.3 (choking at least once in the past week to needing a feeding tube), 2.4 (needing help with many eating tasks to needing help with most or all), 2.5 (needing help for many dressing tasks to needing help for most or all), 2.6 (needing help with many hygiene tasks to needing help with most or all), 2.8 (having major problems doing hobbies/activities to unable to do most or all), or 3.1 (some speech difficult to understand to most is difficult or unintelligible). (**D**) Time to MoCA score ≤ 23. 95% CI, 95% confidence interval; HR, hazard ratio; HY, Hoehn and Yahr; SE ADL, Schwab and England Activities of Daily Living; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment. [Color figure can be viewed at wileyonlinelibrary.com]

of the predicted Progressive group was also classified as PIGD at baseline (Supplementary Table S7). There was more overlap, however, in the Tracking cohort; 54.5% of the predicted Progressive group was also baseline PIGD (Supplementary Table S8).

Time-To-Clinical Milestones

In PPMI, the occurrences of reaching key clinical milestones over ~4 years follow-up were greater in the predicted Progressive versus Stable groups. An HY ≥3 was reached by 18.4% of PPMI participants (36.4% Progressive and 11.1% Stable), with a rate four times higher in the Progressive group (hazard ratio [HR], 4.2 [95% CI, 2.6, 6.6]) (Fig. 2A). An ADL <80% was reached by 19.9% of PPMI participants (32.2% Progressive and 14.9% Stable), with a rate more than two times higher in the Progressive group (HR, 2.6 [95% CI, 1.7, 4.0]) (Fig. 2B). Scoring moderate or worse severity on select functional MDS-UPDRS items occurred in 19.7% of PPMI participants (38.1% Progressive and 12.1% Stable), and was nearly four times higher among the Progressive group (HR, 3.9 [95% CI, 2.5, 6.0]) (Fig. 2C). Cognitive impairment (MoCA ≤23), occurred in 31.0% of PPMI participants (44.9% Progressive and 25.3% Stable), at a rate two times higher for the Progressive group (HR, 2.0 [95% CI, 1.4, 2.9]) (Fig. 2D). The proportional hazards assumption for each outcome was confirmed by Schoenfeld residual tests (Supplementary Fig. S6).

In the Tracking cohort, similar patterns and HRs were observed for each of these clinical milestones as well as for HY ≥2.5 (Supplementary Fig. S7). However,

TABLE 2 *Comparison of various biomarker values between predicted "Progressive" and "Stable" trajectories in the PPMI cohort that were not included as features*

Biomarker (n for progressive; n for stable)[a]	Model-predicted progression trajectory		*P*-value[b]
	Progressive	Stable	
Baseline striatal binding ratios from dopamine transporter imaging			
Mean striatum (116; 287)	1.29 (1.22, 1.37)	1.45 (1.40, 1.49)	**0.0006**
Left striatum (116; 287)	2.56 (2.40, 2.72)	2.88 (2.78, 2.98)	**0.0009**
Right striatum (116; 287)	2.62 (2.46, 2.78)	2.91 (2.81, 3.01)	**0.0003**
Mean putamen (116; 287)	0.75 (0.70, 0.80)	0.84 (0.81, 0.87)	**0.004**
Left putamen (116; 287)	0.73 (0.67, 0.80)	0.83 (0.79, 0.87)	**0.01**
Right putamen (116; 287)	0.77 (0.71, 0.83)	0.86 (0.82, 0.90)	**0.02**
Mean caudate (116; 287)	1.84 (1.73, 1.94)	2.05 (1.99, 2.11)	**0.0007**
Left caudate (116; 287)	1.83 (1.72, 1.94)	2.05 (1.99, 2.12)	**0.0007**
Right caudate (116; 287)	1.85 (1.73, 1.96)	2.05 (1.98, 2.12)	**0.003**
Baseline cerebrospinal fluid biomarkers			
A-β 1–42, pg/mL (113; 281)	908.2 (818.8, 997.7)	913.8 (868.9, 958.8)	0.9
α-Synuclein, pg/mL (114; 283)	1588 (1450, 1727)	1475 (1401, 1549)	0.2
Phosphorylated τ, pg/mL (113; 274)	16.4 (15.2, 17.6)	14.1 (13.6, 14.6)	**0.0009**
Total τ, pg/mL (120; 291)	184.5 (171.8, 197.2)	162.2 (156.6, 167.9)	**0.002**
Albumin, mg/L (94; 241)	242.6 (187.6, 297.6)	171.9 (157.7, 186.1)	**0.02**
IgG, mg/L (94; 241)	25.6 (21.8, 29.3)	22.5 (19.4, 25.5)	0.2
IL-6, pg/mL (54; 152)	4.3 (3.3, 5.3)	3.9 (3.5, 4.4)	0.5
NfL, pg/mL (55; 159)	118.8 (103.1, 134.5)	95.8 (87.1, 104.4)	**0.01**
Baseline blood, plasma, serum measures			
Serum NfL, pg/mL (109; 267)	16.3 (14.7, 18.0)	11.6 (10.9, 12.3)	**<0.0001**
Serum urate, mg/dL (116; 286)	320.2 (305.0, 335.4)	315.6 (306.8, 324.5)	0.61
Plasma HDL, mg/dL (48; 105)	55.5 (50.7, 60.2)	57.0 (53.2, 60.8)	0.62
Plasma LDL, mg/dL (48; 104)	103.5 (93.6, 113.4)	109.1 (102.0, 116.2)	0.37
Plasma triglycerides, mg,dL (48; 105)	124.6 (105.9, 143.4)	110.1 (101.1, 119.2)	0.18
Plasma total cholesterol, mg/dL (48; 105)	183.1 (172.1, 194.1)	189.4 (180.7, 198.1)	0.4
Whole blood GCase activity, umol/L/hr (88; 208)	11.2 (10.5, 11.9)	11.4 (10.9, 11.8)	0.7
DJ-1 RNA, counts (47; 168)	1062 (974, 1150)	1102 (1043, 1160)	0.5
Genetics			
Genetic risk score[33] (115; 282)	−0.01038 (−0.01114, −0.00963)	−0.00889 (−0.00937, −0.00842)	**0.001**
GBA1, n (%) (117; 288)			
Carrier of pathogenic variant	2 (1.7)	12 (4.2)	0.22[c]
LRRK2, n (%) (118; 288)			
Carrier of pathogenic variant	1 (0.8)	6 (2.1)	0.39[c]
APOE, n (%) (118; 289)			
E2/E2 or E2/E3 genotype	19 (16.1)	34 (11.8)	0.24[c,d]

(Continues)

TABLE 2 *Continued*

Biomarker (n for progressive; n for stable)[a]	Model-predicted progression trajectory		*P*-value[b]
	Progressive	Stable	
E3/E3 genotype	75 (63.6)	178 (61.6)	0.18[c,e]
E2/E4, E3/E4, E4/E4 genotype	24 (20.3)	77 (26.6)	
Digital sensor-based assessment of mobility and gait (Verily Watch sub-study)			
Average hourly step count (26, 58)	131.9 (89.3, 174.5)	232.7 (196.7, 268.7)	**0.0005**
Average hourly ambulatory minutes (26, 60)	3.46 (2.88, 4.03)	4.36 (3.90, 4.81)	**0.016**

Abbreviations: PPMI, Parkinson's Progression Markers Initiative; IgG, immunoglobulin G; IL-6, Interleukin 6; Nfl, neurofilament light; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Values presented as mean (95% confidence interval) unless otherwise noted.
[b]Unpaired *t* test unless otherwise noted; bolded *P*-values are those <0.05.
[c]χ^2 test.
[d]E2/E3 and E2/E2 carriers versus others.
[e]E4 carriers versus E4 non-carriers.

the overall proportions of Tracking participants reaching each milestone was higher than in PPMI likely because of slightly longer follow-up times and greater baseline disease duration (Supplementary Table S9): 26.5% reached HY ≥3; 33.0% reached ADL <80%; 26.2% reached MDS-UPDRS function ≥3; and, 39.6% reached MoCA ≤23.

In PPMI, when using baseline motor phenotype (PIGD, TD) as a stratifying factor in the Cox proportional hazards models instead of the model-predicted trajectory groups (Stable, Progressive), the HRs were either reduced (time to HY ≥3: HR, 2.3 [95% CI, 1.4, 3.8]), or were no longer statistically significant (time to ADL <80%: HR, 1.6 [0.96, 2.8]; time to MDS-UPDRS functional item ≥3: HR, 1.7 [0.98, 2.9]; time to MoCA ≤23: HR, 0.8 [0.5, 1.4]) (Supplementary Fig. S8). The HRs in Tracking, however, were more equivalent when comparing between the motor phenotype and model-predicted estimates (Supplementary Fig. S9).

Exploratory Biomarkers

Comparison of baseline biomarker data from PPMI between predicted Progressive and Stable trajectories are summarized in Table 2 and Supplementary Table S10. The predicted Progressive trajectory had significantly reduced mean striatal binding ratios on 123-I Ioflupane dopamine transporter imaging compared to the Stable trajectory. Cerebrospinal fluid (CSF) concentrations of total τ and phosphorylated τ181 (p-τ181) were both increased in the predicted Progressive trajectory. Ratios between p-τ181 and α-synuclein and β-amyloid 1–42 (Aβ1-42) were also elevated among the Progressive trajectory (Supplementary Table S10). CSF and serum concentrations of neurofilament light (NfL) chain were both higher in the predicted Progressive trajectory. The Progressive trajectory group had a more negative PD genetic risk score,[33] but there were no significant differences in the proportions of individuals carrying *GBA1* or *LRRK2* pathogenic variants, and *APOE* genotypes. In a digital sensor substudy, the predicted Progressive trajectory had significantly lower average hourly step counts, and shorter time being ambulatory per hour.

Levodopa responsiveness and levodopa equivalent daily doses (LEDD) were also evaluated where possible. In PPMI, there were no differences in levodopa responsiveness of ambulatory capacity scores between the predicted trajectory groups (Supplementary Table S11). For LEDD, in the Tracking cohort, the Progressive group had higher mean LEDD at baseline versus Stable (361 vs. 301; $P < 0.0001$); however, LEDD did not differ by the final visit (617 vs. 601; $P = 0.35$). Results were similar for LEDD in PPMI at the final visit (Supplementary Results).

Clinical Trial Enrichment

A clinical trial endpoint of minimal clinically meaningful change in MDS-UPDRS part III or initiation of dopamine therapy over 18 months occurred in 94.1% and 91.0% of PPMI participants with predicted Progressive and Stable trajectories, respectively (HR, 1.3; 95% CI, 1.1, 1.7) (Supplementary Fig. S10A). Sample size calculations with this part III/treatment outcome measure were reduced on average by 15.9% when enriching enrollment for predicted Progressive versus no enrichment (Fig. 3A). Results were similar for the endpoint combining the part III/treatment outcome plus a three-point change in MDS-UPDRS part II (Supplementary Figs. S10B and S11). A composite endpoint of minimal clinically meaningful changes in each of the MDS-UPDRS parts I, II, and III/treatment outcome occurred in 52.5% and 37.4% of individuals with a predicted Progressive trajectory and Stable trajectory, respectively (HR, 1.7; 95% CI, 1.3, 2.4)

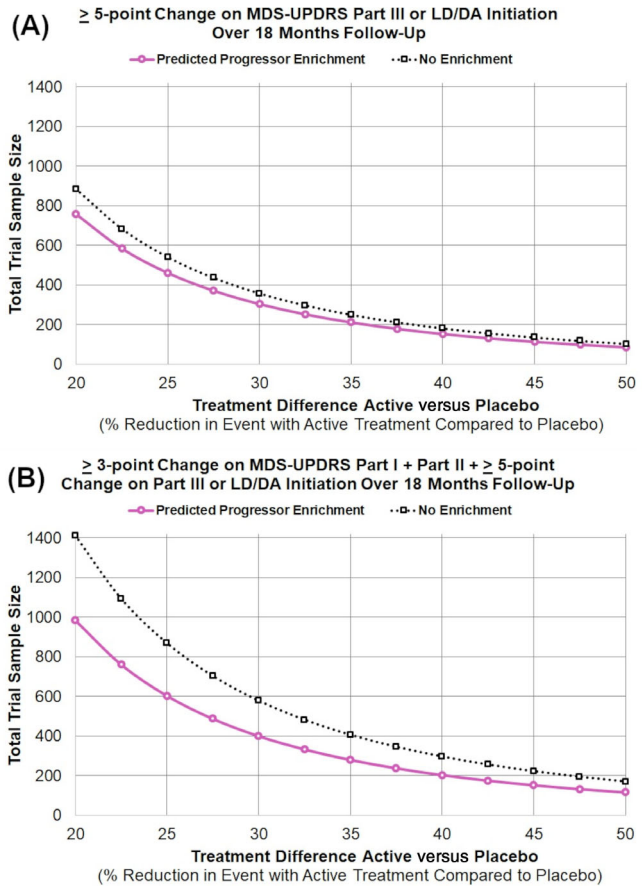

FIG. 3. Comparisons of sample size estimates with corresponding treatment differences when enriching enrollment for predicted "Progressors" (solid pink line) versus no enrichment (dotted black line). Study design scenario is for a randomized (1:1), placebo-controlled trial with follow-up time of 18 months to detect treatment differences between hypothetical active and placebo arms ranging from 20% to 50% ($\alpha = 0.05$ and power of 80%). Scenarios are based on observed data from Parkinson's Progression Markers Initiative (PPMI). (**A**) Time to ≥5 point change on MDS-UPDRS part III or initiation of levodopa (LD) or dopamine agonist (DA) therapy; (**B**) time to ≥5 point change on MDS-UPDRS part III or initiation of LD/DA therapy, and ≥ 3 point change on MDS-UPDRS part II, and ≥ 3 point change on MDS-UPDRS part I. [Color figure can be viewed at wileyonlinelibrary.com]

(Supplementary Fig. S10C). Average sample size savings were 31.2% using this composite endpoint when enriching for a population with a predicted Progressive trajectory (Fig. 3C).

Discussion

We developed and validated a model to predict clinically relevant PD progression trajectories of ambulatory ability from baseline clinical assessments and self-reported symptoms. Having a predicted Progressive trajectory was associated with a rapid and severe course of disease, including loss of functional abilities, and worse cognition over 4 years compared to the Stable trajectory. In the early untreated PD cohort from PPMI, the model-based predicted categories were not simply a recapitulation of the PIGD/TD classifications, which are known to be unstable as disease progresses.[15,16,34] Our predicted trajectory groups in PPMI showed little overlap with baseline PIGD/TD phenotypes, and PIGD/TD was less informative as a stratification factor in time-to-clinical milestones. Interestingly, there was better congruence between the predicted trajectory groups and motor phenotypes in the Tracking cohort. This could be because of the Tracking cohort being slightly more advanced and treated, allowing for clearer differentiation of the PIGD/TD subtypes, which can substantially evolve even during the first year of follow-up.[16] All of this suggests that our models can identify more lasting progression trajectories of ambulation early in disease.

The predicted Progressive and Stable trajectories showed differences in baseline biomarkers. The Progressive group in PPMI had reduced striatal DAT binding, increased CSF τ, p-τ181, and albumin, and elevated serum and CSF NfL concentrations. "Copathologies" are common in people with PD, and aggregation of specific proteins such as Aβ1-42, p-τ, and α-synuclein have been associated with gait and balance disturbances in some, but not all studies of PD.[35-40] In addition, prior studies have linked amyloid and τ with gait disturbances in other populations, such as cognitively impaired cohorts and older persons without PD.[41-43] The CSF p-τ181 levels reported in our Progressive PD group appear to be lower than those reported in Alzheimer's disease patients (26–37 pg/mL),[44,45] so it is not clear whether specific biomarker values from one disease would be informative for prediction in other diseases. A next step to improve model discriminability could be to specifically incorporate these biomarkers as baseline predictors but this requires a separate cohort with the same clinical and biomarker measurements.

Concomitant medication use is another source of information that could be useful toward future efforts in predicting ambulatory progression. Cholinergic loss is linked to mobility impairment in PD,[46-48] and several small randomized controlled trials demonstrate beneficial effects on gait, balance, and falls with acetylcholinesterase inhibitors.[49-52] In contrast, anticholinergic drugs are associated with freezing of gait and increased fractures in PD.[53,54] Pharmacological interventions treating other PD symptoms, such as depression (eg, serotonergic drugs), or interventions targeting other neurotransmitter systems, such as the noradrenergic system, could provide prognostic insights as these have had some effects on freezing and mobility deficits in PD.[55-58]

The model-based predictions were tested for their usefulness in clinical trial enrichment scenarios. Enriching trial enrollment for participants that are more

likely to reach an endpoint of interest has been used in other neurodegenerative diseases.[59] The development of edaravone for amyotrophic lateral sclerosis used an enrichment strategy based on clinical parameters, like our approach, to exclude "minimal Progressors," thereby enhancing the ability to detect a treatment effect and ultimately gain regulatory approval.[60] Our models demonstrated ~16% sample size savings with enrichment when using a time to motor change endpoint that has similarities to one being used in an ongoing phase 2 study in early PD (n = 575).[61] However, enriching for predicted Progressives would require a large screening sample and may be less generalizable to the greater PD population. Additional analyses that factor these extra screening costs would be helpful to conclude whether optimal trial efficiency is attained with this approach. As an alternative, one could consider using the predicted Stable and Progressive trajectory groups as separate sub-cohorts in a trial so that there would be more homogenous progression patterns within cohorts. It is also important to remember that the model-predicted Progressive and Stable groups presented here are clinically rooted rather than biomarker-oriented. Therefore, enrichment strategies that aim to derive more biologically homogenous groups for targeting specific therapeutic pathways would likely be better served with a model or assay specifically designed for this purpose (eg, identifying progressive individuals with high τ levels for testing an anti-τ therapy).

The development of stratification tools that define more homogenous cohorts with emphasis on slow- versus fast-progressing PD has been a high priority area of research.[17,62] We focused on predicting ambulatory capacity trajectories, because ambulatory impairment is burdensome to people living with PD, worsens over time, and is largely resistant to dopaminergic treatments.[13,63,64] However, the ambulatory capacity scores were derived from the MDS-UPDRS, and is not a scale specifically designed to measure ambulation alone in PD. Repurposing the MDS-UPDRS in this fashion could lead to measurement restrictions. For example, most people with PD do not have significant gait and balance issues until later in the disease, increasing the chance of floor effects with the ambulatory capacity scale. Floor effects result in difficulties in differentiating among those at the lowest end of the scale. Therefore, it is possible that there could be undetected progression earlier in disease because of scale crudeness, and that more refined ambulatory trajectories could be detected with more sensitive measures (eg, sensors, gait tracking pads). Interestingly, the predicted Progressive group from our models demonstrated lower step counts and time ambulatory, suggesting at least some alignment of our models with these more precise measures of movement.

We took steps to minimize any effects of misdiagnosis, which may have contributed to the Progressive group, by excluding data from individuals who had revised diagnoses after inclusion in the studies. For PPMI data, we used a consensus committee analytic dataset, which involved clinical diagnosis adjudication with an expert committee that reviewed the clinical, imaging, and other available biomarker data on all PD participants where site investigators indicated a change in diagnosis (eg, progressive supranuclear palsy, multiple system atrophy, etc.). For Tracking, individuals were removed from the original dataset based on the principal investigator re-diagnosis to a non-PD diagnosis (D.G.G. personal communication, January 27, 2023). We acknowledge this may be imperfect, but when levodopa responsiveness was evaluated, we saw no differences between the model categories.

In summary, the modeling approaches used in this study were able to predict ambulatory capacity progression Stable and Progressive subtypes, using a combination of clinical assessments and patient self-reported symptoms. The predictive performance of our models demonstrated relatively good discriminability in identifying these trajectories on external validation, which is crucial to evaluate the generalizability of a model's prognostic capabilities, and which few studies in PD have performed.[62] Although the Progressive group was generally over-predicted, likely because of class imbalance of our target, the overall performance of our model was in-line with prior PD progression subtype prognostic models, which typically report accuracies in the low-to-high 70s.[65,66] Although we acknowledge there is room for improvement in model performance, the Progressive and Stable trajectory groups consistently aligned with clinical progression milestones, and exhibited potential use for clinical trials. ■

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Conflicts of Interest/Financial Disclosures

The authors declare there are no conflicts of interest relevant to this work.

Data Availability Statement

The data supporting the findings of this study are available at the Parkinson's Progression Marker Initiative website (https://www.ppmi-info.org/). Tracking Parkinson's accept and review applications from external researchers who wish to use the data for their own independent research (https://www.trackingparkinsons.org.uk/about-1/collaborations/data-sharing/).

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

C.S.V.: 1A, 1B, 1C, 2A, 2B, 3A.
G.S.: 1B, 1C, 2A, 2B, 3B.
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