Supplementary Material

Parkinson's Progression Markers Initiative: A Milestone-Based Strategy to Monitor Parkinson's Disease Progression

Supplementary Table 1. Baseline demographic and disease characteristics

Characteristic	Data Source	
	Annual Visits (N = 376)	**All Visits** (N = 385)
Age at enrollment, mean (SD)	61.5 (9.8)	61.5 (9.8)
Sex, n (%)		
Female	127 (33.8%)	130 (33.8%)
Male	249 (66.2%)	255 (66.2%)
Clinical site, n (%) *		
Non-US	69 (18.4%)	70 (18.2%)
US	307 (81.6%)	315 (81.8%)
Race, n (%) **		
Asian	8 (2.1%)	8 (2.1%)
Black or African American	6 (1.6%)	6 (1.6%)
Multiracial	6 (1.6%)	6 (1.6%)
White	355 (94.7%)	364 (94.8%)
Ethnicity, n (%)		
Hispanic or Latino	5 (1.3%)	5 (1.3%)
Not Hispanic or Latino	371 (98.7%)	380 (98.7%)
Years of education, mean (SD)	15.6 (2.9)	15.6 (2.9)
Body mass index (kg/m^2), mean (SD)	27.2 (4.7)	27.2 (4.7)
Orthostatic systolic blood pressure change, mean (SD)	4.8 (12.4)	4.8 (12.4)
Disease duration from diagnosis (months), mean (SD)	6.7 (6.5)	6.6 (6.5)
Family history of PD (first-degree relatives), n (%)	48 (12.8%)	50 (13.0%)
MDS-UPDRS total score, mean (SD)	31.5 (12.8)	31.5 (12.7)
Hoehn & Yahr stage, mean (SD)	1.6 (0.5)	1.6 (0.5)
Schwab & England, mean (SD)	93.5 (5.6)	93.5 (5.6)
Montreal Cognitive Assessment score, mean (SD)	27.2 (2.2)	27.2 (2.2)
SCOPA-AUT, mean (SD)	9.0 (5.5)	9.0 (5.5)
DAT-SPECT mean striatum SBR, mean (SD)	1.40 (0.39)	1.40 (0.39)
Serum urate (mg/dL), mean (SD)	5.4 (1.3)	5.4 (1.3)

Columns include participants who were milestone-free at baseline and subsequently completed at least one annual follow-up visit (i.e., 12, 24, 36, 48, and/or 60 months) or at least one annual or interim follow-up visit (i.e., 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months). *Non-US participants were recruited from sites in Australia (3), Austria (7), England (5), Germany (45), and Italy (10). **Multiracial subgroup includes 4 participants who self-identified as American Indian or Alaska Native and White and 2 who self-identified as Asian and White; race is missing for 1 participant. DAT-SPECT, dopamine transporter single photon emission computed tomography; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; SBR, specific binding ratio; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic.

Supplementary Table 2. Proportion of PPMI *de novo* PD cohort that *ever* met progression milestone criteria within five years.

Variable	Data Source	
	Annual Visits * (N = 376)	**All Visits **** (N = 385)
Any domain		
Overall (any milestone)	166 (44.1%)	193 (50.1%)
Cognitive domain		
Overall (any milestone)	71 (18.9%)	82 (21.3%)
By milestone		
Cognitive impairment (MoCA)	37 (9.8%)	37 (9.8%)
Dementia (composite)	25 (6.7%)	25 (6.7%)
Apathy	20 (5.3%)	32 (8.3%)
Cognitive impairment (MDS-UPDRS)	26 (6.9%)	34 (8.8%)
Dementia (clinical diagnosis)	18 (4.9%)	18 (4.9%)
Hallucinations	6 (1.6%)	7 (1.8%)
Functional dependence domain		
Overall (Schwab & England < 80)	72 (19.1%)	89 (23.1%)
Autonomic dysfunction domain		
Overall (any milestone)	60 (16.0%)	65 (16.9%)
By milestone		
Incontinence	34 (9.1%)	36 (9.4%)
Syncope (SCOPA-AUT)	31 (8.2%)	33 (8.6%)
Syncope (MDS-UPDRS)	4 (1.1%)	7 (1.8%)
Orthostatic hypotension	5 (1.3%)	5 (1.3%)
Walking and balance domain		
Overall (any milestone)	41 (10.9%)	55 (14.3%)
By milestone		
Postural instability	29 (7.8%)	39 (10.1%)
Walking and balance	22 (5.9%)	28 (7.3%)
Gait	21 (5.6%)	25 (6.5%)
Hoehn & Yahr	15 (4.0%)	16 (4.2%)
Freezing	10 (2.7%)	14 (3.6%)
Freezing of gait	4 (1.1%)	5 (1.3%)
Motor complications domain		
Overall (any milestone)	33 (8.8%)	48 (12.5%)
By milestone		
Fluctuations (complexity)	15 (4.0%)	22 (5.7%)
Fluctuations (functional impact)	23 (6.1%)	35 (9.1%)
Dyskinesias	2 (0.5%)	3 (0.8%)
Activities of daily living domain		
Overall (any milestone)	29 (7.7%)	52 (13.5%)
By milestone		
Choking	13 (3.5%)	24 (6.2%)
Speech	11 (2.9%)	12 (3.1%)
Dressing	9 (2.4%)	21 (5.5%)
Eating	6 (1.6%)	13 (3.4%)
Hygiene	4 (1.1%)	5 (1.3%)

Data indicates the proportion of participants who ever met criteria for each individual milestone within five years of follow-up irrespective of the order of occurrence (i.e., regardless of whether a different milestone was reached first). Columns include participants who were milestone-free at baseline and subsequently completed at least one of the specified follow-up visits. *Derived from follow-up data collected at 12, 24, 36, 48, and 60 months. **Derived from follow-up data collected at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months. MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic.

Supplementary Table 3. Stability (overall and by domain) of milestone criteria at subsequent annual visits

	Domain first reached						
Variable	**Overall (any domain)**	**Cognition domain**	**Functional dependence**	**Autonomic dysfunction**	**Walking and balance**	**Motor complications**	**ADLs domain**
Met criteria by 60-month visit, n *	166	53	45	41	25	19	17
Withdrew before next annual visit, n	14	3	6	1	4	2	3
N subsequent visits completed, mean **	3.6 (1.8)	3.5 (1.7)	3.6 (1.8)	3.6 (1.6)	3.9 (2.1)	3.1 (1.7)	2.9 (2.0)
Median (min, max) **	3 (1, 8)	3 (1, 7)	3 (1, 7)	3.5 (1, 7)	4 (1, 7)	3 (1, 6)	2 (1, 8)
Met *any* domain criteria at *any* visit, n (%) **	125 (82%)	43 (86%)	33 (85%)	31 (78%)	21 (100%)	12 (71%)	12 (86%)
Met *any* domain criteria at *next* visit, n (%) **	84 (55%)	27 (54%)	24 (62%)	21 (53%)	18 (86%)	10 (59%)	9 (64%)
Met *same* domain criteria at *next* visit, n (%) **	—	25 (50%)	17 (44%)	15 (38%)	12 (57%)	5 (29%)	6 (43%)

Reflects data collected at *annual* visits only and includes all corresponding data captured in the PPMI database as of June 30, 2020 (maximum duration of follow-up: 96 months). *Indicates how many participants met the corresponding criteria at the *initial* event (i.e., first visit at which criteria for at least one milestone from any domain were met). **Calculations exclude anyone who withdrew before completing another follow-up. ADLs, activities of daily living.

Supplementary Figure 1. Flow chart summarizing which participants from PPMI *de novo* PD cohort were included in the analysis and how many participants were assessed at each study time point.