Weighting MDS-UPDRS motor items for optimal sensitivity to Parkinson's Disease progression in untreated patients using Parkinson's Progression Markers Initiative data

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CONCLUSIONS

1. Endpoints derived from the motor composite scale (MCS) reflect items from combined domains which measure clinically meaningful progression with greater sensitivity compared to the original Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II and III.
2. The top three items retained in the MCS were: turning in bed, speech, and rest tremor amplitude, indicating that these are the items most reflecting disease progression in untreated patients with Parkinson's Disease (PD).
3. Composite scales (CS) developed using these methods can improve detection of clinical decline when applied in similar patient populations and are valuable for the assessment of disease modifying therapies (DMT).

References:

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Data Acknowledgment:

PPMI: https://ppmi-info.org

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INTRODUCTION

- PD is a complex degenerative disease, affecting motor abilities across multiple domains. Symptoms can vary substantially across individuals based on the stage of disease.[1]
- Currently, no DMTs for PD are available.
- Clinical trials assessing outcomes in PD patients typically use scales designed to comprehensively measure a range of PD symptoms that occur across the spectrum of disease, of which the MDS-UPDRS is a cornerstone measure.
- The variability of PD symptoms and the use of all-encompassing measures in clinical trials complicate the assessment of disease modifying treatments in clinical trials. Measurement of clinical decline is particularly difficult, in early stages of PD where symptoms are subtle.
- CS have been developed previously in other neurodegenerative diseases, and can be optimized according to disease stage, treatment status, and symptom presentation.[2,3] This allows them to be more sensitive to small but meaningful changes in disease progression.

OBJECTIVE **To demonstrate how CS can better detect meaningful changes in motor progression among untreated PD patients.**

METHODS

Study Participants and Data

- Data were obtained from the PD cohort of the Parkinson's Progression Markers Initiative (PPMI) - an ongoing, international, multicenter natural history cohort which is primarily funded by the Michael J. Fox Foundation. Data were available from July 1, 2010 to July 1, 2023.
- For the current analysis, subject met the following baseline criteria: Hoehn & Yahr stage 1 or 2; no previous or current dopaminergic therapy (DT) use; and time from PD diagnosis less than two years.
- Patients were censored from the analysis once any DT was initiated, other than monoamine oxidase-B (MAO-B) inhibitors.
- MDS-UPDRS scale (© 2008 International Parkinson and Movement Disorder Society) Part II (motor experiences of daily living, 13 items) and Part III (motor examination, 33 scores based on 18 items) were used to develop the MCS.
- The analytic dataset included patients who had baseline and ≥1 post-baseline visits with complete data on Part II and Part III within 3 years.

Statistical Analysis

- A linear decline model was fit to the data using partial least squares (PLS) regression methods in R, where temporal change was the outcome variable and Parts II and III items were the explanatory variables.
- The MCS was generated by combining scale items from Parts II and III, selected from the PLS regression, with PLS coefficients serving as weighting factors. Wold's criterion was used to remove scale items with a variable importance in projection (VIP) threshold of <0.5.
- Each patient had this weighted score calculated and the change from baseline of the new score summarized.
- The mean to standard deviation ratio (MSDR) was computed for change scores, and power calculation.

RESULTS

- Baseline characteristics of the cohort (N=426) are presented in **Table 1**. The cohort included predominantly white males aged 63 years, diagnosed in the previous year with Hoehn & Yahr Stage 2.
- 28 items had positive VIP scores and met the Wold's >0.5 (61% of original scale items) (presented in **Table 2**).
- Items from Part II and III contributed to 37.9% and 61.9% of the weighed MCS, respectively.
- The three most responsive items (with their combined weights) were: turning in bed, getting out of bed/car/chair, and tremor (19.6%) for Part II, and speech, rest tremor amplitude – left upper extremity, and leg agility – left leg (21.1%) for Part III.
- The total MSDR increased 13.1%, from 0.7615 for the original MDS-UPDRS Parts II and III items, to 0.8612 for the weighted MCS.
- The increase in scale sensitivity corresponded to a sample size decrease of 22%, reflecting a power improvement of 8 percentage points at 80% initial power.

Table 1. Demographic and baseline characteristics for untreated patients with PD, from the PPMI dataset

	N=426
Age in years, mean (SD)	62.7 (9.1)
Sex, n (%)	
Male	293 (69)
Female	133 (31)
Age at diagnosis, mean (SD)	61.7 (9.1)
Race	
White	396 (93)
Multiracial	10 (2)
Black/African American	8 (2)
Asian	5 (1)
Native American	1 (0)
Not specified	6 (1)
Time since diagnosis (years), mean (SD)	0.6 (0.5)
Hoehn and Yahr stage, n (%)	
1	159 (37)
2	267 (63)
MDS-UPDRS part II score, mean (SD)	5.3 (4.0)
MDS-UPDRS part III score, mean (SD)	20.8 (8.9)

MDS-UPDRS, movement disorder society unified Parkinson's disease rating scale; SD, standard deviation.

Figure 1: Change in MSDR for the MDS-UPDRS Parts II and III, untreated PD patients

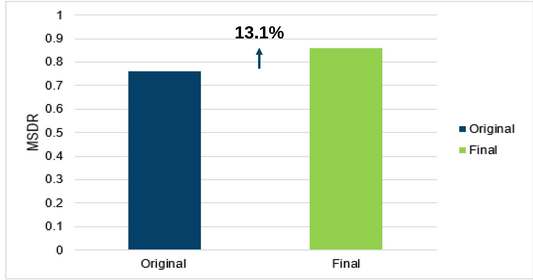

Table 2. VIP scores and corresponding PLS coefficients for the MDS-UPDRS Part II and III PPMI untreated population, VIP cut-off 0.5

Item	MSDR at 1 year	VIP	PLS weight	% contribution
2.9 Turning in bed	0.3498	0.8853	0.7619	9.4
3.1 Speech	0.3683	0.9706	0.6261	7.7
3.17b Rest tremor amplitude - LUE	0.3329	1.0614	0.5510	6.8
3.8b Leg agility - Left leg	0.3061	1.3672	0.5328	6.6
3.17a Rest tremor amplitude - RUE	0.2711	1.0651	0.5075	6.3
2.11 Getting out of bed, a car, or a deep chair	0.2208	0.9876	0.4674	5.8
3.6b Pronation-Supination - Left hand	0.3842	1.3425	0.4484	5.5
2.10 Tremor	0.2322	0.8414	0.3556	4.4
2.12 Walking and balance	0.2723	0.6476	0.3358	4.2
3.13 Posture	0.1708	0.7745	0.3251	4.0
3.2 Facial expression	0.2019	1.0356	0.3164	3.9
2.1 Speech	0.2420	0.6893	0.3144	3.9
3.5b Hand movements - Left hand	0.3332	1.4373	0.3107	3.8
2.7 Handwriting	0.2456	1.1884	0.3042	3.8
3.3e Rigidity - LLE	0.1430	1.1031	0.2782	3.4
3.7a Toe tapping - Right foot	0.1784	1.3510	0.2586	3.2
2.2 Saliva and drooling	0.2288	0.8720	0.2335	2.9
3.18 Constancy of rest tremor	0.3316	1.5598	0.2289	2.8
2.4 Eating tasks	0.2947	0.7090	0.2227	2.8
3.3b Rigidity - RUE	0.1834	0.8314	0.2116	2.6
3.14 Global spontaneity of movement	0.2734	0.9049	0.1519	1.9
3.3c Rigidity - LUE	0.3370	1.0914	0.0694	0.9
3.7b Toe tapping - Left foot	0.2227	1.3155	0.0597	0.7
2.5 Dressing	0.3113	0.7396	0.0599	0.7
3.5a Hand movements - Right hand	0.2268	1.1942	0.0464	0.6
3.3a Rigidity – Neck	0.2428	0.9632	0.0521	0.6
3.4b Finger tapping - Left hand	0.3876	1.3037	0.0279	0.3
3.4a Finger tapping - Right hand	0.2000	1.1148	0.0240	0.3
Overall MSDR	**0.8612**			0 1

LLE, Left lower extremity; LUE, Left upper extremity; MDS-UPDRS, movement disorder society unified Parkinson's disease rating scale; MSDR, mean to standard deviation ratio; PLS, partial least squares; RUE, Right upper extremity; SD, standard deviation; VIP, variable importance of projection.

DISCUSSION

- Data from the MDS-UPDRS Parts II and III from the PPMI PD cohort were used to derive a MCS that enhanced the ability to detect meaningful disease progression in untreated PD patients.
- The scale is optimized for patients with early PD who have not initiated levodopa. An MCS derived in treated patients with PD would be expected to differ, in terms of the items included and their relative contribution to the overall CS.
- The improved MSDR in the MCS indicates a more sensitive scale for disease progression in untreated PD patients based on a shorter tool (28 items vs. 46).
- Scales optimized for responsiveness in measuring disease progression across target populations can have significant implications for clinical trial design, including reduced sample size requirements and increased statistical power.
- Given the difficulties in accurately measuring PD progression during the typical length of a DMT trial, the potential benefit of measures optimized to clinical decline cannot be understated.