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Short-term disability progression in two multiethnic multiple sclerosis centers in the treatment era

Ilya Kister, Tamar E. Bacon and Gary R. Cutter

Abstract

Background: Short-term disease progression is well documented in clinical trials, but there are limited published data on disease course in real-life practice.

Methods: Patient-derived Multiple Sclerosis Severity Score (PMSSS), a disease severity rank score, was computed at each visit for consecutive MS patients attending two large, ethnically diverse MS centers in New York metropolitan area. Disability was assessed *via* Patient-Determined Disease Steps (PDDS). Clinicians recorded disease subtype and relapse status at each visit, but did not rate disability. PMSSS change from the first to the last visit was calculated for the cohort as a whole and for subgroups of interest. Multivariable regression models were constructed for predicting final PMSSS based on readily available predictor variables collected at the initial visit and relapse history during follow up.

Results: A total of 1740 consecutive patients from New York University (n = 1079) and Barnabas (n = 661) MS Care Centers were included. During follow up (mean 2.4 $\pm$ 0.82 years, range 1–4 years), mean PDDS score increased from 1.9 $\pm$ 2.2 to 2.3 $\pm$ 2.2 ($p < 0.0001$), while PMSSS remained roughly unchanged (initial PMSSS = 3.71 $\pm$ 2.73, last PMSSS = 3.81 $\pm$ 2.76, paired t test, p = 0.28). The only major predictor of final PMSSS was the initial PMSSS. Demographic variables (age, sex, race) or relapse status did not predict final severity score.

Conclusions: Baseline disability in two MS clinics was much lower than in the reference population from which PMSSS was derived. We observed no discernable slowing of disability accumulation during the short-term follow up in our cohort compared with the reference cohort. Overwhelmingly the most important predictor of final disease severity rank score was the initial disease severity rank score.

Keywords: disability, disease-modifying therapy, multiple sclerosis, observational cohort study, relapse

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Introduction

Short-term multiple sclerosis (MS) progression in clinical trials is well documented,[1,2] but there is paucity of published data on disease progression in real-life contemporary practice. These data are needed to answer the question of whether there has been a discernable slowing of disability progression in the contemporary MS clinic population. To address this question, one needs a practical tool for assessing disease progression in the clinical setting. The Patient-derived Multiple Sclerosis Severity Score (PMSSS) is such a tool.[3] PMSSS is a decile rank of the Patient-Determined Disease Steps (PDDS) among patients with similar disease duration in the North American Research Committee on Multiple Sclerosis (NARCOMS) registry. Determining PMSSS places minimal demands on the patient or the clinician: the patient records their disability on a single-question PDDS questionnaire, while the clinician reads out PMSSS corresponding to the patient's PDDS and disease duration from the

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published reference table.[3] PMSSS could thus be realistically obtained on nearly all patients with MS without compromising clinical operation. We used PMSSS to track disease progression in consecutive patients with MS attending two large, ethnically diverse MS centers and identified predictors of the final PMSSS based on readily available variables collected at the initial visit and relapse history during follow up.

Methods

We included consecutive patients from the urban New York University (NYU) MS Care Center in New York, NY, USA and the suburban Barnabas MS Care Center in Livingston, NJ, USA who were evaluated between June 2010 and November 2016. All patients were diagnosed with MS by their treating neurologists (2010 McDonald's criteria)[4] and completed two or more self-rated disability assessments (PDDS) more than one year apart. PDDS is a freely available, self-reported eight-point scale that measures global neurological impairment in MS.[5] PDDS correlates strongly with the Expanded Disability Status Scale (EDSS), the 'gold standard' of disability assessment in MS.[6,7] We required that the patient's disease duration at the time of the last visit be less than 45 years as PMSSS can only be calculated for disease durations up to 45 years. At each visit, baseline and follow up, the treating neurologist documented disease subtype and recorded whether the patient had a relapse within 3 months of the visit.

The study received an exemption determination from the institutional review boards (IRBs) of NYU Langone Medical Center (New York) and Barnabas Medical Center (Livingston, NJ). No informed consent was required by the IRBs as this was a retrospective study. In order to meet the IRB exempt review status, we excluded patients younger than 18 years old and those who could not follow written instructions in English.

PMSSS was computed for each patient visit using the published reference table.[3] In addition, we assigned each patient to their respective 'severity grade', as described previously.[8] In brief, the PMSSS scale is divided into six equal grades and each grade (sextile), by design, comprises around one sixth of the reference NARCOMS population. The six-grade classification allows for an easy comparison between distributions of severity scores in our clinic populations and the reference population.

Initial and final PMSSS scores for the cohort as a whole and subgroups of interest were compared using t tests. Linear multivariable regression was conducted predicting final PMSSS from age, sex, race (white *versus* African American *versus* Hispanic *versus* other), duration of follow up, relapse status (yes/no relapse during follow up), interaction terms of initial PMSSS × disease duration and of relapse status (yes/no) × age × sex. Since our aim was to assess longer-term effects of relapses on PMSSS rather than their immediate impact, we have excluded from the model any PMSSS measurements taken within 3 months of a relapse. All analyses were carried out using JMP and SAS software; $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

1740 consecutive patients from NYU (n = 1,079) and Barnabas (n = 661) MS Care Centers met our inclusion criteria. Demographic characteristics for each center as well as for the combined cohort are shown in Table 1. Compared with Barnabas, NYU patients were slightly younger (mean age 44 *versus* 46 years), less likely to be female (72% *versus* 77%) and more ethnically diverse (white patients comprised 52% of those at NYU *versus* 74% at Barnabas). The two centers were similar with respect to disability: median PDDS in each center was 1, corresponding to 'mild disability', and the percentage of patients with ambulatory assistance (PDDS >3) was around 25% in both centers. Identities of disease-modifying therapies (DMTs) at baseline were available for patients from NYU MS Center only and were as follows: 20% infusible medications (natalizumab, rituximab, alemtuzumab); 29% oral agents (fingolimod, dimethyl fumarate); 27% first-line injectables (interferon β and glatiramer acetate); 22% no DMTs; and the remaining 3% nonapproved or 'unknown' therapies. DMTs were not recorded on subsequent visits in the database, so duration on therapy could not be estimated. Initial DMTs were not collected for Barnabas patients, but would be expected to parallel NYU experience, as practice patterns were similar among physicians in the two centers.

Table 1. Baseline demographic characteristics of the BMSC, the NYUMSC and the cohort as a whole (total).

	BMSC	NYUMSC	Total	*p* value*
N	661	1079	1740	–
Female, %	77.2	71.6	73.7	**$p = 0.0116$**
Initial disease duration, average (SD)	11.3 (8.9)	11.2 (9.2)	11.2 (9.0)	$p = 0.8699$
Age in years, average (SD)	46.0 (12.2)	43.5 (12.2)	44.5 (12.2)	**$p < 0.0001$**
Follow up in days, average (SD)	935.9 (301.3)	856.6 (295.9)	886.7 (300.4)	**$p < 0.0001$**
Initial PDDS, average (SD)	2.1 (2.1)	1.9 (2.2)	1.9 (2.2)	$p = 0.0899$
Ambulatory assist (PDDS >3), %	25.6	23.6	24.4	$p = 0.3882$
Initial PMSSS	3.9 (2.7)	3.6 (2.7)	3.7 (2.7)	$p = 0.0806$
Race, %				
White	74.0	51.5	60.1	**$p < 0.0001$**
AA	15.7	22.4	19.9	**$p = 0.0007$**
HA	8.2	15.4	12.6	**$p < 0.0001$**
Other	2.1	10.7	7.4	**$p < 0.0001$**

* p values represent differences between NYU and Barnabas cohorts; values<0.05 are shown in bold.
'Severe disability is defined as 'assistance needed for ambulation', or PDDS>3.
AA, African American; BMSC, Barnabas Multiple Sclerosis Center; HA, Hispanic American; NYUMSC, New York University Multiple Sclerosis Center; PDDS, Patient-Determined Disease Steps; PMSSS, Patient-derived Multiple Sclerosis Severity Score; SD, standard deviation.

Percentage of patients in each of the sextile severity grades at the initial visit is shown in Figure 1 (the dotted line represents expected percentage based on the NARCOMS population). Distributions of patients across the severity grades were similar at NYU and Barnabas. Both centers had notable overrepresentation of patients in the two milder sextile grades (1 and 2): combined total in our clinics was 56% (*versus* 33% in NARCOMS); and underrepresentation of patients in the two most severe grades (5 and 6): a combined total of 20% (*versus* 33% in NARCOMS).

Longitudinal follow up

Mean duration of follow up was 2.4 ± 0.82 years and over 99% of patients had follow up between 1 and 4 years. Mean PDDS score at the initial visit was 1.9 ± 2.2. The final PDDS score was higher than the initial score, 2.3 ± 2.2, $p < 0.0001$. Mean PMSSS rank score for the cohort was similar at baseline (3.71 ± 2.73) and last follow up (3.81 ± 2.76; *t* test, $p = 0.28$).

Figure 2 shows the distribution of final severity grades stratified by the initial severity grade. In total, 51.3% of patients stayed in their original severity grade at the last follow up, 86.9% of patients were within one grade of their original severity grade and 96.1% were within two grades of their original grade. Of the patients in the 'mild MS' group (first sextile) at baseline, 68% remained in the mild sextile at last follow up and 20% moved up to the second severity sextile. Of the patients with 'aggressive MS' (sixth sextile), 76% remained in the sixth sextile and 17% moved down to the fifth severity sextile.

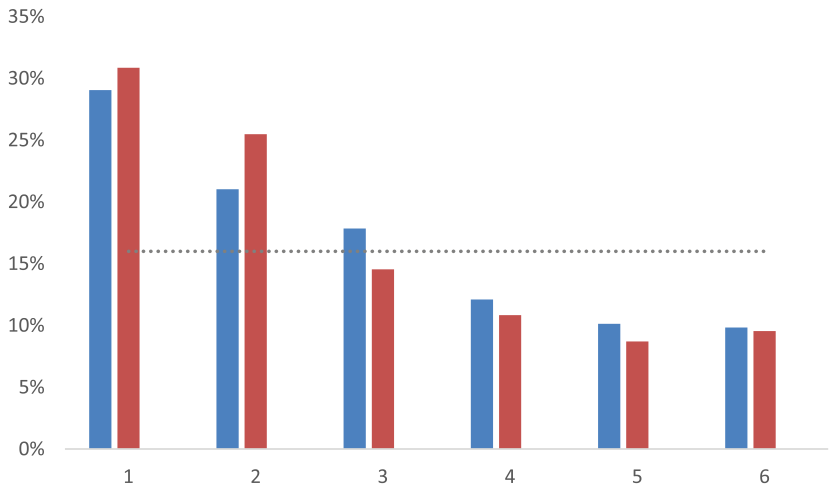

Figure 1. Baseline severity grade distributions in the New York University (NYU) (red) and Barnabas (blue) MS centers.
Distribution of sextile severity grades in Barnabas (blue) and NYU (red) MS centers. Grade severity increases from '1' (PMSSS <1.67, 'mild MS') to '6' (PMSSS <8.33, most severe, 'aggressive MS'). The horizontal dotted line crossing the *y* axis at 16.6% represents the percentage of patients in each severity grade in the reference NARCOMS population and is provided for comparison purposes. MS, multiple sclerosis; NARCOMS, North American Research Committee on Multiple Sclerosis; PMSSS, Patient-derived Multiple Sclerosis Severity Score.

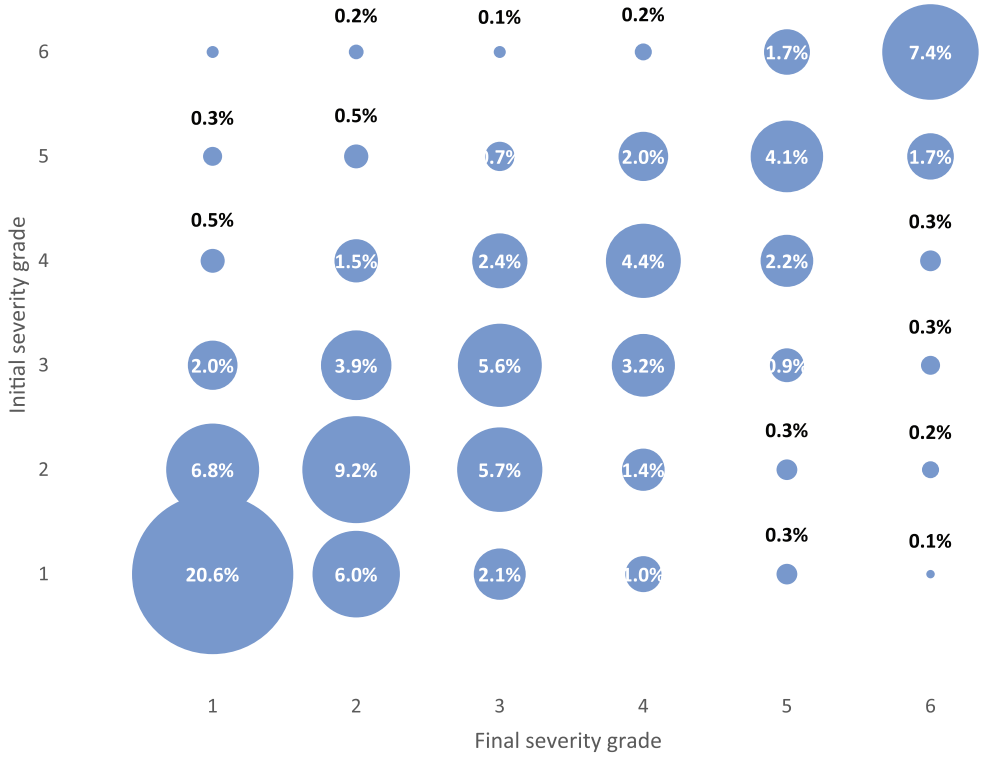

Figure 2. Distribution of final severity grade stratified by the initial severity grade.
Bubble size represents proportion of patients in the cohort with the corresponding initial and final grades. For example, the first column includes all patients with final severity grade of 1: 20.6% of all patients had initial and final severity grade of 1 (left lower corner); 6.8% of patients had initial grade of 2 and final grade of 1; 2.0% had initial grade of 3 and final grade of 1, etc."

Table 2. Initial and final PMSSS in MS center cohorts and subgroups of interest.

	NYUMSC				BMSC				Total cohort			
	Initial	**Final**	**Δ**	***p****	**Initial**	**Final**	**Δ**	***p****	**Initial**	**Final**	**Δ**	***p****
PMSSS cohort	3.61 (2.73)	3.69 (2.71)	0.04	NS	3.87 (2.72)	4.09 (2.80)	0.22	NS	3.73 (2.73)	3.84 (2.75)	0.11	NS
<45	3.18 (2.42)	3.22 (2.35)	0.03	NS	3.41 (2.53)	3.64 (2.57)	0.23	NS	3.26 (2.46)	3.37 (2.44)	0.11	NS
45+	4.18 (2.95)	4.23 (2.99)	−0.06	NS	4.27 (2.83)	4.48 (2.93)	0.21	NS	4.21 (2.9)	4.33 (2.96)	0.12	NS
Male	3.91 (2.87)	3.90 (2.85)	−0.01	NS	4.35 (2.78)	4.59 (2.91)	0.24	NS	4.05 (2.84)	4.12 (2.88)	0.07	NS
Female	3.53 (2.66)	3.61 (2.65)	0.08	NS	3.73 (2.69)	3.94 (2.75)	0.21	NS	3.61 (2.67)	3.74 (2.69)	0.13	NS
No relapse	3.56 (2.72)	3.59 (2.73)	0.03	NS	3.84 (2.74)	4.02 (2.83)	0.18	NS	3.67 (2.73)	3.76 (2.78)	0.09	NS
Yes relapse	3.95 (2.71)	4.09 (2.6)	0.14	NS	4.05 (2.63)	4.54 (2.58)	0.49	NS	3.98 (2.69)	4.22 (2.6)	0.24	NS
Relapsing	3.17 (2.46)	3.22 (2.44)	0.05	NS	3.37 (2.49)	3.47 (2.49)	0.1	NS	3.24 (2.47)	3.31 (2.46)	0.07	NS
Progressive	6.32 (2.64)	6.41 (2.60)	0.09	NS	5.71 (2.76)	6.36 (2.69)	0.65	**$p = 0.04$**	6.03 (2.71)	6.39 (2.64)	0.36	**$p = 0.09$**
White	3.37 (2.61)	3.47 (2.65)	0.1	NS	3.70 (2.68)	3.87 (2.76)	0.17	NS	3.52 (2.64)	3.66 (2.71)	0.14	NS
AA	4.28 (2.97)	4.39 (2.93)	242	NS	4.59 (2.79)	4.94 (2.83)	0.35	NS	4.37 (2.92)	4.56 (2.91)	0.19	NS
HA	4.03 (2.66)	3.76 (2.57)	166	NS	4.08 (2.8)	4.30 (2.63)	0.22	NS	4.04 (2.69)	3.89 (2.59)	−0.15	NS

**p* Values represent differences between baseline and final scores for each subgroup of interest; Δ represents change from final to initial PMSSS.
AA, African American; BMSC, Barnabas Multiple Sclerosis Center; HA, Hispanic American; NS, nonsignificant; NYUMSC, New York University Multiple Sclerosis Center; PDDS, Patient-Determined Disease Steps; PMSSS, Patient-derived Multiple Sclerosis Severity Score.

Initial and final PMSSS for subgroups of interest are shown in Table 2. Baseline PMSSS differed across the subgroups as expected (e.g. higher in progressive *versus* relapsing disease; higher in racial/ethnic minorities *versus* white). No significant change in PMSSS was observed in the subgroups of interest in either center, except for a borderline significant increase in PMSSS among patients with progressive MS in the Barnabas MS center, and a trend toward an increase in PMSSS among all patients with progressive MS (PMSSS increase of 0.36, $p = 0.09$).

We also compared patients whose PMSSS had increased over the period of observation (accelerated accumulation of disability, $N = 607$) with patients whose PMSSS had decreased (slowing in accumulation of disability, $N = 1133$). The two groups were similar with respect to age, percent female, percent white, but relapses were more frequent in those whose PMSSS increased (21.6%) compared with those whose PMSSS declined (15.9%, rate ratio 1.36, $p < 0.0001$).

Predictors of final PMSSS: a multivariate regression model

We constructed a multivariable ordinal regression model with final PMSSS as an outcome variable, with age, sex, race, initial PMSSS, relapse status and duration of follow up as predictor variables. The single most important predictor of final PMSSS in our model was the initial PMSSS ($p < 0.0001$). Initial PMSSS by far dominated all other predictor variables, explaining 66% of the variance, while the additional variables contributed less than 1%. Neither age nor relapse during follow up (and <3 months of the assessment) were predictive of the final PMSSS. However, age × relapse interaction term was a significant predictor of the final score ($p < 0.0025$). The impact of a relapse was greater the younger the patient. This effect was driven by women (interaction term age × sex × relapse was only significant for women and not for men). Interaction term initial PMSSS × duration of follow up was not significant ($p = 0.3139$), implying that lack of change in PMSSS was unlikely to be due to differential follow-up times among our patients.

We also modeled 'two-grade increase' (33.3% increase in PMSSS) as a categorical outcome variable in a logistic regression model that used same predictor variables as the linear model of the PMSSS ordinal data. Initial PMSSS remained the most important predictor of two-grade increase. Age, relapse status, and the relapse × age term were not significant predictors, while African-American race was associated with higher odds of a two-grade increase.

Discussion

Distributions of patients into sextile grades in the two MS centers were similar to each other but milder compared with the reference MS population.[3] Only one in four patients in our centers needed an assistive device for ambulation. These data are in line with contemporaneous reports that document low disability in patients attending MS clinics.[9,10] The reference population, on the other hand, derives from a longitudinal registry and is subject to cohort effects from earlier decades of diagnosis.

During mean follow up of 2.4 years, the average PDDS disability score for the cohort increased from 1.9 to 2.3, while the severity score remained largely unchanged for both centers. The lack of change in PMSSS implies that disability accumulation in our patients proceeded as would be expected for patients with similar baseline scores in the reference NARCOMS population.[11] How do we reconcile the fact that baseline severity scores in our cohort were much lower than in NARCOMS and yet there was no evidence in a slowing of disability accumulation over the short term compared with the NARCOMS population? One plausible explanation is that the follow-up period in our study was insufficient to detect a downward beneficial change in disease trajectory, which would only become apparent with a longer timescale. Indeed, a recent model showed lower disability (EDSS) scores in a treated cohort compared with what would be expected in natural history studies, but the effect was apparent only after 6 years of treatment.[12] Milder disability at baseline also makes it more challenging to detect potential treatment benefit due to 'floor effect'. Milder disability in a contemporary setting could also be partly due to 'stage migration', wherein people who would not have been classified as having MS based on the clinical Poser criteria are now so classified using the less restrictive McDonald criteria at an earlier stage of the disease.[13] Finally, learning effect with the PDDS scale is a potential bias, with greater accuracy on subsequent administrations, but this

seems unlikely as PDDS data collected in our clinics yielded expected results; for example, higher scores in patients with progressive disease *versus* relapsing disease, and higher scores in patients of African descent compared with white patients, as shown previously.[14]

A lack of improvement in severity rank scores in our cohort contrasts with decreases in severity rank scores seen in clinical trials of two highly effective DMTs, natalizumab[15] and alemtuzumab.[16] These discrepant results may be partly due to differences between patients enrolled in these trials *versus* an unselected clinic population. Patients who participated in the trials of these high-efficacy agents had relapsing disease and above average inflammatory disease at enrollment. Our clinic patients, however, are much more like the MS population as a whole: they represent all disease subtypes; have had disease for variable time periods (on average, for a decade or more); and most were receiving a variety of DMTs. Moreover, patients enrolled in the clinical trials are required to have recent disease activity, so some diminution of disease activity in the trials is expected due to regression-to-the-mean phenomenon, which is independent of drug effect.[17]

The large sample size of our cohort allowed us to compare baseline disease severity and disability progression in several subgroups of interest. As expected, baseline severity rank scores were highest in patients with progressive disease subtype and those needing assistance to ambulate. Among racial/ethnic subgroups, African Americans had the highest baseline severity scores, followed by Hispanic Americans, followed by white Americans, in agreement with our prior analyses.[18] Interestingly, no change in severity scores was observed for any of the subgroups of interest, including patients with relapses 3 months or more from the last visit. Patients with progressive disease showed a trend for worsening PMSSS with time.

Multivariable regression analysis identified initial PMSSS as by far the most robust predictor of final PMSSS. This may be due, in part, to statistical considerations: regression to the mean and the fact that change in PMSSS, and therefore the final PMSSS, is determined, in part, on the initial PMSSS. From a clinical point of view, it is remarkable that the initial PMSSS explained 66% of the variance in the final PMSSS, while all additional factors accounted for less than 1% of the variance. Age and other demographic factors were not significant predictors of final PMSSS in our regression model, but if the initial PMSSS was omitted from the model then older age and duration of follow up became significant predictors of higher final PMSSS (data not shown). These data imply that the known, modest predictors of MS course, such as male sex, older age at onset, early sphincter involvement, or even progressive from onset form of the disease,[19] may not be nearly as important for prognosis as the current severity score, at least for short-term prognostication.

We observed that interaction of age $\times$ relapse status had a small, but significant impact on the final PMSSS score, implying that when relapses occurred in younger persons with MS, they tended to have a greater impact on severity rank score. This is in line with a prior study that found that relapses occurring later in the disease course, especially after the onset of the progressive phase, have little or no impact on the accumulation of disability.[20] Interestingly, age $\times$ relapse interaction term was only significant for women and not for men. Perhaps, this was partly due to the fact that a smaller proportion of older men experienced relapses during follow up (8.6% of those who were >45 years old *versus* 10.7% of women), and relatively more men were in the progressive phase.

The strength of our study is the use of two large clinic-based patient populations, which allowed us to check for reproducibility of findings. Notwithstanding, the clinic population may underrepresent some subgroups of patients, such as untreated patients, older patients or bedbound patients. Moreover, though we made an effort to collect data from every patient, we have inevitably missed some of our patients who did not wish to or were not able to respond to the disability questionnaire. Another limitation of the study is the exclusive reliance on patients for disability rating; the clinician's rating of disability was not recorded. We, and others, have shown that PDDS correlates highly with EDSS,[6,7] yet patients' self assessment may not always agree with that of the physician due to cognitive impairment or misattributing debility from non-MS causes to MS. Finally, PDDS, as EDSS, is a scale that is heavily weighted toward ambulation and does not reflect

'invisible disability' due to fatigue, depression, anxiety, cognitive impairment and pain. Symptom progression in the 'invisible' domains warrants a separate study.

Our work illustrates the utility of the PMSSS for studying disease progression in a real-life setting in real time. We show that unlike disability (PDDS scores), which worsened over time, PMSSS remained approximately unchanged during the 1–4-year follow up. This apparent discrepancy is not unexpected: disability in MS is known to increase with disease duration in MS,[1–3] while PMSSS, a relative rank of disability scores adjusted for disease duration, remains constant over time so long as disease progression of the cohort of interest is comparable to that of the reference NARCOMS population. Thus, a decrease of PMSSS would signify that the patient cohort accumulated disability at a slower rate than reference NARCOMS populations, while PMSSS stability, as observed in our cohort, indicates a similar rate of disability accumulation relative to the reference population.

Importantly, baseline PMSSS was overwhelmingly the most important predictor of future PMSSS in our model than any other previously recorded predictors, such as male sex or even progressive disease subtype. Therefore, baseline severity rank score should be included in any study of prognostic factors in MS.

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Conflict of interest statement

This study was supported by an investigator-initiated grant from Sanofi Genzyme. IK has served on advisory boards for Biogen and Genentech and received research support for investigator-initiated grants from Sanofi Genzyme, Biogen, EMD Serono, National MS Society and Guthy Jackson Charitable Foundation. TEB has nothing to disclose. GC has served on data and safety monitoring boards for AMO Pharmaceuticals, Apotek, Horizon Pharmaceuticals, Merck, Merck/Pfizer, Modigenetech/Prolor, Neurim, Opko Biologics, Reata Pharmaceuticals, Receptos/Celgene, Sanofi, Teva Pharmaceuticals, NHLBI (Protocol Review Committee), and NICHD (OPRU oversight committee); has received compensation for consulting or advisory boards from Argenix, Atara Biotherapeutics, Biogen, Bioeq GmbH, the Consortium of MS Centers (grant), Sanofi Genzyme, Genentech, Innate Therapeutics, Klein-Buendel Incorporated, MedDay, Medimmune, Novartis, Opexa Therapeutics, Roche, Savara Inc., Somahlution, Teva Pharmaceuticals, TG Therapeutics, and Transparency Life Sciences; and is president of Pythagoras, Inc., a private consulting company.

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References

1. O'Connor P, Wolinsky JS, Confavreux C, *et al*. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011; 365: 1293–1303.
2. Ontaneda D, Fox RJ and Chataway J. Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives. *Lancet Neurol* 2015; 14: 208–223.
3. Kister I, Chamot E, Salter AR, *et al*. Disability in multiple sclerosis: a reference for patients and clinicians. *Neurology* 2013; 80: 1018–1024.
4. Polman CH, Reingold SC and Banwell B. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald Criteria. *Ann Neurol* 2011; 69: 292–302.
5. Hohol M, Orav E and Weiner H. Disease steps in multiple sclerosis: a simple approach to evaluate disease progression. *Neurology* 1995; 45: 251–255.
6. Learmonth YC, Motl RW and Sandroff BM. Validation of Patient Determined Disease Steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol* 2013; 13: 8
7. Pandey KS, Cutter G, Green R, *et al*. *Single-question patient-reported disability strongly correlates with Expanded Disability Status Scale. Presented orally at the 31st Congress European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)*, October 2015, Barcelona, Spain.
8. Charlson RE, Herbert J and Kister I. Severity grading in multiple sclerosis: a proposal. *Int J MS Care* 2016; 18: 265–270.

9. Cree B, Gourraud P-A and Oksenberg J. Long-term evolution of multiple sclerosis disability in the treatment era. *Ann Neurol* 2016; 80: 499–510.
10. Rotstein DL, Healy BC and Malik MT. Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort. *JAMA Neurol* 2015; 72: 152–158.
11. Roxburgh RH, Seaman SR, Masterman T, *et al.* Multiple sclerosis severity score: using disability and disease duration to rate disease severity. *Neurology* 2005; 64: 1144–1151.
12. Tilling K, Lawton M, Robertson N, *et al.* Modelling disease progression in relapsing-remitting onset multiple sclerosis using multilevel models applied to longitudinal data from two natural history cohorts and one treated cohort. *Health Technol Assess* 2016; 20: 1–48.
13. Sormani MP. The Will Rogers phenomenon: the effect of different diagnostic criteria. *J Neurol Sci* 2009; 287(Suppl. 1): S46–S49. DOI: 10.1016/S0022–510X(09)71300–0.
14. Kister I, Chamot E, Bacon JH, *et al.* Rapid disease course in African Americans with multiple sclerosis. *Neurology* 2010; 75: 217–223. DOI: 10.1212/WNL.0b013e3181e8e72a.
15. Herbert J, Kappos L, Calabresi P, *et al.* Natalizumab reduces multiple sclerosis severity: analysis of patients from the AFFIRM and SENTINEL studies using the multiple sclerosis severity scale (abstract). *Neurology* 2008; 70(Suppl. 1): A212.
16. Giovannoni G, Cohen JA, Coles AJ, *et al.* Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients. *Neurology* 2016; 87: 1985–1992.
17. Martínez-Yélamos S, Martínez-Yélamos A, Martín Ozaeta G, *et al.* Regression to the mean in multiple sclerosis. *Mult Scler* 2006; 12: 826–829.
18. Ventura RE, Antezana AO, Bacon T, *et al.* Hispanic Americans and African Americans with multiple sclerosis have more severe disease course than Caucasian Americans. *Mult Scler J*. 2016. DOI: 1352458516679894.
19. Bergamaschi R. Prognostic factors in multiple sclerosis. *Int Rev Neurobiol* 2007; 79: 423–447.
20. Tremlett H, Yousefi M, Devonshire V, *et al.*; UBC Neurologists. Impact of multiple sclerosis relapses on disease progression diminishes with time. *Neurology*. 2009; 73: 1616–1623.

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