Clinically meaningful performance benchmarks in MS

Timed 25-Foot Walk and the real world

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ABSTRACT

Objective: Identify and validate clinically meaningful Timed 25-Foot Walk (T25FW) performance benchmarks in individuals living with multiple sclerosis (MS).

Methods: Cross-sectional study of 159 MS patients first identified candidate T25FW benchmarks. To characterize the clinical meaningfulness of T25FW benchmarks, we ascertained their relationships to real-life anchors, functional independence, and physiologic measurements of gait and disease progression. Candidate T25FW benchmarks were then prospectively validated in 95 subjects using 13 measures of ambulation and cognition, patient-reported outcomes, and optical coherence tomography.

Results: T25FW of 6 to 7.99 seconds was associated with a change in occupation due to MS, occupational disability, walking with a cane, and needing “some help” with instrumental activities of daily living; T25FW ≥ 8 seconds was associated with collecting Supplemental Security Income and government health care, walking with a walker, and inability to do instrumental activities of daily living. During prospective benchmark validation, we trichotomized data by T25FW benchmarks (< 6 seconds, 6–7.99 seconds, and ≥ 8 seconds) and found group main effects on 12 of 13 objective and subjective measures ($p < 0.05$).

Conclusions: Using a cross-sectional design, we identified 2 clinically meaningful T25FW benchmarks of ≥ 6 seconds (6–7.99) and ≥ 8 seconds. Longitudinal and larger studies are needed to confirm the clinical utility and relevance of these proposed T25FW benchmarks and to parse out whether there are additional benchmarks in the lower (< 6 seconds) and higher (> 10 seconds) ranges of performance. **Neurology® 2013;81:1856–1863**

GLOSSARY

EDSS = Expanded Disability Status Scale; **IADL** = instrumental activities of daily living; **LL-FDI** = Late-Life Function and Disability Inventory; **MS** = multiple sclerosis; **MSWS-12** = Multiple Sclerosis Walking Scale-12; **O₂ cost** = oxygen cost of walking; **PASAT** = Paced Auditory Serial Addition Task; **PS** = Performance Scales; **SDMT** = Symbol Digit Modalities Test; **SI** = Symptom Inventory; **6MWT** = Six-Minute Walk Test; **SSST** = Six Spot Step Test; **T25FW** = Timed 25-Foot Walk; **TUG** = Timed Up and Go.

Walking is an essential feature of independence and one of the most valued functions in persons with multiple sclerosis (MS).¹ Walking dysfunction is an almost ubiquitous finding over the MS disease course² and is reported as the most challenging aspect of the disease.³

Among the available tools to measure walking function in MS, the Timed 25-Foot Walk (T25FW) is considered one of the best measures across a wide range of MS-related disability⁴ and has gained popularity for use in both clinical and research settings.^{5,6} The T25FW score is averaged over 2 consecutive walks and reported in seconds. Available research supports a $> 20\%$ change in T25FW as statistically significant^{7–9} and clinically meaningful.^{7,10} Change in the T25FW is predictive of disability in progressive patients and sensitive to change over the length of progressive MS trials.^{11,12}

What remains uncertain is how any “specific” T25FW score relates to an individual’s life and function. We hypothesized that T25FW thresholds or benchmarks of real-world disability could be defined within the MS population (e.g., loss of employment or functional independence) by

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exploring the relationship between T25FW scores and real-life anchors. A similar approach has been used for the development of a clinically meaningful reference point for cognitive function in MS.¹³

METHODS **Standard protocol approvals, registrations, and patient consents.** A cross-sectional study design was used to identify clinically meaningful T25FW performance benchmarks (identification step) using real-life anchors. We then validated these benchmarks in a second independent population (validation step). Study protocols were approved by the University of Virginia and University of Illinois at Peoria institutional review boards. All participants provided informed written consent.

Table 1 Identification step demographics (n = 159)

	Frequency	Values ^a
Age, y, mean (SD)		48.3 (12.58)
T25FW, s, mean (SD)		8.2 (7.89)
Female	108	67.9
Race		
Caucasian	132	83
African American	25	15.7
Marital status		
Single	26	16.4
Married	108	68
Live with partner	9	5.6
Divorced	9	5.6
Employment status		
Working full-time	60	80 ^b
Working part-time	15	20 ^b
Employed outside the home	68	42.8
Disabled (self-report)	58	36.5
Retired	12	7.6
Change in occupation due to MS	86	54.1
No change in occupation due to MS	73	45.9
PDDS		
0 = normal	37	23.3
1 = mild disability	25	15.7
2 = moderate disability	11	6.9
3 = gait disability	26	16.4
4 = early cane	28	17.6
5 = late cane	11	6.9
6 = bilateral support	18	11.3
7 = wheelchair/scooter	3	1.9

Abbreviation: MS = multiple sclerosis; PDDS = Patient Determined Disease Steps; T25FW = Timed 25-Foot Walk.

^a Values indicate percentage unless otherwise indicated.

^b Calculated with denominator as total number reporting any employment (n = 75).

MS populations. For benchmark identification, we recruited by mail 300 individuals with confirmed MS diagnosis (relapsing or progressive forms) who had a T25FW test performed during routine clinical care in the prior 15 months. We mailed a questionnaire battery to collect current information regarding marital status, employment (full-time/part-time/unemployed), role of MS in employment status, instrumental activities of daily living (IADL),¹⁴ and use of walking assistive devices. Also included were surveys of disability (Patient Determined Disease Steps and Performance Scales [PDS]),^{15,16} walking function (MS Walking Scale-12 [MSWS-12]),^{17–19} and depression (Beck Depression Inventory–Fast Screen).^{20,21}

We determined the mean and median T25FW scores for the MS populations grouped by real-life anchor categories (e.g., employed vs unemployed; married vs divorced; IADL independence). Using mean and median T25FW scores, we identified and grouped subjects by candidate benchmarks, next calculating the proportion of subjects in a real-life anchor category (e.g., proportion employed vs unemployed) within a candidate benchmark group. Once identified, we then validated these T25FW benchmarks in a separate group of persons with MS.

The benchmark validation step recruited 95 subjects from 3 area neurologists. All had confirmed MS (relapsing or progressive form). Inclusion criteria included ability to ambulate independently or with assistive device. Participants completed all testing in a single, 2-hour session, which included the following: Expanded Disability Status Scale (EDSS), ambulation testing (T25FW, Timed Up and Go [TUG],²² Six Spot Step Test [SSST],²³ Six-Minute Walk Test [6MWT]^{24,25} with associated oxygen cost of walking [O₂ cost],^{26,27} and a 7.9-m GAITRite electronic mat [CIR Systems Inc., Havertown, PA] for gait kinematics),^{28,29} cognitive function (3-second Paced Auditory Serial Addition Task [PASAT] and Symbol Digit Modalities Test [SDMT]),^{30,31} and axonal loss (retinal nerve fiber layer thickness via time domain optical coherence tomography [Zeiss Stratus OCT 3; Carl Zeiss Meditec, Dublin, CA]).³² Individual eyes were excluded from OCT for the following reasons: a) ocular disease (history of optic neuritis, glaucoma, macular degeneration, etc.), or b) high myopia (−7.5 or higher). Subjective measures included the MSWS-12, functional limitations portion of the Late-Life Function and Disability Inventory (LL-FDI),³³ and Symptom Inventory (SI).¹⁶ Participants then wore a triaxial accelerometer during the waking hours of a 7-day period to capture free-living ambulation. Accelerometers were returned through the US Postal Service.

Statistical analysis. Identification step data were analyzed using SAS 9.2 software (SAS Institute Inc., Cary, NC). Descriptive statistics of demographics and real-life anchor T25FW scores were used to identify candidate T25FW performance benchmarks. Candidate T25FW benchmark-defined group differences on real-life anchors and self-report measures were completed using analysis of variance and χ^2 test, as appropriate. During the benchmark validation step using SPSS 19.0 (IBM Corp., Armonk, NY), a second sample of MS participants was trichotomized by T25FW benchmarks (group 1: <6 seconds; group 2: 6–7.99 seconds; group 3: ≥8 seconds). We performed analysis of variance with group as a between-subjects factor on the different outcomes; the univariate *F* ratios and partial η^2 values were used to examine the magnitude of differences per dependent outcome; η^2 is analogous with *R*² and reflects variance that explains the outcome variable. We assessed specific differences in means between groups using Bonferroni analyses, expressing the magnitude of differences based on Cohen *d*.

Table 2 Identification step real-life anchor categories

Variable	No.	Median T25FW, s	Difference, %
Marital status			
Married	108	5.24	144
Divorced	9	12.8	
Employment status			
Working outside home	68	4.6	50
Disabled by self-report	58	6.9	
Government health care			
Not receiving	110	4.9	69
Receiving	49	8.3	
Occupation change due to MS			
No	73	4.8	28
Yes	86	6.14	
Occupation change due to walking disability			
Yes	41	8.95	86.4
Mobility assistance			
No assistance	102	4.8	N vs C, 35 ^a N vs W, 169 ^b
Cane	24	6.5	C vs W, 98 ^c
Walker	16	12.9	
Housework, IADL survey			
Need no help	67	4.5	NNH vs NSH, 41 ^d NNH vs UTD, 113 ^e
Need some help	73	6.34	NSH vs UTD, 51 ^f
Unable to do	19	9.6	

Abbreviations: IADL = instrumental activities of daily living; MS = multiple sclerosis; T25FW = Timed 25-Foot Walk.

^aNo assistance vs cane.

^bNo assistance vs walker.

^cCane vs walker.

^dNeed no help vs need some help.

^eNeed no help vs unable to do.

^fNeed some help vs unable to do.

RESULTS During the benchmark identification step, we received 169 completed surveys of the 300 sent, a 56.3% response rate, which is similar to other mail surveys (mean 60% $\pm$ 21%) in the medical literature.³⁴ For analyses, we included only those subjects with a T25FW recorded within 6 months of survey completion, which resulted in exclusion of 8 subjects. Two additional subjects were excluded, one for a T25FW of >2 minutes and one who was no longer walking at the time of the survey. This netted 159 subjects with MS for analyses.

Of the 159 subjects, 68% were women and the average age was 48 $\pm$ 12.6 years. For survey responders, the T25FW median was 5.4 seconds (mean 8.2 seconds, SD 7.89, range 3.25–65 seconds). Importantly, the T25FW performance for survey nonresponders was similar (median 5.9 seconds, mean 8.55 seconds, SD 9.79, range 3.12–104 seconds). Forty-five percent of survey

responders were employed, either outside of the home or within the home; an additional 37% described themselves as disabled. Only 37.8% of all responders were working full-time (60/159 subjects). Fifty-four percent reported a change in occupational status due to MS. Additional demographic details can be found in table 1.

T25FW benchmarks were identified using the median T25FW performance across life anchors and IADL categories (table 2 and figure 1). We recognized that a T25FW time of 6 to 7.99 seconds was associated with a change in occupation due to MS, disabled by self-report, requiring assistance (“some help”) with IADL, cane use for outside walking, and “early cane use” on mobility PS. A T25FW time of $\geq$ 8 seconds was associated with permanent disability (collecting Supplemental Security Income), government health care assistance (Medicaid/Medicare), change in occupational status due to MS, inability to perform IADL, and use of a walker. These associations were statistically significant (table 3). We grouped subjects by T25FW benchmarks (<6.0, 6–7.99, and $\geq$ 8 seconds) and assessed the proportion of subjects in real-life anchor and functional independence categories (table 3). T25FW benchmark groups significantly differed by age, marital status, MSWS-12 scores, and several real-life anchor and IADL categories (table 3). Of note, there were no significant group differences on depression (Beck Depression Inventory–Fast Screen) (table 3). Nonambulatory IADL (e.g., managing money or using telephone), as expected, did not co-vary with T25FW performance.

Table 2 provides median T25FW scores within and percent differences between real-life anchor categories. We found a 28% difference associated with change in occupation due to MS. T25FW performance correlated with patient’s self-report of disability on the PS; the strongest relationship was between T25FW and PS-Mobility ($p < 0.001$). Report on PS-Mobility of increased need for assistance was tightly associated with worsening in T25FW performance (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). There was approximately a 20% difference in T25FW between minimal and mild gait disability, 30% between mild gait disability and occasional cane, 80% between occasional and frequent cane, and 55% between frequent cane and severe gait disability. Using a measure of IADL, T25FW performance differed on average by 43% between those who required “no help” vs “some help” (figure 1). There was an overall statistically significant relationship between T25FW and IADL scores ($p < 0.0001$). In comparing the “no help” and “some help” groups, we found a significant difference for laundry, grocery shopping, and getting places beyond walking distance ($p < 0.025$). The identification step results supported a T25FW performance of $\geq$ 6 seconds (6–7.99) and $\geq$ 8 seconds to represent clinically

Figure 1 Instrumental activities of daily living

ADL = activities of daily living; T25FW = Timed 25-Foot Walk.

meaningful benchmarks of MS-related gait impairment. To confirm and validate these findings, we applied these T25FW benchmarks to a second, independent MS sample.

During the benchmark validation step, 95 subjects with MS completed all assessments. The average age of the population was 52.7 years (SD = 11.1) and the median EDSS score was 4.5 with a range between 2 and 6.5. The median T25FW was 6.0 seconds with a mean of 6.8 seconds (SD = 3.1). Approximately 50% of the population had a T25FW <6.0 seconds (group 1, $n = 47$), 22% had a T25FW of 6 to 7.99 seconds (group 2, $n = 21$), and 28% had a T25FW of ≥ 8 seconds (group 3, $n = 27$). Median EDSS scores differed significantly across groups ($p < 0.0001$) with median (interquartile range: 25%, 75%) values for T25FW groups as follows: group 1: <6 seconds = 3.5 (2.5, 4.5); group 2: 6–7.99 seconds = 5.0 (4.0, 6.0); and group 3: ≥ 8 seconds = 6.0 (6.0, 6.5).

We then tested all measures for expected between-group differences (table 4). There were statistically significant group main effects for trichotomized T25FW benchmarks across both objective and subjective measures: 6MWT ($p < 0.0001$), TUG ($p < 0.0001$), SSST ($p < 0.0001$), MSWS-12 ($p < 0.0001$), accelerometer counts per day ($p < 0.0001$) and steps per day, Functional Ambulation Performance score from the GAITRite ($p < 0.0001$), PASAT ($p < 0.05$), SDMT ($p < 0.0001$), LL-FDI ($p < 0.0001$), and SI ($p < 0.0001$). There were also statistically significant group main effects for individual spatial and temporal parameters from the GAITRite (all $p \leq 0.05$), with the exception of base of support ($p = 0.80$) (table e-1).

There was no difference in retinal nerve fiber layer thickness between groups ($p = 0.34$).

The Bonferroni follow-up analyses indicated that significant differences between groups varied by both objective and subjective measures as detailed in table 4. All 3 groups significantly differed on 6MWT, TUG, SSST, and MSWS-12 scores. Significant between-group differences existed for group 1 vs 2 and group 1 vs 3 for accelerometer counts per day and steps per day, SDMT, and LL-FDI. There were significant group differences for group 1 vs 3 and group 2 vs 3 for the Functional Ambulation Performance and O_2 cost measures. Differences for group 1 vs 3 were significant only for the PASAT and SI.

To expand our understanding of subjects in the <6 seconds group, we trichotomized T25FW groups as follows: 3–3.99 seconds ($n = 23$); 4–4.99 seconds ($n = 39$); and 5–5.99 seconds ($n = 29$). In these exploratory analyses, no significant differences were found across the 3 groups for marital status, depression, Patient Determined Disease Steps, employment status, or change in work due to MS or walking impairment (table e-2). However, we did find significant group differences for the MSWS-12 ($p = 0.0015$) and PS-Mobility ($p = 0.0229$). PS-Mobility group differences were driven by the T25FW 5–5.99 seconds group with 38% reporting “mild gait disability.” We also noted a higher percentage (approximately 30%) of patients having government health care assistance in the 5–5.99 seconds group. There was no overall difference in IADL in these three <6 seconds groups, but there was a difference for meal preparation ($p = 0.0326$) with 31% of those with T25FW 5–5.99 seconds reporting the need for some assistance. Additional analyses of the <6 seconds subjects in the validation step revealed significant decrease in accelerometer counts and steps per day in the 5–5.99 seconds group (table e-2).

DISCUSSION The T25FW is among the best characterized objective measures of walking in MS⁴ with extensive use in clinical practice and research. Our data build on previous work by defining 2 clinically meaningful T25FW performance benchmarks based on real-life anchors and physiologic objective measures; specifically, we report that T25FW walk times slower than 6 and 8 seconds represent clinically meaningful and distinct performance benchmarks. The impact of MS disability on the loss of employment, functional independence, and the societal cost of government health insurance are well documented in the medical literature.^{35–38} Mobility impairment has been specifically recognized as an important factor affecting employment and functional independence.³⁸ Using the NARCOMS (North American Research Committee on Multiple Sclerosis), researchers have reported that impairments

Table 3 Identification step: T25FW benchmarks and survey results

	T25FW			p Value ^a
	<6.0 s	6–7.99 s	≥8 s	
Subject no.	91	28	40	
Age, mean y	45.1	51.5	53.3	0.0008
Marital status, %				0.083 ^a
Married (n = 108)	69.2	75	60	0.39 ^b
Divorced (n = 9)	4.4	0	12.5	0.065 ^c
MSWS-12 score	24.9	59.1	77.8	<0.001
Beck Depression Inventory, mean score	3	3.6	3.8	0.486
Employed outside home, %	59.3	28.6	15	<0.001
If employed, working full-time, n	48	6	6	0.5459
Occupation change due to MS, %	42.9	71.4	67.5	0.0043
Has government health care assistance, %	15.4	35.7	62.5	<0.001
Activities of daily living, mean score	14.5	13	10.6	<0.001
Groceries, %				<0.001
Independent	79.1	60.7	12.5	
Needs help	18.7	35.7	67.5	
Unable to do	2.2	3.6	20	
Housework, %				<0.001
Independent	62.6	25	7.5	
Needs help	33	64.3	62.5	
Unable to do	4.4	10.7	30	
Preparing a meal, %				<0.001
Independent	83.5	57.1	30	
Needs help	16.5	42.9	60	
Unable to do	0	0	10	
PDDS				<0.0001
0 = normal	39.5	3.6	0	
1 = mild disability	22	17.9	0	
2 = moderate disability	7.7	7.1	5	
3 = gait disability	18.7	21.4	7.5	
4 = early cane	11	35.7	20	
5 = late cane	1.10	7.1	20	
6 = bilateral support	0	7.1	40	
7 = wheelchair/scooter	0	0	7.5	

Abbreviations: MS = multiple sclerosis; MSWS-12 = MS Walking Scale-12; PDDS = Patient Determined Disease Steps; T25FW = Timed 25-Foot Walk.

^aThe p value for a) marital status category (married, divorced, single, widowed, etc.); b) married vs not married; c) divorced vs not divorced.

in mobility (measured by PS-Mobility) were associated with changes in IADL and employment status. The researchers reported that the impact of mobility on employment was greater than that of demographic variables and translates to loss of household income, even at low levels of disability (PS <2).³⁸ We similarly report that mobility limitations measured by T25FW performance correspond to changes in employment and

functional independence and propose benchmarks at which individuals with MS are more likely to be functionally impaired.

Patients with MS who complete the T25FW in ≥6 seconds (6–7.99) are more likely to be unemployed, have a change in occupation due to MS and walking, use a cane, and require assistance with IADL. A second cohort of patients with MS who had the same T25FW time (6–7.99 seconds) performed poorly on objective measurements of ambulatory function (6MWT, TUG, SST) and had reduced community ambulation as measured by accelerometer. Social, occupational, and ambulatory disabilities are further worsened in patients with MS who perform the T25FW in ≥8 seconds. This level of performance was associated with unemployment, government health care assistance (Medicaid/Medicare), divorce, walking with a walker, and more than a 70% likelihood of being unable to perform IADL including house cleaning, grocery shopping, laundry, and cooking. Based on these findings, we propose that a T25FW performance of ≥6 seconds (6–7.99) and ≥8 seconds represent clinically meaningful benchmarks of MS progression.

Within our data set, ≥6 seconds on the T25FW was a clear threshold. Of note, our exploratory analysis of the <6.0 subgroups (3–3.99, 4–4.99, 5–5.99 seconds) identified a significant difference in some measures, notably MSWS-12 and PS-Mobility, and about a third of subjects in the 5–5.99 seconds group reported difficulty with meal preparation and received government health care assistance. An important percentage of individuals with T25FW scores in the range of 5–5.99 seconds are already showing impairment in some IADL. However, the majority are still able to engage in functional independence and remain in the workforce. We believe that there is merit in exploring possible additional clinically meaningful benchmarks of disease progression in individuals with T25FW of <5 seconds and >10 seconds.

These occupational and social functional differences were coupled with measurable increases in MS-related disability progression in the validation step. Comparing the T25FW benchmarks (≥6 seconds and ≥8 seconds), we found statistically significant group main effect differences across a breadth of ambulatory, gait, and disease-related measures (including cognition). In comparing among the benchmark-defined groups, there were variable outcome differences: whereas groups 1 and 2 differed by community ambulation (accelerometer), there was no difference in O₂ cost among them. By comparison, groups 2 and 3 differed by O₂ cost, but not in community ambulation. We interpret this to mean that reaching the first benchmark of ≥6 seconds (6–7.99) results in a loss of functional community ambulation despite relatively preserved energetic cost of walking, which may allow for continued functionality

Table 4 Benchmark step outcomes

	Group			p Values/effect sizes			
	1: T25FW <6.0 s	2: T25FW 6.0–7.99 s	3: T25FW ≥8 s	Overall p value/ η^2	Group 1 vs 2	Group 1 vs 3	Group 2 vs 3
6MWT, m	501.8 (76.4)	375.4 (55.7)	262.1 (77.8)	0.0001/0.67	0.001/1.80	0.001/3.12	0.001/1.66
TUG, s	6.4 (1.7)	9.1 (2.0)	14.3 (5.7)	0.0001/0.50	0.007/1.55	0.001/2.48	0.001/1.26
SSST, s	7.5 (2.7)	11.5 (2.4)	16.9 (5.4)	0.0001/0.56	0.001/1.55	0.001/2.58	0.001/1.33
MSWS-12	30.4 (26.8)	47.4 (20.8)	67.4 (15.0)	0.0001/0.33	0.017/0.68	0.001/1.64	0.010/1.14
Accelerometer counts/d	179,915 (90,750)	121,200 (61,402)	89,117 (50,639)	0.0001/0.23	0.012/0.71	0.001/1.19	0.432/0.57
Accelerometer steps/d	5,284 (2,525)	3,441 (1,794)	2,407 (1,676)	0.0001/0.26	0.005/0.80	0.001/1.30	0.311/0.60
FAP score	95.8 (4.4)	91.2 (6.9)	74.6 (13.1)	0.0001/0.55	0.084/0.88	0.001/3.02	0.001/1.67
O ₂ cost, mL/kg/m	0.190 (0.029)	0.216 (0.030)	0.288 (0.097)	0.0001/0.36	0.250/0.90	0.001/1.83	0.001/1.06
PASAT	44.2 (11.2)	39.7 (12.1)	36.5 (15.5)	0.043/0.07	0.548/0.39	0.044/0.60	1.000/0.23
SDMT	49.2 (10.4)	41.7 (7.0)	38.8 (11.5)	0.0001/0.18	0.017/0.81	0.001/0.97	0.982/0.30
RNFL thickness, μ m	92.5 (15.5)	86.1 (16.1)	89.8 (13.5)	0.340/0.03	0.449/0.41	1.000/0.17	1.000/0.26
LL-FDI	59.2 (11.3)	49.1 (9.6)	42.7 (7.2)	0.0001/0.35	0.001/0.94	0.001/1.68	0.086/0.78
SI	31.7 (20.8)	42.0 (15.2)	50.8 (13.5)	0.0001/0.18	0.094/0.53	0.001/1.05	0.272/0.62

Abbreviations: FAP = Functional Ambulation Performance; LL-FDI = Late-Life Function and Disability Inventory; MSWS-12 = Multiple Sclerosis Walking Scale-12; O₂ cost = oxygen cost of walking; PASAT = Paced Auditory Serial Addition Task; RNFL = retinal nerve fiber layer; SDMT = Symbol Digit Modalities Test; SI = Symptom Inventory; 6MWT = Six Minute Walk Test; SSST = Six Spot Step Test; T25FW = Timed 25-Foot Walk; TUG = Timed Up and Go. Values are mean (SD). Effect sizes for between-group differences are an absolute value of Cohen *d*.

in the home (e.g., preserved ability to do some IADL). However, when an individual reaches the second benchmark (≥ 8 seconds), there is no further loss of community ambulation, but there is an increase in the energetic cost of walking, which we speculate is reflected by this group's inability to do household activities. Further data will be needed to confirm and expand our understanding of differences among benchmark groups.

Previous research suggests that a $>20\%$ change in the T25FW is significant and may be clinically meaningful.^{7–11} In our sample, the T25FW group differences were $\geq 20\%$, depending on the anchor being compared. It is clear that a 20% change in T25FW represents a statistical change during longitudinal follow-up (change above the “noise”). Our analysis indicates that for certain life events, a meaningful T25FW performance change may equal 20%. For example, the difference between minimal to mild mobility impairment corresponds to a T25FW difference of 20% (figure e-1). Importantly, for other life events, the difference is $>20\%$. For example, the difference in T25FW between those who did and did not have a change in occupation due to MS was 28% (table 2). Furthermore, depending on the baseline T25FW score, worsening $>20\%$ may be needed before one experiences a breakdown in gait dynamics or increase in the energetic cost of walking. Thus, there may be differential changes that are meaningful depending on where each individual is on the T25FW performance continuum (e.g., <6 seconds or >8 seconds).

The utility and application of any outcome will be weakened or strengthened by researcher familiarity. For example, the EDSS has been an extensively used outcome measure for several decades³⁹; whereas it has many limitations that are well described, one of its strengths and endearing values is its familiarity. Those familiar with the EDSS can quickly “picture” a subject that has an EDSS score of 2.0 compared with a subject who has a score of 6.0. We are currently lacking the same familiarity with the T25FW. Our research provides a better understanding of what a person with a T25FW of >6 seconds “looks like” compared with one who has a T2FW >8 seconds. While these T25FW performance benchmarks were well-defined in our cross-sectional study in 2 separate MS cohorts, further research is needed to understand the longitudinal nature of change in these benchmarks and the consequences of moving up or down from one benchmark group to the next. Future studies are needed to characterize the prospective relationship between movement among these T25FW benchmarks and changes in real-life anchors and functional independence. As well, larger longitudinal studies across the entire performance T25FW continuum are needed to expand our understanding of the clinical meaningfulness of observed changes in this very important MS outcome.

AUTHOR CONTRIBUTIONS

M.D. Goldman and R.W. Motl: study design, data collection, analysis and interpretation, manuscript drafting and revising. J. Scagnelli: data collection, manuscript drafting and revising. J.H. Pula and J.J. Sosnoff:

data collection and manuscript revising. D. Cadavid: study design, analysis and interpretation, manuscript drafting and revising.

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