

Multiple Sclerosis Treatment Decisions: EDSS Independent Disease Impact/Reserve and the Use of Additional Milestones that Really Matter To People with MS

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Objective: Utilize objective examination independent computerized cognitive outcome measures to identify an economically important Multiple Sclerosis (MS) disability trajectory in people with MS (PwMS) as it relates to important disease impact not readily apparent by reported relapse, EDSS or MRI findings. Explore disability milestones beyond EDSS and neurological examination.

Background/Rationale: MS, usually characterized by relapses and physical disability progression, is traditionally measured by reported relapse rate reduction, as well as EDSS & MRI changes. EDSS change is primarily driven by physical findings or walking impairment, neither of which accounts for cognitive impact, reserve, or accumulation of cognitive impairment. Cognitive impairment is not typically quantified or tracked in PwMS in routine care or clinical trials. EDSS is also insensitive to the degree and/or types of cognitive impairment. Cognitive impairment impacts economically important abilities not addressed by traditional metrics (e.g. employment, ability to drive, and fall risk for both simple & complex daily activities). There are multiple available disease modifying therapies (DMT) of varied routes, frequency and efficacy making individual treatment choice and effective timing of DMT change problematic. A patient centric objective analysis of disease trajectory of the loss of such economically important milestones relating to predictive loss of ability can supplement and perhaps improve alternative approaches to guide treatment choice, change and timing. This objective quantitative patient centric and granular EDSS independent approach of likely disability trajectory might also improve decision making regarding DMT choice and timing of change and offer a path to compare outcome measures across clinical trials and possibly allow pre-empting the appearance of such important disabilities that result in significant increased cost of care needed and reduced quality of life. Objective comprehensive analytics documenting unseen disease impact and change offer such unique opportunities to improve care and outcomes as well as reduce disability related costs.

Methods: Retrospective cross-sectional review of a prospective digital MS registry obtained in the course of routine care utilizing standardized computerized cognitive testing (NeuroTrax) to evaluate the relationship of cognitive impairment (**number of cognitive domains impaired (CDI) >1 standard deviation from age/education normal**) on patient reported outcome disability [unemployment, loss of driving, freedom from falls (FOF)] in a **cohort of PwMS EDSS<6, (less obvious physical disability)**.

Results: Increasing accumulated number of CDI in PwMS EDSS<6 is associated with likely progressive loss of: **employment (N=543, CDI-0=61%, CDI-1=50%, CDI-2=43%, CDI-3=32%), driving (N=115, CDI-0=100%, CDI-1=66%, CDI-2=53%, CDI-3=21%)** and **reduced safety** by an **increased fear of falling - FOF (N=159) for simple daily activities [(FOF-SDA) CDI-0=77%, CDI-1=65%, CDI-2=37%, CDI-3=39%]** and increased FOF for **complex daily activities [(FOF-CDA), CDI-0=72%, CDI-1=58%, CDI-2=36%, CDI-3=33%]**.

Conclusions: Tracking disease impact in PwMS by predictable loss of economically important milestones trajectory, beyond what can be documented by EDSS, MRI or apparent or reported relapse, can be accomplished by use of objective multi-domain cognitive testing to provide such patient centric information predicting loss likelihood of economically impactful abilities that are not completely dependent upon EDSS nor currently obtained in the course of traditional MS care or clinical trials. This objective approach might provide a pathway towards actionable change by objectively monitoring disease progression in a way that EDSS and MRI are unable and that will likely impact therapy choice as well as timing of DMT change. This approach can be incorporated into routine care and also can be utilized to easily and quantitatively track examiner independent multi-domain cognitive impact longitudinally in PwMS to perhaps improve care outcomes and reduce economic costs that accompany such increased disease burden.

