ACTA SCIENTIFIC NEUROLOGY (ISSN: 2582-1121)

Volume 7 Issue 6 June 2024

Research Article

Potential Therapeutic Benefits of Using the BeCare MS Link App Frequently

Charisse Litchman, Caroline Stowe*, Larry Rubin, Joseph DiTrapani and Sharon Stoll

School of Public Health, George Mason University, United States

***Corresponding Author:** Caroline Stowe, School of Public Health, George Mason University, United States.

DOI: 10.31080/ASNE.2024.07.0738

Received: March 14, 2024

Published: May 16, 2024

© All rights are reserved by **Caroline Stowe., *et al.***

Abstract

Objective: BeCare MS Link App quantitatively measures neurologic function on a mobile phone and calculates Expanded Disability Status Scale (EDSS) through AI. Previous peer-reviewed studies demonstrated a convergence validity of the clinical EDSS. The primary objective of this study is to assess the therapeutic benefits of frequent use of the BeCareLink App activities.

Design/Methods: Data was collected from the use of the BeCareLink mobile device app by subjects with MS. Subjects were enrolled over three months beginning at the time of IRB approval. Patients were divided into two groups: the first group of 100 patients was asked to perform all the activities 3 or more days per week (Frequent Use Arm), and the second group of 25 patients was asked to perform all the activities only twice during the 12-week period- day 0 and day 90 (Infrequent Use Arm).

Results: The results show that of subjects with very mild disease (EDSS of 0.5-1.5), 33% had unchanged EDSS scores, 38% showed improvement and 29% worsened when remeasured 3 months from the initial date. Of Patients with more significant disease (EDSS of > 2.0), 70% remained clinically unchanged or improved and 30% worsened. Infrequent users showed less significant change in function (25% improved, 36% stayed the same, and 39% worsened).

Conclusions: Frequent use of BeCareLink's activities may have a therapeutic benefit for patients with demonstrable disability.

Keywords: Digital Therapeutics; Multiple Sclerosis; Mobile Therapeutic App; Multiple Sclerosis Remote Therapy

Introduction

Multiple sclerosis (MS) is an autoimmune central nervous system (CNS) disorder that affects approximately 900,000 people in the United States [1]. MS can present with a broad range of symptoms including pain, depression, fatigue, weakness, sensory changes, or difficulty ambulating. Fifteen to twenty percent of all MS patients have progressive disease course from the onset, and 80% of patients with relapsing disease will exhibit secondary progressive disease after 20 years [2]. Evidence suggests that treating MS with disease-modifying therapy as soon as the patient is diagnosed leads to decreased long-term disabilities and mortality [3]. Because of this, metrics used to monitor patients for signs of disease progression and guide therapy are essential in preventing cumulative disability from MS.

The Expanded Disability Status Scale (EDSS) is currently the gold standard of these metrics used to quantify disability progression and neurologic dysfunction in MS [4]. This instrument is a clinician-administered assessment scale that evaluates the functional systems of the central nervous system. However, the EDSS is time-consuming and cumbersome [5]. In addition, the EDSS does not objectively measure cognitive impairment, which is likely affected during relapses in patients with MS. The EDSS sub-score developed to measure cognition has low reproducibility and is primarily reliant on clinician judgment or patient self-report [6]. Because of this, there is an opportunity to increase the sensitivity of metrics used to assess disease progression in MS. Another limitation of the EDSS is that it requires an in-person neurological examination. Given the increased utilization of telemedicine because of the COVID-19 pandemic, this has the possibility of delaying treatment for patients in need of disease-modifying therapy.

The BeCare MS Link App, compatible with both Apple and Android operating systems, was originally developed as a digital equivalent to the EDSS with the addition of a cognitive assessment component not routinely performed during follow-up clinical visits. The app-directed activities reflect the functionality of components of the nervous system (pyramidal, cerebellar, sensory, visual, mental, and motor) that are measured by the EDSS.

After receiving patient reports of functional improvement from performing the BeCare MS Link app frequently, BeCareLink decided to investigate the benefits of performing some of the activities as a digital therapeutic tool.

The notion that resistance and endurance exercise promote healthier aging in terms of brain function is not new. One systematic review explored the relationship between resistance exercises, structural brain changes, and cognitive improvements in a healthy aging population. It highlighted the potential benefits of resistance training for healthy aging and brain preservation. The analyses suggested improvement in executive function, lower white matter atrophy, and smaller white matter lesion volumes [7]. Faster reaction time has been shown to correlate with improved information processing speed, attention, language skills, and visual-spatial orientation in healthy college students [8]. In addition, there have been numerous studies addressing functional improvement in neurologic function from neurodegenerative disease with the use of smartphone mobile apps. One study assessed improvement in mobility and subjective outcome measures after following an 8-week independent, video-guided exercise using a mobile app for Parkinson's disease. The outcome measures employed were all suggestive of clinical improvement [9].

This study investigated the clinical improvement of MS patients gained from frequent use of the BeCare MS Link app over a 12-week period.

Objective

The BeCare MS Link App quantitatively measures neurologic function on a mobile phone and calculates disability scores (EDSS) of MS patients through AI. Previous peer-reviewed studies demonstrated a convergence validity of clinical EDSS with BeCareLink-derived EDSS [10]. The primary objective of this study is to assess the therapeutic benefit of frequent use of the BeCare MS Link app activities.

Design/Methods

Study design

Subjects were enrolled over three months beginning at the time of IRB approval. Patients were divided into two groups: the first group of 100 patients was asked to perform the activities 3 or more days per week (Frequent Use Arm) and the second group of 25 patients was asked to perform all the activities only twice during the 12-week period-day 0 and day 90 (Infrequent Use arm).

Inclusion criteria

Inclusion criteria included patients who were between the ages of 18 and 60 years with clinically definite relapsing remitting multiple sclerosis based on revised McDonald criteria. Additional criteria included the ability to provide informed consent, mild to moderate disability in one or more of the modalities assessed by the BeCare MS App, corrective visual acuity better than or equal to 20/200, and the ability to perform five or more of the BeCare MS App tasks independently.

Exclusion criteria

Exclusion criteria included the inability to independently use the BeCare MS App, EDSS > 6.5, inability to provide informed consent, neurologic impairment due to an illness other than MS, impairment in mobility or function due to rheumatologic or other illnesses, congenital or traumatic loss of the index finger or thumb, any chronic illness that has not been stable for at least six months (medication changes for that condition during the past year are not exclusionary), malignancy/previous chemotherapy treatment for neoplastic disease, untreated or unstable major depression or bipolar disease, clinic diagnosis of primary progressive MS or secondary progressive MS, patients previously treated with Tysabri, or acute COVID-19 infection with persisting symptoms for the last 6 weeks.

Informed consent

The details of the study protocol were reviewed with each patient and all questions were addressed. If a patient agreed to enroll in the study an informed consent form was signed. The informed consent was kept in a study binder and a digital copy was made and stored on a secure server in compliance with the Health Insurance Portability and Accountability Act.

Assessments

Subjects completed twelve different app-based assessments on the BeCare MS App, testing various components of the neurological examination including motor mobility, fine motor function, upper extremity coordination, auditory comprehension, time to walk predetermined distance, visual tracking of objects, cognitive function, memory, and vibration sense as well as questionnaires. The twelve app-based assessments are listed and described below

- **Timed up and go:** The subject is seated in a regular chair with no chair armrests. The Subject will hold their mobile device in their hand during the test. They will stand up and walk five steps, turn around, and sit back down in the same chair. The time it takes to do this activity is recorded by the app.
- **Fine motor function/rapid finger movements:** The Subject is presented with a game on their mobile phone that requires them to tap a designated spot as frequently as possible for ten seconds. The phone will record the number of taps, the regularity of their spacing and any consistent change over time (fatigue). This is repeated three times.
- **Path test:** The Subject is asked to move an object with their index finger such that it stays within the boundaries of a moving path. The app will measure deviations outside the path as well as circumstances in which these deviations occur. The test will be repeated three times on each side.
- **Transcription test or auditory-comprehension-typing test:** The Subject is given a short auditory phrase and then must type that phrase using a virtual keyboard. The time to complete typing the phrase as well as the time interval and time variance between keystrokes is compiled and compared to serial app users. To control for fine motor function, the virtual keyboard records the time and variance for tapping a series of keys that spontaneously change color, which is termed the maximal keystroke velocity (strokes/second).
- **Timed 25-foot walk:** The Subject holds their mobile device in their hand, and the time the Subject takes to walk twenty-five feet is measured. It also measures the number of steps per second.
- **Code message cognitive test:** The Subject is asked to decode a message using a decoding key. A series of symbols are paired with letters or words to be used as the key. The coded message is provided in symbols. The test ends when the Subject completes the decoded message.
- **Contrast sensitivity:** The Subject is asked to discern or read letters/numbers on the screen with varying contrast sensitivity. The number of correct assignments is recorded.
- **Arm elevation test:** The Subject is asked to raise the arm holding the mobile device repeatedly as fast as possible for thirty seconds. This will be repeated in both arms.
- **Memory test:** The Subject is presented with five animals in five colors that appear in boxes in two rows. Two of the boxes with animals are randomly selected and, after ten seconds, one of the two choices is closed. The subject must remember the animal and the color in the box that was closed from the choices that appeared, and, on the next round, the subject must remember the previous animal and color from the box that was not presented on the previous round. The choice as to the box that is closed will be mathematically determined to pose the same difficulty for each subject. The number of errors and correct choices are recorded.
- **Stroop test:** The Subject will see words written in different colors and will be asked to name the color of the text.
- **Vibration test:** The Subject will be asked to hold their phone first in their right hand and then in their left hand. The phone will vibrate, and the vibration frequency will change several times during the test. Participants will be instructed to tap a box every time they sense a vibration change.
- **Six minute walk:** The Subject holds their mobile device in their hand, and the distance the Subject travels in 6 minutes is measured. It also measures the number of steps per second.

Assessments on the BeCare App were designed to correspond to standard clinical tests that assess for functional abilities performed during a neurological examination. For example, the Timed 25-foot Walk and Six Minute Walk tests measure the ability to walk, and the arm elevation tests measure repetitive arm movements and motor strength. These tests are considered the gold standard tests for determining mobility function in patients with MS [7]. BeCare app-based assessments were designed to reflect these gold standard tests, and results were compared between the clinical and app-based evaluations among the subjects in the study. The app uses the accelerometer, gyroscope, or magnetic sensor in the patient's phone to determine when they took a step, transitioned their position or orientation, or moved their arms. The remaining app-based assessments correspond to other measurements rated by the EDSS and the fatigue severity scale, which are the most widely used assessment tools by clinicians in this patient population [8,9].

After a subject completed an assessment on the app, the corresponding data was sent to the BeCare Link Cloud when an internet connection was available. A machine learning algorithm then analyzed the data collected from the app and produced an independent EDSS for each subject.

Statistical analysis

The analysis was a population analysis of subjects categorized by starting EDSS and Weekly Frequency of App use. The EDSS categories were (All subjects, Subjects starting with an EDSS > 1.5 and Subjects starting with an EDSS > 2.0). Weekly Frequency was grouped by subjects who performed all the activities 3 or more days per week (Frequent) and the second group of subjects (Frequent) who performed all the activities only twice during the 12-week period or skipped more than 1-week usage during the trial without a catch-up week. We used the Mann-Whitney U test, also known as the Wilcoxon rank-sum test to compare the populations of Frequent vs Infrequent users for changes in EDSS as these changes are not normally distributed, and these sample sets are independent. Comparing Frequent vs Infrequent Users with starting EDSS > 1.5 yielded a p-value = 0.294 and for EDSS > 2.0 yielded a p-value = 0.365 rejecting the hypothesis that the changes were selected from the same sample set (see figures 4,5,6).

Results

The results show that of all subjects with very mild disease (EDSS of 0.5-1.5), (frequent and infrequent users), 33% had unchanged EDSS scores, 38% showed improvement and 29% had an increase in their EDSS scores when remeasured after 3 months, suggesting that patients with mild disease show close to a random distribution of changed scores when measured in the near future. For patients with more significant disease (EDSS of >1.5), 68% had unchanged or improved EDSS scores and 32% had increase of their EDSS scores. For Patients with EDSS > 2.0, 77% had unchanged or improved EDSS while 23% had increased scores. With infrequent users, there was a less significant change in function (45% improved, 21% remained stable, and 34% worsened).

efirst	elast	chg
2.139	0.186	-1.953
2.577	1.041	-1.536
2.202	1.059	-1.143
2.775	1.747	-1.028
2.01	1.019	-0.991
2.098	1.117	-0.981
2.82	1.889	-0.931
2.431	1.789	-0.642
2.598	2.041	-0.557
2.201	1.673	-0.528
2.439	2.029	-0.41
2.399	2.16	-0.239
2.084	1.917	-0.167
2.116	1.976	-0.14
2.13	2.006	-0.124

Figure 1: EDSS scores of users.

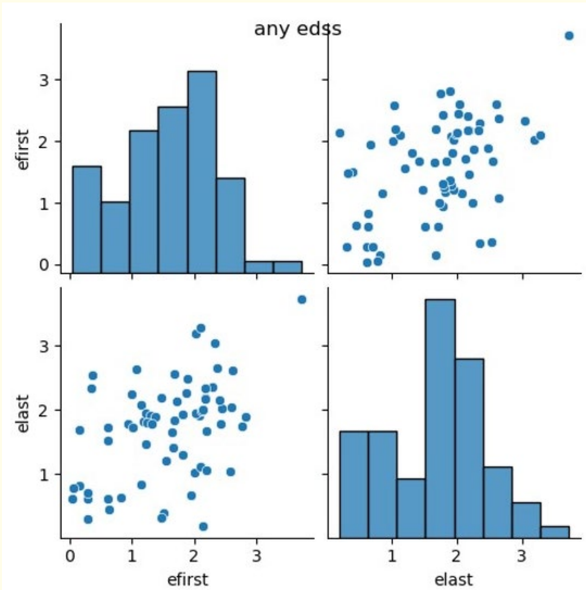
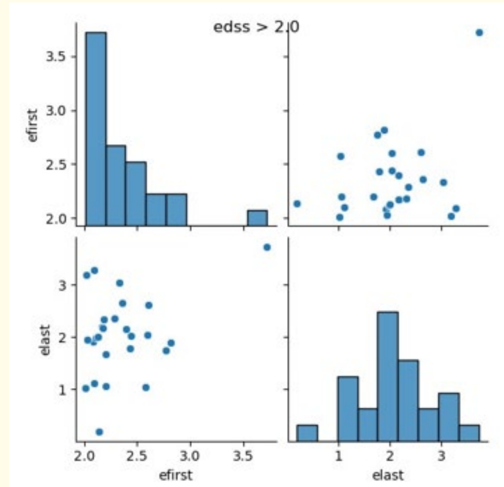


Figure 2: EDSS scores.



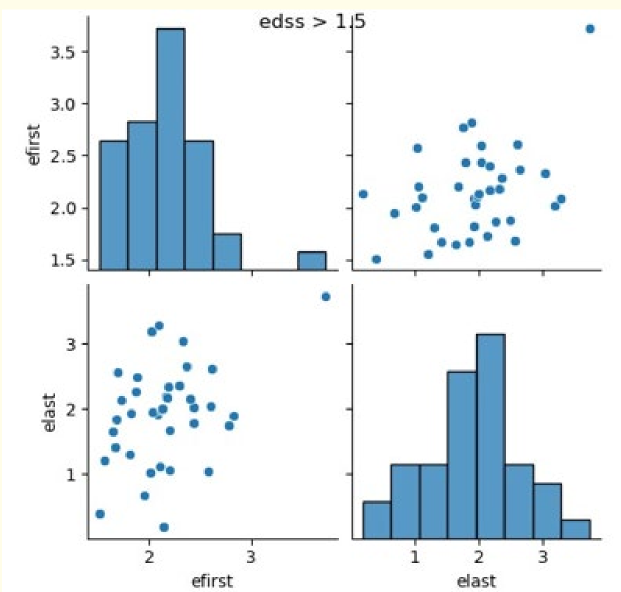


Figure 3: EDSS scores >1.5 and >2.0.

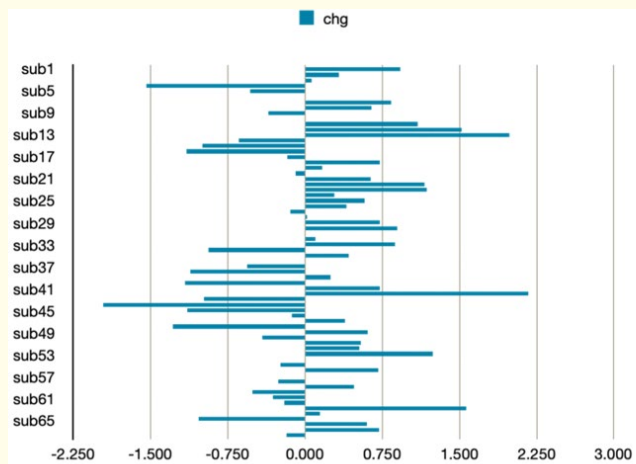
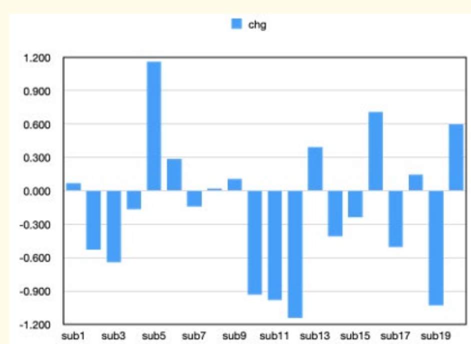


Figure 4: Change in EDSS over 12 weeks for all users (A negative change in EDSS shows improvement in their final EDSS from their initial EDSS).



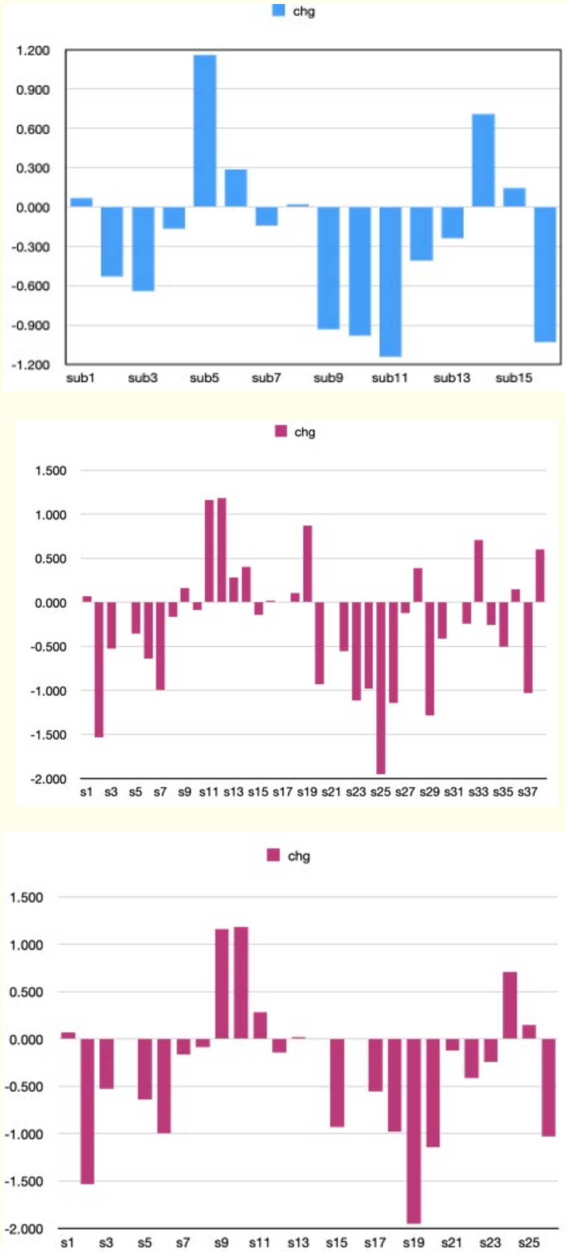


Figure 5: Frequent user change starting EDSS > 1.5, Frequent user change starting EDSS > 2.0 Fig. 6. All user change starting EDSS > 1.5, All user change starting EDSS > 2.0.

Discussion

Physical therapy has been the mainstay for improving the functional status of MS patients following distinct flares. Individuals with multiple sclerosis having mild-to-moderate disability (i.e., Expanded Disability Status Scale [EDSS] scores 1.0-5.5), who performed exercise training reported significant improvements in disability, physical fitness, physical function, mobility and fatigue [14,15].

Many patients are unable to access in-person physical therapy due to financial concerns and/or geographic unavailability, while most patients are not prescribed physical therapy between flares to improve function. Fortunately, patients have been able to find ways to promote their own health from home. Prior research has shown cognitive improvement in patients with MS after performing repetitive activities such as computer-assisted programs, memory activities; cognitive rehabilitation, and videogames [16,17].

The AI algorithm used by the BeCare MS App has been shown to calculate EDSS which correlates well with clinical EDSS. This study suggests that frequent use of the BeCare MS App promotes stabilization or reduction of EDSS when compared to only infrequent use. Participants in this study performed the complete set of BeCare activities. These activities measure movement (TUG, T25, Six Minute Walk, arm movement, fine movement: (finger tapping, pushing a tiger up a path on the screen), and other functional skills such as memory, cognition, sensation, and vision. The BeCare AI algorithm uses data from these activities to compute a participant's EDSS. The BeCare EDSS is based on more objective data than an in-person clinical EDSS.

An important potential conclusion of this study is that frequent use of the BeCare MS App may confer similar benefit to traditional physical therapy with the added benefit that the BeCare MS App can be performed remotely and at any time. This not only addresses the issues of access for all socioeconomic groups, but it also empowers patients to pursue ongoing therapy at home to stabilize and even improve their neurologic function.

This study has limitations, including sample size and some subject noncompliance performing activities in-window. A follow-up study could help determine which of the many activities the BeCare MS App offers confers the best functional benefits to users, which would enable us to develop a new app dedicated to therapeutic benefit that can offer a longer duration of such activities at each use.

Conclusion

Frequent use of BeCare MS activities may confer a therapeutic benefit for patients with demonstrable disability. The potential impact is great as not only will it augment and even guide physical therapy after an MS flare, but it can empower patients to maximize their functional state between flares and between visits with their clinicians. The lessons learned from inadequate monitoring of disease activity and delayed therapeutic interventions, especially in rehabilitation, bolster the need for patient-guided remote therapy for MS patients to improve functional outcomes.

As the starting EDSS increases, the final mean EDSS score shows greater improvement for frequent app users.

Acknowledgments

Patient recruitment and engagement was supported by Claudia Chen, Be Care Link's Business Analyst, and Beth Sanford, BeCareLink's Marketing Specialist. Data analysis was conducted by Jessica Buell, BeCare Link's Senior Project Development Engineer.

Financial Disclosures

Dr Stoll has served on scientific advisory boards for Bristol Myers Squibb; F. Hoffmann-La Roche Ltd; Forepont Capital Partners; Genentech, Inc; Horizon Therapeutics, Inc; and TG Therapeutics, Inc; received research support from BeCare Link, LLC and MedDay Pharmaceuticals SA; has received compensation for consulting services, served on scientific advisory boards, and received speaker honorarium for Alexion Pharmaceuticals, Inc; Biogen, Inc; Bristol Myers Squibb; EMD Serono, Inc; Horizon Therapeutics, Inc; Novartis AG; Roche's Genentech, Inc; and Sanofi Genzyme; is CEO of Global Consultant MD; and has served on the steering committee of Horizon Therapeutics, Inc and Roche's Genentech, Inc. Dr Litchman has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Amgen, Inc; holds stock and/or stock options in BeCare Link, LLC, which sponsored this research; and has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Amgen, Inc. ONLINE. Dr Larry Rubin has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with BeCare Link, LLC; has received compensation for serving on the board of directors of BeCare Link, LLC; and has received royalty, license fees, or contractual rights payments from BeCare Link, LLC. Dr. Caroline Stowe has no conflict of interest to disclose.

Funding/Support

Funding for this study was provided by BeCare Link, LLC.

Prior Presentation

None

Bibliography

1. McGinley MP., *et al*. "Diagnosis and Treatment of Multiple Sclerosis". *JAMA* 325.8 (2021): 765.
2. Bosma LV., *et al*. "Clinical scales in progressive MS: predicting long-term disability. *Multiple Sclerosis Journal* 18.3 (2021): 345-350.
3. Cerqueira JJ., *et al*. "Time matters in multiple sclerosis: can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis?" *Journal of Neurology, Neurosurgery and Psychiatry* 89.8 (2018): 844-850.
4. Kurtzke JF. "Disability rating scales in multiple sclerosis". *Annals of the New York Academy of Sciences* 436 (1984): 347-360.
5. Alves P., *et al*. "Validation of a machine learning approach to estimate expanded disability status scale scores for multiple sclerosis". *Multiple Sclerosis Journal-Experimental, Translational and Clinical* 8.2 (2022): 205521732211086.
6. Morrow SA., *et al*. "Quantifying cognition and fatigue to enhance the sensitivity of the EDSS during relapses". *Multiple Sclerosis Journal* 27.7 (2020): 1077-1087.
7. Herold F., *et al*. "Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements – a systematic review". *European Review of Aging and Physical Activity* 16.1 (2019).
8. Prabu Kumar A., *et al*. "How does cognitive function measured by the reaction time and critical flicker fusion frequency correlate with the academic performance of students?" *BMC Medical Education* 20.1 (2020).
9. ClinicalTrials.gov. clinicaltrials.gov. Accessed (2024).

10. Stoll S., *et al*. "Validated, Quantitative, Machine Learning-Generated Neurologic Assessment of Multiple Sclerosis Using a Mobile Application". *International Journal of MS Care* (2023).

11. Fritz NE., *et al*. "Distinguishing among multiple sclerosis fallers, near-fallers and non-fallers. *Multiple Sclerosis and Related Disorders* 19 (2018): 99-104.

12. Krupp LB. "The Fatigue Severity Scale". *Archives of Neurology* 46.10 (1989): 1121.

13. Kurtzke JF. "Disability rating scales in multiple sclerosis". *Annals of the New York Academy of Sciences* 436 (1984): 347-360.

14. Edwards T and Pilutti LA. "The effect of exercise training in adults with multiple sclerosis with severe mobility disability: A systematic review and future research directions. *Multiple Sclerosis and Related Disorders* 16 (2017): 31-39.

15. Sandroff BM., *et al*. "Systematic, Evidence-Based Review of Exercise, Physical Activity, and Physical Fitness Effects on Cognition in Persons with Multiple Sclerosis". *Neuropsychology Review* 26.3 (2016): 271-294.

16. Charvet LE., *et al*. "Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. Friede T, ed". *PLOS ONE* 12.5 (2017): e0177177.

17. Bossa M., *et al*. "Non-Pharmacological Treatments of Cognitive Impairment in Multiple Sclerosis: A Review". *Journal of Neuroscience* 3.3 (2022): 476-493.