Validation of the Scoring Algorithm for a Novel Integrative MS Progression Discussion Tool

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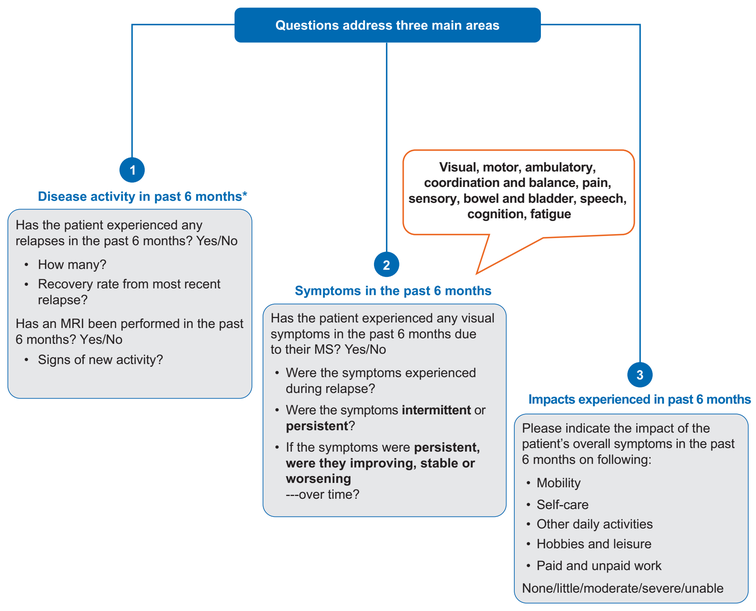
Tjalf Ziemssen[1], Daniela Piani Meier[2], Bryan Bennett[3], Chloe Johnson[3], Katie Tinsley[3], Andrew Trigg[3], Thomas Hach[2], Frank Dahlke[2], Davorka Tomic[2], Chloe Tolley[3], Mark S. Freedman[4]

[1]Center of Clinical Neuroscience, Neurological University Clinic Carl Gustav Carus, TU Dresden, Dresden, Germany; [2]Novartis Pharma AG, Basel, Switzerland; [3]Adelphi Values, Macclesfield, United Kingdom; [4]University of Ottawa and Ottawa Health Research Institute, Ottawa, ON, Canada

Introduction

- At onset, approximately 85% of patients are diagnosed with relapsing-remitting MS (RRMS)[1] and with time, patients enter a secondary progressive disease course (SPMS); large variations in time-to-onset of SPMS are observed with a median time ranging from 10–23 years[2-5]
- The mechanisms of transition from RRMS to SPMS are not clearly understood. Disease progression is a continuous process[6] that may start early in the disease course, sometimes identifiable even at a Disability Status Scale of 2.0[7]
- SPMS is also difficult to diagnose in real time due to the lack of clear diagnostic criteria or reliable imaging and biological markers, resulting in substantial diagnostic delays[8,9]
- The MS progression discussion tool is a clinician-completed digital tool to educate and sensitize about the risk of transitioning from RRMS to SPMS.[10,11] It facilitates physician-patient discussion and evaluation of subtle early signs of progression based on neurological history, symptoms and impacts experienced in the past 6 months (**Figure 1**)
- The three sections assessing disease activity including age (optional Expanded Disability Status Scale [EDSS] if available), symptoms and impacts produce a total score out of 100, with a higher score indicating a higher level of progression linked to a traffic light system – (●, unlikely; ●, possible; ●, likely)

Figure 1. Tool questionnaire



*Including age and optional EDSS
EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis

Objective

- To determine the sensitivity and specificity of the MS progression discussion tool in differentiating between RRMS and SPMS patients and to evaluate its psychometric properties and usefulness to clinicians

Methods

- The MS progression discussion tool was developed using a mixed-methods approach based on qualitative research with clinicians and patients and quantitative assessment of real-world evidence
- Twenty experienced MS neurologists from the US, Germany and Canada completed a web-based version of the tool for 198 patients (up to 10 patients for each) with a diagnosis of RRMS, SPMS or those suspected to be progressing to SPMS ('transitioning')
- Sample size was calculated based on the planned Receiver Operating Characteristic (ROC) analyses. A sample size of ≥150 would produce 90% power to detect an Area Under the Curve (AUC)≥0.68, which is considered moderate performance. When the AUC=0.50, the measure is discriminating at chance levels; the closer to 1.00 the AUC is, the better the tool is at distinguishing between patient groups. An AUC>0.9 is considered excellent performance
- The neurologists completed the following:
  - Two case report forms, one to capture the diagnosis (RRMS, SPMS or transitioning) and other clinical information for each patient
  - A separate form to capture the neurologist's clinical experience and a usability questionnaire about the tool
  - Each neurologist was also shown two video vignettes, with each showing an interaction between a clinician and a patient with RRMS/SPMS. The clinician was asked to rate each of those patients using the tool for the purpose of evaluating intra-rater reliability

Determining cut-off scores

- ROC analysis was used to evaluate the sensitivity (true positive rate) and specificity (true negative rate) of different cut-off scores on the tool
  - The thresholds were estimated based on the following comparisons:
    - **SPMS vs. not SPMS (transitioning/RRMS)** to obtain an upper threshold of those patients who are likely to be showing signs of progression, i.e. SPMS
    - **RRMS vs. not RRMS (transitioning/SPMS)** to obtain a lower threshold of those patients who are unlikely to be showing signs of progression to SPMS, i.e. RRMS
    - Any values between the lower and upper thresholds would indicate a patient who may possibly be showing signs of progression, i.e. transitioning to SPMS
- Two different statistical methods were considered to determine the optimal cut-off values that placed equal weight on sensitivity and specificity - Youden's J index and sum of squares

Psychometric properties

- Psychometric properties of the MS progression discussion tool were evaluated, including inter-rater reliability and construct validity (known-group comparisons)

Usability findings

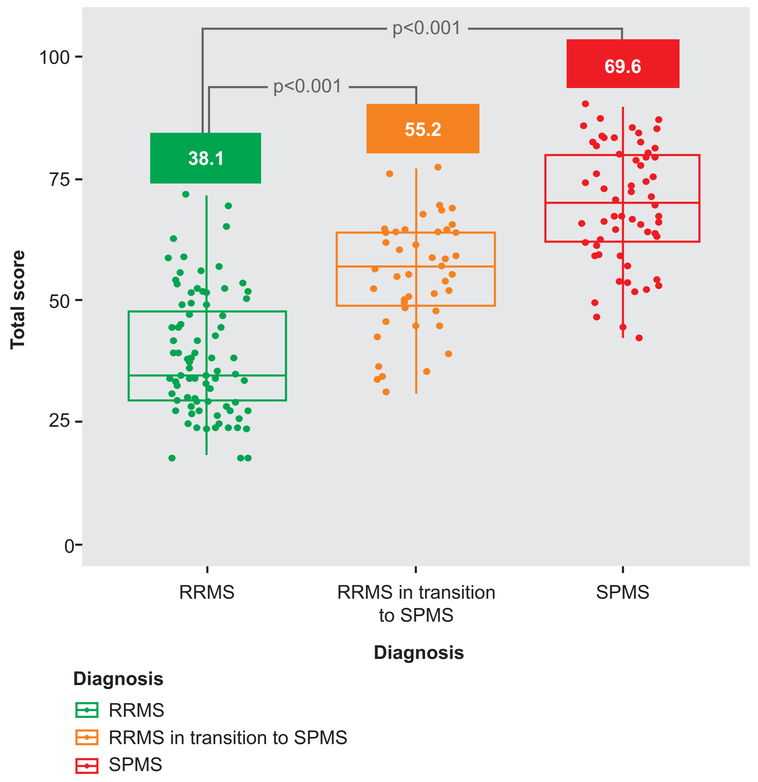
- Responses to the usability questionnaire, including ease of use, usefulness of the output and feasibility of implementing in clinical practice, were qualitatively assessed
- Qualitative responses to the usability questionnaire were coded using thematic analysis methods on Atlas Ti[12]

Results

Patient demographics and clinical characteristics

- A total of 20 neurologists across a number of settings, including private practice (70%), academic settings (40%), hospital (30%) and primary care (10%), completed the tool for 198 MS patients. The mean (range) of the monthly workload dedicated to MS was 36.6% (8.0–80.0%)
- The mean age of patients was 44.8 years (38.1 for RRMS, 53.4 for SPMS) and mean EDSS was 4.0 (2.6 for RRMS, 5.6 for SPMS). The duration (mean) of RRMS and SPMS diagnosis was 11.8 years (range: <1.0–50.5 years) and 6.3 years (range: <1.0–22.1 years), respectively
- The most frequent symptoms experienced by MS patients were fatigue (n=138), ambulatory (n=130), motor (n=129), sensory (n=128), coordination and balance (n=120), bowel and bladder (n=85), and cognition (n=78)
  - The most pronounced differences in SPMS and transitioning patients versus RRMS were observed for ambulatory/motor symptoms (94% vs. 35%) and coordination/balance (89% and 79% vs. 31%) followed by cognitive symptoms (66% and 45% vs. 18%) and bowel and bladder symptoms (65% and 57% vs. 20%)
  - The impact of symptoms was experienced by more SPMS and transitioning patients compared to RRMS patients
- Patients with a physician diagnosis of SPMS scored higher on the tool (mean: 69.6), followed by patients in transition to SPMS (55.2) and those with RRMS (38.1; p<0.001; **Figure 2**)

Figure 2. Distribution of total scores according to HCP MS diagnosis

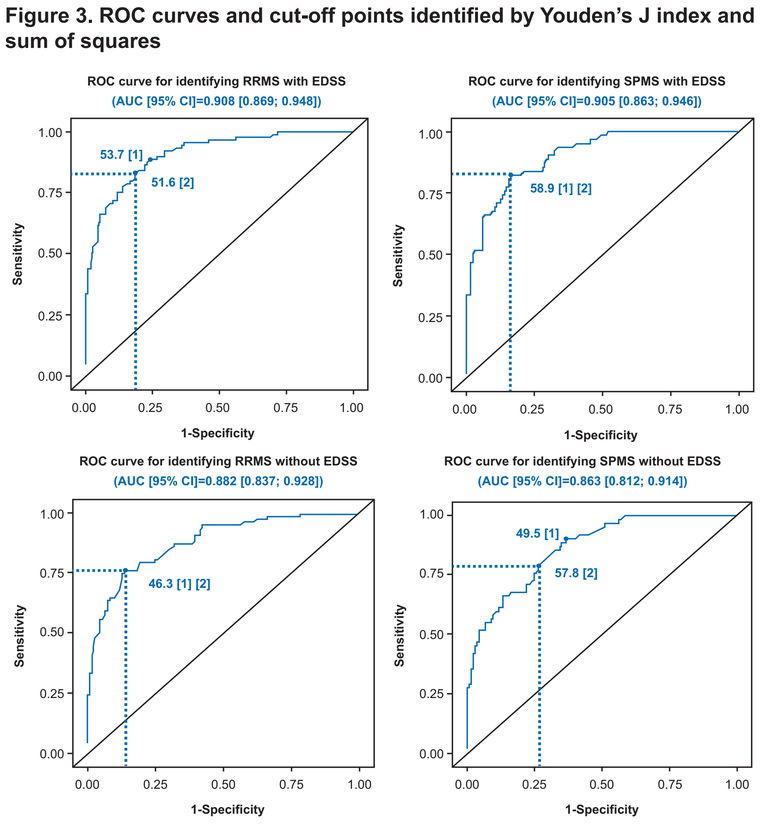


HCP, health care professional; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Optimal cut-off points for differentiation between SPMS and RRMS (ROC curves, including and excluding EDSS from the algorithm)

- AUC was very good, both including/excluding EDSS: SPMS, 0.905/0.863; RRMS, 0.908/0.882 (**Figure 3**)
- A cut-off point of ≥58.9 identified SPMS patients with high sensitivity (0.82) and specificity (0.84). For RRMS patients, high sensitivity (0.83) and specificity (0.82) were obtained using the cut-off point ≤51.6 (**Figure 3**)
- When EDSS was removed, sensitivity (0.79) and specificity (0.735) for SPMS were reduced but still good (cut-off point ≥57.80); for RRMS patients, a sensitivity of 0.76 and a specificity of 0.86 was achieved with a lower cut-off point ≤46.3 (**Figure 3**)
- Since EDSS is often not recorded in routine clinical practice, cut-off points without EDSS were chosen and the feasibility of applying the same cut-off points (≤46.3 and ≥57.8) for the algorithm with/without EDSS was explored. Sensitivity/specificity was still very good, ranging between 0.72 and 0.89. Sensitivity for SPMS was consistently around 80% (true positive rate) and specificity (true negative rate) for RRMS was above 86% (**Table 1**)

Figure 3. ROC curves and cut-off points identified by Youden's J index and sum of squares



[1] Youden's J Index; [2] Sum of squares; AUC, area under the curve; CI, confidence interval; EDSS, Expanded Disability Status Scale; ROC, Receiver Operating Characteristic; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Table 1. Sensitivity and specificity applying the same cut-off points for algorithm including and excluding EDSS

	Cut-off point	Sensitivity	Specificity
SPMS vs. transitioning and RRMS (upper cut-off)			
With EDSS	≥57.8	0.823	0.809
Without EDSS		0.790	0.735
RRMS vs. transitioning and SPMS (lower cut-off)			
With EDSS	≤46.3	0.719	0.890
Without EDSS		0.764	0.862

EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Psychometric properties

- The total score demonstrated excellent inter-rater reliability intraclass correlation coefficient (ICC)=0.950 (95% CI, 0.772;1). In the known-groups comparisons, a significant difference was observed in total score between EDSS groups (≥1 and ≤4.5; >4.5 and <9.5) and physician diagnosis groups (RRMS; SPMS)

Usability findings

- All neurologists confirmed that items included in the tool were relevant to progression to SPMS (**Table 2**)
- The neurologists found the traffic light signal related to the level of progression to be clear and useful and were satisfied by the time taken to complete the tool

Table 2. Usability findings from a neurologist perspective

Usability	n (%)
Items relevant to progression to SPMS	20 (100)
Typically collect tool data in clinical practice	18 (90)
Time to complete satisfactory	17 (85)
Traffic light style output useful and clear	16 (80)
Feasible to implement tool in clinical practice	17 (85)

n, number of neurologists who provided a positive response; SPMS, secondary progressive multiple sclerosis

Conclusions

- The MS progression discussion tool provides a comprehensive assessment of patients' current disease status based on disease activity, symptoms and associated impacts experienced in the past 6 months
- The tool has demonstrated the ability to differentiate between patients with RRMS and those transitioning to SPMS with high sensitivity and specificity, suggesting that the items included in the tool are of relevance to evaluate early signs of progression and also demonstrated reliability and validity
- Neurologists have responded positively to the tool, supporting implementation in clinical practice to facilitate physician-patient discussion and evaluation of subtle signs of progression to SPMS complementing routine neurological assessment

The online version of the MSProDiscuss tool can be accessed on Neuro-Compass website:
www.neuro-compass.education/en-gb/msprodiscuss/ (or) www.msprodiscuss.com

The tool does not provide medical advice, diagnosis, prediction, prognosis, or treatment. The tool and its content are being provided for general information purposes only. Any medical advice, diagnosis or treatment should be made by the appropriate healthcare professional

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Scan the QR Code to Access the Online Version of the MSProDiscuss Tool

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