***Table S1.* Summary of Studies Identified Following Targeted Literature Review**

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| Study | Number of patients evaluated | Measure | Assessment | Main finding(s) |
| Horakova 200910 | 181 patients with early RRMS | Brain volume measures | –Percentage of brain volume loss  | –Predictive of increase in EDSS observed over 5-year period |
| –Lateral ventricle volume loss  |
| Uher 201913 | 964 patients with RRMS | –Annualized percent whole brain volume loss–Annualized percent thalamic volume loss–Annualized percent corpus callosum volume loss | –Correlation with annualized absolute increase in EDSS |
| –Annualized gray matter volume loss | –Correlation with higher annualized absolute EDSS |
| Lavorgna 201412 | 241 patients with RRMS | –Reduction in gray matter fraction1 | Predictive of:–Higher probability of conversion from RRMS to SPMS–Higher probability of EDSS progression2–Achievement of EDSS score of 4–Higher risk of reaching EDSS score of 4 |
| –Lower gray matter fraction | Association with:–Conversion from RRMS to SPMS–Achievement of EDSS score of 4 |
| –Lower white matter fraction–Higher abnormal white matter fraction | Association with:–Conversion from RRMS to SPMS–Achievement of EDSS score of 4 |
| –Higher cerebrospinal fluid fraction | Association with:–Conversion from RRMS to SPMS–Achievement of EDSS score of 4 |
| Deloire 201114 | 44 patients with MS | –Brain parenchymal fraction–Ventricular fraction–Normal-appearing brain tissue-magnetization transfer ratio | No predictive evidence of:–Change in memory *z* score–Change in information processing speed |
| Pulido-Valdeolivas 202011 | 161 patients with MS |  | –Annualized rates of brain volume loss (MRI, T1 and T2 lesions) and retinal thinning (optical coherence tomography) | –Predictive of early MS progression (within 5 years) |
| Popescu 201317 | 97 patients with RRMS | Lesions | –Higher T2-lesion volume–Increase in annualized T2-lesion volume | Assessments predictive of:–Higher EDSS (year 10)–Higher MS Severity Scale Score (year 10) |
| Horakova 200910 | 181 patients with early RRMS | –Higher T2-lesion volume | –Correlated with an increase in EDSS (over 5 years) |
|   |   | –T2-lesion volume  | –Not correlated with an increase in EDSS (over 5 years) |
| Deloire 201114 | 44 patients with MS | –Lesion load–Lesion magnetization transfer ratio | No predictive evidence of:–Change in memory *z* score–Change in information processing speed |
| Rio 20185 | 283 patients with RRMS | –3 or more new T2 lesions–2 or more gadolinium-enhancing lesions | –Predictive of sustained EDSS worseningof at least 2 points (year 8) |
| Goodin 20169 | 376 patients with MS | –T2 burden of disease–Change in T2 burden of disease | –Predictive of negative disability outcomes (year 16) |
| Prosperini 20176 | 987 patients with RRMS | NEDA | –Evidence of disease activity3,4–Minimal evidence of disease activity3,5 | –Predictive of higher risk of reachingEDSS score of 6 or higher (year 10) |
| Uher 20177 | 162 patients following first demyelinating event suggestive of MS | –Loss of NEDA-36 | Assessment predictive of–Sustained disability progression (year 10)7–Greater T2 lesion volume loss (year 10)–Greater whole brain volume loss (year 10)–Greater corpus callosum volume loss (year 10) |
|  |  | –NEDA-48 | –No predictive evidence of sustained disability progression (year 10) 7 |
| Kappos 20168 | 2355 patients with RRMS | –NEDA-49 | –Predictive of longer time to secondary progressive MS conversion (over 8 years) |
|  |  | –NEDA-310 | –No predictive of evidence of longer time to secondary progressive MS conversion (over 8 years) |
| Goodin 20169 | 376 patients with MS | –Clinical NEDA11 | –Predictive of negative disability outcomes (year 16) |
|  |  |  | – No predictive evidence of time to death (over 21 years) |
|  |  | –NEDA-3a12–NEDA-3b13–NEDA-414 | –No predictive evidence of negative disability outcomes (year 16) |
|  |  | –NEDA-3a–NEDA-3b–NEDA-4 | – No predictive evidence of survival (year 21) |
| Rio 20185 | 283 patients with RRMS | –Minimal evidence of disease activity-115 | –Predictive of sustained EDSS worsening of at least 2 points (year 8) |
|  |  | –Minimal evidence of disease activity-216–Evidence of disease activity | –No predictive evidence of sustained EDSS worsening of at least 2 points (year 8) |
| Chitnis 201818 | 122 patients with MS | Serum neurofilament light | –Higher average yearly NfL measurements–Higher average yearly NfL levels–Higher NfL levels–Yearly and average yearly NfL measurements–Average yearly NfL–NfL at each year | Assessments were predictive of:–Reduction in brain parenchymal fraction–Higher T2-lesion load–Higher MFIS but only years 1-3 were predictive over the 10-year period evaluatedAssessments correlated with:–Lower BPF (year 10)No predictive evidence was found for:–MFIS (year 10)–SDMT (year 10 and change over 10 years)–T25-FW (year 10 and change over 10 years)–EDSS (year 10) |
| Moccia 201616 | 155 patients with RRMS | Cognitive impairment | –Lower SDMT– Higher number of failed impaired tests of the BRB-N– Cognitive impairment (measured within 6 months from MS diagnosis)– Lower SDMT–Higher number of failed impaired tests of the BRB-N–Lower SRT-D–Failure of at least 3 tests of the BRB-N | Assessment predicted:–Achievement of EDSS score of 4 (year 10)–Conversion from RRMS to SPMS (year 10)No predictive evidence of:–Occurrence of clinical relapse (year 10) |
| Lavorgna 201412 | 241 patients with RRMS | Demographics | –Higher age | Association with:–Achievement of EDSS score of 4Not associated with:–Conversion from RRMS to SPMS |
| Moccia 201616 | 155 patients with RRMS | –Higher age–Gender | Association with:–Achievement of EDSS score of 4Not associated with:–Conversion from RRMS to SPMS |
| Deloire 201114 | 44 patients with MS | –Age–Gender–Education | –No predictive evidence of change in:–Memory *z* score–Change in information processing speed |
| Jokubaitis 201519 | 2271 patients with MS | Pregnancy | –Pregnancy | –Predictive of a decrease in median EDSS score (over 8 years) |
| Jokubaitis 201519 | 2271 patients with MS | Annualized relapse rate | –Higher annualized relapse rate | –Predictive of an increase in mean EDSS score (over 8 and 10 years) |
| Moccia 201616 | 155 patients with RRMS | –Higher annualized relapse rate | –Association with achievement of EDSS score of 4 (year 10)–Not associated with a conversion from RRMS to SPMS (year 10) |
| Rio 20185 | 283 patients with RRMS | Relapse | –Presence of one relapsewithout changes in EDSS score (year 1) | Predictive of: –Conversion from RRMS to secondary MS (year 12)–Five-step EDSS worsening (year 12) |
|  |  |  | –Presence of one or more relapses | –Predictive of sustained EDSS worseningof at least 2 points (year 8) |
| Lavorgna 201412 | 241 patients with RRMS | Disease duration | –Longer disease duration | –Association with achievement of EDSS score of 4 |
| Moccia 201616 | 155 patients with RRMS | –Disease duration | No association with:–Achievement of EDSS score of 4.0 **(**year 10)–Conversion from RRMS to SPMS (year 10) |
| Rothman 201915 | 140 patients with RRMS | Macular volume | –Lower total macular volume | –Predictive of EDSS worsening–Correlated with higher EDSS (year 10) |
| Deloire 201114 | 44 patients with MS | Montgomery-Åsberg Depression Rating Scale | –Montgomery-Åsberg Depression Rating Scale | No predictive evidence of:–Change in memory *z* score–Change in information processing speed |

BRB-N, Rao Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (version A); MFIS, Modified Fatigue Impact Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity; NfL, neurofilament light; RRMS, relapsing remitting MS; SDMT, Symbol Digit Modalities Test; SRT-D, Selective Reminding Test-Delayed; T25-FW, Timed 25-Foot Walk

1 Fraction of intracranial volume

2 One-point increase for EDSS score ≤ 5.5 and a 0.5-point increase (confirmed after at least 3 months) for EDSS score > 5.5

3 Compared to patients with NEDA (absence of relapses, of confirmed EDSS worsening and of MRI activity)

4 Evidence of disease activity: occurrence of ≥ 1 relapses with either confirmed EDSS worsening or ≥ 1 gadolinium-enhancing lesions or ≥ 3 new T2 lesions

5 Minimal evidence of disease activity: either 1 relapse with ≤ 2 new T2 lesions or < 3 new T2 lesions or < 2 gadolinium-enhancing lesions, in the absence confirmed EDSS worsening

6 NEDA-3: absence of new clinical relapse, disability progression, and active MRI lesions during follow-up, and no evidence of disease activity

7 Sustained disability progression was defined as an increase in EDSS by 1.0 point (if baseline EDSS score > 0) or 1.5 points (if baseline EDSS score = 0), confirmed after 12 months

8 NEDA-4: absence of new clinical relapse, disability progression, active MRI lesions as well as increased whole brain volume loss during follow-up

9 NEDA-4: no MRI lesion activity, no relapses, no confirmed progression of disability, and annual brain volume loss < 0.4%

10 NEDA-3: no MRI lesion activity, no relapses, and no confirmed progression of disability

11 Clinical NEDA: no relapses, and no EDSS worsening

12 NEDA-3a: no relapses and no new T2-active lesions during treatment, and no confirmed 1-point EDSS progression

13 NEDA-3B: no relapses and no EDSS/T2 burden of disease worsening

14 NEDA-a4: no relapses, no EDSS/T2 burden of disease worsening, and no enlargement in 3rd ventricle size

15 Minimal evidence of disease activity-1: presence of one relapse with 0 or 1–2 new T2 lesions

16 Minimal evidence of disease activity-2: presence of < 3 new T2 lesions or < 2 gadolinium-enhancing lesions