Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF
NEUROLOGY®

Performance of the 2017 and 2010 Revised McDonald Criteria in Predicting MS Diagnosis After a Clinically Isolated Syndrome: A MAGNIMS Study

Author(s):

Massimo Filippi, MD, FEAN, FAAN[1,2,3,4,5]; Paolo Preziosa, MD, PhD[1,2]; Alessandro Meani, MSc[1]; Gloria Dalla Costa, MD[3,5]; Sarlota Mesaros, MD, PhD[6]; Jelena Drulovic, MD[6]; Jovana Ivanovic, MD[6]; Alex Rovira, MD[7]; Mar Tintorè, MD[8]; Xavier Montalban, MD[8]; Olga Ciccarelli, MD[9]; Wallace Brownlee, MD[9]; Katherine Miszkiel, MD[9]; Christian Enzinger, MD[10]; Michael Khalil, MD, PhD[10]; Frederik Barkhof, MD, PhD[11,12]; Eva M.M. Strijbis, MD, PhD[13]; Jette L Frederiksen, MD, DMSci[14]; Stig P Cramer, MD[15,16]; Enrico Fainardi, MD[17]; Maria Pia Amato, MD[18,19]; Claudio Gasperini, MD[20]; Serena Ruggieri, MD[20]; Vittorio Martinelli, MD[2]; Giancarlo Comi, MD[5]; Maria A. Rocca, MD[1,2,5] on behalf of MAGNIMS Study Group

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for

publication. This manuscript will be published in its final form after copyediting, page

composition, and review of proofs. Errors that could affect the content may be corrected

during these processes.

Corresponding Author:
Massimo Filippi
filippi.massimo@hsr.it

Affiliation Information for All Authors: 1. Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy; 2. Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; 3. Neurorehabilitation Unit IRCCS San Raffaele Scientific Institute, Milan, Italy; 4. Neurophysiology Service, IRCCS San Raffaele Scientific Institute, Milan, Italy; 5. Vita-Salute San Raffaele University, Milan, Italy; 6. Clinic of Neurology, Faculty of Medicine, University of Belgrade, Serbia; 7. Section of Neuroradiology, Department of Radiology, Hospital Universitari Vall d Hebron, Barcelona, Spain; 8. Department of Neurology/Neuroimmunology, Multiple Sclerosis Center of Catalonia, Hospital Universitari Vall d Hebron, Barcelona, Spain; 9. NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, UK; 10. Department of Neurology, Medical University of Graz, Graz, Austria; 11. Department of Radiology and Nuclear Medicine, MS Center Amsterdam, Amsterdam Neuroscience Amsterdam UMC, location VUmc, Amsterdam, The Netherlands; 12. Institutes of Neurology and Healthcare Engineering, University College London, London, UK; 13. Department of Neurology, MS Center Amsterdam, Amsterdam Neuroscience Amsterdam UMC, location VUmc, Amsterdam, The Netherlands; 14. Clinic of Optic Neuritis and Clinic of Multiple Sclerosis, Department of Neurology, Rigshospitalet - Glostrup, University of Copenhagen, Copenhagen, Denmark; 15. Department of Clinical Physiology, Nuclear Medicine and PET, FIU unit, Rigshospitalet Glostrup, Copenhagen University Hospital, Copenhagen, Denmark; 16. Department of Clinical Physiology and Nuclear Medicine, Centre for Functional and Diagnostic Imaging and Research, Hvidovre Hospital, Hvidovre, Denmark; 17. Neuroradiology Unit, Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', University of Florence, Florence, Italy; 18. Department of Neurofarba, University of Florence, Florence, Italy; 19. IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy;20. Department of Neurosciences, San Camillo Forlanini Hospital, Rome, Italy.

Contributions:
Massimo Filippi: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data; Additional contributions: Study supervision
Paolo Preziosa: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Alessandro Meani: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data; Additional contributions: statistical analysis
Gloria Dalla Costa: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Sarlota Mesaros: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Jelena Drulovic: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Jovana Ivanovic: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Alex Rovira: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Mar Tintorè: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Xavier Montalban: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Olga Ciccarelli: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Wallace Brownlee: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Katherine Miszkiel: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Christian Enzinger: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Michael Khalil: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Frederik Barkhof: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Eva M.M. Strijbis: Drafting/revision of the manuscript for content, including medical writing for content;

Major role in the acquisition of data

Jette L Frederiksen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Stig P Cramer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Enrico Fainardi: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Maria Pia Amato: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Claudio Gasperini: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Serena Ruggieri: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Vittorio Martinelli: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Giancarlo Comi: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Maria A. Rocca: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Number of characters in title: 88

Abstract Word count: 246

Word count of main text: 4357

References: 50

Figures: 5

Tables: 2

Abstract

Background and Objective. To compare the performance of the 2017 revisions to the McDonald criteria with the 2010 McDonald criteria in establishing MS diagnosis and predicting prognosis in patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS).

Methods. CSF examination, brain and spinal cord MRI obtained ≤5 months from CIS onset, and a follow-up brain MRI acquired within 15 months from CIS onset were evaluated in 785 CIS patients from 9 European centers. Date of second clinical attack and of reaching Expanded Disability Status Score (EDSS)≥3.0, if they occurred, were also collected. Performance of the 2017 and 2010 McDonald criteria for dissemination in space (DIS), time (DIT) (including oligoclonal bands assessment) and DIS+DIT for predicting a second clinical attack (clinically definite [CD]

MS) and EDSS≥3.0 at follow-up was evaluated. Time to MS diagnosis for the different criteria was also estimated.

Results. At follow-up (median=69.1 months), 406/785 CIS patients developed CDMS. At 36 months, the 2017 DIS+DIT criteria had higher sensitivity (0.83 *vs* 0.66), lower specificity (0.39 *vs* 0.60) and similar area under the curve values (0.61 *vs* 0.63). Median time to MS diagnosis was shorter with the 2017 *vs* the 2010 or CDMS criteria (2017 revision=3.2; 2010 revision=13.0; CDMS=58.5 months). The two sets of criteria similarly predicted EDSS≥3.0 milestone. Three periventricular lesions improved specificity in patients ≥45 years.

Discussion. The 2017 McDonald criteria showed higher sensitivity, lower specificity and similar accuracy in predicting CDMS compared to 2010 McDonald criteria, while shortening time to diagnosis of MS.

Classification of Evidence. This study provides Class II evidence that the 2017 McDonald Criteria more accurately distinguish CDMS in patients early after a CIS when compared to the 2010 McDonald criteria.

Introduction

In 2001, MRI was formally included in the criteria for multiple sclerosis (MS) diagnosis to demonstrate dissemination in space (DIS) and time (DIT) of MS lesions.[1] Subsequent iterations of the McDonald criteria[2, 3] have simplified MS diagnosis, while maintaining sensitivity, specificity and accuracy. The McDonald criteria shorten the time from onset of symptoms to MS diagnosis in patients with a clinically isolated syndrome (CIS) suggestive of MS, without waiting for the occurrence of a second clinical event.[4] This is crucial since an increasing number of therapies have been demonstrated to be effective in favorably modifying MS disease course especially if started early.[5]

Recently, new evidence regarding the utility of MRI and CSF analysis for MS diagnosis has become available. The MAGNIMS network proposed modified MRI criteria for DIS in 2016.[6] The performance of these evidence-based recommendation was evaluated in a large multicenter MAGNIMS study[7] that informed the 2017 revisions to MS diagnostic criteria,[8] including removing the distinction between symptomatic and asymptomatic lesions and combining cortical and juxtacortical lesions in DIS (data available from Dryad: Table e-1 https://doi.org/10.5281/zenodo.5566178). Additionally, in CIS patients fulfilling DIS criteria, the presence of CSF-specific oligoclonal bands (OCBs) allows a diagnosis of MS, in the absence of clinical or MRI evidence of DIT (data available from Dryad: Table e-1 https://doi.org/10.5281/zenodo.5566178).[8] An additional modification proposed by the MAGNIMS network[6] to improve the criteria specificity,[7] but not included in the 2017 revisions, was to increase the number of lesions needed to establish periventricular involvement from one to three.

After their publication, several studies compared the performance of the 2017 and 2010 revisions to the McDonald criteria in adult[9-14] and pediatric CIS patients.[15-17] Globally, they showed that the 2017 McDonald criteria have higher sensitivity but lower specificity compared with the 2010 criteria in predicting clinically definite (CD) MS, but a shorter time to MS diagnosis.

Several aspects related to the performance of the 2017 revision of the McDonald criteria still need to be fully evaluated. The performance of these criteria has mainly been assessed in small, monocentric cohorts of CIS patients. Different outcomes have been used, including the estimation of CDMS after a relatively short or heterogeneous follow-up, or by combining clinical (CDMS) with MRI (new lesions) status. Additionally, some important aspects have been only partially explored. These include the influence of age and CIS topography on criteria performance, and the impact of treatment initiation on the risk of developing CDMS. Finally, the ability of the 2017 revisions to predict disability accumulation has not been investigated yet.

To clarify all these important aspects, we compared the performance of the 2017 McDonald criteria in predicting CDMS development and MS prognosis, and in enabling an earlier MS diagnosis, with that of the 2010 McDonald criteria, in a large multicenter study of patients with a typical CIS suggestive of MS. The influence of type of CIS onset and increasing the number of periventricular lesions needed to demonstrate DIS from one to three (which might have a different relevance according to age at onset) was also evaluated.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents. Approval was received from the institutional ethical standards committee on human experimentation of each participating center for any experiments using human subjects. Written informed consent was obtained from all patients participating in the study at the time of data acquisition.

Primary Research Question and Classification of Evidence. Primary research question: in patients with a typical CIS suggestive of MS, do the 2017 revision to the McDonald criteria outperform the 2010 McDonald criteria for the diagnosis of MS?

This study provides Class II evidence that the 2017 McDonald Criteria more accurately distinguish CDMS in patients early after a CIS when compared to the 2010 McDonald criteria.

Patients. This project was run within the European MAGNIMS network (http://www.magnims.eu/) and involved nine highly specialized MS centers, which were : a) the Neuroimaging Research Unit and Department of Neurology, San Raffaele Scientific Institute, Milan, Italy; b) MS Centre Amsterdam, VU University Medical Centre, the Netherlands; c) the Centre d'Esclerosi Múltiple de Catalunya (Cemcat), the Department of Neurology/Neuroimmunology and the Section of Neuroradiology, Department of Radiology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain; d) the Clinics of Neurology and Radiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; e) the Department of Neurology, Rigshospitalet Glostrup and University of Copenhagen, Copenhagen, Denmark; f) the Department of Neurology, Medical University of Graz, Graz, Austria; g) the Queen Square MS Centre, University College London (UCL) Institute of Neurology, London, UK; h) the Department of Neurosciences, San Camillo-Forlanini Hospital, Rome, Italy; i) the Department NEUROFARBA, University of Florence, Florence, Italy/IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy.

The study design was similar to that of previous studies aimed at assessing the performance of MS diagnostic criteria.[7, 18]

Centers identified CIS patients recruited into local prospective clinical and MRI follow-up studies from June 1995 to October 2020 with: a) age between 18 and 60 years; b) a diagnosis of CIS suggestive of MS;[19] c) a typical clinical presentation of relapse-onset MS;[20] d) a complete neurological examination, with scoring of the Expanded Disability Status Scale (EDSS), performed within 5 months from the clinical onset; e) baseline brain and spinal cord MRI scans obtained within 5 months from the clinical onset; f) a follow-up brain MRI obtained ≤15 months from CIS onset. Development of CDMS was defined as the occurrence of a second clinical event attributable to demyelination lasting more than 24 hours and after an interval ≥1 month from the first attack, with evidence of two separate lesions. Time to CDMS was calculated as the interval between the first two clinical events.

The following information was collected: age at CIS onset, sex, presence of CSF-specific OCBs (where available), date and topography of CIS onset, dates of the second event and of last available follow-up, date of reaching EDSS≥3.0, date of initiation and type of disease-modifying treatment (DMT), dates of MRI scans and field strengths of the scanners used.

MRI analysis and CSF examination. For the brain, axial dual-echo (DE) and/or fast fluid-attenuated inversion recovery (FLAIR) and post-contrast (0.1 mmol/kg of gadolinium [Gd]-DTPA; acquisition delay: ≈ 10 minutes) T1-weighted sequences were acquired at baseline and at follow-up. Slice thickness varied between 3 and 5 mm, in-plane resolution between 0.45 and 1.0 mm, no gap between slices. A brain double inversion recovery (DIR) sequence was available for 337/785 (42.9%) CIS patients from three centres (Barcelona, Belgrade and Milan). For the spinal cord, sagittal short tau inversion recovery (STIR) and/or T2-weighted and post-contrast T1-weighted sequences (0.1 mmol/kg of gadolinium [Gd]-DTPA; acquisition delay: 5 minutes) with 3 mm slice thickness, in-plane resolution between 0.4375 and 1.0 mm, no gap between slices, covering the cervical and thoracic cord were acquired. For 120/785 (15.3%) CIS patients, baseline SC involvement was established using available MRI reports, due to missing or corrupted raw MRI data.

All images were assessed by consensus by two experienced observers (PP and MAR), blinded to the patients' identity and MS status at the Neuroimaging Research Unit (Milan, Italy). Brain white matter (WM) lesions were identified on dual-echo/FLAIR images and were defined as hyperintensities involving at least 3 voxels, present on at least two slices and visible on two different sequences (e.g., FLAIR and T2 or proton density and T2). Spinal cord lesions were identified on sagittal short tau inversion recovery (STIR) and/or T2-weighted sequences. Total number of WM lesions, number of periventricular (abutting the lateral ventricles without intervening WM), juxtacortical (touching the cortex), cortical (within the cortex), posterior fossa (located in the brainstem, cerebellar peduncles and cerebellar hemispheres) and spinal cord lesions were evaluated following published recommendations.[21] Cortical lesions and juxtacortical lesions

identified from double inversion recovery (available in 337/785 [43%]) and T2 and FLAIR sequences were combined.[8] Gd-enhancing lesions (area of hyperintensity on post-contrast T1-weighted images)[21] were identified on post-contrast T1-weighted scans.

On the MRI scan acquired at follow-up, the numbers of new T2-hyperintense and Gd-enhancing lesions were quantified.

OCBs were evaluated in 670/785 (85%) CIS patients in the CSF and serum at the time of baseline clinical evaluation by agarose isoelectric focusing combined with immunoblotting. When bands were present only in the CSF, they were considered CSF-specific.

DIS and DIT criteria. The 2010[3] and 2017[8] McDonald DIS criteria were assessed on baseline MRI scans, whereas the 2010[3] and 2017[8] McDonald DIT criteria were defined on baseline and follow-up MRI and according to CSF-specific OCB status (data available from Dryad: Table e-1 https://doi.org/10.5281/zenodo.5566178). Although presence of OCBs does not reflect DIT, but is an alternative to DIT, we used the definition of DIT including OCBs. The fulfilment of DIS plus DIT criteria for both the 2010 and 2017 was also assessed.

The performance of the 2017 McDonald criteria[8] was evaluated also without OCB assessment.

As additional analyses, we compared the performances of 2017 and 2010 McDonald criteria according to the type of CIS at onset (i.e., optic neuritis, brainstem/cerebellar syndrome, or spinal cord syndrome). The performance in CIS patients with a hemispheric or multifocal onset was not evaluable due to their limited number. Finally, we evaluated criteria performance using three instead of one periventricular lesions to define periventricular involvement, according to age at onset (<25, 25-34, 35-44, and ≥45 years).

Statistical analysis. Cumulative/dynamic time-dependent receiver operating characteristic (ROC) curve analysis[22] for censored survival data was applied to assess the performance of the MRI criteria for DIS, DIT and DIS plus DIT (also without OCB assessment), using the clinical status (CDMS or CIS) over time as outcome. Sensitivity, specificity, accuracy, positive and negative

predictive values at months 36 and 60 were calculated. Bias-corrected and accelerated bootstrap method[23] was used to estimate 95% confidence intervals (CIs). Analyses were repeated after excluding all CIS patients receiving DMT before the second clinical event.

The cumulative risk of CDMS development from the first clinical event to the last available follow-up was represented using Kaplan-Meier survival curves (patients censored according to their follow-up). Extended Cox regression models using time to CDMS as the outcome and adjusted for age (continuous), sex (binary), treatment (binary, time-dependent, i.e., treatment effects were modeled considering the time when a patient started any treatment [thus considering two conditions: without or under treatment]), and disease onset type (optic neuritis, brainstem/cerebellar, spinal cord, hemispheric, multifocal), were performed to obtain adjusted hazard ratios (aHRs) and 95% CIs. A shared gamma-frailty term was also included to address center effects, accounting for unobserved heterogeneity and statistical dependence between clustered time-to-event data.[24] The possible interactions between MRI criteria and treatment or type of onset were explored by estimating similar models including a specific interaction term.

Similar models were also estimated using time to reach EDSS$\geq$3.0 as the outcome.

Median time to MS diagnosis according to different criteria (i.e., 2017 or 2010 McDonald criteria or CDMS) were estimated using Kaplan-Meier survival curves.

Data Availability. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The anonymized dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

Results

Demographic, clinical and MRI data. From 958 CIS patients, the final cohort comprised 785 CIS patients fulfilling inclusion criteria. Figure 1 shows study flow chart and Table 1 summarizes the main baseline demographic, clinical and MRI findings of these patients.

Seven hundred and forty-five out of 785 (95%) CIS patients had a monofocal onset, including optic neuritis in 286/745 (38%), a brainstem/cerebellar syndrome in 169/745 (23%), a spinal cord syndrome in 239/745 (32%) and a hemispheric syndrome in 51/745 (7%).

At the last evaluation (median=69.1 months; IQR=39.8-112.1), 406/785 (52%) CIS patients had experienced a second clinical episode (median time to conversion=13.2 months, IQR=5.2-31.5), and 101/785 (13%) CIS patients reached an EDSS≥3.0; 437/785 (56%) CIS patients started DMTs (235 after the first clinical episode; 202 after the second): 141 (32%) of them did not develop CDMS.

At baseline, 78/785 (10%) CIS patients had a normal brain MRI (24 [31%] of whom had an abnormal spinal cord MRI), and 398/785 (51%) had normal spinal cord MRI (346 [87%] of whom had an abnormal brain MRI). CSF-specific OCBs were found in 459/670 (69%) CIS patients.

At follow-up MRI 386/785 (79%) patients developed new T2-hyperintense or Gd-enhancing lesions.

Performances of different sets of criteria. For DIS at month 36, the 2017 McDonald criteria had higher sensitivity (0.86 [95% CI=0.82-0.90] *vs* 0.78 [95% CI=0.73-0.82]), lower specificity (0.32 [95% CI=0.28-0.37] *vs* 0.38 [95% CI=0.33-0.43]), and similar area under the curve (AUC) values (0.59 [95% CI=0.56-0.62] *vs* 0.58 [95% CI=0.55-0.62]) than the 2010 McDonald criteria, for predicting CDMS (Table 2, Figure 2).

For DIT at month 36, the 2017 vs 2010 McDonald criteria showed higher sensitivity (0.95 [95% CI=0.92-0.97] vs 0.77 [95% CI=0.72-0.82]), lower specificity (0.20 [95% CI=0.16-0.25] vs 0.53 [95% CI=0.47-0.58])] and slightly lower AUC values (0.58 [95% CI=0.55-0.60] vs 0.65 [95% CI=0.61-0.68]) for predicting CDMS (Table 2).

For DIS plus DIT at month 36, the 2017 McDonald criteria had higher sensitivity (0.83 [95% CI=0.79-0.87] *vs* 0.66 [95% CI=0.61-0.71]), lower specificity (0.39 [95% CI=0.34-0.44] *vs* 0.60 [95% CI=0.55-0.65]), and similar AUC values (0.61 [95% CI=0.58-0.64] *vs* 0.63 [95% CI=0.59-0.67]) (Table 2, Figure 2).

The evaluation at month 36 of the 2017 McDonald criteria without CSF-specific OCB assessment decreased sensitivity (0.74 [95% CI=0.69-0.78]), increased specificity (0.54 [95% CI=0.49-0.59]) and preserved AUC values (0.64 [95% CI=0.60-0.67]) (Table 2, Figure 2).

At month 60, the performance of the 2017 and 2010 McDonald criteria were comparable to what observed at month 36 (Table 2).

The analysis evaluating DIS, DIT and DIS plus DIT in CIS patients not receiving DMT before the second clinical event (n=550) showed, for both sets of criteria, a slight decrease in sensitivity together with increased specificity and AUC values, with the 2017 McDonald criteria showing a higher sensitivity, a lower specificity and similar AUC values compared to the 2010 McDonald criteria (data available from Dryad: Table e-2 https://doi.org/10.5281/zenodo.5566178).

For DIS plus DIT, the 2017 vs 2010 McDonald criteria showed higher sensitivity, lower specificity and similar AUC values in CIS patients presenting with optic neuritis (Figure 3, data available from Dryad: Table e-3 https://doi.org/10.5281/zenodo.5566178). In CIS patients with brainstem/cerebellar syndromes, the 2017 vs 2010 McDonald criteria for DIS and DIS plus DIT had higher AUC values. Although these differences were more evident at month 36 than at month 60, overall accuracy of the 2017 vs 2010 McDonald criteria was constantly superior over time (Figure 3, data available from Dryad: Table e-3 https://doi.org/10.5281/zenodo.5566178). Finally, in CIS patients with a spinal cord syndrome, the 2017 vs 2010 McDonald criteria for DIS plus DIT had lower AUC values (Figure 3, data available from Dryad: Table e-3 https://doi.org/10.5281/zenodo.5566178).

When assessing diagnostic criteria performance according to age groups at M36, the 2017 modified DIS criteria with 3 instead of 1 periventricular lesions resulted in slightly lower sensitivity (0.76 [95% CI=0.57-0.89] vs 0.79 [95% CI=0.6-0.91]), but improved specificity (0.32 [95% CI=0.19-0.46] vs 0.18 [95% CI=0.08-0.32]) and accuracy (0.54 [95% CI=0.44-0.63] vs 0.49 [95% CI=0.40-0.57]) in CIS patients aged ≥45 years (Figure 4, data available from Dryad: Table e-4 https://doi.org/10.5281/zenodo.5566178). These results were confirmed when considering CDMS at

month 60 as the outcome, although these differences were marginal for DIS plus DIT (data available from Dryad: Figure e-1, Table e-4 https://doi.org/10.5281/zenodo.5566178).

Prediction of CDMS and EDSS≥3.0. Although the cumulative risk of CDMS development was similar for the different sets of criteria, the lack of fulfilment of the 2017 McDonald criteria was associated with a higher risk of non-converting to CDMS when compared to the 2010 McDonald criteria (Figure 2, Table 2, data available from Dryad: Table e-5 https://doi.org/10.5281/zenodo.5566178). The adjusted hazard ratios (aHRs) were higher for the 2017 compared with the 2010 McDonald criteria, for DIS only (aHR=3.25 [95% CI=2.43-4.34] and 2.45 [95% CI=1.91-3.15]) and for DIS plus DIT (aHR=3.59 [95% CI=2.71-4.76] and 2.68 [95% CI=2.15-3.35]).

The aHRs of both sets of criteria were not affected by disease onset type, whereas the interaction between the different criteria and treatment status was statistically significant (p ranging from <0.001 to 0.009), with aHRs being lower under vs without treatment (data available from Dryad: Table e-5 https://doi.org/10.5281/zenodo.5566178).

Cumulative risk of reaching EDSS≥3.0 and aHRs were similar for both sets of criteria (data available from Dryad: Figure e-2, Table e-6 https://doi.org/10.5281/zenodo.5566178).

Time to MS diagnosis. The median time to MS diagnosis was shorter with the 2017 compared with the 2010 McDonald and CDMS criteria (2017 McDonald criteria=3.2 months [95% CI=3.0-3.7]; 2017 McDonald criteria without OCBs=11.4 months [95% CI=7.3-12.7]; 2010 McDonald criteria=13.0 months [95% CI=12.0-14.5]; CDMS=58.5 months [95% CI=49.6-76.0]) (Figure 5).

Discussion

By evaluating a large, multicenter cohort of patients with typical CIS,[8] our study demonstrated that the 2017 McDonald criteria had higher sensitivity, lower specificity and overall similar accuracy in predicting conversion to CDMS than the 2010 McDonald criteria. This validation study extends previous studies,[9-12, 14] which are characterized by high between-study

variability performance of the different criteria, possibly due to the heterogeneity in the demographic and clinical characteristics of the patients evaluated, the MRI protocols used to define MRI criteria, lengths of the follow-ups, statistical approaches used and the influence of treatment.

We confirmed that the inclusion of OCB assessment[25] increased the sensitivity, reducing the specificity, while preserving the accuracy of the criteria. The decreased specificity derived from OCB evaluations, not done in all cases but requested according to local protocols, could raise some concerns regarding the risk of MS overdiagnosis.[26] Our analysis also showed that although the performance of the 2017 McDonald criteria seems slightly worse in the short term than the 2010 McDonald criteria, due to a lower specificity, the overall accuracy increases over time, thus the presence of OCBs contributes to correctly identify patients developing CDMS when longer follow-up are considered, underlying the relevance of longer evaluation to better evaluate the performance of the diagnostic criteria. The progressive improvement of criteria performance with time could be due to the effects of DMTs that, if started, may delay the occurrence of a second event, thus negatively influencing the specificity of the criteria when the follow-up is limited to a few years.

The performance of the 2017 and 2010 McDonald criteria was similar in CIS patients with optic neuritis. This is expected, also considering the limited relevance in distinguishing symptomatic from asymptomatic lesions in patients with optic neuritis, with the slight differences mainly due to the inclusion of OCB assessment. Accordingly, the evaluation of optic nerve involvement could improve the diagnostic accuracy in this type of onset.[6, 7, 27, 28]

Interestingly, considering especially the pointwise evaluation at month 36 more than that at month 60, and the overall accuracy over time, it seems clear that, compared to the 2010 McDonald criteria, the 2017 McDonald criteria showed a better performance in predicting CDMS development in CIS patients with a brainstem/cerebellar syndrome. The inclusion of infratentorial lesions irrespective of being symptomatic in patients with this type of CIS allows to capture the contribution of the infratentorial site, which is known to be clinically relevant, in respect to CDMS development[29, 30] and MS prognosis.[31, 32] In CIS patients with a spinal cord syndrome, the 2017

McDonald criteria had higher sensitivity, lower specificity and slightly lower accuracy than the 2010 McDonald criteria. This may seem counterintuitive, since the presence of spinal cord lesions facilitates MS diagnosis and predicts CDMS conversion as well as disability accumulation.[33, 34] A previous study showed that the presence of spinal cord lesions helped in predicting CDMS particularly in CIS patients presenting with a non-spinal symptomatology, with the highest risk (up to 14.4 times) found in patients who did not fulfill brain DIS criteria.[34]

Periventricular lesions increase with age, especially in subjects with cerebrovascular risk factors[35] and occur in several neurological conditions characterized by WM lesions and mimicking MS, including small-vessel disease,[36] and migraine.[37-39] In previous studies the requirement for three periventricular lesions improved specificity of the 2010[7, 40, 41] and 2017[12] McDonald criteria for DIS, especially in older CIS patients.[41] Additionally, a threshold of three or more periventricular lesions was found to be one of the most accurate predictors of CDMS conversion.[29, 42, 43] In line with this, we found that three periventricular lesions improved the specificity and accuracy of the 2017 McDonald DIS criteria, but slightly reduced sensitivity, especially in CIS patients aged ≥45 years. The main aim of the subsequent iterations of the McDonald criteria is to allow an earlier and more accurate MS diagnosis in people who present with a CIS, but it remains essential to reduce the risk of misdiagnosis due to a combination of increased sensitivity and reduced specificity, i.e. an oversimplification of MS criteria.[26] Among the proposed modifications, the evaluation of three periventricular lesions appears easily implementable in the clinical setting and may present a distinctive criterion to improve the specificity and the accuracy of the diagnostic criteria at least in older CIS patients who do not not satisfy DIT criteria - as suggested by a previous study -[41] and/or patients with comorbidities.

Survival analyses showed that the cumulative risk of CDMS development was similar in CIS patients fulfilling the criteria independently from the set of criteria investigated. Conversely, CIS patients who did not fulfil the 2017 McDonald criteria had a higher risk of not developing CDMS than patients who met the criteria. These findings, combined with those of a previous study,[9]

suggest that the 2017 McDonald criteria could be useful to identify CIS patients at low risk of developing a second relapse.

Of note, the significant interaction found between the different criteria and treatment status, with lower aHR found under treatment, further confirms that the use DMTs worsens the performance of the criteria and can explain, at least in part, differences in the performances of the criteria compared with previous reports.[18, 40, 44, 45] This hypothesis is also confirmed by the sensitivity analyses performed excluding all CIS patients starting a DMT before the occurrence of a second clinical event that showed an improvement of the specificity of both the 2017 and 2010 revisions of the McDonald criteria compared to the analyses who evaluated the whole cohort of CIS patients included in the study.

Regarding the prognostic value for disability accumulation, survival probability analyses showed that CIS patients fulfilling either the 2010 or the 2017 McDonald criteria had a significantly higher risk to reach an EDSS$\geq$3.0 than patients who did not meet the criteria, and that the two sets of criteria had similar performance, with a slight superiority of the 2017 McDonald criteria. This is in line with previous studies[45] and supports the relevance of infratentorial,[31, 32] spinal cord[33, 34, 46] and Gd-enhancing lesions[46] but also of CSF-specific OCBs[47-49] as relevant predictors of clinical disability.

Finally, consistent with previous studies[9-11, 13, 50] our results confirmed that, with the 2017 McDonald criteria, more CIS patients reached a diagnosis of MS already after the first clinical manifestation, with a single MRI scan. In our study, the 2017 McDonald criteria shortened the median time to MS diagnosis by 4.6 years compared with the clinical criterion alone and by 10 months compared with the 2010 McDonald criteria. This has substantial implications in the management of CIS patients. An earlier MS diagnosis may facilitate earlier treatment, with beneficial effects on MS prognosis, since therapies have demonstrated to reduce the risk of CDMS conversion roughly by 30-55% and could exert long-term benefits to CIS patients.{Forster, 2019 5} Further studies are still needed to demonstrate that treatment start after clinical onset instead of

waiting until a second clinical relapse may also positively limit long-term disability progression.[5] Clearly, this aspect could be negatively counterbalanced by the risk of misdiagnosis.[26] It should be noted that the apparent lower specificity of the 2017 McDonald criteria could reflect earlier treatment with a lower chance of developing DIT – calling into question the appropriateness of the CDMS outcome. It should be also noted that, although quite lower at month 36, specificity of the 2017 revisions of the McDonald criteria increased at month 60 (0.46) and further improved at month 120 (0.53), approaching that of the 2010 McDonald criteria (0.62), but still remaining lower.

Nevertheless, the 2017 McDonald criteria must be applied in the right context, after the exclusion of differential diagnoses, in patients who present with symptoms and signs which are typical of MS[26] and with the proper assessment of lesions on MRI.[21] In fact, a lower specificity may determine a higher prevalence of MS misdiagnosis and unnecessary initiation of DMT may be associated with unnecessary risks and morbidity in misdiagnosed patients.[26]

This study has some limitations. First, the analyses have been performed retrospectively. Despite this, all CIS patients included are part of ongoing prospective studies performed by each participating center allowing us to have long follow-up to better investigate the performance of the different sets of criteria. Second, CIS patients were collected from highly specialized centers, thus possibly selecting patients with higher lesion number and risk of CDMS conversion (52% in our cohort). However, the multicenter setting with MRI exams acquired with both 1.5 and 3.0 Tesla and different sequence parameters, allowed us to evaluate the MRI criteria in a cohort of CIS patients that should be representative of the European clinical scenario. Third, cortical lesion and OCB assessment were not available for all patients. However, cortical lesion evaluation was found to not significantly contribute to DIS criteria performance,[7] whereas OCB assessment was missing only in a minority (2.2%) of CIS patients not fulfilling DIT criteria. Fourth, no formal statistical testing have been performed between the performances of the 2017 and 2010 revisions to the McDonald criteria and no adjustment for multiplicity was applied. Accordingly, our observations - particularly

the sub-group analyses - should be regarded as exploratory and require replication in an independent dataset.

Overall, this study confirms that the 2017 McDonald criteria have higher sensitivity, lower specificity and overall similar accuracy compared with the 2010 McDonald criteria in predicting CDMS development independently from the type of clinical onset. These criteria simplify the clinical use of MRI criteria without reducing accuracy and allow an earlier diagnosis of MS. Three periventricular lesions should be considered in future revisions of the McDonald criteria to improve the specificity and the accuracy in older CIS patients.

Appendix 1. Authors

Name	Location	Contribution
Massimo Filippi, MD	San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy	study concept, analysis and interpretation of the data, drafting/revising the manuscript. He also acted as study supervisor.
Paolo Preziosa, MD, PhD	San Raffaele Scientific Institute, Milan, Italy	study concept, analysis and interpretation of the data, drafting/revising the manuscript.
Alessandro Meani, MsC	San Raffaele Scientific Institute, Milan, Italy	analysis and interpretation of the data, statistical analysis, and drafting/revising the manuscript.
Gloria Dalla Costa, MD	San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy	acquisition of the data and drafting/revising the manuscript
Sarlota Mesaros, MD, PhD	University of Belgrade, Belgrade, Serbia	acquisition of the data and drafting/revising the manuscript
Jelena Drulovic, MD	University of Belgrade, Belgrade, Serbia	acquisition of the data and drafting/revising the manuscript
Jovana Ivanovic, MD	University of Belgrade, Belgrade, Serbia	acquisition of the data and drafting/revising the manuscript
Alex Rovira, MD	Hospital Universitari Vall d'Hebron, Barcelona, Spain	acquisition of the data and drafting/revising the manuscript
Mar Tintorè, MD	Hospital Universitari Vall d'Hebron, Barcelona, Spain	acquisition of the data and drafting/revising the manuscript
Xavier Montalban, MD	Hospital Universitari Vall d'Hebron, Barcelona, Spain	acquisition of the data and drafting/revising the manuscript
Olga Ciccarelli, MD	UCL Institute of Neurology, London, UK	acquisition of the data and drafting/revising the manuscript
Wallace Brownlee, MD	UCL Institute of Neurology, London, UK	acquisition of the data and drafting/revising the manuscript
Katherine Miszkiel, MD	UCL Institute of Neurology, London, UK	acquisition of the data and drafting/revising the manuscript
Christian Enzinger, MD	Medical University of Graz, Graz, Austria	acquisition of the data and drafting/revising the manuscript
Michael Khalil, MD, PhD	Medical University of Graz, Graz, Austria	acquisition of the data and drafting/revising the manuscript
Frederik Barkhof, MD, PhD	Amsterdam UMC, location VUmc, Amsterdam, The Netherlands; University College London, London, UK.	acquisition of the data and drafting/revising the manuscript
Eva M.M. Strijbis, MD, PhD	Amsterdam UMC, location VUmc, Amsterdam, The Netherlands	acquisition of the data and drafting/revising the manuscript
Jette L. Frederiksen, MD, DMSci	Rigshospitalet - Glostrup, University of Copenhagen, Denmark	acquisition of the data and drafting/revising the manuscript
Stig Cramer, MD	Rigshospitalet Glostrup, Copenhagen University Hospital;	acquisition of the data and drafting/revising the manuscript

	Hvidovre Hospital, Hvidovre, Denmark.	
Enrico Fainardi, MD	University of Florence, Florence, Italy	acquisition of the data and drafting/revising the manuscript
Maria Pia Amato, MD	University of Florence, Florence, Italy; IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy	acquisition of the data and drafting/revising the manuscript
Claudio Gasperini, MD	San Camillo Forlanini Hospital, Rome, Italy	acquisition of the data and drafting/revising the manuscript
Serena Ruggieri, MD	San Camillo Forlanini Hospital, Rome, Italy	acquisition of the data and drafting/revising the manuscript
Vittorio Martinelli, MD	San Raffaele Scientific Institute, Milan, Italy	acquisition of the data and drafting/revising the manuscript
Giancarlo Comi, MD	Vita-Salute San Raffaele University, Milan, Italy	acquisition of the data and drafting/revising the manuscript
Maria A. Rocca, MD	San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy	study concept, analysis and interpretation of the data, drafting/revising the manuscript.

Appendix 2. Coinvestigators

Name	Location	Role	Contribution
Nicola De Stefano, MD	University of Siena, Siena, Italy	Co-investigator	Study design and interpretation of the data
Jacqueline Palace, MD	University of Oxford, Oxford, UK	Co-investigator	Study design and interpretation of the data
Ludwig Kappos, MD	University of Basel, Basel, Switzerland	Co-investigator	Study design and interpretation of the data
Jaume Sastre-Garriga, MD	Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain	Co-investigator	Study design and interpretation of the data
Tarek Yousry, MD	Queen Square MS Centre, UCL Institute of Neurology, London, UK	Co-investigator	Study design and interpretation of the data

References

1.   McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-127.

2.   Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840-846.

3.   Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.

4.   Brownlee WJ, Swanton JK, Altmann DR, Ciccarelli O, Miller DH. Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria. J Neurol Neurosurg Psychiatry 2015;86:584-585.

5.   Forster M, Graf J, Mares J, Aktas O, Hartung HP, Kremer D. Drug Treatment of Clinically Isolated Syndrome. CNS Drugs 2019;33:659-676.

6.   Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. The Lancet Neurology 2016;15:292-303.

7.   Filippi M, Preziosa P, Meani A, et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. The Lancet Neurology 2018;17:133-142.

8.   Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology 2018;17:162-173.

9.   van der Vuurst de Vries RM, Mescheriakova JY, Wong YYM, et al. Application of the 2017 Revised McDonald Criteria for Multiple Sclerosis to Patients With a Typical Clinically Isolated Syndrome. JAMA Neurol 2018;75:1392-1398.

10.   Hyun JW, Kim W, Huh SY, et al. Application of the 2017 McDonald diagnostic criteria for multiple sclerosis in Korean patients with clinically isolated syndrome. Mult Scler 2019;25:1488-1495.

11.   Habek M, Pavicic T, Ruska B, et al. Establishing the diagnosis of multiple sclerosis in Croatian patients with clinically isolated syndrome: 2010 versus 2017 McDonald criteria. Mult Scler Relat Disord 2018;25:99-103.

12.   Miclea A, Salmen A, Wiest R, et al. Prediction of conversion to multiple sclerosis using the 2017 McDonald and 2016 MAGNIMS criteria in patients with clinically isolated syndrome: a retrospective single-centre study. Ther Adv Neurol Disord 2019;12:1756286419835652.

13.   Lee DH, Peschke M, Utz KS, Linker RA. Diagnostic value of the 2017 McDonald criteria in patients with a first demyelinating event suggestive of relapsing-remitting multiple sclerosis. Eur J Neurol 2019;26:540-545.

14.   Souissi A, Mrabet S, Nasri A, et al. Multiple sclerosis 2017 McDonald criteria are also relevant for Tunisians. Mult Scler Relat Disord 2020;43:102161.

15.   Fadda G, Brown RA, Longoni G, et al. MRI and laboratory features and the performance of international criteria in the diagnosis of multiple sclerosis in children and adolescents: a prospective cohort study. Lancet Child Adolesc Health 2018;2:191-204.

16.   Hacohen Y, Brownlee W, Mankad K, et al. Improved performance of the 2017 McDonald criteria for diagnosis of multiple sclerosis in children in a real-life cohort. Mult Scler 2020;26:1372-1380.

17.   Wong YYM, de Mol CL, van der Vuurst de Vries RM, et al. Real-world validation of the 2017 McDonald criteria for pediatric MS. Neurol Neuroimmunol Neuroinflamm 2019;6:e528.

18.   Swanton JK, Rovira A, Tintore M, et al. MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study. The Lancet Neurology 2007;6:677-686.

19.   Miller D, Barkhof F, Montalban X, Thompson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. The Lancet Neurology 2005;4:281-288.

20.   Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. Lancet 2017;389:1336-1346.

21.   Filippi M, Preziosa P, Banwell BL, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain 2019;142:1858-1875.

22.   Hung H, Chiang C. Estimation models for time-dependent AUC with survival data. Canadian Journal of Statistics 2010;38:8-26.

23.   Efron B. Better Bootstrap Confidence Intervals. Journal of the American Statistical Association 1987;82:171-185.

24.   Glidden DV, Vittinghoff E. Modelling clustered survival data from multicentre clinical trials. Stat Med 2004;23:369-388.

25.   Arrambide G, Tintore M, Espejo C, et al. The value of oligoclonal bands in the multiple sclerosis diagnostic criteria. Brain 2018;141:1075-1084.

26.   Solomon AJ, Naismith RT, Cross AH. Misdiagnosis of multiple sclerosis: Impact of the 2017 McDonald criteria on clinical practice. Neurology 2019;92:26-33.

27.   Brownlee WJ, Miszkiel KA, Tur C, Barkhof F, Miller DH, Ciccarelli O. Inclusion of optic nerve involvement in dissemination in space criteria for multiple sclerosis. Neurology 2018;91:e1130-e1134.

28.   Vidal-Jordana A, Rovira A, Arrambide G, et al. Optic Nerve Topography in Multiple Sclerosis Diagnosis: The Utility of Visual Evoked Potentials. Neurology 2021;96:e482-e490.

29.   Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997;120 (Pt 11):2059-2069.

30.   Filippi M, Rocca MA, Calabrese M, et al. Intracortical lesions: relevance for new MRI diagnostic criteria for multiple sclerosis. Neurology 2010;75:1988-1994.

31.   Minneboo A, Barkhof F, Polman CH, Uitdehaag BM, Knol DL, Castelijns JA. Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. Arch Neurol 2004;61:217-221.

32.   Tintore M, Rovira A, Arrambide G, et al. Brainstem lesions in clinically isolated syndromes. Neurology 2010;75:1933-1938.

33.   Arrambide G, Rovira A, Sastre-Garriga J, et al. Spinal cord lesions: A modest contributor to diagnosis in clinically isolated syndromes but a relevant prognostic factor. Mult Scler 2018;24:301-312.

34.   Sombekke MH, Wattjes MP, Balk LJ, et al. Spinal cord lesions in patients with clinically isolated syndrome: a powerful tool in diagnosis and prognosis. Neurology 2013;80:69-75.

35.   Nyquist PA, Bilgel M, Gottesman R, et al. Age differences in periventricular and deep white matter lesions. Neurobiol Aging 2015;36:1653-1658.

36.   Del Brutto OH, Mera RM, Costa AF, Silva P, Del Brutto VJ. Dawson Fingers in Older Adults with Cerebral Small Vessel Disease: A Population Study. Eur Neurol 2020;83:421-425.

37.   Absinta M, Rocca MA, Colombo B, et al. Patients with migraine do not have MRI-visible cortical lesions. Journal of neurology 2012;259:2695-2698.

38.   Lapucci C, Saitta L, Bommarito G, et al. How much do periventricular lesions assist in distinguishing migraine with aura from CIS? Neurology 2019;92:e1739-e1744.

39.   Liu S, Kullnat J, Bourdette D, et al. Prevalence of brain magnetic resonance imaging meeting Barkhof and McDonald criteria for dissemination in space among headache patients. Mult Scler 2013;19:1101-1105.

40.   Brownlee WJ, Miszkiel KA, Altmann DR, Ciccarelli O, Miller DH. Periventricular lesions and MS diagnostic criteria in young adults with typical clinically isolated syndromes. Mult Scler 2017;23:1031-1034.

41.   Arrambide G, Tintore M, Auger C, et al. Lesion topographies in multiple sclerosis diagnosis: A reappraisal. Neurology 2017;89:2351-2356.
42.   Ruet A, Deloire MS, Ouallet JC, Molinier S, Brochet B. Predictive factors for multiple sclerosis in patients with clinically isolated spinal cord syndrome. Mult Scler 2011;17:312-318.
43.   Ruet A, Arrambide G, Brochet B, et al. Early predictors of multiple sclerosis after a typical clinically isolated syndrome. Mult Scler 2014;20:1721-1726.
44.   Brownlee WJ, Swanton JK, Miszkiel KA, Miller DH, Ciccarelli O. Should the symptomatic region be included in dissemination in space in MRI criteria for MS? Neurology 2016;87:680-683.
45.   Tintore M, Otero-Romero S, Rio J, et al. Contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. Neurology 2016;87:1368-1374.
46.   Brownlee WJ, Altmann DR, Prados F, et al. Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. Brain 2019;142:2276-2287.
47.   Dobson R, Ramagopalan S, Davis A, Giovannoni G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. J Neurol Neurosurg Psychiatry 2013;84:909-914.
48.   Tintore M, Rovira A, Rio J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015;138:1863-1874.
49.   Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: A large multicentre study. Mult Scler 2015;21:1013-1024.
50.   Gaetani L, Prosperini L, Mancini A, et al. 2017 revisions of McDonald criteria shorten the time to diagnosis of multiple sclerosis in clinically isolated syndromes. Journal of neurology 2018;265:2684-2687.

Table 1. Main baseline demographic, clinical, and MRI findings from the final cohort of CIS patients.

		All cases (n=785)
Demographic and clinical data		
Number (%) of Men / Women		255 (32%) / 530 (68%)
Median age at onset (IQR) [years]		32.0 (26.0-39.0)
Median time since onset at baseline MRI (IQR) [months]		1.9 (0.8-3.0)
Median EDSS at baseline (IQR)		1.5 (1.0-2.0)
Clinical presenting symptom(s) (%): Monofocal		745 (95%)
• Optic neuritis		• 286/745 (38%)
• Brainstem/cerebellar syndrome		• 169/745 (23%)
• Spinal cord syndrome		• 239/745 (32%)
• Hemispheric syndrome		• 51/745 (7%)
Multifocal		40 (5%)
Number (%) of patients	With CSF analysis	670 (85%)
	With OCBs	459/670 (69%)
	Receiving treatment at FU	437 (56%)
	• After the first clinical episode	• 235/437 (54%)
	• After the second clinical episode	• 202/437 (46%)
	CDMS at FU (%)	406 (52%)
Median time to CDMS in converters (IQR) [months]		13.3 (5.2-31.5)
Median FU duration in all patients (IQR) [months]		69.1 (39.8-112.1)
Median FU duration in non-converters (IQR) [months]		54.0 (34.0-86.5)
Number (%) of patients reaching EDSS≥3.0 at FU		101 (13%)
MRI data		
MRI field strength (%): 1.5 T / 3.0 T		645 (82%) / 140 (18%)
Baseline number (%) of patients with lesions [brain and cord]		731 (93%)
Number (%) of patients with DIR		337 (43%)
Median lesion number (IQR) [brain and cord]		9 (3-19)

Median time to FU MRI (IQR) [months]		12.1 (7.7-14.3)
MRI criteria		
Baseline number (%) of patients with	≥ 1 PV lesion	590 (75%)
	≥ 1 JC lesion	502 (64%)
	≥ 1 CL	116/337 (34%)
	≥ 1 CL/JC	519 (66%)
	≥ 1 PF lesion	358 (46%)
	≥ 1 SC lesion	387 (49%)
	≥ 1 Gd-enhancing lesion	320 (41%)
Number (%) of patients with ≥ 1 new T2/Gd-enhancing lesion at FU MRI		386 (49%)

Abbreviations: CDMS=clinically definite multiple sclerosis; CIS=clinically isolated syndrome;

CL=cortical lesion; CSF=cerebrospinal fluid; DIR=double inversion recovery; EDSS=Expanded

Disability Status Scale; FU=follow-up; Gd=gadolinium; IQR=interquartile range; JC=juxtacortical;

MRI=magnetic resonance imaging; OCBs=oligoclonal bands; PF=posterior fossa;

PV=periventricular; SC=spinal cord; T=tesla.

Table 2. Performance of the different combined MRI criteria for DIS, DIT and DIS plus DIT also according to the evaluation of OCBs for development of CDMS in the final cohort (n=785) at 36 and 60 months' follow-up.

Criteria	Timepoint	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS only						
2010 McDonald[3]	M36	0.78 (0.73-0.82)	0.38 (0.33-0.43)	0.58 (0.55-0.62)	0.48 (0.44-0.53)	0.70 (0.64-0.76)
	M60	0.78 (0.74-0.82)	0.47 (0.40-0.53)	0.62 (0.58-0.66)	0.60 (0.55-0.65)	0.67 (0.61-0.73)
2017 McDonald[8]	M36	0.86 (0.82-0.90)	0.32 (0.28-0.37)	0.59 (0.56-0.62)	0.49 (0.44-0.53)	0.76 (0.69-0.82)
	M60	0.85 (0.81-0.88)	0.38 (0.31-0.45)	0.61 (0.58-0.65)	0.59 (0.54-0.63)	0.71 (0.64-0.78)
DIT only						
2010 McDonald[3]	M36	0.77 (0.72-0.82)	0.53 (0.47-0.58)	0.65 (0.61-0.68)	0.55 (0.50-0.59)	0.76 (0.71-0.81)
	M60	0.75 (0.71-0.80)	0.59 (0.52-0.65)	0.67 (0.63-0.71)	0.65 (0.6-0.7)	0.70 (0.64-0.75)
2017 McDonald[8]	M36	0.95 (0.92-0.97)	0.20 (0.16-0.25)	0.58 (0.55-0.60)	0.48 (0.44-0.52)	0.83 (0.75-0.90)

	M60	0.94 (0.91-0.97)	0.28 (0.22-0.35)	0.61 (0.58-0.65)	0.59 (0.54-0.63)	0.82 (0.73-0.89)
2017 McDonald without OCBs[8]	M36	0.80 (0.76-0.85)	0.47 (0.41-0.52)	0.63 (0.60-0.67)	0.53 (0.48-0.57)	0.76 (0.71-0.81)
	M60	0.79 (0.75-0.84)	0.53 (0.46-0.60)	0.66 (0.62-0.70)	0.64 (0.58-0.68)	0.71 (0.65-0.77)
DIS plus DIT						
2010 McDonald[3]	M36	0.66 (0.61-0.71)	0.60 (0.55-0.65)	0.63 (0.59-0.67)	0.55 (0.50-0.60)	0.71 (0.66-0.75)
	M60	0.65 (0.59-0.69)	0.66 (0.59-0.72)	0.65 (0.61-0.69)	0.66 (0.60-0.72)	0.64 (0.59-0.69)
2017 McDonald[8]	M36	0.83 (0.79-0.87)	0.39 (0.34-0.44)	0.61 (0.58-0.64)	0.51 (0.46-0.55)	0.76 (0.70-0.81)
	M60	0.82 (0.78-0.86)	0.46 (0.40-0.53)	0.64 (0.60-0.68)	0.61 (0.56-0.66)	0.71 (0.65-0.77)
2017 McDonald without OCBs[8]	M36	0.74 (0.69-0.78)	0.54 (0.49-0.59)	0.64 (0.60-0.67)	0.54 (0.49-0.59)	0.73 (0.68-0.78)
	M60	0.72 (0.67-0.76)	0.59 (0.53-0.66)	0.66 (0.62-0.70)	0.65 (0.59-0.7)	0.67 (0.61-0.73)

Abbreviations: AUC=area under the curve; CDMS=clinically definite MS; CI=confidence interval; DIS=dissemination in space; DIT=dissemination in time; M=month; MRI=magnetic resonance imaging; NPV=negative predictive value; OCBs=oligoclonal bands; PPV=positive predictive value.

Figure legends

Figure 1. Study flow chart. See text for further details. Abbreviations: CIS=clinically isolated syndrome; MRI=magnetic resonance imaging.
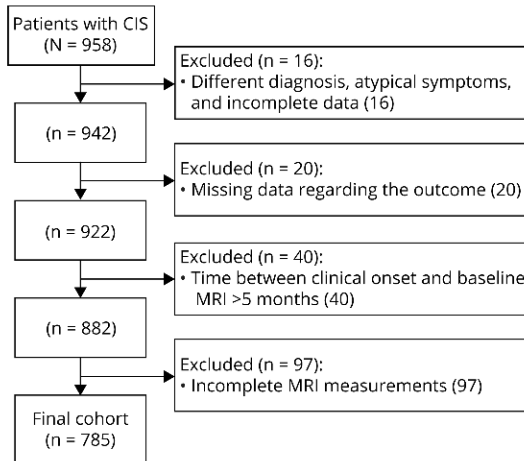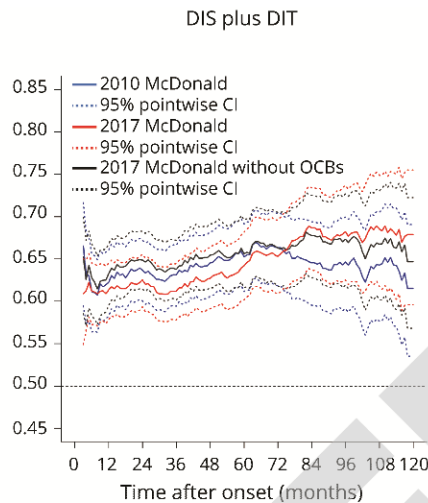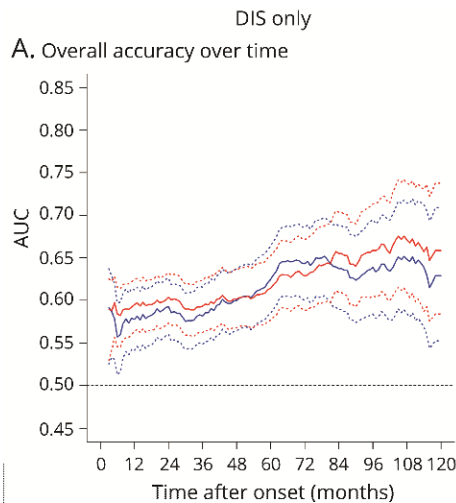
Figure 2. Overall accuracy over time and survival probability estimates of not developing CDMS according to the different sets of criteria investigated. (A) Overall accuracy of the 2010 McDonald (blue line) and 2017 McDonald criteria (red line), also without OCBs assessment (gray line), determined by the AUC over time, up to 10 years, from disease onset, to the development of CDMS, considering DIS only or DIS plus DIT. (b) Kaplan-Meier curves showing the survival probability estimates of not developing CDMS up to 10 years from disease onset considering DIS only or DIS plus DIT according to the 2010 McDonald and 2017 McDonald criteria, with or without OCBs assessment. aHRs with their corresponding 95% CI obtained from extended Cox regression models using time to CDMS as the outcome are also shown.

Abbreviations: aHR=adjusted hazard ratios; AUC=area under the curve; CDMS=clinically definite MS; CI=confidence interval; DIS=dissemination in space; DIT=dissemination in time; OCBs=oligoclonal bands.

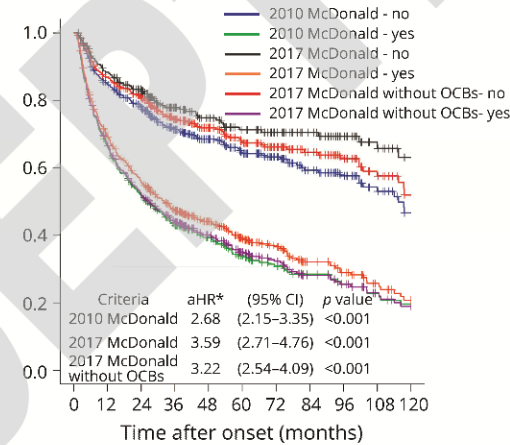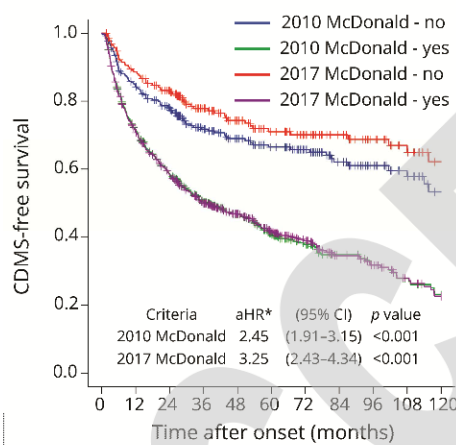*=adjusted for age, sex, centre, treatment, and type of onset.

DIS only

DIS plus DIT

A. Overall accuracy over time

AUC

0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45

0 12 24 36 48 60 72 84 96 108 120
Time after onset (months)

0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45

— 2010 McDonald
···· 95% pointwise CI
— 2017 McDonald
···· 95% pointwise CI
— 2017 McDonald without OCBs
···· 95% pointwise CI

0 12 24 36 48 60 72 84 96 108 120
Time after onset (months)

Number at risk:

Converters	0	189	268	320	339	362	370	380	386	393	400
Survivors	785	578	474	361	277	214	170	122	96	65	45
Censored	0	18	43	104	169	209	245	283	303	327	340

0	189	268	320	339	362	370	380	386	393	400	
785	578	474	361	277	214	170	122	96	65	45	
0	18	43	104	169	209	245	283	303	327	340	

B. Survival probability estimates of not developing CDMS

CDMS-free survival

1.0
0.8
0.6
0.4
0.2
0.0

— 2010 McDonald - no
— 2010 McDonald - yes
— 2017 McDonald - no
— 2017 McDonald - yes

Criteria	aHR*	(95% CI)	p value
2010 McDonald	2.45	(1.91–3.15)	<0.001
2017 McDonald	3.25	(2.43–4.34)	<0.001

0 12 24 36 48 60 72 84 96 108 120
Time after onset (months)

1.0
0.8
0.6
0.4
0.2
0.0

— 2010 McDonald - no
— 2010 McDonald - yes
— 2017 McDonald - no
— 2017 McDonald - yes
— 2017 McDonald without OCBs- no
— 2017 McDonald without OCBs- yes

Criteria	aHR*	(95% CI)	p value
2010 McDonald	2.68	(2.15–3.35)	<0.001
2017 McDonald	3.59	(2.71–4.76)	<0.001
2017 McDonald without OCBs	3.22	(2.54–4.09)	<0.001

0 12 24 36 48 60 72 84 96 108 120
Time after onset (months)

Number at risk:

264 (0)	215 (8)	187 (21)	138 (56)	117 (72)	100 (85)	85 (99)	61 (119)	48 (131)	34 (143)	22 (153)
521 (0)	363 (10)	287 (22)	223 (48)	160 (97)	114 (124)	85 (146)	61 (164)	48 (172)	31 (184)	23 (187)
213 (0)	183 (6)	160 (18)	117 (52)	97 (67)	81 (79)	69 (90)	55 (104)	44 (114)	32 (124)	21 (134)
572 (0)	395 (12)	314 (25)	244 (52)	180 (102)	133 (130)	101 (155)	67 (179)	52 (189)	33 (203)	24 (206)

Number at risk:

405 (0)	328 (16)	282 (37)	217 (80)	176 (113)	141 (138)	115 (162)	80 (191)	63 (206)	43 (222)	28 (233)
380 (0)	250 (2)	192 (6)	144 (24)	101 (56)	73 (71)	55 (83)	42 (92)	33 (97)	22 (105)	17 (107)
252 (0)	216 (7)	187 (24)	136 (64)	114 (81)	95 (95)	79 (110)	64 (125)	49 (139)	34 (152)	23 (162)
516 (0)	348 (11)	274 (19)	213 (40)	152 (88)	110 (114)	84 (134)	54 (155)	43 (161)	28 (172)	20 (175)
354 (0)	294 (14)	256 (33)	195 (75)	160 (104)	127 (128)	103 (150)	77 (174)	60 (189)	41 (204)	27 (215)
431 (0)	284 (4)	218 (10)	166 (29)	117 (65)	87 (81)	67 (95)	45 (109)	36 (114)	24 (123)	18 (125)

Figure 3. Overall accuracy over time according to the different sets of criteria investigated in CIS patients with different types of onset. Overall accuracy of the 2010 McDonald (blue line) and 2017 McDonald criteria, with (red line), also without OCBs assessment (gray line), determined by the AUC over time, up to 10 years, from disease onset, to the development of CDMS, considering DIS only, DIT only or DIS plus DIT in CIS patients with (A) optic neuritis, (B) brainstem/cerebellar syndrome, or (C) spinal cord syndrome as type of onset. See text for further details.

Abbreviations: AUC=area under the curve; CI=confidence interval; DIS=dissemination in space; DIT=dissemination in time; OCBs=oligoclonal bands.

DIS only | DIS plus DIT

A. Optic neuritis
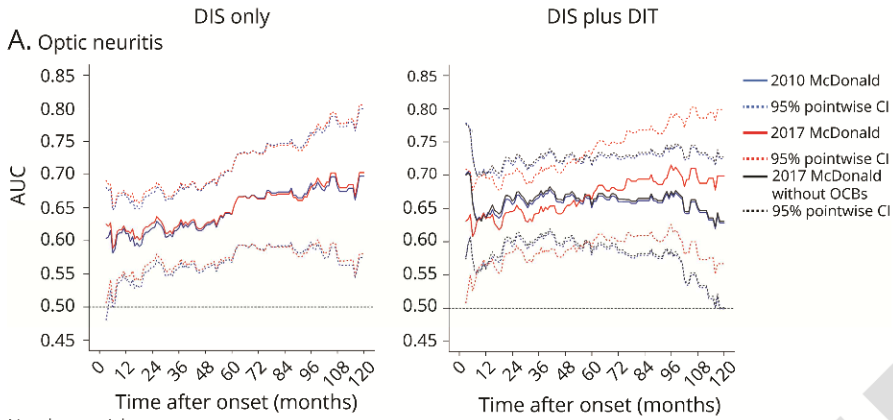
Number at risk:
Converters   0   59   94 115 122 130 132 135 138 142 145   0   59   94 115 122 130 132 135 138 142 145
Survivors 286 222 178 133 103 78 62 51 42 27 21   286 222 178 133 103 78 62 51 42 27 21
Censored   0   5   14 38 61 78 92 100 106 117 120   0   5   14 38 61 78 92 100 106 117 120

B. Brainstem/cerebellar syndrome
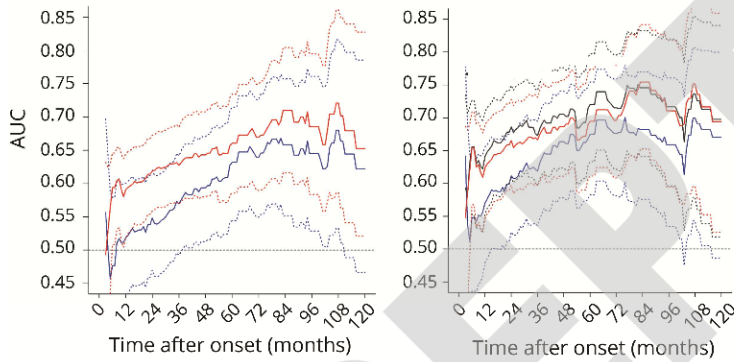
Number at risk:
Converters   0   39   51 62 65 71 72 75 75 77 77   0   39   51 62 65 71 72 75 75 77 77
Survivors 169 127 108 82 64 51 44 31 23 14 11   169 127 108 82 64 51 44 31 23 14 11
Censored   0   3   10 25 40 47 53 63 71 78 81   0   3   10 25 40 47 53 63 71 78 81

C. Spinal cord syndrome
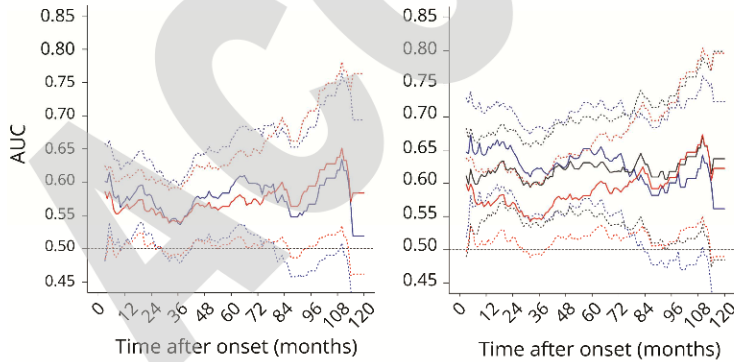
Number at risk:
Converters   0   62   87 103 107 115 119 122 124 125 127   0   62   87 103 107 115 119 122 124 125 127
Survivors 239 168 139 109 81 65 48 30 23 18 11   239 168 139 109 81 65 48 30 23 18 11
Censored   0   9   13 27 51 59 72 87 92 96 101   0   9   13 27 51 59 72 87 92 96 101

Figure 4. Overall accuracy over time of DIS criteria according to age at onset and to 3 instead of 1 periventricular lesions. Overall accuracy of the 2010 McDonald (blue line), 2017 McDonald criteria, with 1 (red line) or 3 (gray line) periventricular lesions, determined by the AUC over time, up to 10 years, from disease onset, to the development of CDMS, considering DIS only in CIS patients aged (A) <25 years, (B) 25-34 years, (C) 35-44 years or ≥45 years at onset. See text for further details.
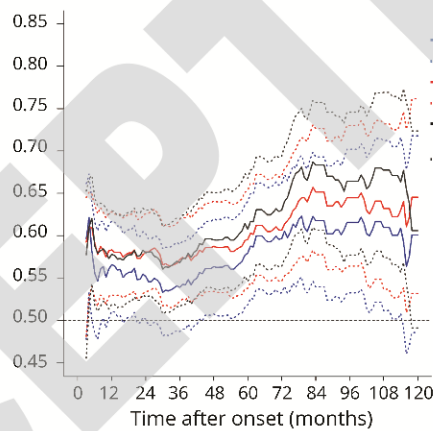
Abbreviations: AUC=area under the curve; CDMS=clinically definite MS; CI=confidence interval; DIS=dissemination in space.

Figure 5. Time to MS diagnosis. Median time to MS diagnosis according to the different criteria investigated estimated using Kaplan-Meier survival curves: CDMS (green line), 2010 McDonald (blue line) and 2017 McDonald criteria (red line), also without OCBs (gray line) assessment. Abbreviations: CDMS=clinically definite MS; CI=confidence interval; MS=multiple sclerosis; OCBs=oligoclonal bands.