Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

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The 2010 McDonald criteria for the diagnosis of multiple sclerosis are widely used in research and clinical practice. Scientific advances in the past 7 years suggest that they might no longer provide the most up-to-date guidance for clinicians and researchers. The International Panel on Diagnosis of Multiple Sclerosis reviewed the 2010 McDonald criteria and recommended revisions. The 2017 McDonald criteria continue to apply primarily to patients experiencing a typical clinically isolated syndrome, define what is needed to fulfil dissemination in time and space of lesions in the CNS, and stress the need for no better explanation for the presentation. The following changes were made: in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space, the presence of CSF-specific oligoclonal bands allows a diagnosis of multiple sclerosis; symptomatic lesions can be used to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate dissemination in space. Research to further refine the criteria should focus on optic nerve involvement, validation in diverse populations, and incorporation of advanced imaging, neurophysiological, and body fluid markers.

Lancet Neurol 2017

Published Online
December 21, 2017
http://dx.doi.org/10.1016/S1474-4422(17)30470-2

See Online/Comment
http://dx.doi.org/10.1016/S1474-4422(17)30461-1

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Introduction

Diagnostic criteria for multiple sclerosis combining clinical, imaging, and laboratory evidence have evolved over time, with the most recent being the 2010 McDonald criteria from the International Panel on Diagnosis of Multiple Sclerosis (referred to as the Panel from here on).[1–5] The increasing incorporation of paraclinical assessments, especially imaging, to supplement clinical findings has allowed earlier, more sensitive, and more specific diagnosis.[6] New data, emerging technology, and evolving consensus necessitate a periodic re-examination of diagnostic criteria and their usefulness. The Panel reconvened under the auspices of the International Advisory Committee on Clinical Trials in Multiple Sclerosis (sponsored by the US National Multiple Sclerosis Society and the European Committee for Treatment and Research in Multiple Sclerosis) for two meetings (Nov 2–5, 2016, in Philadelphia, PA, USA, and May 20–21, 2017, in Berlin, Germany). In this Position Paper, we discuss issues related to misdiagnosis, differential diagnosis, and appropriate application of the McDonald criteria, with a particular emphasis on diagnosis in diverse populations and in patients with atypical presentations. With the 2017 McDonald criteria, we present recommendations concerning the diagnostic process for multiple sclerosis, make specific revisions to the 2010 McDonald criteria, and outline research that should be done to inform future refinements of the criteria.

Rationale and methods for the 2017 revisions

The Panel meetings to consider revisions to the 2010 McDonald criteria were motivated by new data in several areas: the performance of the 2010 McDonald criteria in diverse populations; the distinction between multiple sclerosis and other diseases with potentially overlapping clinical and imaging features, such as neuromyelitis optica spectrum disorders (NMOSDs); challenges in making the diagnosis in individuals with presentations other than a typical clinically isolated syndrome; the frequency and consequences of misdiagnosis; and CSF and other paraclinical tests that could be used to diagnose multiple sclerosis. The meetings were further informed by the proposed 2016 revisions of MRI criteria for the diagnosis of multiple sclerosis by the European Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) network.[7]

The 2017 Panel membership (ie, the authors of this Position Paper) was expanded considerably compared with previous panels to include broader representation from different geographical regions and additional expertise in clinical, imaging, and laboratory aspects of multiple sclerosis diagnosis, while maintaining some members of previous panels. At the meetings, Panel members reviewed past criteria and made brief presentations covering proposed revisions. Relevant published and unpublished data guided subsequent group discussion and agreement on proposed revisions. Consensus was reached on all points.

The Panel agreed that the 2010 McDonald criteria performed well based on their use in clinical and research settings and in regulatory approval of several disease-modifying therapies for multiple sclerosis; major changes were not anticipated. Rather, the 2017 McDonald criteria are intended to simplify or clarify components of the 2010 McDonald criteria (panels 1, 2), to facilitate earlier diagnosis when multiple sclerosis is likely but not diagnosable with the 2010 McDonald criteria, and to preserve the specificity of the 2010 McDonald criteria and promote their appropriate application to reduce the

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Panel 1: Glossary

Attack
Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonyms. See clinically isolated syndrome and relapse for descriptions.

Clinically isolated syndrome
A monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection; similar to a typical multiple sclerosis relapse (attack and exacerbation) but in a patient not known to have multiple sclerosis.[8–10] Thus, if the patient is subsequently diagnosed with multiple sclerosis (by fulfilling dissemination in space and time, and ruling out other diagnoses), the clinically isolated syndrome was that patient's first attack. A clinically isolated syndrome can be monofocal (reflecting pathology in a single location) or multifocal; the specific manifestations of a clinically isolated syndrome depend on the anatomical location (or locations) of the pathology. Typical presentations include unilateral optic neuritis, focal supratentorial syndrome, focal brainstem or cerebellar syndrome, or partial myelopathy; examples of atypical presentations include bilateral optic neuritis, complete ophthalmoplegia, complete myelopathy, encephalopathy, headache, alteration of consciousness, meningismus, or isolated fatigue.[6]

Cortical MRI lesions
Lesions within the cerebral cortex. Typically, special MRI techniques such as double inversion recovery, phase-sensitive inversion recovery, and magnetisation-prepared rapid acquisition with gradient echo sequences are required to visualise these lesions.[7,11,12] The lesions detected by these techniques are primarily of the leukocortical type; subpial lesions are rarely detected. Care is needed to distinguish potential cortical lesions from neuroimaging artefacts.[7]

Dissemination in space
The development of lesions in distinct anatomical locations within the CNS—ie, indicating a multifocal CNS process.

Dissemination in time
The development or appearance of new CNS lesions over time.

Exacerbation
Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonyms. See clinically isolated syndrome and relapse for descriptions.

Infratentorial MRI lesion
A T2-hyperintense lesion in the brainstem (typically near the surface), cerebellar peduncles, or cerebellum.[6]

Juxtacortical MRI lesion
A T2-hyperintense cerebral white matter lesion abutting the cortex, and not separated from it by white matter.[6,7,13]

Lesion
An area of hyperintensity on a T2-weighted or proton-density-weighted MRI scan that is at least 3 mm in long axis.[14]

Objective clinical or paraclinical evidence (as it relates to a current or historical attack)
An abnormality on neurological examination, imaging (MRI or optical coherence tomography), or neurophysiological testing (visual evoked potentials) that corresponds to the anatomical location suggested by the symptoms of the clinically isolated syndrome—eg, optic disc pallor or a relative afferent pupillary defect, optic nerve T2 hyperintensity on MRI, retinal nerve fibre layer thinning on optical coherence tomography, or P100 latency prolongation on visual evoked potentials in a patient reporting a previous episode of self-limited, painful, monocular visual impairment. Caution should be exercised in accepting symptoms accompanied only by patient-reported subjective alteration as evidence of a current or previous attack.

Periventricular MRI lesion
A T2-hyperintense cerebral white matter lesion abutting the lateral ventricles without white matter in between, including lesions in the corpus callosum but excluding lesions in deep grey matter structures.[6,13]

Progressive course
A multiple sclerosis course characterised by steadily increasing objectively documented neurological disability independent of relapses. Fluctuations, periods of stability, and superimposed relapses might occur. Primary progressive multiple sclerosis (a progressive course from disease onset) and secondary progressive multiple sclerosis (a progressive course following an initial relapsing-remitting course) are distinguished.[10]

Radiologically isolated syndrome
MRI findings strongly suggestive of multiple sclerosis in a patient with no neurological manifestations or other clear-cut explanation.

Relapse
A monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection. Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonyms.

Relapsing-remitting course
A multiple sclerosis course characterised by relapses with stable neurological disability between episodes.[10]

Spinal cord MRI lesion
A hyperintense lesion in the cervical, thoracic, or lumbar spinal cord seen on T2 plus short tau inversion recovery, proton-density images, or other appropriate sequences, or in two planes on T2 images.[6,7,14]

frequency of misdiagnosis. The Panel strived to ensure that proposed changes were supported by reasonable evidence, not merely expert opinion.

Usefulness and applicability of the 2010 McDonald criteria

Misdiagnosis and differential diagnosis

Before considering potential revisions of the 2010 McDonald criteria, the Panel reviewed issues related to the diagnosis of multiple sclerosis, appropriate use of the McDonald criteria, and performance of the criteria across patient populations.

Misdiagnosis of multiple sclerosis remains an issue in clinical practice,[15–18] and the Panel identified several factors that potentially increase this risk. Multiple sclerosis has heterogeneous clinical and imaging manifestations, which differ between patients and change within individual patients over time. There is no single pathognomonic clinical feature or diagnostic test; diagnosis of multiple sclerosis relies on the integration of clinical, imaging, and laboratory findings. MRI abnormalities associated with other diseases and non-specific MRI findings, which are common in the general population, can be mistaken for multiple sclerosis. The increasingly strong focus on timely diagnosis to alleviate uncertainty for patients and allow initiation of disease-modifying therapies might also increase the risk of misdiagnosis.[19]

As with any diagnostic criteria, a trade-off exists between sensitivity (to allow efficient diagnosis in patients with multiple sclerosis) and specificity (to avoid erroneous diagnosis in patients who do not have the disease).[19] The positive and negative predictive power of diagnostic tests depends on the pre-test probability (likelihood) of the disorder, which has important implications for the interpretation of the available data concerning the usefulness of such tests (panel 2).

The clinician must remain vigilant for clinical features or diagnostic test results that suggest the possibility of an alternative diagnosis, so-called red flags.[9,13,20,21] A recent multicentre case series[18] demonstrated that a wide range of conditions can be mistaken for multiple sclerosis. Aside from NMOSDs, the most frequent reason for misdiagnosis as multiple sclerosis was misinterpretation of non-specific symptoms, neurological signs, or MRI findings in common disorders (eg, migraine) that, when reviewed carefully, in most patients, would not fulfil the 2010 McDonald criteria. Misdiagnosis had harmful consequences in some patients, emphasising the importance of appropriate application of the McDonald criteria (panel 3).

Interpretation and integration of the history, physical examination, and results of imaging and laboratory testing by a clinician with expertise in multiple sclerosis remain fundamental in making a reliable diagnosis of multiple sclerosis or an alternative diagnosis. It is important to re-emphasise that the McDonald criteria should be applied primarily in patients with a typical clinically isolated syndrome (panel 1)—ie, patients who already have a high likelihood of having multiple sclerosis. Care should be exercised in accepting historical events in the absence of contemporaneous or current objective evidence that corroborates those events (panel 3). As with past McDonald criteria, the Panel's discussion emphasised rigour in interpreting clinical features and results of diagnostic tests to ensure the absence of atypical features and that there is no more appropriate diagnosis.

Applicability of the 2010 McDonald criteria in diverse populations

Original development of the McDonald criteria and subsequent revisions were largely based on data from adult white European and North American populations with a typical clinically isolated syndrome[9] and age younger than 50 years. The applicability of the 2010 McDonald criteria has been reported in patients from

Panel 2: Validation of the McDonald criteria

In the context of validation of proposed diagnostic criteria for multiple sclerosis, the typical approach is to study (retrospectively or, preferably, with prospective follow-up) a population of patients experiencing a first symptom suggestive of multiple sclerosis (ie, a clinically isolated syndrome) and to categorise these patients on the basis of whether they fulfil the proposed diagnostic criteria and subsequently develop a second clinical attack that is typical of a multiple sclerosis relapse and indicates involvement of an anatomical location distinct from the initial attack. It is necessary to determine the rates of true positives (patients who fulfil the proposed diagnostic criteria and develop a second attack), false positives (patients who fulfil the proposed diagnostic criteria and do not develop a second attack), true negatives (patients who do not fulfil the proposed diagnostic criteria and do not develop a second attack), and false negatives (patients who do not fulfil the proposed diagnostic criteria and develop a second attack). Sensitivity is calculated as the number of true positives divided by the total of true positives plus false negatives; specificity is calculated as the number of true negatives divided by the total of true negatives plus false positives.

The performance of a diagnostic test (or, in this example, proposed diagnostic criteria) in terms of positive and negative predictive value depends on the likelihood of the condition of interest (in this example, multiple sclerosis) in the study population. The McDonald criteria and proposed revisions have largely been validated in patient populations that have a high likelihood of multiple sclerosis by virtue of their demographic features, their mode of recruitment, and their having had a typical clinically isolated syndrome. Their positive predictive value will be lower in populations with a lower likelihood of multiple sclerosis.

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Canada,[22] Italy,[23] the Netherlands,[24] Spain,[25] and Russia.[26] Additional studies evaluating the applicability of the 2010 McDonald criteria in Asian,[27–29] Middle Eastern,[30,31] and Latin American[32] populations have been published since 2010, although these studies tended to be small. These data provide no evidence that the 2010 McDonald criteria cannot be used in these populations. Vigilance is needed to exclude alternative diagnoses, particularly NMOSDs in populations such as African American, Asian, Latin American, and paediatric patients, in which multiple sclerosis is less common than in adult white European and North American populations. In Latin America, infectious diseases and nutritional deficiencies that mimic multiple sclerosis also remain important considerations.[33]

Several studies[34–41] support the applicability of the 2010 McDonald criteria in children. The criteria are generally most applicable to patients who are 11 years of age or older; special care is needed in patients younger than 11 years old, in whom the likelihood of multiple sclerosis is lower.[35] Acute disseminated encephalomyelitis is more common in children than in adults, and, although it is typically monophasic, some children with this disease have recurrent clinical episodes or MRI evidence of accrual of new lesions, which can lead to a diagnosis of multiple sclerosis.[42] The Panel agreed that the 2017 McDonald criteria should not be applied to children at the time of acute disseminated encephalomyelitis presentation and that occurrence of a subsequent attack characteristic of multiple sclerosis is necessary to diagnose multiple sclerosis.[43] Alternative diagnoses, including NMOSDs, need to be excluded in all children in whom the diagnosis of multiple sclerosis is being considered. Tests for antibodies reactive with myelin-oligodendrocyte glycoprotein (MOG) could be useful to aid diagnosis of children with NMOSDs who are aquaporin 4 (AQP4) seronegative, children with acute disseminated encephalomyelitis followed by recurrent optic neuritis, and children with chronic relapsing optic neuritis.[44–46] Particular care to reach a final diagnosis is required in children with presentations with features overlapping those of acute disseminated encephalomyelitis, NMOSDs, and multiple sclerosis.

Although multiple sclerosis typically presents between the ages of 20 years and 50 years, approximately 0·5% of adults with this disease have symptom onset at the age of 60 years or older.[47,48] Older individuals are more likely to have a progressive course at presentation—progressive either from onset or following retrospectively recognised attacks—but occasionally they present with an acute attack. Careful attention to alternative diagnoses and particularly comorbidities is necessary. Age-related vascular white matter lesions might occasionally be periventricular, and seeking more than one periventricular lesion with a morphology characteristic of multiple sclerosis might be prudent in this setting. Consideration of multiple sclerosis in an older individual is an example of a diagnostic scenario in which spinal cord MRI or CSF examination to look for findings that support a multiple sclerosis diagnosis or suggest a different diagnosis is advised. With these caveats, the Panel agreed that the 2010 McDonald criteria are likely to be applicable in older patients, but recommended further studies to validate the 2017 McDonald criteria in this population.

***Panel 3*: Considerations to help avoid misdiagnosis of multiple sclerosis**

- Recognise that the McDonald criteria were not developed to differentiate multiple sclerosis from other conditions but to identify multiple sclerosis or a high likelihood of the disease in patients with a typical clinically isolated syndrome once other diagnoses have been deemed unlikely.
- Integration of the history, examination, imaging, and laboratory evidence by a clinician with multiple sclerosis-related expertise remains fundamental in making a reliable diagnosis of multiple sclerosis or an alternative diagnosis. In addition to confirming dissemination in space and time, diagnostic rigour in the interpretation of clinical data, imaging findings, and test results is necessary.
- In the absence of a clear-cut typical clinically isolated syndrome (panel 1), caution should be exercised in making the diagnosis of multiple sclerosis, and the diagnosis should be confirmed by further clinical and radiological follow-up. In such cases, the clinician should consider postponing making a definitive diagnosis and initiation of long-term disease-modifying therapies, pending longer follow-up to accumulate additional evidence supporting the diagnosis.
- Caution should be taken in accepting a historical event as an attack in the absence of contemporaneous or current objective evidence providing corroboration.
- The threshold for additional testing should be low, including for spinal cord MRI or CSF examination in the following situations: when clinical and brain MRI evidence supporting a diagnosis of multiple sclerosis is insufficient, particularly if initiation of long-term disease-modifying therapies are being considered; when there is a presentation other than a typical clinically isolated syndrome, including patients with a progressive course at onset (primary progressive multiple sclerosis); when there are clinical, imaging, or laboratory features atypical of multiple sclerosis; and in populations in which multiple sclerosis is less common (eg, children, older individuals, or non-white populations).

Neuromyelitis optica spectrum disorders

Substantial data concerning NMOSDs have emerged since the publication of the 2010 McDonald criteria. Although clinical, imaging, and CSF features of multiple sclerosis and NMOSDs can overlap, these disorders are now understood to be distinct.[49] Diagnosis of NMOSDs has been facilitated by the development and use of serological testing for antibodies reactive with the AQP4 water channel and validation of the antibodies not only as markers of NMOSDs but also as pathogenic factors.[50,51] The range of recognised clinical and MRI manifestations of AQP4-associated NMOSDs is wide and still evolving. Data suggest that some AQP4-seronegative patients with NMOSD features have antibodies reactive with MOG.[52–56] However, the diagnostic sensitivity and specificity of anti-MOG antibody testing have not been fully validated.

The Panel agreed that the 2010 McDonald criteria and 2015 International Panel for Neuromyelitis Optica

Diagnosis criteria[57] largely distinguish multiple sclerosis from NMOSDs, although uncertainty can occur, particularly with AQP4-seronegative patients. Because the treatments for multiple sclerosis and NMOSDs are different (eg, interferon beta, fingolimod, and natalizumab can exacerbate NMOSDs[58]), the Panel recommended that NMOSDs should be considered in any patient being evaluated for multiple sclerosis. Serological testing for AQP4 and for MOG should be done in all patients with features suggesting NMOSDs (such as bilateral optic neuritis, severe brainstem involvement, longitudinally extensive spinal cord lesions, large cerebral lesions, or normal brain MRI or findings not fulfilling dissemination in space [DIS]), and considered in groups at higher risk of NMOSDs (such as African American, Asian, Latin American, and paediatric populations).

Role of MRI in diagnosis of multiple sclerosis

MRI has been increasingly used to support the diagnosis of multiple sclerosis and to look for atypical radiological features arguing against this diagnosis. MAGNIMS and the Consortium of Multiple Sclerosis Centers recently proposed standardised MRI protocols for the diagnostic process, to determine prognosis, and for follow-up.[14,59,60] Brain and spinal cord MRI remain the most useful paraclinical tests to aid the diagnosis of multiple sclerosis and can substitute for clinical findings in the determination of DIS or dissemination in time (DIT) in patients with a typical clinically isolated syndrome.

The Panel recommended that brain MRI be obtained in all patients being considered for a diagnosis of multiple sclerosis, recognising that it might at times not be possible because of availability, cost, or contraindication. There was general agreement that, although spinal MRI is not mandatory in all cases, it is advisable when the presentation suggests a spinal cord localisation, when there is a primary progressive course, when considering multiple sclerosis in a population in which the disease is less common (eg, older individuals or non-white populations), or when additional data are needed to increase diagnostic confidence (eg, when brain MRI findings only just fulfil the criteria for DIS).[14,60] Spinal MRI seems to be less useful in the diagnosis of multiple sclerosis in children than in adults.[39]

Role of CSF examination in diagnosis of multiple sclerosis

Although CSF examination has been de-emphasised in successive iterations of the McDonald criteria, it remains a valuable diagnostic test.[61] In the appropriate clinical setting, evidence of intrathecal antibody synthesis, although not specific for multiple sclerosis, supports the diagnosis.[62] Conversely, CSF findings atypical of multiple sclerosis (eg, an elevated protein concentration of >100 mg/dL, pleocytosis with >50 cells per mm^3, or the presence of neutrophils, eosinophils, or atypical cells) suggest other diseases.[63]

The Panel's discussion of CSF recognised the importance of using appropriate and standardised technology.[62–64] The qualitative demonstration of two or more CSF-specific oligoclonal bands more reliably indicates intrathecal antibody synthesis than do other tests, such as the IgG index.[62–64] Positive results on these other tests should be interpreted with caution when testing for oligoclonal bands is negative or not done. The sensitivity of oligoclonal band testing depends on the method used; agarose gel electrophoresis with isoelectric focusing and immunoblotting or immunofixation for IgG is the most sensitive approach at present.[62–64] Importantly, analysis of paired CSF and serum samples is essential to confirm that the oligoclonal bands are unique to CSF.

Although CSF examination is not mandatory in some cases (eg, a patient with a typical clinically isolated syndrome supported by characteristic MRI findings [panel 1], unequivocal demonstration of DIS and DIT, and an absence of atypical clinical or imaging features), the threshold for CSF examination should be low to increase diagnostic confidence. CSF examination is strongly recommended in the following situations: when clinical and MRI evidence is insufficient to support a diagnosis of multiple sclerosis, particularly if initiation of disease-modifying therapies is being considered; when there is a presentation other than a typical clinically isolated syndrome, including a progressive course at onset (primary progressive multiple sclerosis); when clinical, imaging, or laboratory features are atypical of multiple sclerosis; and in populations in which multiple sclerosis is less common (eg, children, older individuals, or non-white populations). Although the absence of CSF oligoclonal bands does not rule out multiple sclerosis, particularly early in the condition and in children,[62,63] caution should be exercised in making this diagnosis when CSF oligoclonal bands are not detected and, certainly, in the presence of atypical clinical, imaging, or CSF findings.

2017 revisions to the McDonald criteria

CSF oligoclonal bands

Numerous studies[65–73] have provided evidence that, in adult patients with a clinically isolated syndrome, CSF oligoclonal bands are an independent predictor of the risk of a second attack when controlling for demographic, clinical, treatment, and MRI variables. After considering these data, the Panel recommended that with a typical clinically isolated syndrome, fulfilment of clinical or MRI criteria for DIS, and no better explanation for the clinical presentation, demonstration of CSF oligoclonal bands in the absence of atypical CSF findings allows a diagnosis of multiple sclerosis to be made, even if the MRI findings on the baseline scan do not meet the criteria for DIT and in the absence of either a second attack or MRI evidence of a new or active lesion on serial imaging (table; panel 4).[73] This consensus recommendation allows the presence of CSF oligoclonal bands to substitute for the

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5. ¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Table: **The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset**

requirement of fulfilling DIT in this situation. This criterion is similar to the laboratory-supported definite multiple sclerosis category in the earlier Poser criteria.[2]

Symptomatic lesions as evidence for dissemination in space and time

Previously, the symptomatic lesion in a patient presenting with brainstem or spinal cord clinically isolated syndrome could not be included as MRI evidence of DIS or DIT, to avoid so-called double counting. Studies in the past year have shown that inclusion of symptomatic lesions in the MRI determination of DIS or DIT increases diagnostic sensitivity with little or no reduction in specificity[74,75] and was proposed in the 2016 MAGNIMS criteria.[7,76] On the basis of these data, the Panel recommended including symptomatic and asymptomatic MRI lesions in the determination of DIS and DIT (panel 5). An exception relates to lesions in the optic nerve in a patient presenting with optic neuritis, as the Panel felt evidence was insufficient to support inclusion of the optic nerve as a site to determine DIS in these patients.

Cortical lesions equivalent to juxtacortical lesions

Juxtacortical white matter is a characteristic location of multiple sclerosis lesions (panel 1), and lesions in this region were incorporated into the MRI criteria for DIS in the 1997 Barkhof imaging criteria.[77] Histopathological studies have shown that cortical lesions and juxtacortical lesions extending into the cortex are typical of multiple sclerosis.[78,79] With the development of improved techniques to identify cortical lesions, their potential to contribute to diagnosis has been appreciated.[11,12,76] The Panel recommended that, in addition to juxtacortical lesions, cortical lesions can be used to fulfil MRI criteria for DIS, although it recognised that standard MRI currently has limited ability to detect cortical lesions or distinguish cortical lesions in multiple sclerosis from those with other causes. In addition, care is needed to distinguish potential cortical lesions from neuroimaging artefacts.

Application in multiple sclerosis subtypes

About 15% of patients with multiple sclerosis have a course that is characterised by gradual progression from onset (primary progressive multiple sclerosis).[10] The original McDonald criteria were developed to make the diagnosis in patients with a clinically isolated syndrome at onset and then modified for use in patients with progression from onset. The diagnostic criteria for primary progressive multiple sclerosis remain the same in the 2017 McDonald criteria as those outlined in the 2010 McDonald criteria,[5] aside from removal of the distinction between symptomatic and asymptomatic MRI lesions and the use of cortical lesions (panel 6).

The 2013 revised classification[10] of the clinical phenotypes and disease course of multiple sclerosis maintained the distinction between multiple sclerosis with an attack onset versus a progressive course from onset. The revised classification incorporated further categorisation as active or not (based on recent clinical relapse or MRI lesion activity) and progressive or not (based on clinical assessment of disability). The intent was for patients to be assessed over time and classified (and reclassified as needed) according to the disease course in a preceding time period (eg, 1 year). The Panel

recommended that a provisional disease course should be specified as soon as the multiple sclerosis diagnosis is made, and periodically re-evaluated based on accumulated information.

Key proposals that require further evidence

Number of periventricular lesions

The 2001[3] and 2005[4] McDonald criteria required three or more periventricular lesions as one of the anatomical locations that could fulfil MRI criteria for DIS. In the 2010 McDonald criteria,[5] this requirement was changed to one or more periventricular lesions as one of the four anatomical locations (periventricular, juxtacortical, and infratentorial brain regions, and the spinal cord). However, non-specific white matter lesions are common in older individuals and in those with vascular risk factors including migraine; a single periventricular lesion is not uncommon.[13] Therefore, the 2016 MAGNIMS criteria[7] suggested that a single lesion might be insufficiently specific and proposed increasing the requirement to three periventricular lesions. In a recent analysis,[76] changing the requirement from one periventricular lesion to three improved specificity of predicting development of a second attack by month 36 from 0·33 to 0·40 but decreased sensitivity from 0·91 to 0·85. The Panel felt the modest improvement in specificity, which is comparable to that achieved when DIS and DIT are considered in combination,[80,81] did not justify the added complexity of requiring a different number of lesions in different anatomical regions. Therefore, the 2017 McDonald criteria maintain the requirement for one periventricular lesion. For some patients—eg, older individuals or those with vascular risk factors including migraine—it might be prudent for the clinician to seek a higher number of periventricular lesions.

Incorporation of the anterior visual system into the criteria

The visual system often provides an early and eloquent clinical sign of multiple sclerosis.[82] The 2016 MAGNIMS criteria[7] proposed the optic nerve as a fifth anatomical location to fulfil MRI criteria for DIS. In the 2017 Panel deliberations, there was substantial discussion concerning the potential advantages and disadvantages of MRI, visual evoked potentials, and optical coherence tomography to demonstrate optic nerve involvement objectively and support a clinical suspicion of current or previous optic neuritis, including changes in the sensitivity of all three tests over time relative to the optic neuritis event.[82] The MAGNIMS analysis[76] showed that adding optic nerve involvement detected by MRI or visual evoked potentials as a fifth anatomical site led to a minor improvement in sensitivity of predicting development of a second attack by month 36, from 0·91 to 0·92, but reduced specificity from 0·33 from 0·26. The analysis did not include optical coherence tomography. Despite recognising optic nerve involvement as an important feature of multiple sclerosis, the Panel felt the data concerning the diagnostic sensitivity and specificity of MRI, visual evoked potentials, or optical coherence tomography to demonstrate optic nerve lesions in patients without a clear-cut history or clinical evidence of optic neuritis were insufficient to support incorporation into the McDonald criteria at this time. Studies to validate MRI, visual evoked potentials, or optical coherence tomography in fulfilling DIS or DIT in support of a multiple sclerosis diagnosis were identified as a high priority.

***Panel 4*: 2017 revisions to the McDonald diagnostic criteria for multiple sclerosis**

- In a patient with a typical clinically isolated syndrome and fulfilment of clinical or MRI criteria for dissemination in space and no better explanation for the clinical presentation, demonstration of CSF-specific oligoclonal bands in the absence of other CSF findings atypical of multiple sclerosis allows a diagnosis of this disease to be made. This recommendation is an addition to the 2010 McDonald criteria.
- Symptomatic and asymptomatic MRI lesions can be considered in the determination of dissemination in space or time. MRI lesions in the optic nerve in a patient presenting with optic neuritis remain an exception and, owing to insufficient evidence, cannot be used in fulfilling the McDonald criteria. In the 2010 McDonald criteria, the symptomatic lesion in a patient presenting with brainstem or spinal cord syndrome could not be included as MRI evidence of dissemination in space or time.
- Cortical and juxtacortical lesions can be used in fulfilling MRI criteria for dissemination in space. Cortical lesions could not be used in fulfilling MRI criteria for dissemination in space in the 2010 McDonald criteria.
- The diagnostic criteria for primary progressive multiple sclerosis in the 2017 McDonald criteria remain the same as those outlined in the 2010 McDonald criteria, aside from removal of the distinction between symptomatic and asymptomatic MRI lesions and that cortical lesions can be used.
- At the time of diagnosis, a provisional disease course should be specified (relapsing-remitting, primary progressive, or secondary progressive) and whether the course is active or not, and progressive or not based on the previous year's history. The phenotype should be periodically re-evaluated based on accumulated information. This recommendation is an addition to the 2010 McDonald criteria.

***Panel 5*: 2017 McDonald criteria for demonstration of dissemination in space and time by MRI in a patient with a clinically isolated syndrome**

- Dissemination in space can be demonstrated by one or more T2-hyperintense lesions* that are characteristic of multiple sclerosis in two or more of four areas of the CNS: periventricular†, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord
- Dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions* at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. †For some patients—eg, individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.

***Panel 6*: 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with a disease course characterised by progression from onset (primary progressive multiple sclerosis)**

Primary progressive multiple sclerosis can be diagnosed in patients with:

- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus two of the following criteria:

- One or more T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions* in the spinal cord
- Presence of CSF-specific oligoclonal bands

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

Applicability of the McDonald criteria in patients with atypical presentations

Radiologically isolated syndrome

With increasing availability and use of MRI, incidental T2 hyperintensities on brain imaging are common;[83] the subset of individuals with MRI findings that are strongly suggestive of multiple sclerosis lesions but with no neurological manifestations or other clear-cut explanation are said to have radiologically isolated syndrome.[84] Data concerning the population-based incidence and prevalence of radiologically isolated syndrome are scarce but suggest that it is uncommon (in Sweden, the incidence is 0·8 cases of radiologically isolated syndrome per 100 000 person-years compared with 10·2 cases of multiple sclerosis per 100 000 person-years[85]), but prevalence is increased in healthy relatives of patients with multiple sclerosis.[86] Approximately a third of individuals with radiologically isolated syndrome are diagnosed with multiple sclerosis within 5 years of presentation, most often with a relapsing-remitting course[84,87] but occasionally with a primary progressive course.[88,89] The factors predicting an increased risk of subsequent multiple sclerosis diagnosis are similar to those associated with a diagnosis of multiple sclerosis after a clinically isolated syndrome: younger age, higher cerebral lesion load, asymptomatic infratentorial or spinal cord lesions, gadolinium-enhancing lesions, CSF-specific oligoclonal bands, and abnormal visual evoked potentials.[88,90]

Some Panel members argued that individuals with radiologically isolated syndrome have a high likelihood of having multiple sclerosis and might already exhibit evidence of putative pathobiology, including fatigue,[91] cognitive impairment,[92] or thalamic atrophy,[93] and that postponing the diagnosis of multiple sclerosis and initiation of disease-modifying therapies might increase the risk of disability. Others argued that the risk of misdiagnosis is high in patients with MRI abnormalities only,[18] and that two-thirds of these patients will not receive a diagnosis of multiple sclerosis within 5 years. The Panel reached a consensus to continue to require clinical manifestations to make the diagnosis of multiple sclerosis and, as in the 2010 McDonald criteria, to allow the use of historical radiological evidence for DIS and DIT in patients with radiologically isolated syndrome to support the diagnosis of multiple sclerosis once a typical clinically isolated syndrome occurs. Although the Panel considered allowing a diagnosis of multiple sclerosis in patients with radiologically isolated syndrome, demonstration of DIS and DIT by MRI, and demonstration of CSF-specific oligoclonal bands, this proposal did not receive general support. Radiologically isolated syndrome was identified as a high-priority area for further research.

Solitary sclerosis

The Panel discussed rare patients who have an inflammatory lesion of the cerebral white matter, cervicomedullary junction, or spinal cord who develop progressive disability that is clinically indistinguishable from progressive forms of multiple sclerosis and who might have CSF-specific oligoclonal bands but have no clinical or radiological evidence of new lesion formation—a condition that has been termed progressive solitary sclerosis.[94] The Panel agreed that despite a progressive course, such patients do not satisfy the McDonald criteria for multiple sclerosis, because they do not have DIS. Like radiologically isolated syndrome, solitary sclerosis was identified as a high-priority area for further research.

Possible multiple sclerosis

The 2010 McDonald criteria[5] include a diagnostic category of possible multiple sclerosis, defined as a suspicion of multiple sclerosis (ie, a patient with a clinically isolated syndrome but not meeting the full criteria). The Panel considered expanding the category of possible multiple sclerosis to include patients with atypical presentations, but did not reach a consensus. Validation of future criteria to inform about presentations that only partially fulfil the 2017 McDonald criteria (such as radiologically isolated syndrome, solitary sclerosis, or other atypical presentations) needs more focused collaborative studies, in particular because such presentations are uncommon.

Other high-priority areas for research

Many of the elements of the McDonald criteria have come from data from academic multiple sclerosis specialty centres and have been derived largely from adult patients of western European genetic or ethnic origins presenting with a typical clinically isolated syndrome (ie, patients with a high likelihood of multiple sclerosis). Validation of the 2017 McDonald criteria, either prospectively or retrospectively, will be needed in diverse populations: patients from Asia, Latin America, the Middle East, Africa, and other relatively less studied geographical locations;

patients with suspected paediatric and late-onset multiple sclerosis; patients with comorbidities that are associated with clinical or imaging manifestations that overlap those of multiple sclerosis; and in non-specialty and general practice clinical settings.

In addition to validation of the 2016 MAGNIMS criteria individually, the Panel identified further studies to evaluate the performance of the 2016 MAGNIMS criteria when applied in aggregate as a high priority. New MRI approaches also will need to be considered for future iterations of the McDonald criteria. Currently, the only feature to assess the chronicity of MRI lesions at the time of first assessment is the presence or absence of gadolinium enhancement. Chronic T1-hypointense lesions (so-called black holes) were shown not to aid in the determination of DIT.[95] The role in multiple sclerosis diagnosis of more sensitive imaging methods to detect grey matter pathology (particularly to demonstrate subpial cortical and deep grey matter lesions[78]) and techniques to distinguish multiple sclerosis lesions from T2 hyperintensities in other conditions (eg, central vein sign on susceptibility-weighted, T2*-weighted, or FLAIR* images[96] or paramagnetic rim on T2*-weighted, phase-weighted, or susceptibility-weighted images[97,98]) are being explored. The role of high field strength imaging requires detailed investigation to determine whether it is useful and practical, particularly in non-academic settings, in view of its improved ability to detect lesions and reveal their anatomical features.

Currently, no laboratory test in isolation confirms the diagnosis of multiple sclerosis. Although AQP4 serological testing generally differentiates NMOSDs from multiple sclerosis,[50] less is known about the performance of testing for MOG antibodies.[46,52–54] Other diagnostic biomarkers have been proposed to differentiate between multiple sclerosis phenotypes or to monitor CNS damage, but none has been shown to diagnose multiple sclerosis reliably in individual patients, representing a major unmet need and area for future research. Finally, the possible contribution of evoked potential investigations besides visual evoked potentials (eg, somatosensory or motor) to diagnostic criteria should be further explored. With the growing interest in precision medicine and rapidly evolving technologies, the multiple sclerosis research community needs to develop an approach for the validation of all paraclinical tests for multiple sclerosis diagnosis and incorporation of these tests into practice when appropriate.

Conclusions

Early diagnostic criteria for multiple sclerosis were based primarily on clinical evidence.[1] Subsequent criteria incorporated imaging and other paraclinical markers in response to technological advances and new data.[2–5] The 2017 revisions to the well established 2010 McDonald criteria revitalise the role of CSF analysis, reconsider the value of imaging findings previously not included (symptomatic and cortical lesions), and articulate more clearly cautions about misdiagnosis and differential diagnosis, all of which were supported by a sound evidence base.

The 2017 McDonald criteria are intended for use both in research settings and clinical practice. The Panel recognised that application of new diagnostic criteria can have an impact on future recruitment into and interpretation of clinical trials and observational studies.[99] The ability to diagnose multiple sclerosis accurately and more rapidly should facilitate enrolment in prospective clinical trials, and could increase the populations of individuals eligible for observational and natural history studies. None of these changes is anticipated to invalidate the diagnosis of multiple sclerosis according to previous versions of the McDonald criteria (ie, any patient diagnosed with the previous criteria should also fulfil the 2017 McDonald criteria), or affect the regulatory-approved indications of disease-modifying therapies for multiple sclerosis.

Although diagnosis of multiple sclerosis is increasingly based on paraclinical tests, optimal diagnosis requires the judgment of a clinician with multiple sclerosis-related expertise, aided by appropriate radiological and other paraclinical assessments. The 2017 McDonald criteria are not treatment guidelines. The goal is to make a rapid and accurate diagnosis of multiple sclerosis to allow appropriate management (initiation of treatment or observation), keeping fully in mind the potential dangers of misdiagnosis in an era with increasing numbers of treatment options for multiple sclerosis, which carry varying degrees of risk. The importance of correct diagnosis is further heightened by the observation that certain disease-modifying therapies for multiple sclerosis are contraindicated in some of the more common differential diagnoses (eg, NMOSDs). The Panel was also mindful of the challenges many patients experience in gaining access to clinicians with multiple sclerosis-related expertise and advocated a concerted global effort to address this crucial workforce gap.

Search strategy and selection criteria

In preparation for the meetings, the Panel conducted literature searches (completed April 15, 2017) in PubMed (English language, using search terms "multiple sclerosis" and "diagnosis" with a focus on publications since 2010 but also including earlier publications as appropriate). It reviewed papers on topics including, but not limited to: the role in diagnosis of MRI, optical coherence tomography, evoked potentials, and CSF analysis; diagnosis in diverse populations (paediatric, Asian, and Latin American); diagnosis in patients with atypical presentations (eg, radiologically isolated syndrome and solitary sclerosis); differential diagnosis between multiple sclerosis, neuromyelitis optica spectrum disorders, and other neurological disorders; and the intersection of diagnosis with disease phenotype designation.

Contributors

JAC, AJT, and SCR drafted meeting agendas, with review and agreement by all Panel members. BLB, FB, GC, JC, MF, KF, SLG, FDL, DHM, XM, EMM, MTi, ALT, and BGW made specific topic-related presentations at the meetings. All Panel members attended both meetings, and actively participated in discussion and reaching a consensus. JAC, AJT, and SCR prepared the initial drafts of this manuscript. All Panel members were given the opportunity to review drafts and make revisions before finalisation, and approved the manuscript for submission.

Declaration of interests

AJT reports personal consultancy fees from MedDay, Novartis, Eisai, Biogen Idec, and Teva; is an Editorial Board member of *The Lancet Neurology*; is Editor in Chief of *Multiple Sclerosis Journal* and receives honoraria from SAGE Publications; chairs the Scientific Advisory Committee of, and receives financial support for travel to international meetings from, the International Progressive MS Alliance; is a member of, and receives financial support for travel to international meetings from, the Research Programs Advisory Committee of the US National Multiple Sclerosis Society; was Chair of the Multiple Sclerosis International Federation (MSIF) International Medical and Scientific Board between 2005 and 2015; has received financial support for travel to international meetings from MSIF; and has been a member of the MSIF International Medical and Scientific Board (since 2015). He has received honoraria and support for travel for lecturing from EXCEMED, and has received support from the University College London Hospitals National Institute for Health Research Biomedical Research Centre. BLB received grants from the Multiple Sclerosis Scientific Research Foundation during the conduct of this study. FB reports consultancy fees from Apitope, Bayer-Schering Pharma, Biogen Idec, GeNeuro, IXICO, Janssen Research, Merck-Serono, Novartis, Roche, Sanofi Genzyme, and Teva; speakers' fees from Biogen Idec and IXICO; and grants or pending grants from AMYPAD (IMI), Dutch MS Society, ECTRIMS-MAGNIMS, EuroPOND (Horizon 2020), University College London Hospitals National Institute for Health Research Biomedical Research Centre, PICTURE (IMDI-NWO), and the UK Multiple Sclerosis Society. WMC reports travel support from Biogen, Genzyme, and Teva; lecture fees from Merck and Roche; and has served as the Asia Pacific Editor for *Multiple Sclerosis Journal*. TC declares no competing interests. GC reports personal fees from Almirall, Biogen, Celgene, EXCEMED, Forward Pharma, Genzyme, Merck, Novartis, Roche, Sanofi, and Teva. JC reports personal fees from Merck Argentina, Merck LATAM, Genzyme LATAM, Genzyme Global, Novartis LATAM, Roche LATAM, and TEVA LATAM; grants and personal fees from Genzyme Argentina and Novartis Argentina; and grants from Biogen Idec. FF reports personal fees from Actelion, Biogen Idec, MedDay, Merck, Novartis, Parexel, Sanofi Genzyme, and Teva Ratiopharm. MF reports personal fees from Biogen Idec, Merck-Serono, Novartis, and Teva Pharmaceutical Industries; and grants from Alzheimer's Drug Discovery Foundation, ARiSLA (Fondazione Italiana di Ricerca per la SLA), Biogen Idec, Cure PSP, Fondazione Italiana Sclerosi Multipla, the Jacques and Gloria Gossweiler Foundation (Switzerland), Italian Ministry of Health, Novartis, and Teva Pharmaceutical Industries. MSF reports grants from Sanofi Genzyme and honoraria from Actelion, Biogen Idec, Chugai, EMD, Genzyme, Merck Serono, Novartis, Roche, Sanofi, and Teva Canada Innovation. KF has received grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Ministry of Health, Welfare and Labor of Japan during the conduct of the study; grants and personal fees from Asahi Kasei Medical, Astellas, Bayer Schering, Biogen, Chugai, Mitsubishi Tanabe, Nihon Pharmaceutical, Takeda, and Teijin; personal fees from Alexion, Daiichi Sankyo, Medimmune, Merck Serono, and Novartis; and grants from Chemo-Sero-Therapeutic Research Institute, Genzyme, Ono, and Teva. SLG reports personal fees from Biogen. HPH reports personal fees from Bayer HealthCare, Biogen, Geneuro, MedDay, Medimmune, Novartis, Octapharma, Receptos Celgene, Roche, Sanofi Genzyme, and Teva. LK reports grants from Actelion, Alkermes, Allergan, Almirall, Bayer HealthCare, Biogen Idec, CSL Behring, df-mp, The European Union, EXCEMED, GeNeuro SA, Genzyme, Merck, Mitsubishi, Novartis, Pfizer, Receptos, Roche, Roche Research Foundations, Sanofi-Aventis, Santhera, Teva, UCB, Vianex, the Swiss Multiple Sclerosis Society, and the Swiss National Research Foundation. FDL reports personal fees from AbbVie, Acorda, Actelion, Akros, Atara Biotherapeutics, Bayer HealthCare, EMD Serono, Forward Pharma, Innate Immunotherapeutics, MedDay, Medimmune, Osmotica, Questcor/Mallinckrodt, Receptos, Roche/Genentech, TG Therapeutics, and Xenoport; grants and personal fees from Biogen Idec, Celgene, Sanofi Genzyme, and Teva Neuroscience; and grants from Transparency Life Sciences. RAM reports research funding from the Canadian Institutes of Health Research, Crohn's and Colitis Canada, Canadian Multiple Sclerosis Scientific Foundation, Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, Research Manitoba, and Rx&D Health Research Foundation; and support paid to her institution by Sanofi-Aventis. AEM reports research support from Biogen Idec, Genzyme/Sanofi, Mallinckrodt (Questcor), MedDay, Novartis, and Roche/Genentech; personal fees from Acorda Therapeutics, Adamas, Alkermes, Biogen Idec, Celgene, EMD Serono (Merck Serono), Genzyme/Sanofi, Mallinckrodt (Questcor), Mapi-Pharma, Novartis, Roche/Genentech, and Teva; and has served on the Speakers Bureaus for Biogen (unbranded disease awareness programmes only) and Roche/Genentech (unbranded disease awareness programmes only). DHM reports grants from Apitope and Biogen Idec; personal fees from Bayer Schering, GlaxoSmithKline, and Mitsubishi Pharma Europe; and grants and personal fees from Novartis. XM reports personal fees from Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi, and Teva. EMM reports grants from Biogen and Genzyme, and free medication for a clinical trial from Teva and royalties for editorial duties from Up-to-Date. PSS reports personal fees from Celgene, Forward Pharma, GlaxoSmithKline, and MedDay; grants and personal fees from Biogen, Merck, Sanofi-Aventis/Genzyme, and Teva; and grants from Roche. MTi reports personal fees from Almirall, Bayer HealthCare, Merck Serono, Novartis, Roche, and Teva Neuroscience; grants and personal fees from Biogen Idec and Sanofi Genzyme. ALT reports grants and personal fees from Biogen Idec, Chugai, F Hoffmann-La Roche, and Sanofi Genzyme; grants from the Canadian Institutes of Health Research and Multiple Sclerosis Society Canada; and personal fees from Novartis, Teva Innovation, and the Consortium of Multiple Sclerosis Centers. MTr reports personal fees from Almirall, Biogen Idec, Merck, Novartis, Roche, Sanofi Genzyme, and Teva; and grants from Biogen Idec, Merck, and Novartis; BMJU reports personal fees from Biogen Idec, Genzyme, Merck Serono, Roche, and Teva. SV reports grants and personal fees from Biogen, Merck-Serono, Novartis, Roche, Sanofi Genzyme, and Teva; personal fees from Geneuro; and grants from MedDay. EW has received honoraria as Co-Chief Editor of *Multiple Sclerosis and Related Disorders* and as Section Editor for *Annals of Clinical and Translational Neurology*. BGW reports personal fees from Alexion, Biogen Idec, Caladrius Biosciences, MedImmune, and Novartis; and has a patent for NMO-IgG for diagnosis of neuromyelitis optica with royalties paid to RSR, the University of Oxford, Hospices Civil de Lyon, and MVZ Labor PD Dr Volkmann und Kollegen GbR. SCR has received personal fees or travel support from the National Multiple Sclerosis Society, the Observatoire Français pour la Sclérose en Plaques, and the European Committee for Treatment and Research in Multiple Sclerosis during the conduct of the study; personal fees and other support from F Hoffmann-La Roche, Ionis Pharmaceuticals, MedDay Pharmaceuticals SA, MedImmune, Merck Serono, Novartis; personal fees from Opexa Therapeutics, Teva Pharmaceuticals Industries, and TG Therapeutics; and personal fees and non-financial support from Scientific and Clinical Review Associates LLC. JAC reports personal fees from Adamas and Celgene, and has served as Co-Editor of *Multiple Sclerosis Journal*.

Acknowledgments

We thank Michael Hutchinson, Catherine Lubetzki, and Jerry Wolinsky for reviewing the manuscript and providing useful suggestions. The International Panel on Diagnosis of Multiple Sclerosis was convened under the auspices of the International Advisory Committee on Clinical Trials in Multiple Sclerosis, and the National Multiple Sclerosis Society and the European Committee for Treatment and Research in Multiple Sclerosis funded its work. The sponsors were not involved in the design, collection, analysis, or interpretation of data included in the publication, in the writing of the manuscript, or in the decision to submit it for publication.

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