MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines

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In patients presenting with a clinically isolated syndrome, MRI can support and substitute clinical information in the diagnosis of multiple sclerosis by showing disease dissemination in space and time and by helping to exclude disorders that can mimic multiple sclerosis. MRI criteria were first included in the diagnostic work-up for multiple sclerosis in 2001, and since then several modifications to the criteria have been proposed in an attempt to simplify lesion-count models for showing disease dissemination in space, change the timing of MRI scanning to show dissemination in time, and increase the value of spinal cord imaging. Since the last update of these criteria, new data on the use of MRI to establish dissemination in space and time have become available, and MRI technology has improved. State-of-the-art MRI findings in these patients were discussed in a MAGNIMS workshop, the goal of which was to provide an evidence-based and expert-opinion consensus on proposed modifications to MRI criteria for the diagnosis of multiple sclerosis.

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Introduction

MRI was formally included in the diagnostic work-up of patients presenting with a clinically isolated syndrome suggestive of multiple sclerosis in 2001 by an international panel of experts.[1] Diagnosis of multiple sclerosis relies on proof of disease dissemination in space and time and exclusion of other disorders that can mimic multiple sclerosis by their clinical and laboratory profile. MRI can support and substitute clinical information for multiple sclerosis diagnosis, enabling an early and accurate diagnosis and, as such, early treatment.

MRI criteria for multiple sclerosis are based on the presence of focal lesions in the white matter of the CNS, which are considered typical for this disorder in terms of distribution, morphology, evolution, and signal abnormalities on conventional MRI sequences (eg, T2-weighted and T2-weighted fluid-attenuated inversion recovery [FLAIR] scans, and pre-contrast and post-contrast T1-weighted scans).[2–4] Several modifications of MRI diagnostic criteria have been proposed, but emphasis has consistently been that such criteria should be applied only in patients who present with a typical clinically isolated syndrome suggestive of multiple sclerosis or symptoms consistent with a CNS inflammatory demyelinating disease. These revisions have simplified lesion-count models for proof of dissemination in space, changed the timing of MRI scanning to show dissemination in time, and increased the value of spinal cord imaging.[5–8] In 2007, the European collaborative research network that studies MRI in multiple sclerosis (MAGNIMS) reviewed the findings of studies that addressed these issues and proposed new MRI criteria to be applied in multiple sclerosis.[9] Those MAGNIMS criteria are included in the most recent diagnostic criteria for multiple sclerosis, known as the 2010 McDonald criteria.[10] Consensus guidelines for clinicians to optimise planning, performance, and interpretation of brain and spinal cord MRI in the multiple sclerosis diagnostic process have also been published and are complementary to the recommendations in this Review.[11]

Since 2011, new data on application of MRI to show dissemination in space and time have become available, and these data deserve consideration for future revisions of the multiple sclerosis diagnostic criteria. Additionally, many improvements in MRI technology have occurred, which have resulted in development of innovative acquisition sequences, identification of novel pathophysiological mechanisms that might help with differential diagnosis, and new insights into multiple sclerosis disease activity from studies using high-field and ultra-high-field scanners. The MAGNIMS members felt the need for timely review of these findings and consideration of how they should be used to modify the MRI criteria for diagnosis of multiple sclerosis. A summary of the main proposed revisions or clarifications to the MRI component of the 2010 McDonald criteria[10] for multiple sclerosis is given in panel 1.

Methods

In March, 2015, an international workshop was held in Milan, Italy, under the auspices of MAGNIMS. The workshop involved clinical and imaging experts in diagnosis and management of patients with multiple sclerosis, including neurologists and neuroradiologists. Before the meeting, two co-chairs (M Filippi and F Barkhof) identified areas in which revision, clarification, or both might be necessary in future diagnostic criteria for multiple sclerosis. Experts for each topic were invited to provide a summary during the meeting of the main findings related to their argument, based on a review of the literature and on their personal experience. They were then asked to define whether such a measure would be useful in the diagnostic process, and whether it would move the field forwards in a promising way, in order to stimulate group discussion. For each measure, a group agreement was reached (100% agreement was achieved in all cases) during the workshop and summarised in a first

Panel 1: **Recommended 2016 MAGNIMS modifications to the 2010 McDonald criteria[10] for MRI in the diagnosis of multiple sclerosis**

Proposed revisions

- Three or more lesions are needed to define the involvement of the periventricular region to establish disease dissemination in space (expert consensus)
- The presence of a lesion in the optic nerve should be added to the criteria for dissemination in space as an additional CNS area (expert consensus)
- The combined term cortical/juxtacortical is recommended to expand the concept of juxtacortical lesion in the criteria for dissemination in space, by including all multiple sclerosis cortical lesion types, involvement of the white matter next to the cortex, or both; when available, advanced imaging sequences should be applied to visualise cortical lesions (expert consensus)
- No distinction needs to be made between symptomatic and asymptomatic MRI lesions for dissemination in time or space (evidence based)[12–15]
- Imaging of the whole spinal cord is recommended to define dissemination in space (especially in patients who do not fulfil brain MRI criteria for dissemination in space); spinal cord imaging has a limited role for identification of dissemination in time (evidence based)[16–19]
- Identical criteria for dissemination in space should be used for primary progressive multiple sclerosis and relapse-onset multiple sclerosis (expert consensus); CSF results should be considered for clinically uncertain cases of primary progressive multiple sclerosis (evidence based)[20]
- In children aged older than 11 years with presentation that does not resemble acute disseminated encephalomyelitis (ADEM), MRI criteria used to establish dissemination in time and space in adults should be applied (evidence based)[21–26]
- Caution is recommended when applying the 2010 criteria[10] solely at baseline in patients younger than age 11 years, even in those with a non-ADEM presentation[27]
- MRI criteria can be applied equally well to patients with multiple sclerosis in Asia or Latin America as to patients from Europe and North America, once alternative neurological disorders (eg, neuromyelitis optica spectrum disorder) have been carefully excluded (evidence based)[28–31]
- MRI criteria used to establish dissemination in time and space in multiple sclerosis should be applied for assessment of radiologically isolated syndromes; when a clinical attack occurs in patients with radiologically isolated syndromes with evidence of dissemination in time (who, by definition, have dissemination in space), a diagnosis of multiple sclerosis can be made (expert consensus)

Additional clarifications and summary statements

- MRI criteria for disease dissemination in time can remain unchanged
- Presence of non-enhancing black holes is not useful as a potential alternative criterion for dissemination in time in adults; the contribution of non-enhancing black holes seems to be more robust in distinguishing children with multiple sclerosis from children with monophasic demyelination (especially ADEM)
- In the case of atypical imaging presentation, other acquired and inherited white matter diseases should always be considered in the differential diagnosis
- At present, insufficient evidence exists to support earlier diagnosis of multiple sclerosis when using high-field or ultra-high-field scanners

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draft of these guidelines, which was circulated among the meeting participants and some additional experts for critical discussion and revision.

Dissemination in space

According to the 2010 McDonald criteria for multiple sclerosis,[10] dissemination in space can be established with at least one T2 lesion in at least two of four locations characteristic for multiple sclerosis (juxtacortical, periventricular, infratentorial, and spinal cord). We propose an increase in the number of lesions necessary to confirm involvement of the periventricular area from one to three, and to add an additional cardinal CNS location, the optic nerve (panel 2). Together with a spinal cord lesion, these changes increase the number of dissemination in space locations from four to five.

Periventricular lesions

A single lesion was deemed not sufficiently specific to determine whether involvement of the periventricular region is due to a demyelinating inflammatory event, and the use of one periventricular lesion for assessing dissemination in space has never been formally validated. Incidental periventricular lesions can be detected in healthy individuals and patients with other neurological disorders, including up to 30% of patients with migraine.[32] Importantly, three or more periventricular lesions was the most accurate threshold identified in a study using receiver-operating curve analysis by Barkhof and colleagues (known as the Barkhof criteria),[4] and was therefore applied in the 2001 and 2005 McDonald criteria.[1,8] Analysis of a large cohort of 652 patients with a clinically isolated syndrome has shown that, in patients who do not meet criteria for dissemination in space for multiple sclerosis, presence of three periventricular lesions, combined with age or presence of oligoclonal bands, is helpful to identify those at risk of multiple sclerosis.[33] In a retrospective study[34] in patients with a clinically isolated syndrome affecting the spinal cord, a prediction model, including those aged 40 years or younger, with three or more periventricular lesions, and with intrathecal immunoglobulin synthesis, identified patients who would develop multiple sclerosis with an accuracy of 78%.[34] In a multicentre trial[35] of 468 patients with a clinically isolated syndrome, presence of at least three periventricular lesions had a strong prognostic value for conversion to multiple sclerosis in 3-year period. In a study comparing patients with multiple sclerosis with those with primary and secondary CNS vasculitis,[36] presence of three or more periventricular lesions was the only individual component of the Barkhof criteria[4] that could be used to distinguish patients with multiple sclerosis from those with systemic lupus erythematosus or Sjögren's syndrome.

However, in paediatric patients, presence of a single periventricular lesion (and one or more T1-hypointense lesions) powerfully distinguished children with multiple sclerosis from children with monophasic demyelination.[37]

Optic nerve lesions

20–31% of patients with a clinically isolated syndrome present with acute optic neuritis.[38–40] Compared with other clinical presentations, adult patients with optic neuritis are more likely than those with acute

demyelination in other CNS locations to have a monophasic illness,[38,41,42] as confirmed by results of a study of 1058 patients with a clinically isolated syndrome.[39] Importantly, in this cohort and in other studies, the likelihood of optic neuritis being a monophasic illness was substantially reduced in the presence of CSF oligoclonal bands or clinically silent brain MRI lesions (with a hazard ratio [HR] of 5·1 for patients with one to three lesions and 11·3 for patients with ten or more lesions). Presence of even one clinically silent T2-hyperintense brain lesion in children with optic neuritis is highly associated with confirmation of a multiple sclerosis diagnosis,[43] whereas the absence of brain lesions strongly predicts a monophasic illness.[27]

Clinical features of optic neuritis (visual impairment, scotoma, red–green desaturation, and pain with ocular movement), MRI evidence of optic nerve inflammation (increased T2 signal, gadolinium enhancement, and optic nerve swelling), abnormalities on optical coherence tomography (evidence of retinal nerve fibre layer thinning), and neurophysiological abnormalities (especially delayed visual evoked potentials) all support inclusion of the optic nerve as an additional CNS area that might be affected at the onset of a clinically isolated syndrome. Clinical documentation of optic nerve atrophy or pallor, neurophysiological confirmation of optic nerve dysfunction (slowed conduction), or imaging features of clinically silent optic nerve inflammation (MRI lesions or retinal nerve fibre layer thinning) support dissemination in space and, in patients without concurrent visual symptoms, dissemination in time.

Cortical lesions

Results of pathology studies have shown extensive involvement of the grey matter in multiple sclerosis.[44–46] According to their location within the grey matter, different cortical lesion locations (subpial, purely intracortical, and leukocortical lesions on the grey matter–white matter border) have been identified.[45] Imaging cortical lesions is challenging, especially with conventional clinical MRI protocols. Different MRI techniques have been proposed and are being compared for their sensitivity for cortical lesion detection, including double inversion recovery,[47] phase-sensitive inversion recovery,[48–50] and magnetisation-prepared rapid acquisition with gradient echo[51] sequences (figure 1). Despite use of these techniques, results of correlative MRI pathology studies have shown that many cortical lesions remain invisible on MRI, at least with 1·5 T and 3·0 T MRI scanners.[52,53]

With double inversion recovery sequences, cortical lesions have been identified in more than 30% of patients with a clinically isolated syndrome.[54,55] In a cohort of 80 patients with a clinically isolated syndrome, with 4-year follow-up, the accuracy of MRI diagnostic criteria for multiple sclerosis increased when the presence of at least one intracortical lesion on baseline scans was considered.[55] Cortical lesion assessment might also help with differential diagnosis between multiple sclerosis and disorders that mimic multiple sclerosis, since cortical lesions have not been reported in patients with migraine with white matter T2 lesions[32] or neuromyelitis optica.[56] Intracortical lesions are also rare in healthy controls (identified in one of 30 individuals who were scanned with phase-sensitive inversion recovery sequences).[49]

Even with these promising results, many unsolved issues remain regarding inclusion of cortical lesion assessment in the diagnostic work-up of patients with a clinically isolated syndrome. First, MRI sequences used in research settings for identification of these lesions might not be available and easily implementable on most clinical scanners. Second, the acquisition parameters for these sequences still need to be standardised across scanning systems from different manufacturers and for various field strengths. Third, agreement among observers in assessment of these sequences is at best moderate (complete agreement 19% for double inversion recovery), and guidelines for their assessment are changing.[49,57] Fourth, different criteria and terms are applied by different research groups for the distinction between intracortical, leukocortical, mixed white matter and grey matter, and juxtacortical lesions.[47–50,55] Finally, subpial demyelination, which can be quite extensive, is usually not scored.[46]

Since intracortical, leukocortical, and juxtacortical lesions cannot be distinguished reliably and consistently on conventional MRI scans using most available MRI scanners in clinical settings, expert consensus was that these lesions should be combined in a single term (cortical/juxtacortical lesions) that indicates involvement of the white matter next to the cortex, the cortex, or both, thereby expanding the term juxtacortical lesion used in the 2010 McDonald criteria[10] for dissemination in space. When available, advanced imaging sequences should be applied to visualise cortical lesions.

Panel 2: Recommended 2016 MAGNIMS MRI criteria to establish disease dissemination in space in multiple sclerosis

Dissemination in space can be shown by involvement* of at least two of five areas of the CNS as follows:

- Three or more periventricular lesions
- One or more infratentorial lesion
- One or more spinal cord lesion
- One or more optic nerve lesion
- One or more cortical or juxtacortical lesion†

*If a patient has a brainstem or spinal cord syndrome, or optic neuritis, the symptomatic lesion (or lesions) are not excluded from the criteria and contribute to the lesion count. †This combined terminology indicates the involvement of the white matter next to the cortex, the involvement of the cortex, or both, thereby expanding the term juxtacortical lesion.

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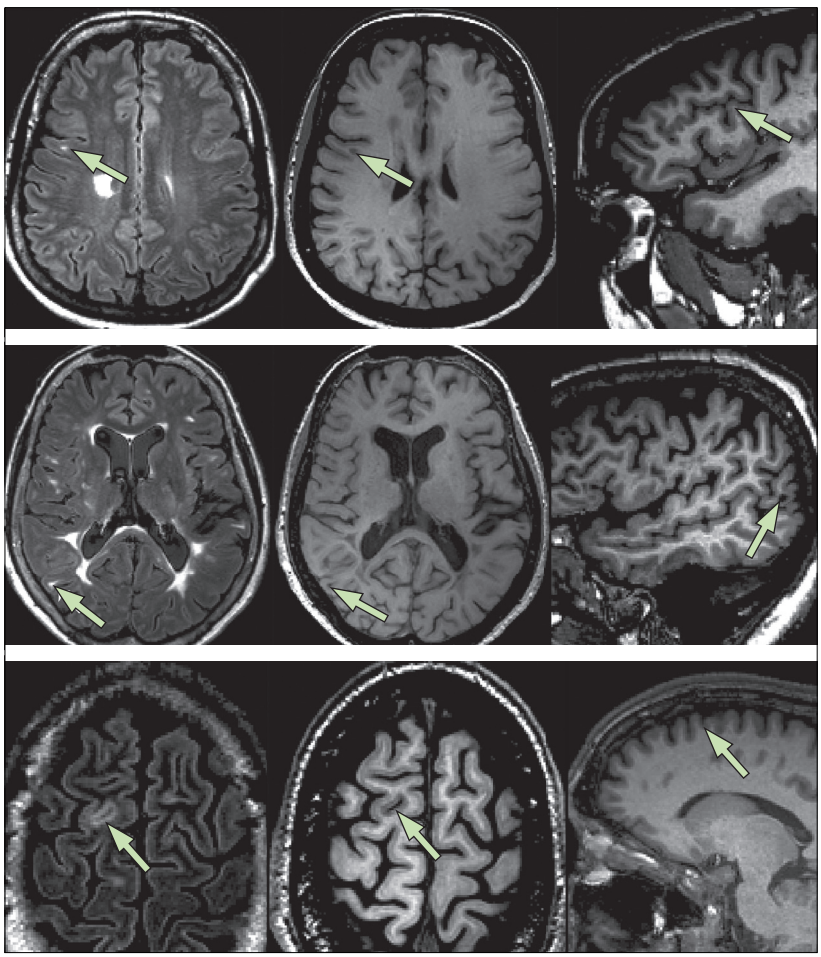

Figure 1: **Cortical and juxtacortical lesion detection with MRI**
Examples of lesion classification based on integrated analysis of double inversion recovery (left column) and magnetisation-prepared rapid acquisition with gradient echo (MPRAGE; middle and right columns) MRI sequences. Top row: a hyperintense lesion close to the cortex (green arrow) is visible on double inversion recovery MRI, but the MPRAGE images show that the lesion is located in the white matter. Middle row: a hyperintense lesion close to the cortex (green arrow) is visible on double inversion recovery MRI, and the MPRAGE images show that the location borders the cortex (juxtacortical). Bottom row: a hyperintense lesion close to the cortex (green arrow) is visible on double inversion recovery MRI, and the MPRAGE images show that the lesion is intracortical. Under the proposed system, the lesions in the middle and bottom rows would be classified as cortical/juxtacortical.

Dissemination in time

According to the 2010 McDonald criteria,[10] disease dissemination in time can be established by the following: presence of at least one new T2 or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI; or the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time.

Non-enhancing T1-hypointense lesions (black holes) are chronic lesions characterised by severe axonal damage.[58] In relapsing-remitting multiple sclerosis, brain T1-hypointense lesion volume increases by about 11% per year and is associated with long-term disability progression.[59,60] T1-hypointense lesion formation is more common in patients with long disease durations and progressive disease subtypes. For that reason, their presence in patients with a clinically isolated syndrome is indicative of an already-established multiple sclerosis disease process. The prevalence of non-enhancing T1-hypointense lesions and their added value for identification of adult patients with multiple sclerosis was analysed in a large multicentre study[61] of 520 patients with a clinically isolated syndrome. Non-enhancing black holes were fairly common in adult patients with a clinically isolated syndrome (36%) and were associated with an increased likelihood of multiple sclerosis diagnosis. However, the value of this magnetic resonance finding for prediction of a second clinical attack in these patients was lost when added to the other criteria.[61] Of note, T1-hypointese lesion assessment is still subjective and highly dependent on the type of T1-weighted sequence and field strength. Nevertheless, in paediatric patients with acute demyelination, presence of one or more T1-hypointense lesions was highly associated with subsequent confirmation of multiple sclerosis.[37]

The criteria for dissemination in time should therefore remain unchanged, and the presence of non-enhancing black holes should not be considered as a potential alternative criterion to show dissemination in time in adult patients with multiple sclerosis, but might be useful to identify multiple sclerosis in paediatric patients.

Symptomatic lesions

In patients with a clinically isolated syndrome, symptomatic lesions that align with an acute clinical deficit do not contribute to the dissemination in time or space components of existing multiple sclerosis diagnostic criteria.[10] Specifically, in patients with brainstem or spinal cord syndromes, lesions within the symptomatic region cannot be counted for dissemination in space. The simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time is a criterion to define dissemination in time.

In patients with a clinically isolated syndrome presenting with brainstem symptoms, results of a 2004 study[62] showed that the specificity of MRI criteria for dissemination in space (Barkhof's criteria[4] at that time) was lower than that reported in other clinically isolated syndromes (myelitis and optic neuritis; 61% *vs* 73%). A 2014 study[12] assessed the likelihood of multiple sclerosis confirmation in 35 (3%) of 954 patients with a single symptomatic lesion in the brainstem or spinal cord with a follow-up of almost 8 years. The HR for a diagnosis of multiple sclerosis was higher for patients with a symptomatic lesion (HR 7·2) than for those with a single asymptomatic lesion (5·7), or with no lesions (1·0), in the same regions. Another retrospective study[13] in 146 patients with a clinically isolated syndrome who fulfilled the 2010 McDonald diagnostic criteria[10] reported that the presence of a symptomatic lesion identified patients with multiple sclerosis with a high sensitivity.[13] In a study of 30 patients with a clinically isolated

syndrome who were followed up for a mean of 7·3 years (SD 1·98) after onset, the sensitivity of the dissemination in space criteria was 73% for the 2010 McDonald criteria, 80% when asymptomatic lesions in the symptomatic region were included, and 87% when any lesion in the symptomatic region was included; specificity was 73% for the 2010 McDonald criteria, 73% when asymptomatic lesions in the symptomatic region were included, and 73% when any lesion in the symptomatic region was included; and accuracy was 73% for the 2010 McDonald criteria, 77% when asymptomatic lesions in the symptomatic region were included, and 80% when any lesion in the symptomatic region was included.[14] These results suggest that inclusion of presence of lesions in the symptomatic region in criteria for dissemination in space might increase the sensitivity of MRI criteria for diagnosis of multiple sclerosis, without compromising specificity.

The diagnostic effect of counting any gadolinium-enhancing and non-enhancing lesions (not only asymptomatic, but also symptomatic) in criteria for dissemination in time has also been analysed.[15] Inclusion of symptomatic lesions in the dissemination in time criteria increased the proportion of patients meeting the MRI diagnostic criteria for multiple sclerosis to 33%, compared with 30% for those diagnosed without inclusion of such lesions, with three additional patients meeting the 2010 McDonald criteria.[10] In fact, deciding what is symptomatic or not is often very difficult. This distinction is fairly straightforward in brainstem and spinal cord presentations but not in other clinical scenarios, and on the basis of the evidence, the expert panel recommends that no distinction needs to be made between symptomatic and asymptomatic MRI lesions to establish dissemination in both space and time.

Spinal cord imaging

As set out in the 2010 McDonald criteria,[10] clinically silent spinal cord lesions can contribute to assessment of dissemination in space and time, and on the basis of the available evidence, the expert panel recommends use of spinal cord MRI to establish dissemination in space. At symptom onset, spinal cord imaging is recommended in patients with clinical features suggestive of spinal cord involvement to exclude alternative cord pathology (eg, compression, spinal cord tumour, neuromyelitis optica, or vasculitides) and in those with non-spinal clinically isolated syndromes that do not fulfil brain MRI criteria for dissemination in space. In patients with a non-spinal clinically isolated syndrome that does not meet brain MRI criteria for dissemination in space, whole cord imaging showed that the presence of one spinal cord lesion can be used to identify patients at high risk of multiple sclerosis confirmation.[16] Imaging of the whole cord, with at least two magnetic resonance sequences (eg, T2 and short T1 inversion recovery, T2 and double inversion recovery, T2 and post-contrast T1 sequences) is preferable to increase confidence in lesion identification, in part because about 40% of spinal cord lesions are identified in the thoracolumbar region (figure 2).[17–19]

The value of spinal cord imaging to establish dissemination in time in patients without accrual of deficits associated with the spinal cord is low, since new clinically silent cord lesions are not frequent; spinal cord imaging in these patients is therefore not recommended by the expert panel.

Primary progressive multiple sclerosis

In all formulations of the diagnostic criteria, diagnosis of primary progressive multiple sclerosis has been separated from that of the more common relapse-onset form of the disease. Since no evidence exists that imaging features differ substantially between patients with relapse-onset multiple sclerosis and patients with primary progressive multiple sclerosis, the expert group agreed that use of similar criteria would simplify the diagnostic work-up of patients with primary progressive multiple sclerosis. In 2009, unification of MRI criteria for dissemination in space was proposed for primary progressive multiple sclerosis and relapsing-remitting multiple sclerosis,[63] which was only partly integrated in the 2010 McDonald criteria.[10] According to these criteria, dissemination in space in primary progressive multiple sclerosis is defined by occurrence of two of the following three criteria: dissemination in space in the brain, based on presence of at least one lesion in at least one area characteristic for multiple sclerosis (periventricular, juxtacortical, or infratentorial regions); dissemination in space in the spinal cord, based on presence of at least two lesions in the spinal cord; and positive CSF examination.

The sensitivity of the spinal cord criteria and the usefulness of CSF examination were retrospectively analysed in a cohort of 95 patients with primary progressive multiple sclerosis.[20] In that study, if the criterion for two or more cord lesions was changed to

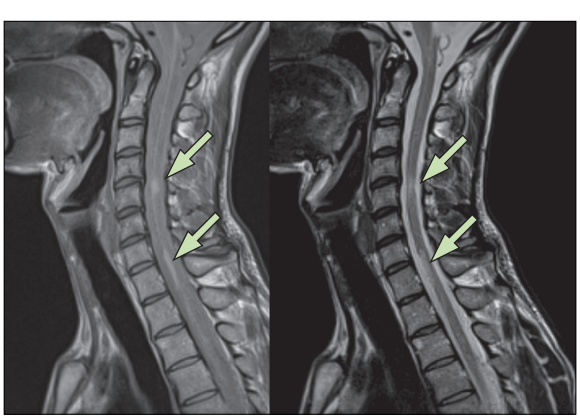

Figure 2: **Spinal cord MRI in a patient with multiple sclerosis**
Sagittal intermediate and T2-weighted dual echo fast-spin echo MRIs of the spinal cord from a female patient aged 45 years with multiple sclerosis. Abnormalities (arrows) are present both at the cervical and thoracic level of the cord.

one or more cord lesions (whether symptomatic or not), an increased number of patients would meet the spinal cord criteria for diagnosis, with increasing sensitivity and simplification of the criteria. However, specificity of these simplified criteria still needs to be tested.

In view of the evidence, the expert consensus was that identical dissemination in space criteria should be used for primary progressive multiple sclerosis and relapse-onset multiple sclerosis, with use of CSF testing for confirmation in uncertain cases.

Paediatric populations

The 2010 consensus was that the proposed MRI criteria[10] could be used for most paediatric patients with multiple sclerosis. An alert specified that use of the 2010 McDonald criteria for multiple sclerosis at baseline was not applicable for children with encephalopathy and multifocal neurological deficits meeting criteria for acute disseminated encephalomyelitis.[10] Such children have many lesions, some of which might enhance; however, when defined with international consensus criteria for acute disseminated encephalomyelitis, 95% have a monophasic illness.[27] Diagnosis of multiple sclerosis in paediatric patients manifesting initially with a first attack that resembles acute disseminated encephalomyelitis relies on clinical or MRI evidence of further non-acute disseminated encephalomyelitis attacks or accrual of clinically silent MRI lesions.

Although results of a study of 52 patients[25] suggested that inclusion of spinal cord imaging at first attack does not increase accuracy of the 2010 McDonald criteria,[10] a retrospective investigation[22] of 85 patients showed that addition of spinal cord MRI was helpful in identification of dissemination in time and space in 10% of cases. Several studies[21–26] have confirmed that the 2010 McDonald criteria perform better than or similar to previously proposed paediatric multiple sclerosis criteria for diagnosis of children with non-acute disseminated encephalomyelitis presentations and paediatric patients older than 11 years, and the consensus group therefore recommend caution when using these criteria in children younger than 11 years. Clinical and MRI serial assessment to confirm new lesions over time might be especially important in this age group.[27]

In line with previous criteria[10] and the above evidence, we agreed that MRI criteria for dissemination in time and space identical to those applied in adults should be used in children aged 11 years or older who have non-acute-disseminated-encephalomyelitis-like presentation.

Non-white populations

The 2010 McDonald criteria have been developed and tested mostly in adult white European and North American populations, and their formulation states that validation is needed in Asian and Latin American populations.[10] Between 2011 and 2015, performance of MRI diagnostic criteria has been tested in Korean,[28] Taiwanese,[29] Argentinean (including a sub-analysis applied only to non-European descendants—ie, mestizos, natives, and zambos),[30] and Russian[31] patients with clinically isolated syndromes, after careful exclusion of alternative neurological disorders, such as neuromyelitis optica and neuromyelitis optica spectrum disorder in Korean patients.[28] All these studies provided evidence that the 2010 McDonald criteria apply well irrespective of world region, and, therefore, the consensus view was that MRI criteria for dissemination in time and space apply equally well to patients from Asia and Latin America as to patients from Europe and North America.

Radiologically isolated syndromes

Availability of MRI assessment for indications unrelated to multiple sclerosis has led to increased recognition of individuals with incidental brain lesions consistent with multiple sclerosis. Criteria have been proposed to identify imaging features that are suggestive of a clinically asymptomatic demyelinating disorder, including fulfilment of at least three of four Barkhof criteria[4] for dissemination in space.[64,65] The 2010 McDonald criteria[10] concluded that "a firm diagnosis of [multiple sclerosis] based on incidental findings on MRI alone, even with additional supportive findings on evoked potentials or typical CSF findings in the absence of [multiple sclerosis]-relevant clinical symptoms, is problematic." We propose that the MRI criteria used to establish dissemination in time and space in multiple sclerosis should be applied for assessment of radiologically isolated syndromes, and that when a clinical attack occurs in patients with radiologically isolated syndromes with evidence of dissemination in time (who by definition have dissemination in space), a diagnosis of multiple sclerosis can be made. Thus, we agreed that people should not be diagnosed with multiple sclerosis on the basis of MRI findings alone, and at least one clinical event consistent with acute demyelination remains a cornerstone for multiple sclerosis diagnosis.

Use of advanced MRI techniques to characterise CNS involvement in patients with radiologically isolated syndromes has shown extensive axonal damage (measured with magnetic resonance spectroscopy)[66] and a perhaps surprisingly high percentage (40%) of patients with cortical lesions (which were more frequent in patients with CSF oligoclonal bands, cervical cord lesions, and dissemination in time on brain MRI).[67]

About two-thirds of patients with radiologically isolated syndromes develop new lesions on longitudinal MRI scans and a third develop neurological symptoms within 5 years, especially those with gadolinium-enhancing or spinal cord lesions.[68] In people with clinically silent brain lesions consistent with multiple sclerosis, presence of oligoclonal bands, younger age (≤37 years), male sex, and abnormal visual evoked potentials were predictors of development of a first clinical attack. Focusing on MRI,

the presence of gadolinium-enhancing lesions[69] and asymptomatic spinal cord lesions (cervical or thoracic) are predictors of clinical change.[68,70]

At present, more specific characterisation of people with radiologically isolated syndromes is needed, and prospective long-term studies should be done to estimate the risk of development of multiple sclerosis in these patients. As a result, a firm recommendation for radiologically isolated syndromes is not possible. However, even at this stage, individuals who have several risk factors clearly need to be distinguished from those without these factors, since they are likely to have a prodromal disorder, and specific criteria are needed for prompt diagnosis when the first symptom of CNS involvement occurs.

Differential diagnosis

Exclusion of alternative diagnoses that can mimic multiple sclerosis, including atypical demyelination and neuromyelitis optica, is imperative when applying the 2010 McDonald criteria.[10] From an imaging perspective, many inherited and acquired disorders could manifest with evidence of dissemination in time or space, or both, and these disorders should be included in the differential diagnosis of multiple-sclerosis-like lesions. A timely recognition of imaging red flags in the work-up of patients suspected of having multiple sclerosis should alert clinicians to reconsider the differential diagnosis more extensively and do some additional analyses.[71] Several reviews discuss imaging features of the main acquired and inherited white matter disorders that can enter the differential diagnosis of multiple sclerosis,[71–73] and, in our view, when atypical imaging presentation occurs, these disorders should be considered.

In the 2010 McDonald criteria,[10] a specific focus was the differential diagnosis between multiple sclerosis and neuromyelitis optica spectrum disorders. Up to 70% of patients with neuromyelitis optica spectrum disorders at onset have brain MRI lesions. Brain, optic nerve, and spinal cord MRI findings of patients with neuromyelitis optica spectrum disorders have been reviewed,[74] and revised diagnostic criteria for neuromyelitis optica spectrum disorders have been proposed.[75] The International Panel for Neuromyelitis Optica Diagnosis proposed use of the unifying term neuromyelitis optica spectrum disorders, which was stratified further by AQP4–IgG testing. According to this revision, for patients with a positive AQP4–IgG test, at least one core clinical characteristic is needed for a diagnosis of neuromyelitis optica spectrum disorder; these characteristics include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. For AQP4–IgG-negative patients or patients with unknown AQP4–IgG status, stringent clinical criteria, with additional neuroimaging findings, are needed. Specifically, for a diagnosis of acute optic neuritis, brain MRI is needed to show either of the following: normal findings or only non-specific white matter lesions; or a T2-hyperintense or T1-weighted gadolinium-enhancing lesion extending for more than half the optic nerve length or involving the optic chiasm. For a diagnosis of acute myelitis, presence of an associated intramedullary MRI lesion extending for more than three contiguous segments (longitudinally extensive transverse myelitis) or three contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis needs to be shown. Diagnosis of area postrema syndrome depends on the presence of associated dorsal medulla or area postrema lesions. Finally, associated peri-ependymal brainstem lesions are needed for a diagnosis of an acute brainstem syndrome.

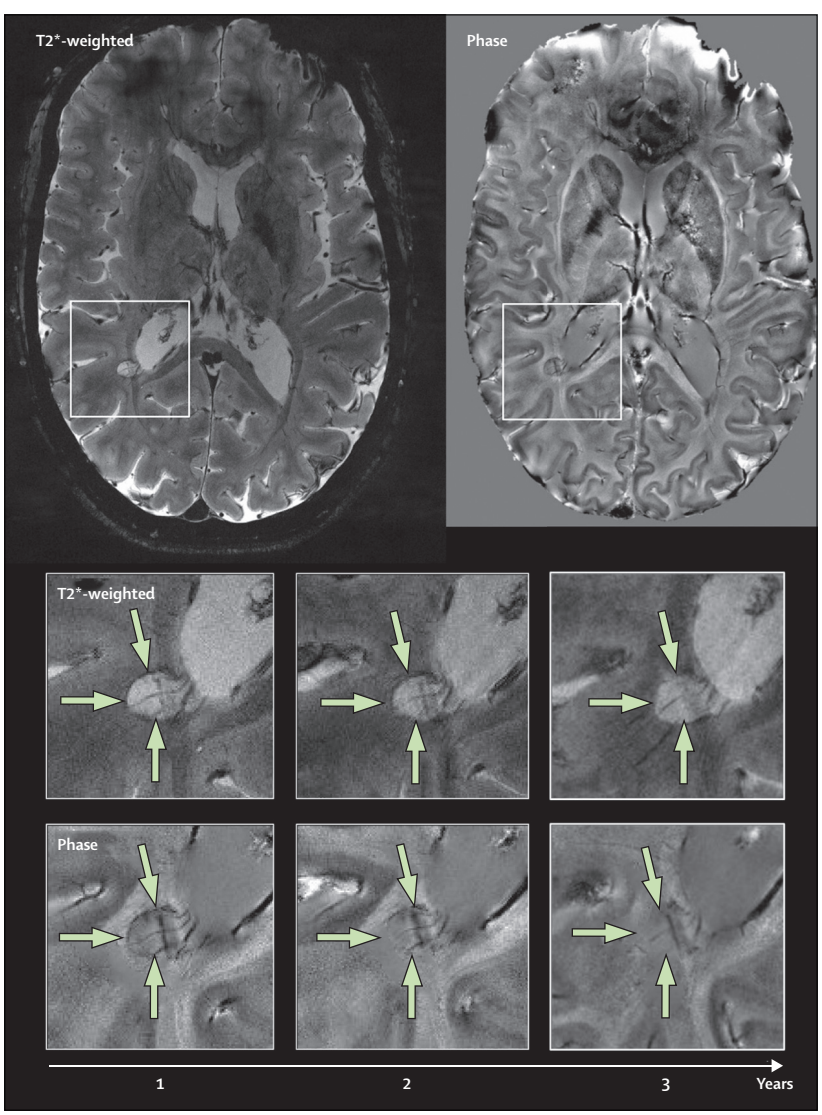

Figure 3: **Ultra-high-field brain MRI in a patient with relapsing-remitting multiple sclerosis**
T2*-weighted gradient-echo and phase axial MRIs, obtained with a 7·0 T scanner, from a 36-year-old woman with relapsing-remitting multiple sclerosis. A periventricular non-enhancing lesion with a paramagnetic rim (green arrows) is shown. A prominent central vein is visible on all images. The lesion maintains the same morphological features at medium-term (3 years) follow-up imaging (magnified boxes).

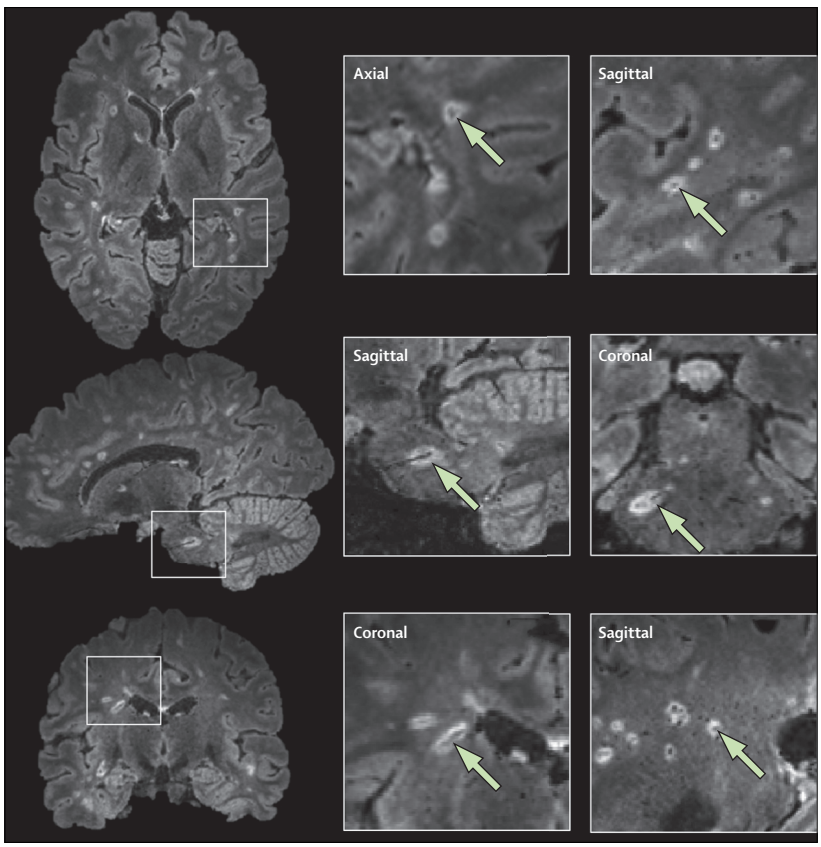

Figure 4: **Identification of the central vessels with MRI**
Non-contrast FLAIR* images (axial, sagittal, and coronal views), obtained with a 3·0 T scanner, from a 33-year-old woman with multiple sclerosis. A conspicuous central vessel is clearly visible in most hyperintense lesions. Visualisation of the central vessel in at least two perpendicular views (arrows in magnified boxes) is needed to define perivenular lesions. FLAIR*=combined T2*-weighted MRI and fluid-attenuated inversion recovery MRI.

Use of high-field and ultra-high-field scanners

High-field scanners (3·0 T)

Compared with 1·5 T scanners, use of high-field-strength scanners (3·0 T) enables detection of a significantly higher number of lesions in patients with clinically isolated syndromes,[76,77] with improved recognition of lesions involving the cortical,[78] infratentorial, and periventricular regions.[76] Comparison of MRI criteria performance at 1·5 T versus 3·0 T in 40 patients with clinically isolated syndromes showed that one additional patient was diagnosed with dissemination in space at high field, without improvement for dissemination in time.[79]

Ultra-high-field scanners (7·0 T)

Ultra-high-field MRI enables detection of a significantly higher number of lesions,[80] and improved definition of lesions located in the white and grey matter with respect to their morphology and association with the vasculature,[81–85] than was previously shown with 1·5 T[86] or 3·0 T[87] scanners. Whether assessment of lesion number and distribution with ultra-high-field MRI scanners helps to make an earlier diagnosis of multiple sclerosis in patients with clinically isolated syndromes has not yet been assessed. Several studies have identified some interesting lesion characteristics, which can aid differential diagnosis between multiple sclerosis and other neurological disorders. The improved definition of the relation between demyelinating lesions and the intraparenchymal venous system, obtained by use of T2*-weighted magnitude and phase imaging, confirms results of pathological studies showing that many multiple sclerosis plaques form around the microvasculature.[81–85,88,89] Perivenular lesion location can help to distinguish white matter lesions in patients with multiple sclerosis from incidental (ischaemic) white matter lesions.[85,89] This finding has been reinforced by investigation of blood–brain barrier abnormalities in multiple sclerosis at 7·0 T and 3·0 T, which showed that most enhancing lesions are perivenular and that the smallest lesions have a centrifugal pattern of enhancement, suggesting that they grow outwards from a central vein.[90,91] The presence of a central small vein and a rim of hypointensity on T2*-weighted magnitude or FLAIR* (combined T2*-weighted and FLAIR) imaging,[85] obtained with a 7·0 T scanner, could be a distinctive feature of multiple sclerosis white matter lesions, which might assist in differentiation from lesions of patients with neuromyelitis optica spectrum disorders[92] or Susac syndrome.[93]

A few studies have tracked the longitudinal changes of the above-mentioned abnormalities (figure 3). Results of a longitudinal study[80] of 29 patients with possible but unclear diagnosis have shown that the presence of a central vein in most lesions can be used to accurately identify patients with multiple sclerosis.[80] Another study[94] showed that phase-ring lesions remained unchanged during a 2·5-year period in five patients with relapsing-remitting multiple sclerosis, whereas such a ring can be transient in acute lesions.[90,91]

In summary, use of high-field or ultra-high-field scanners is not likely to result in an earlier diagnosis. However, lesion features distinctive of multiple sclerosis could emerge from use of these scanners and might eventually enhance differentiation of multiple sclerosis from other diseases.

Future perspectives

The expert panel noted that some promising measures deserve further investigation before being moved (or not) to diagnostic criteria in the future.

For identification of the central vein, sequences capable of showing these features on 3·0 T and 1·5 T scanners need to be standardised, and standardised definitions need to be created for identification of central vessels. So far, central vessels have been identified if they could be visualised in at least two perpendicular planes, appeared linear in at least one plane, and were completely surrounded by hyperintense signal in at least one plane (figure 4).[89] Whether central veins are confirmatory for

multiple sclerosis lesions needs further study with appropriate disease comparisons.

For identification of the hypointense lesional rim on T2*-weighted magnitude or phase images, longitudinal studies need to be done at 3·0 T and 7·0 T; magnetic resonance sequences across 3·0 T scanners from different manufacturers need to be standardised and clinically implemented; value in predicting conversion to multiple sclerosis and disability progression in patients with clinically isolated symptoms needs to be analysed; and different multiple sclerosis clinical phenotypes and other neurological disorders that can mimic multiple sclerosis need to be studied.

For identification of cortical pathology, high-field-strength imaging is expected to enable identification of cortical lesions more reliably than conventional MRI but is not likely to be available in clinical practice in the near term. More advanced techniques for cortical lesion identification at 3·0 T might prove valuable in multiple sclerosis diagnosis. The definition of standardised, up-to-date guidelines for cortical lesion classification is also pending.

Conclusions

Assessment of MRI scans should be done in the appropriate clinical context. The premise of these guidelines and criteria is that we assume a basic knowledge of what constitutes a lesion. The largest linear measurement for lesion definition should be 3 mm or more in at least one plane. Therefore, lesion identification should be done by trained, expert personnel. Image quality should be of a high standard. A conservative approach to identification of lesions should be used.

In the diagnostic work-up of patients with suspected multiple sclerosis, use of post-contrast sequences provides important information for differential diagnosis. However, the US Food and Drug Administration has issued a safety communication for the long-term effects of repeated administration of gadolinium-based contrast agents, after the description of deposition of gadolinium in the brains of some patients who underwent several contrast-enhanced MRI scans. The effect of these safety concerns is unknown at present.

MRI remains a valuable tool for identification of children and adults with multiple sclerosis, both at the time of an incident attack and when applied serially to confirm the chronic nature of this disease. Advanced imaging techniques provide information about regional CNS involvement with greater sensitivity than conventional MRI and might add to diagnostic specificity. Whether MRI features consistent with multiple sclerosis in the absence of clinical involvement can confirm multiple sclerosis diagnosis remains an area of debate that needs further study and deliberation, especially in view of evidence that some such individuals have focal and global loss of tissue integrity but are not eligible for multiple-sclerosis-directed therapies at present. Since high-field-strength imaging and more recently developed sequences enable improved pathology-level interrogation of the CNS, the fundamental question of what defines a disease such as multiple sclerosis will need to be answered.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "clinically isolated syndrome", "multiple sclerosis", "McDonald criteria", "diagnosis", "differential diagnosis", "cortical lesions", "white matter", "lesions", "cortical lesions", "brain", "spinal cord", "MRI", "optic nerve", "disease dissemination in space", "disease dissemination in time", "radiologically isolated syndromes", "pediatric MS", "T1-hypointense lesions", "symptomatic lesions", "primary progressive multiple sclerosis", "non-caucasian populations", "neuromyelitis optica", "neuromyelitis optica spectrum disorders", "high field", and "ultra-high field" from Jan 1, 1979, to Nov 15, 2015. Articles were also identified through searches of our own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Contributors

MF and FB developed the idea for the meeting, organised it, chaired it, and framed the structure of this Review. AR, FB, JS-G, LK, MAR, MT, NDS, NE, and OC participated in the meeting, summarised different aspects for the discussions, and took part in the discussions. JLF, CG, JP, and DSR participated in the meeting and discussions. BB and XM were involved after the meeting for critical discussion and revision. The complete Review was commented on, revised, and approved by all authors.

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Declaration of interests

Travel expenses for the workshop were paid by Novartis through a provider. The speakers did not receive direct reimbursement. MF serves on scientific advisory boards for Teva Pharmaceutical Industries, has received compensation for consulting services and speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries, and receives research support from Biogen Idec, Teva Pharmaceutical Industries, and Novartis. MAR has received speakers honoraria from Biogen Idec, Novartis, Genzyme, Sanofi-Aventis, and Excemed. OC serves as a consultant for GE, Biogen Idec, and Novartis, and all the payments are made to the institution (Queen Square MS Centre, UCL Institute of Neurology, London, UK). NDS has received honoraria from Schering, Biogen Idec, Teva Pharmaceutical Industries,

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Novartis, Genzyme, and Merck Serono SA for consulting services, speaking, and travel support. He serves on advisory boards for Biogen Idec, Merck Serono SA, and Novartis. NE has received honoraria from Biogen Idec, Novartis, and Genzyme for consulting services, speaking, and travel support. He serves on advisory boards for Biogen Idec, Merck Serono, and Novartis. LK's institution (University Hospital Basel) has received in the past 3 years and used exclusively for research support steering committee, advisory board, and consultancy fees from Actelion, Addex, Bayer HealthCare, Biogen Idec, Biotica, Genzyme, Eli-Lilly & Company, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva Pharmaceutical Industries, UCB, and Xenoport, speaker fees from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis, and Teva Pharmaceutical Industries, support of educational activities from Bayer HealthCare, Biogen Idec, CSL Behring, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, and Teva Pharmaceutical Industries, royalties from Neurostatus Systems GmbH, and grants from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis, Roche, and Roche Research Foundations. AR serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, has received speaker honoraria from Bayer HealthCare Pharmaceuticals, Genzyme, Bracco, Merck Serono, Teva Pharmaceutical Industries, OLEA Medical, Stendhal, Novartis, and Biogen Idec, and has research agreements with Siemens AG. JS-G has received compensation for serving on scientific advisory boards or on speaker's bureaus from Biogen Idec, Merck Serono, Novartis, Teva Pharmaceutical Industries, and Sanofi-Aventis. MT has received compensation for consulting services and speaker's fees from Bayer Schering, Merck Serono, Biogen Idec, Teva Pharmaceutical Industries, Sanofi-Aventis, and Novartis. JLF has served on scientific advisory boards for, and received funding of travel for participation in scientific advisory boards and honoraria from, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Takeda, and Teva Pharmaceutical Industries. CG has received compensation for consulting from Bayer HealthCare Pharmaceuticals and Biogen Idec and as a speaker for lectures from Biogen Idec, Bayer HealthCare Pharmaceuticals, Genzyme, Merck Serono, Novartis, and Teva Pharmaceutical Industries. JP reports personal fees from Biogen Idec, Teva Pharmaceutical Industries, Merck Serono, Bayer Schering, Novartis, Chugai Pharma, Ono Pharmaceuticals Co, and CI consulting, and grants from Merck Serono, Bayer Schering, and Novartis. DSR reports grants from Vertex Pharmaceuticals and patents PCT/US2012/067997 and PCT/US2013/033334 pending for development of lesion segmentation algorithms. BB serves as a centralised MRI reviewer for Novartis, and an unpaid advisor regarding paediatric multiple sclerosis clinical trial design for Novartis, Biogen Idec, and Teva Neuroscience. XM has received speaker's honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past 5 years with Actelion, Almirall, Bayer, Biogen Idec, Genzyme, Merck Serono, Novartis, Octapharma, Receptos, Roche, Sanofi-Genzyme, Teva Pharmaceutical Industries, and Trophos. FB serves as a scientific consultant to Bayer Schering Pharma, Sanofi-Aventis, Biogen Idec, Teva Pharmaceutical Industries, Merck Serono, Novartis, Roche, Synthon BV, Janssen, Genzyme, and Toshiba Medical systems, and has served on speakers' bureaus for Serono Symposia Foundation and MedScape.

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