Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria

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Advances in the understanding of multiple sclerosis and the development of biomarkers of pathophysiology prompted a substantial revision of the 2017 McDonald diagnostic criteria. The new 2024 McDonald criteria provide a unified approach for diagnosing multiple sclerosis in individuals with relapsing or progressive courses throughout the lifespan (ie, from paediatric to late-life presentations). The optic nerve can now serve as a fifth anatomical location within the CNS for diagnosis. The central vein sign, paramagnetic rim lesions, and kappa free-light chain concentrations in CSF can be used, when available, to provide supportive evidence and confer specificity for a diagnosis of multiple sclerosis in specific situations. In certain cases, radiologically isolated syndrome or neurological symptoms that do not constitute a clear attack or progression of disability can fulfil the criteria for a multiple sclerosis diagnosis. We also provide guidance for the diagnosis of multiple sclerosis in older individuals (≥50 years) and those with comorbidities. The 2024 revised criteria should expedite the diagnosis of multiple sclerosis, while maintaining specificity.

Introduction

Diagnosing multiple sclerosis requires a balance between facilitating early recognition of disease and avoiding misdiagnosis. Historically, the diagnosis of multiple sclerosis was based on clinical symptoms.[1–5] However, the advent of MRI has enabled the identification of characteristic lesions in typical CNS regions suggestive of multiple sclerosis. Laboratory findings (eg, the presence of CSF-restricted oligoclonal bands) can now identify the existence of an inflammatory process within the CNS.[6] Within the past two decades, diagnostic criteria were revised to enable earlier diagnosis of multiple sclerosis by incorporating these MRI and CSF biomarkers. The evolution of the criteria has facilitated earlier initiation of disease-modifying therapy and improved clinical outcomes.[7–9]

The 2001 McDonald revisions incorporated detailed MRI assessment into the diagnostic criteria for the first time. Subsequent revisions of the criteria incorporated new evidence that progressively improved their performance. The 2001 McDonald criteria and its 2005 revision introduced and further refined the concept of clinical progression as a requirement for diagnosing progressive multiple sclerosis.[2,3] The 2010 criteria refined the definition of dissemination in space to include four anatomical locations within the CNS (ie, periventricular, juxtacortical, infratentorial, and spinal cord), and dissemination in time (ie, shown by the presence of new lesions on follow-up MRI or simultaneous gadolinium-enhancing and non-enhancing lesions on a single MRI).[4]

The 2017 revisions of the McDonald criteria further facilitated earlier diagnosis with the inclusion of CSF-oligoclonal bands as a substitute for dissemination in time (DIT) in patients fulfilling only criteria for dissemination in space (DIS). Cortical lesions and both symptomatic and asymptomatic MRI lesions can also show DIS and DIT.[5] The high sensitivity and specificity of the 2017 McDonald criteria are now well-established across a range of MRI field strengths, clinical settings, ages (eg, paediatric and late-onset cases), and ethnically diverse and geographically diverse populations.[10–16] Consequently, the time from the first clinical attack to multiple sclerosis diagnosis and treatment initiation has markedly decreased and could be one of several factors contributing to improved clinical outcomes.[7,9] With the 2024 McDonald criteria, we aim at expediting diagnosis even further, and diminish time to treatment initiation.

Rationale and methods for the 2024 revisions

Since the publication of the 2017 revision of the McDonald criteria, substantial progress has been made in several areas. First, evidence has shown added diagnostic sensitivity without losing specificity by including the optic nerve among the potential anatomical locations for diagnosing multiple sclerosis.[16–20]

Second, a typical clinical presentation is currently required to diagnose multiple sclerosis. However, clinicians might encounter individuals with radiologically isolated syndrome (appendix pp 1–3) or patients with neurological symptoms that do not constitute a clear typical attack or progression of disability (eg, paroxysmal symptoms or other non-specific neurological symptoms).[21] Recent studies suggest that some of these patients display MRI and CSF features similar to people

with established multiple sclerosis, and have the same risk for subsequent clinical or radiological activity.[22–25] The lack of initial typical clinical findings in radiologically isolated syndrome and in other non-specific presentations might reflect complex interactions between the locations of injury and compensatory mechanisms in the brain rather than the absence of biological disease. Other fields, such as research in Parkinson's disease and Alzheimer's disease, are moving toward biologically based diagnostic criteria.[26–28]

Third, multiple sclerosis is a diagnosis of exclusion and should be reassessed periodically, considering the harmful consequences of not only underdiagnosis, but also of misdiagnosis.[29] Previously, diagnosing multiple sclerosis was possible entirely on the basis of clinical grounds, according to the presence of at least two attacks with clinical or historical evidence in different anatomical locations and in the absence of a better explanation for the symptoms.[5] However, the typical clinical presentations of multiple sclerosis can overlap with those of other conditions. For instance, differentiation between multiple sclerosis, neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) might only be possible with imaging and antibody testing.[30–32] Although the 2017 McDonald criteria allowed for the diagnosis of multiple sclerosis without an MRI if there were two or more clinical attacks, MRI was highly recommended because of the heightened risk of misdiagnosis.[5]

Fourth, although DIT enhances diagnostic specificity, it is not always required and could unnecessarily delay initiation of treatment to avoid further disease activity. The 2017 McDonald criteria already included CSF-oligoclonal bands as a substitute tool for DIT, with marked improvements in diagnostic accuracy. This development has prompted further consideration of the necessity of showing DIT for the diagnosis of multiple sclerosis.[10–16]

Fifth, evidence suggesting that the various clinical presentations of multiple sclerosis form part of a continuum, and that progressive-onset and relapsing-onset multiple sclerosis share similar disease mechanisms, challenge the need for continued use of separate diagnostic criteria for progressive-onset multiple sclerosis.[33]

Sixth, the potential for misdiagnosis exists in relation to comorbidities across the age spectrum, particularly with respect to paediatric demyelination, and the increased awareness of MOGAD as a dominant presentation in children with demyelination.[34] Besides advances in these six areas, substantial knowledge and evidence have also accumulated on disease mechanisms and related imaging and laboratory markers.[33,35–37] Collectively, these advances lay the foundation for the 2024 revision of the diagnostic criteria.

The International Advisory Committee on Clinical Trials, sponsored by the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the US National Multiple Sclerosis Society (NMSS), hereinafter the Committee, served as the convening body for the development of the 2017 McDonald criteria and continued in this role for the 2024 revisions. Four virtual meetings of the Committee were convened in 2022 and 2023, during which the invited experts reviewed evidence and provided their interpretation of the available evidence related to the six aforementioned topics.

A consensus conference (Nov 29–Dec 2, 2023, in Barcelona, Spain) brought together 56 contributors, with a broad representation of expertise in neurology, neuroradiology, neuro-ophthalmology, laboratory testing, clinical management, and epidemiology, and people with lived experience of multiple sclerosis. The conference included 32 members of the Committee and additional contributors from several countries with high-resource, mid-resource, or low-resource settings. The additional participants were selected by the steering committee (XM, PAC, TC, CLF, JO, and AJT). Particular attention was given to incorporating the opinions from experts working with populations or in geographic regions known to have an historically underappreciated yet epidemiologically significant burden of multiple sclerosis.

The conference used the modified-nominal group technique to make consensus recommendations.[38] 66 voting statements were developed by the conference steering committee on the basis of information presented in preparatory meetings (see the appendix pp 4–5 for the voting statements and results). After evidence related to individual topics was presented by an expert, all conference participants anonymously voted electronically on a series of general statements and recommendations using a five-point Likert scale (ie, strongly agree, agree, neither agree or disagree, disagree, or strongly disagree). Consensus was defined as 90% of conference participants recording a vote and if there was 80% agreement (ie, strongly agree and agree). Statements receiving approval of 70–79% of participants were eligible for further discussion and a revote. Of the 76 voting statements, four were considered for revote following further discussion during the same meeting. The revoted statements are noted in the appendix (p 6). Subsequently, the criteria were presented at various meetings, including at a plenary session at ECTRIMS 2024 in Copenhagen (Denmark), where they were circulated among all conference participants to generate further feedback before an agreed-upon final summary.

Participants of the consensus conference affirmed two general principles for the diagnosis of multiple sclerosis: (1) the worldwide applicability of the diagnostic criteria; and (2), the essential role of paraclinical tests in the diagnosis of multiple sclerosis (panel 1). These principles serve as the foundation for the 2024 revisions to the criteria.

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Panel 1: **The two fundamental principles for the diagnosis of multiple sclerosis**

Worldwide applicability of diagnostic criteria

A central tenet of our approach is that multiple sclerosis is a global disease. While multiple sclerosis prevalence differs across geographic regions and ethnicities, there are no substantial differences in clinical presentations or MRI or CSF findings that could affect the sensitivity and specificity of diagnosis, suggesting that the same set of criteria should be applied worldwide.[10–15,39–43] Conference participants recognised the challenges associated with restricted global access to MRI, laboratory testing, and treatments; and endeavoured to facilitate the application of the revised criteria by incorporating new and potentially more accessible paraclinical tools, while simplifying some requirements. Guidance related to global implementation in different settings of the 2024 criteria will be addressed in subsequent publications.

Essential role of paraclinical diagnostic tests

The diagnosis of multiple sclerosis is conventionally based on the presence of symptoms typical of demyelinating disease, objective evidence of CNS white matter lesions typical of multiple sclerosis, and no better explanation.[5,21,44] The definitions of symptoms and signs of demyelinating disease are based on accurate medical history, neurological examination, and exclusion of other diagnostic possibilities.[21] The exclusion of mimics has been the most challenging aspect across different sets of criteria. Presentations considered non-specific (eg, seizures) or typical symptoms of multiple sclerosis (eg, trigeminal neuralgia) in patients without a clear attack or objective progression is sometimes caused by focal demyelination, and multiple sclerosis can be discovered incidentally; for example, while investigating unspecific symptoms, such as headache.[45,46] In contrast, typical presentations, such as optic neuritis and myelitis, can be due to other CNS inflammatory diseases.[21] Some disorders that can present with multiple sclerosis-like symptoms, including neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein antibody-associated disease, are diagnosed on the basis of paraclinical evidence of biological mechanisms (eg, MRI features and disease-specific antibodies).[30–32] Therefore, while clinical history and examination remain fundamental, the diagnosis of multiple sclerosis should be corroborated by paraclinical tests, with brain and spinal cord MRI being the most useful diagnostic paraclinical tools. Nonetheless, in exceptional circumstances, a pragmatic approach can be appropriate.

The optic nerve as a fifth anatomical location

Approximately 25% of people with multiple sclerosis present with optic neuritis as the initial manifestation, and most patients with multiple sclerosis exhibit optic nerve involvement postmortem.[47,48] Optic nerve involvement can be established from different structural (eg, MRI and optical coherence tomography [OCT]) or functional (eg, visual evoked potentials [VEPs]) modalities, as paraclinical adjuncts to careful and thorough neuro-ophthalmological examinations.

OCT is very sensitive and specific for the detection of retinal thinning following symptomatic optic neuritis (with maximal retinal thinning usually detectable at least 6 months post-optic neuritis) and detection of asymptomatic or subclinical remote demyelinating optic nerve injury.[17,18,49,50] Furthermore, OCT can detect optic nerve pathology whether it is unilateral or bilateral. Conservative and device-agnostic support for an abnormal OCT in identifying optic nerve involvement includes an inter-eye difference in the peripapillary retinal nerve fibre layer or composite macular ganglion cell inner plexiform layer thickness of 6 µm or more or 4 µm or more, respectively, with no better explanation. It is imperative that the OCT scan interpretation is done according to the quality control criteria and other parameters outlined in the accompanying companion paper focused on evaluation of the visual pathways for diagnosis of multiple sclerosis.[51]

An abnormal VEP for detection of optic nerve demyelinating injury is defined as a delayed latency (or asymmetric inter-ocular latencies) 2·5 standard deviations greater than the mean for both absolute peak P100 latency and inter-ocular latency, whose exact numerical measures depend on technical and methodological factors, and are also dependent on centre and device. For illustrative purposes only, absolute P100 latency of 118 ms and longer and of 115 ms and longer, and inter-ocular latency differences of 5 ms or longer and of 8 ms and longer are considered abnormal at the University of California San Francisco and Vall d'Hebron University Hospital laboratories, respectively. However, it is imperative that each centre determines its specific VEP cutoffs. As for OCT, it is paramount that quality standards are maintained when acquiring and interpreting VEPs. Abnormal VEPs can identify symptomatic and asymptomatic optic nerve lesions.

OCT and VEPs are widely available in many regions; thus, their inclusion in the new criteria could be applied immediately in diverse settings.[51] However, the OCT and VEP studies that supported the inclusion of the optic nerve in the diagnostic criteria were conducted in adult cohorts. The performance of these tests in children, in whom other conditions such as MOGAD are more prevalent, remains to be explored. Moreover, OCT inter-eye differences might be insensitive to bilateral optic nerve involvement, and caution should be exercised when interpreting bilateral VEP delays since both pre-chiasmal and retro-chiasmal lesions can contribute to bilateral VEP abnormalities. The accompanying paper provides further details.[51]

Although optic nerve lesions can also be seen on brain MRI scans, optic nerve MRI with fat saturation can better show symptomatic and asymptomatic T2-hyperintense lesions and could be included in the conventional diagnostic MRI work-up of multiple sclerosis.[52] Moreover,

Panel 2: Principles and recommendations regarding the optic nerve

- The optic nerve can serve as a fifth anatomical location to demonstrate dissemination in space (DIS) if no better explanation exists for optic nerve pathology
- Provided rigorous quality control is applied, optical coherence tomography-derived peripapillary retinal nerve fibre layer or macular ganglion cell inner plexiform layer inter-eye differences of 6 µm or more and 4 µm or more, respectively, support unilateral optic nerve involvement to demonstrate DIS
- Delayed visual evoked potential latency or asymmetric inter-ocular latencies (2·5 standard deviations greater than the mean for both absolute peak P100 latency and inter-ocular latency), the exact numerical measures of which depend on technical and methodological factors and are also centre and device dependent, support demyelinating optic nerve injury to demonstrate DIS
- One or more intrinsic optic nerve lesions with no better explanation (eg, without prominent chiasmal involvement, optic perineuritis, or longitudinally extensive lesion) identified by MRI might indicate optic nerve involvement to demonstrate DIS

optic nerve MRI can differentiate multiple sclerosis from other causes of optic neuropathy and, thus, might be necessary in the presence of clinical red flags, such as atypical visual symptoms, severe visual loss, or progressive course.[21,52,53] More information on optic nerve MRI is provided in the accompanying papers.[51,54]

Studies evaluating the inclusion of the optic nerve as an additional site for demonstration of DIS have consistently shown increased diagnostic sensitivity without notable loss of specificity.[18–20,55] Caution is always required when considering the differential diagnosis of optic neuritis and optic neuropathy, which includes more than 60 known aetiologies, and can be region specific and include regional infections.[21,53]

The consensus recommendations for incorporating the optic nerve into the 2024 McDonald criteria are listed in panel 2. Overall, our recommendations include that the optic nerve serves as a fifth anatomical location (ie, in addition to the periventricular, cortical or juxtacortical, infratentorial brain, and the spinal cord). Optic nerve involvement supporting a diagnosis of multiple sclerosis can be shown using OCT, VEPs, or MRI, provided no better aetiological explanation exists. Further details regarding the optic nerve as an additional site to show DIS can be found in the accompanying papers on the visual system and MRI.[51,54]

There was no consensus on the role of longitudinal changes in OCT, nor on VEP measures of optic nerve pathology for showing DIT, due to the absence of supporting data. The ability of the optic nerve to show DIT is recognised as an area warranting further study.

Panel 3: Dissemination in space

- Dissemination in space (DIS) is fulfilled when two of the five regions (ie, optic nerve, intracortical or juxtacortical, periventricular, infratentorial, and spinal cord) show typical lesions, regardless of whether these lesions are symptomatic
- In patients with progressive disease, two spinal cord lesions are enough to identify DIS
- Fulfilment of DIS and dissemination in time (DIT) are sufficient to diagnose multiple sclerosis, as per the 2017 McDonald criteria
- Fulfilment of DIS plus positive CSF (eg, oligoclonal bands or kappa free light chain index) is sufficient to diagnose multiple sclerosis
- In patients with typical clinical presentations, the presence of typical lesions in at least four anatomical locations is sufficient to diagnose multiple sclerosis
- In patients with typical clinical presentations and typical lesions in one region, a positive select 6 central vein sign or presence of one or more paramagnetic rim lesions plus DIT or CSF positivity is sufficient to diagnose multiple sclerosis

Modifications to the use of dissemination in space

With the inclusion of the optic nerve in the current revisions, the demonstration of DIS spans five possible anatomical locations.

Consensus recommendations for showing DIS in the 2024 criteria are listed in panel 3. DIS can be fulfilled when at least two of five regions (eg, juxtacortical or cortical, periventricular, infratentorial brain, spinal cord, and optic nerve) have typical lesions, regardless of whether these lesions are symptomatic. Multiple sclerosis can be diagnosed after showing DIS plus DIT on MRI or CSF-restricted oligoclonal bands or kappa free-light chains (kFLC).[5,6,11,43,56,57] Conference participants highlighted the importance of correctly identifying lesions typical of multiple sclerosis, as described in previous imaging and differential diagnosis publications.[5,21,58,59]

Several studies have shown a heightened risk of presenting with a second attack or new or enhancing MRI lesions with greater numbers of typical lesions in CNS regions.[45,60] In particular, having typical lesions in three or four CNS areas increases diagnostic sensitivity and has up to 100% specificity.[61] On the basis of current evidence, the conference participants agreed that multiple sclerosis can be diagnosed when at least four of the five anatomical locations are affected in patients who present with clinically isolated syndrome or with steadily increasing neurological disability independent of relapses (ie, progression) for at least 12 months, without any further requirements, provided there is no better explanation. If only one typical CNS site is affected by characteristic lesions, we advise the use of

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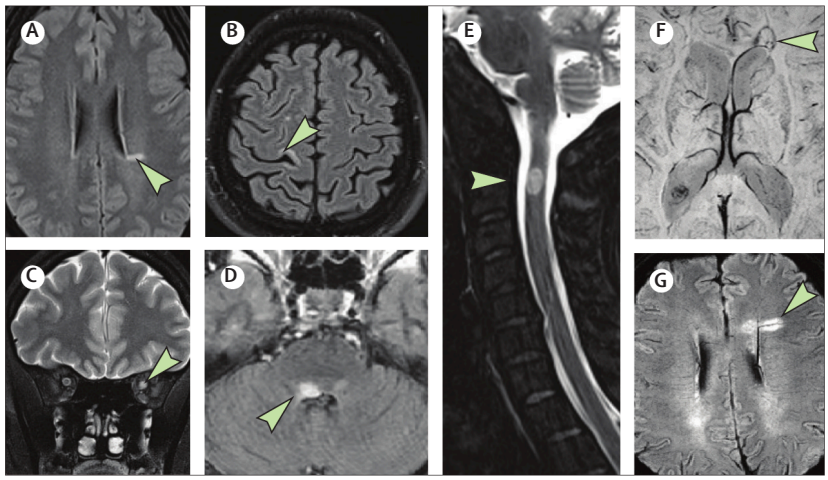

Figure 1: **Typical MRI appearance of multiple sclerosis lesions**
Characteristic anatomical locations of multiple sclerosis lesions identified on T2-weighted images, including (A) periventricular, (B) cortical or juxtacortical, (C) optic nerve, (D) infratentorial, and (E) spinal cord lesion (arrows). Novel MRI features identified on susceptibility-based images, including the (F) paramagnetic rim lesion and (G) central vein sign (arrows).

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See **Online** for appendix

highly specific tools (in addition to DIT or oligoclonal bands).

Dissemination in time is no longer necessary

The concept of DIT was incorporated into previous diagnostic criteria to differentiate multiple sclerosis from other inflammatory syndromes, such as monophasic acute disseminated encephalomyelitis, isolated myelitis, or monophasic optic neuritis.[2–5,62–64] However, DIT is not as specific as first assumed. Some clinical trials and natural history studies show that most patients with clinically isolated syndrome and typical MRI lesions will develop clinical or radiological DIT.[65,66] Other reasons for reconsidering the use of DIT for the diagnosis of multiple sclerosis include that other diseases can also exhibit DIT and that technical issues or inter-rater variability can affect the assessment of new or enlarging lesions on MRI for radiological DIT.[21,67] In keeping with the notion that DIT is not as specific as once believed, the 2017 McDonald criteria already included CSF-oligoclonal bands as a substitute tool for DIT. Hereby, the presence of new or simultaneous gadolinium-enhancing and non-enhancing typical lesions on MRI increases the specificity of the diagnostic criteria and, together with relapses, should be retained in the diagnostic process of multiple sclerosis, but not as a mandatory additional requirement to DIS, as discussed earlier.[68,69] DIT is now considered not essential.

Central vein sign can be diagnostic

The formation of multiple sclerosis plaques around venules has been shown in pathological studies since the 19th century.[70] However, plaque detection inside multiple sclerosis lesions in vivo has only been possible since the development of non-conventional MRI techniques.[70,71] Demonstration of the central vein sign (CVS) by MRI (figure 1) can increase diagnostic specificity by differentiating multiple sclerosis from vascular or other CNS inflammatory conditions.[54]

The optimal method for assessing the CVS is to calculate the proportion of the total number of lesions that have a central vein.[72] However, this approach can be very labour intensive if there are many lesions. Several simplified rating methods for CVS, which take a short time to complete, have been evaluated in cross-sectional or prospective multicentre studies.[35,73,74] In general, these methods show excellent diagnostic performance using sequences, such as susceptibility-weighted imaging or T2*-weighted 3D segmented echo planar imaging, with the select 3 rating method having greater sensitivity and the select 6 rating method having greater specificity (sensitivity 62–93% *vs* 59–89%; specificity 63–92% *vs* 75–98%, respectively) for the diagnosis of multiple sclerosis. Given that select 6 has an optimal balance of sensitivity, specificity, and feasibility, conference participants agreed that, for people with clinically isolated syndrome or radiologically isolated syndrome with at least two regions affected, the presence of CVS using select 6 is sufficient for diagnosing multiple sclerosis, without any further requirements. The select 6 method is considered positive when six or more white matter lesions are CVS positive; if fewer than ten white matter lesions are detected on MRI, the number of CVS positive lesions should be the majority.[75]

Some studies have shown that the CVS and oligoclonal bands have similar diagnostic properties individually, and that the positive predictive value of having both oligoclonal bands and select 6 positivity approaches 100% (80–100%).[76–78] Conference participants agreed that in patients with clinically isolated syndrome and only one anatomical location affected, and either positive CSF or DIT on MRI, the presence of CVS with the select 6 method is sufficient for the diagnosis of multiple sclerosis.

Despite the high specificity of the CVS for differentiating multiple sclerosis from other diseases with white matter involvement, conference participants emphasised that CVS is not a mandatory tool for diagnosing multiple sclerosis (panel 4). The assessment of the CVS in clinical practice has potential limitations, including time constrains in MRI acquisition and reporting. The frequency of CVS in paediatric patients with multiple sclerosis is less well studied than in adults, although CVS lesions have also been reported in children.[79–82]

Although the CVS can be observed on images acquired with 1·5T MRI, the proportion of detected CVS is lower (56–58%) than with 3T (74 –79%) or 7T (79–82%). Therefore, on 1·5T scanners, optimised sequences or paramagnetic contrast administration can be required for adequate CVS detection. Although T2* 3D echo planar imaging sequences are most sensitive for CVS detection (82–84%), this and other imaging sequences might have limited utility as they might not be readily

available at all centres or they might not have received regulatory approval for use in some circumstances. Lastly, the prevalence of CVS is highest in periventricular (up to 94%) and deep white matter (up to 84%) lesions. There is little evidence on the proportion of lesions with CVS in the cortical or juxtacortical, infratentorial, and spinal cord regions.[72] Overall, identification of the CVS is not required to diagnose multiple sclerosis but can, when available, be helpful in some cases, such as in patients with white matter lesions due to vascular disease or migraine, by increasing specificity. Furthermore, CVS can discriminate 87% of people incorrectly diagnosed with multiple sclerosis.[83]

Paramagnetic rim lesions can be used

Chronic active multiple sclerosis lesions are characterised by an inactive core surrounded by activated iron-laden microglia.[36,84–87] Susceptibility sensitive images can identify such paramagnetic rim lesions (PRLs), which are present in many cases (even at the earliest stages of multiple sclerosis), by the presence of a characteristic rim that is typically rendered as hypointense or hyperintense on phase images and often appear as hypointense on T2*-weighted images.[36,84–89]

Many PRL studies have been done using 7T MRI scanners, which are not readily accessible in clinical practice.[88,90] However, numerous recent studies have shown that PRLs can also be detected at 3T and 1·5T using the appropriate susceptibility sensitive sequences.[57,88,91] At experienced centres, inter-rater agreement for PRL detection between 3T and 7T has been reported to be as high as 90%, and inter-rater agreement between 1.5T and 3T as high as 97%.[36,85] However, no evidence exists as to whether these reported agreements are valid in non-experienced centres.

Evidence supporting the specificity of PRLs in multiple sclerosis diagnosis is still preliminary but is accumulating rapidly. A recent systematic review and meta-analysis found that the composite specificity of PRLs for a diagnosis of multiple sclerosis was 98%, and sensitivity ranged from 10% to 92·3%.[88] In one prospective longitudinal study, specificity and sensitivity were 100% and 59%, respectively.[57] Importantly, PRLs are rarely found in other radiological mimics of multiple sclerosis.

Despite the general agreement that the presence of PRLs can help diagnose multiple sclerosis, the evidence concerning their added value and specifically in clinically isolated syndrome when only DIS is fulfilled, was considered insufficient. Only one longitudinal study in people with a clinically isolated syndrome evaluated the diagnostic properties of PRLs, and found that combining 2017 MRI DIS plus one or more PRL had a sensitivity of 59% and a specificity of 83% for multiple sclerosis diagnosis, outperforming DIS and oligoclonal bands.[57] Moreover, the reported prevalence of PRLs in clinically isolated syndrome varies substantially across studies, and PRLs are most often found in periventricular lesions, with limited data on PRLs in other locations.[57,86,91]

On the basis of the available evidence, conference participants agreed that identifying PRLs on MRI can increase the specificity of a diagnosis of multiple sclerosis. In people with clinically isolated syndrome and abnormal MRI showing typical lesions in only one anatomical location and who have either DIT on MRI or CSF-restricted oligoclonal bands, the presence of one or more PRL is sufficient to diagnose multiple sclerosis (panel 4). While the evidence that PRL could serve as a paraclinical tool for multiple sclerosis diagnosis is robust, conference participants agreed that identifying PRLs is not required to diagnose multiple sclerosis and might hold similar limitations to CVS. PRLs can also be recommended to reduce misdiagnosis in presentations with symptoms that are not specific for multiple sclerosis.[55]

kFLC index as an appropriate paraclinical diagnostic test

Demonstration of CSF-restricted oligoclonal bands is a valuable diagnostic tool;[6,92] however, their detection

***Panel 4:* General principles and recommendations related to the central vein sign, paramagnetic rim lesions, and kappa free light chains**

Central vein sign (CVS)

- Demonstrating the CVS by MRI can be used to diagnose multiple sclerosis in specific situations
- Demonstrating the CVS by MRI can increase the specificity of the diagnosis
- Demonstration of the CVS is not required for diagnosis
- In patients with typical clinical presentations and dissemination in space, the presence of CVS is defined using select 6 and is sufficient for diagnosis
- In patients with typical clinical presentations and typical lesions in one region, the presence of the select 6 CVS plus dissemination in time or positive CSF is sufficient for diagnosis

Paramagnetic rim lesions (PRLs)

- Demonstrating one or more PRLs by MRI can be used to diagnose multiple sclerosis in specific situations
- Demonstrating one or more PRLs by MRI can increase the specificity of the diagnosis
- Demonstrating PRLs is not required for diagnosis
- In patients with typical symptoms and typical lesions in one region, the presence of one or more PRLs plus dissemination in time or positive CSF is sufficient for diagnosis

Kappa free-light chains (kFLC)

- The kFLC index is an appropriate paraclinical test for the diagnosis of multiple sclerosis
- The kFLC-index is interchangeable with oligoclonal bands and consequently can substitute for oligoclonal bands for diagnosis (ie, positive CSF)

Panel 5: **Recommendations related to radiologically isolated syndrome, paediatric multiple sclerosis, and primary progressive multiple sclerosis**

Radiologically isolated syndrome (RIS)

- RIS is identified by the incidental discovery of CNS white matter T2-weighted hyperintense foci on MRI, which are highly typical of multiple sclerosis in the absence of typical clinical symptoms related to inflammatory demyelination or findings on clinical examination
- In patients with RIS, fulfilling dissemination in space (DIS) and dissemination in time is sufficient for diagnosing multiple sclerosis
- In patients with RIS, fulfilling DIS and positive CSF is sufficient for diagnosing multiple sclerosis
- In patients with RIS fulfilling DIS, the presence of the select 6 central vein sign (CVS) is sufficient for diagnosing multiple sclerosis
- These recommendations can also apply to patients with other non-specific presentations

Paediatric multiple sclerosis

- Paediatric and adult-onset multiple sclerosis can be diagnosed using a single diagnostic criteria framework
- In patients with an acute disseminated encephalomyelitis (ADEM) presentation, a second clinical attack consistent with typical multiple sclerosis attacks or new T2 lesions in typical multiple sclerosis anatomical locations longer than 90 days post-ADEM onset is required before the multiple sclerosis diagnostic criteria can be applied
- In children and adolescents (younger than 18 years), the presence of CVS in more than 50% of T2 lesions strongly supports a diagnosis of multiple sclerosis
- Myelin oligodendrocyte glycoprotein (MOG)-IgG testing using a cell-based assay is strongly recommended in children with incident CNS demyelination younger than 12 years
- In people aged 12 years and older with an incident demyelinating event, MOG-IgG testing using a cell-based assay is recommended in presentations with symptoms not specific to multiple sclerosis or suggestive of myelin oligodendrocyte glycoprotein antibody-associated disease, but not for all people being investigated for multiple sclerosis

Primary progressive multiple sclerosis (PPMS)

- PPMS requires evidence of clinical progression extending at least 12 months
- A single, framework of diagnostic criteria should be used to diagnose relapsing and progressive multiple sclerosis
- Two or more spinal cord lesions are evidence of DIS in diagnosing primary progressive multiple sclerosis

method (eg, isoelectric focusing, followed by IgG immunodetection—mostly immunoblotting) is time-consuming and rater-dependent, limiting this assessment to laboratories with specialised expertise.[93] kFLC have emerged as another diagnostic biomarker. Multiple studies have reported increased intrathecal production of kFLC in people with multiple sclerosis compared with controls.[94,95] In contrast to oligoclonal bands, kFLC measurement can be conducted in hospitals and institutions with access to nephelometry or turbidimetry, which are cost-effective platforms that return objectively quantifiable and rater-independent results.[96] Intrathecal production of kFLC can be identified by different methods, such as the kFLC index, the percentage of intrathecal kFLC fraction, the CSF kFLC concentration, and the kFLC quotient. The most frequently investigated method is the kFLC index (ie, kFCL concentrations proportioned to albumin concentrations), which is more sensitive than isolated kFLC measurements in CSF if concentrations are low.[97,98] Patients with radiologically isolated syndrome and clinically isolated syndrome with a positive kFLC index are at increased risk of an attack or fulfilling the 2017 McDonald criteria.[99–101] The diagnostic accuracy of the kFLC index are similar to those of oligoclonal bands when assessed in clinically isolated syndrome cohorts, and, importantly, the concordance between oligoclonal bands and the kFLC index is about 87·0%.[100] In primary progressive multiple sclerosis, a retrospective multicentre study showed a concordance between oligoclonal bands and kFLC index of 90·0% when using a cutoff of 6·1.[102] An international expert panel had recommended the inclusion of the kFLC index as an additional diagnostic tool to show intrathecal antibody production.[103]

The IgG index, included in previous versions of the McDonald criteria as an alternative to oligoclonal bands to aid diagnosis, was not considered for voting, but was discussed.[1–4] Although specific, studies have shown a much lower sensitivity and accuracy of the IgG index compared with both oligoclonal bands and the kFLC index.[104,105] As such, only the kFLC index was considered as an equivalent tool to oligoclonal bands in the 2024 McDonald criteria (panel 4).

It is important to note that, as with oligoclonal bands, the kFLC index can identify intrathecal antibody production in other diseases, including MOGAD and NMOSD, albeit with considerably lower index values; the greatest overlap is between multiple sclerosis and NMOSD.[30,31,106,107] As always, the kFLC index should be interpreted in the context of clinical and MRI findings. kFLC index testing could be particularly helpful in centres where oligoclonal bands determinations are unavailable. Further details regarding oligoclonal bands and kFLC index will be published separately.[108]

Radiologically isolated syndrome

Radiologically isolated syndrome is characterised by incidental findings on MRI of T2-hyperintense lesions in the CNS white matter, in a pattern typical of multiple sclerosis, but in the absence of clinical symptoms suggestive of inflammatory demyelination.[22,109] Observational studies have shown that slightly more than half of individuals (51·2%) with radiologically isolated syndrome will develop clinical symptoms within 10 years of follow-up.[24] Risk factors for developing multiple sclerosis symptoms are similar to those observed in clinically isolated syndrome cohorts and include younger age (<37 years), infratentorial or spinal cord lesions, gadolinium-positive lesions, oligoclonal bands, or altered VEP consistent with demyelination. The more the risk factors, the greater and earlier risk of developing multiple sclerosis symptoms.[23,109,110] This evidence indicates that

radiologically isolated syndrome is part of the multiple sclerosis continuum and shares the same pathology.[33] As such, radiologically isolated syndrome should be included in the multiple sclerosis diagnostic criteria.

Additional characteristics highlighting the inflammatory nature of the lesions, including the presence of DIT or intrathecal antibody production by oligoclonal bands or kFLC, enhance the specificity of incidental T2 lesions fulfilling DIS.[24,110,111] Therefore, individuals with radiologically isolated syndrome or other non-specific presentations should have MRI lesions in at least two anatomical locations and at least one additional feature among DIT or positive CSF to be diagnosed with multiple sclerosis (panel 5).

CVS should be considered in patients with or without symptoms who have not had an attack or objective progression. In radiologically isolated syndrome, up to 75% of lesions have a CVS, with a median proportion of CVS per case of 87%. A larger proportion of CVS lesions corresponds to a higher risk of developing multiple sclerosis, and about 95% of people with radiologically isolated syndrome fulfill the select 6 criteria.[78,112] These findings, along with the previously described evidence in clinical multiple sclerosis, led the conference participants to agree on using the CVS select 6 rule in radiologically isolated syndrome cases with lesions in at least two anatomical locations to diagnose multiple sclerosis (figure 2). These criteria also apply to patients with other symptoms, such as paroxysmal symptoms, seizures, or other non-specific neurological symptoms that do not constitute a clear attack or progression of disability.

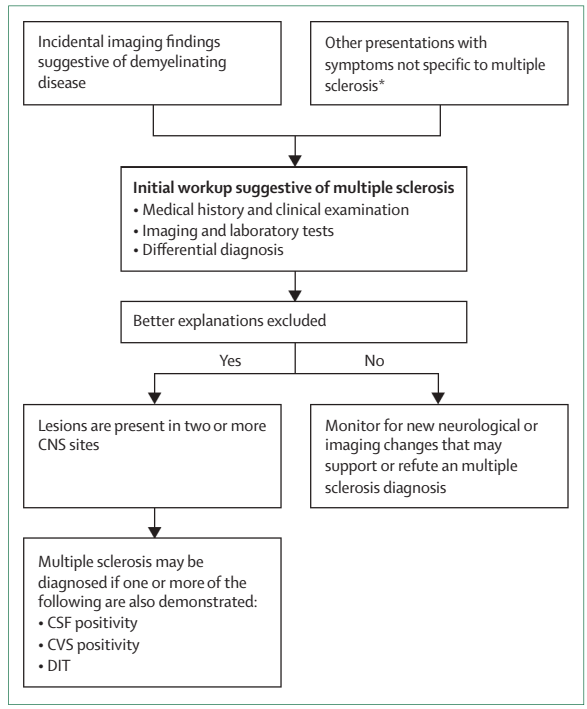

Figure 2: **Diagnostic algorithm for radiologically isolated syndrome and other non-specific presentations**
CVS=central vein sign. DIT=dissemination in time. *Presentations might include: (1) symptoms or signs overlapping those of multiple sclerosis but with no characteristic attack; or (2) paroxysmal symptoms (eg, trigeminal neuralgia), seizures, and other symptoms.

A single diagnostic criterion for paediatric-onset and adult-onset multiple sclerosis

Conference participants agreed that a single diagnostic criteria framework should be applied to adult-onset and paediatric-onset multiple sclerosis (onset younger than age 18 years). Specific considerations apply to differential diagnoses in children and adolescents with acquired demyelinating syndromes. MRI, CSF, and serum myelin oligodendrocyte glycoprotein (MOG) antibody serostatus are the most robust features to distinguish children with multiple sclerosis from those with non-multiple sclerosis diagnoses.[13,113]

Pediatric-onset multiple sclerosis (POMS) and adult-onset multiple sclerosis share similar pathobiological mechanisms, risk of clinical worsening, and MRI features.[114–117] However, POMS is characterised by a high inflammatory burden and by clinical and MRI features of active relapsing multiple sclerosis.[118,119] Optic nerve involvement in POMS is common, although formal analyses evaluating the contribution of the optic nerve as the fifth location need to be completed in large cohorts. While recovery from relapse-associated worsening is generally more complete in POMS, disability milestones might nevertheless be reached at a younger age than in adult-onset multiple sclerosis, thus requiring early identification and treatment.[116,120]

The periventricular, infratentorial, spinal cord, juxtacortical, and cortical lesions in POMS have features similar to those in adult-onset multiple sclerosis. CVS-positive lesions are common in POMS and can support differentiation from other conditions, including MOGAD.[81] However, considering the often-high lesion burden and the dearth of evidence evaluating select 6 CVS criteria in POMS, in individuals younger than age 18 years, CVS should be considered only when 50% or more of lesions show this sign. PRLs are less common than CVS lesions and their diagnostic value in POMS is yet to be established.[81,121] The diagnostic performance of the kFLC index in POMS was very similar to that in adults in a small but robust study, that included patients with NMOSD and MOGAD as controls.[122]

Just as in adults, criteria for diagnosing multiple sclerosis should be applied with care to children (younger than age 12 years) and adolescents with acquired demyelinating syndromes due to the risk of misdiagnosis. In particular, these criteria should not be applied to children presenting with acute disseminated encephalomyelitis, as this presentation might require additional work-up for differential diagnosis, such as anti-MOG testing and CSF examination.[123] If a follow-up MRI scan shows resolution or near-complete resolution

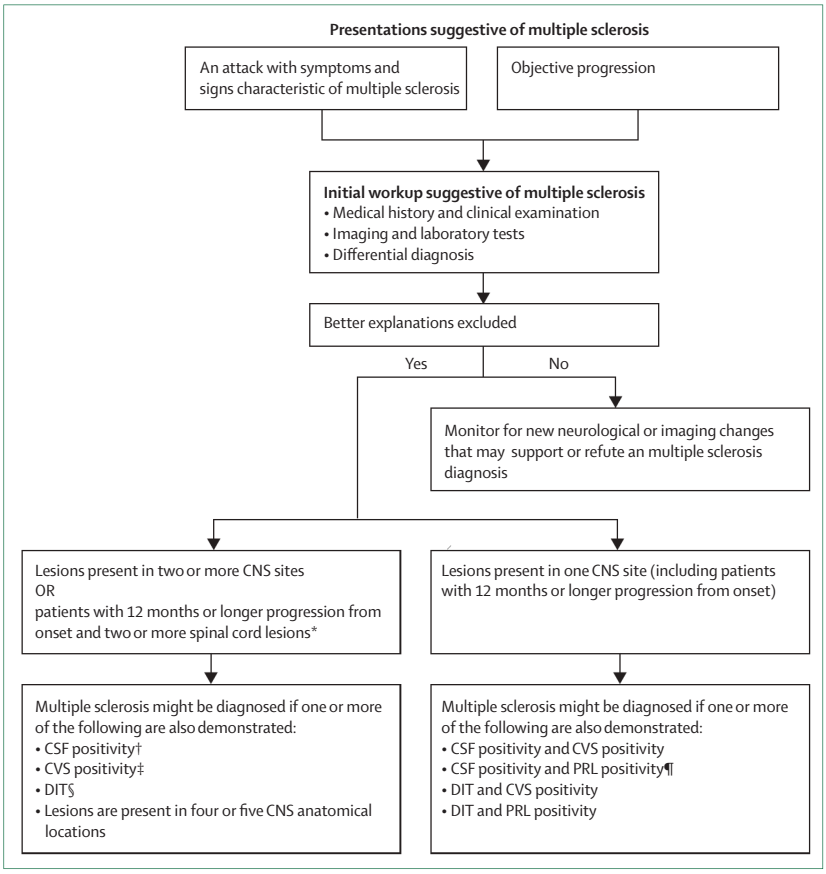

Figure 3: **Diagnostic algorithm for relapsing and progressive presentations of multiple sclerosis**
CVS=central vein sign. DIT=dissemination in time. PRL=paramagnetic rim lesion. *In patients presenting with 12 months or longer disease progression from symptom onset, the presence of two or more spinal cord lesions is considered evidence of dissemination in space and meets criteria for the presence of lesions in two CNS locations. †CSF positivity is demonstrated by presence of oligoclonal bands or kappa free-light chains. ‡CVS positivity is demonstrated by the presence of six or more lesions with CVS; if fewer than ten white matter lesions are seen on MRI, the number of CVS positive lesions should outnumber the CVS negative lesions. §DIT is demonstrated by the presence of one or more new T2 lesions or one or more gadolinium-positive lesions or a clinical attack. ¶PRL positivity is demonstrated by the presence of one or more PRL.

of all or most of the previous T2 lesions, these findings should prompt consideration of alternative diagnoses. In paediatric presentations, standard inclusion of serum MOG-IgG testing, using fixed or live cell assays, at the time of first attack can identify children with MOGAD and increase sensitivity and specificity of multiple sclerosis criteria.[13] As such, while the 2017 criteria showed excellent sensitivity and specificity in POMS, so-called no better explanation considerations should include MOG-IgG testing because of the higher relative incidence of MOGAD compared with multiple sclerosis in the (especially younger) paediatric population and their overlap in clinical and MRI presentations.[113,124,125] MOG-IgG testing using a cell-based assay is strongly recommended in all children younger than 12 years with an incident CNS demyelinating event (panel 5). MOG-IgG testing using a cell-based assay (where available) is advocated in the context of presentations with symptoms not specific to multiple sclerosis (eg, either at onset or based on clinical and MRI evolution) in children with a clinical or radiographic presentation suggestive of MOGAD. It is not advocated to routinely test for MOG-IgG in all patients aged 12 years or older with suspected demyelination and it is noted that low titre MOG-IgG can infrequently be present in POMS, just as in adult-onset multiple sclerosis.[30,106] While aquaporin 4-positive NMOSD is rare in paediatric patients, testing for aquaporin 4 antibodies might be warranted in some cases, depending on the clinical context.

A unified framework for the diagnosis of relapsing and progressive forms

Progressive-onset multiple sclerosis has conventionally had a separate set of diagnostic criteria, which have been minimally revised in years.[126] However, pathological and imaging studies have identified quantitative, not qualitative, differences between the various clinical forms, suggesting that the disease course should be considered as a continuum.[33,127–129] Hence, if diagnostic criteria are rooted in the biological mechanisms of multiple sclerosis, they could be applied equally to relapsing-onset and progressive-onset multiple sclerosis (figure 3).[130]

In a recent study by the MAGNIMS network, the 2017 McDonald criteria for relapsing-onset multiple sclerosis performed well for progressive-onset multiple sclerosis, also when including the optic nerve as an additional anatomical location.[61] The spinal cord is frequently affected in progressive-onset multiple sclerosis, and two or more spinal cord lesions might be sufficient to fulfil DIS criteria and provide increased diagnostic sensitivity.[61] Cautious interpretation of isolated spinal cord and CSF findings in progressive presentations is encouraged, since several progressive neurological disorders can present similarly.

A single diagnostic criteria framework should be applied to relapsing-onset and progressive-onset multiple sclerosis, including the five anatomical locations and additional paraclinical tools described earlier (panel 5). This framework would maintain high sensitivity and specificity while reducing complexity. With progressive-onset multiple sclerosis, the presence of a second spinal cord lesion can substitute for an additional brain anatomical location. Whether this approach could also be applied to relapsing-onset multiple sclerosis warrants exploration.

Diagnosis in individuals aged 50 years and older or with comorbidities

Comorbidity is common at multiple sclerosis symptom onset and diagnosis, and prevalence increases with age.[131] As such, an older age of onset and comorbidities associated with clinical or imaging features that overlap with those seen in multiple sclerosis increase the risk of misdiagnosis.[15,69,131–133] Diseases potentially producing

Panel 6: **Recommendations related to older age and comorbidities in the diagnosis of multiple sclerosis**

- In patients being considered for a diagnosis of multiple sclerosis presenting at age 50 years and older, multiple sclerosis is more likely to be misdiagnosed
- Small vessel ischaemic disease, psychiatric disorders, and some autoimmune diseases are associated with an increased risk of misdiagnosed multiple sclerosis
- Headache disorders, particularly migraine, are associated with periventricular lesions and an increased risk of misdiagnosis of multiple sclerosis
- In patients who are being considered for a diagnosis of multiple sclerosis presenting at age 50 years and older or with significant vascular risk factors (eg, hypertension, smoking, diabetes, hyperlipidaemia, or known macrovascular disease), additional features are strongly recommended to confirm the diagnosis:
  - A spinal cord lesion
  - CSF positivity by demonstration of intrathecal antibody production with oligoclonal bands or kappa free-light chain index
  - Central vein sign positivity

Panel 7: **Revisions to the 2017 McDonald criteria in the 2024 McDonald Criteria**

- The optic nerve might serve as a fifth anatomical location to demonstrate dissemination in space (DIS) if no better explanation exists for optic nerve pathology as detected by MRI, optical coherence tomography, or visual evoked potentials
- DIS is fulfilled when two of five anatomical locations (ie, optic nerve, intracortical or juxtacortical, periventricular, infratentorial, and spinal cord) show typical lesions, regardless of whether these lesions are symptomatic
- DIT is not mandatory for a diagnosis of multiple sclerosis in specific situations
- The demonstration of central vein sign positivity by MRI can be used to diagnose multiple sclerosis in specific situations
- The demonstration of paramagnetic rim lesions by MRI can be used to diagnose multiple sclerosis in specific situations
- The kappa free-light chain index is interchangeable with oligoclonal bands and consequently can replace oligoclonal bands for diagnosing multiple sclerosis
- Radiologically isolated syndrome and other presentations with non-specific symptoms are multiple sclerosis when specific criteria are fulfilled
- Paediatric-onset and adult-onset multiple sclerosis can be diagnosed using a single diagnostic criteria framework
- Progressive and relapsing multiple sclerosis represent a unified diagnosis and require unified diagnostic criteria
- Additional recommendations should be considered for confirming the diagnosis of multiple sclerosis in individuals aged 50 years and older with vascular comorbidities

MRI findings leading to misdiagnosis of multiple sclerosis include: vascular white matter changes (eg, small vessel disease); neurovascular pain syndromes (eg, migraine); and other inflammatory diseases (eg, Behçet's disease).[29,134]

Periventricular lesions are not specific to multiple sclerosis and can be seen in different conditions, including small-vessel ischaemia, migraine, infection, and metabolic disorders.[135] Increasing the threshold to three or more periventricular lesions helps to differentiate people with multiple sclerosis from those with migraine, but cannot distinguish multiple sclerosis from age-related changes and does not improve sensitivity and specificity in older patients.[69,136,137] Also, cortical or juxtacortical and periventricular regions are simultaneously affected in up to a third of individuals with migraine, thus only partly address the risk of misdiagnosis.[138,139] Similarly, infratentorial lesions can occur secondary to vascular disorders and non-multiple sclerosis inflammatory disorders.[140] Spinal cord lesions are generally not found in patients with cerebrovascular disease. Gadolinium-enhancing lesions or CSF oligoclonal bands or kFLCs can improve the likelihood of multiple sclerosis diagnosis across all age groups.[69] The CVS is specific for multiple sclerosis pathology and can support the differentiation of multiple sclerosis lesions from vascular disorders.[141,142] Older people and those with comorbidities (ie, including headache and vascular disorders) might define a subset of patients at a higher risk for misdiagnosis, requiring additional diagnostic tests.

Additional tests for a multiple sclerosis diagnosis are strongly recommended in individuals aged 50 years and older or with vascular risk factors (eg, including hypertension, smoking, diabetes, hyperlipidaemia, or known macrovascular disease; panel 6). Such additional test findings might include one or more spinal cord lesions or positive CSF or CVS-positive (select 6). These considerations apply to all our previous recommendations, including those for radiologically isolated syndrome. A consensus was not reached about using PRL for diagnosis in older people or in those with comorbidities.

Conclusion

Diagnosing multiple sclerosis requires a balance between facilitating early recognition and avoiding misdiagnosis, without unnecessary complexity and considering the diversity of clinical settings worldwide. Periodic revision of the diagnostic criteria has directly affected long-term outcomes of people with multiple sclerosis. Consistent with these principles, the 2024 McDonald criteria are based on the most recent robust evidence, extend the boundaries of previous criteria, and lay the groundwork for future innovations based on the updated mechanistic framework for disease progression

Search strategy and selection criteria

References for this Position Paper were identified by searches of PubMed between Jan 1, 2017, and Dec 31, 2024, and references from relevant articles. The search terms "multiple sclerosis", "MRI", "OCT", "VEP", "CVS", "PRL", "diagnosis", and "PPMS" were used. The final reference list was generated on the basis of relevance to the diagnostic criteria.

(panel 7).[33] The applicability of the revised diagnostic criteria might vary across regions because of differences in epidemiological context. As such, research to understand how the criteria perform in different settings and the prevalence of multiple sclerosis mimics should be prioritised.

Demonstrating typical lesions by MRI in characteristic anatomical locations is now the cornerstone of diagnosis. The optic nerve can now serve as a fifth CNS region for diagnosis, and can be assessed by OCT, VEP, or MRI. CVS and PRLs can be used to diagnose multiple sclerosis in specific situations to reduce the risk of misdiagnosis. The kFLC index can be an alternative to oligoclonal bands to support the diagnosis of multiple sclerosis. The 2024 McDonald criteria provide a unified approach to diagnose multiple sclerosis in patients experiencing typical relapsing or progressive presentations and radiologically isolated syndrome, across the lifespan. Moving toward a unifying biological framework of disease, radiologically isolated syndrome and symptoms in the absence of a typical relapsing or progressive course can be considered multiple sclerosis in specific situations. Additional recommendations for diagnosing multiple sclerosis in older people and in those with vascular comorbidities are incorporated to reduce misdiagnosis. Further detail regarding implementation of the new criteria can be found in the companion papers discussing the visual system, MRI, and CSF and other body fluid biomarkers.[51,54,108] The 2024 McDonald criteria are expected to facilitate the diagnosis of multiple sclerosis, thereby improving clinical outcomes of people with multiple sclerosis worldwide.

Contributors

XM, AJT, and TC drafted the conference agendas with the agreement of steering committee members, CL-F, JO, and PAC. XM, TC, SO-R, ÀM, JAC, AJT, HT, RAM, FL, AS, BW, RM, PAC, JS-G, AJG, SS, FB, GA, JO, DO, DR, CG, CL-F, MF, FD, BB, MPA, and OC made topic-related presentations at the consensus conference. All conference participants actively participated in discussion and reaching consensus. XM, TC, AJT, JO, CL-F, PAC, GA, and MM prepared the initial drafts of this manuscript. All conference participants were given the opportunity to review drafts and make revisions before finalisation, and approved the manuscript for submission.

Declaration of interests

GA received compensation for consulting services, speaking honoraria, or participation in advisory boards from Roche, Horizon Therapeutics, and Bristol Myers Squibb; travel support for scientific meetings from Novartis, Roche, ECTRIMS and EAN; GA serves as Editor for *Europe of the Multiple Sclerosis Journal – Experimental, Translational and Clinical*; is a member of the editorial and scientific committee for Acta Neurológica Colombiana; is a member of the International Women in Multiple Sclerosis (iWiMS) network executive committee, the European Biomarkers in Multiple Sclerosis (BioMS-eu) steering committee, the MOGAD Eugene Devic European Network (MEDEN) steering group, and the Platform Adaptive Trial for remyelination and neuroprotection in multiple Sclerosis (PLATYPUS) steering committee. 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