REVIEW OPEN ACCESS

Application of the 2024 McDonald Criteria

Earlier Diagnosis and Avoiding Misdiagnosis of Multiple Sclerosis in a Global Setting

Andrew J. Solomon,[1] Wallace J. Brownlee,[2,3] Shanthi Viswanathan,[4] Giulia Fadda,[5] Julie Fiol,[6] Lorna M. Galleguillos Goiry,[7] Thomas Griffin,[8] Mohammad Ali Sahraian,[9] Deanna R. Saylor,[10,11] Àlex Rovira,[12] Eoin P. Flanagan,[13] and Sudarshini Ramanathan,[14,15] as the International Advisory Committee on Clinical Trials in Multiple Sclerosis

Correspondence
Dr. Solomon
andrew.solomon@uvmhealth.org

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Abstract

The evolution of multiple sclerosis (MS) diagnostic criteria over the past 4 decades has shortened the time to diagnosis of MS, enabling earlier institution of immunomodulatory therapy and therefore improved clinical outcomes. In response to a recent expansion of knowledge related to approaches and paraclinical tools that may aid diagnosis of MS and identify causes of MS misdiagnosis, the 2024 McDonald criteria reflect substantive changes and introduce new pathways to MS diagnosis. These revisions carry potential for both earlier and more accurate diagnosis of MS, yet require expertise for their appropriate application in clinical practice and introduce new challenges for global implementation. These changes include expansion of anatomical locations that represent dissemination in space, new paraclinical findings that can substitute for dissemination in time, inclusion of patients with asymptomatic or nonspecific clinical presentations, and recommendations for diagnostic approaches in specific patient populations. These changes also incorporate new paraclinical tools for the first time, including MRI central vein sign and paramagnetic rim lesions, CSF kappa free light chains, and optical coherence tomography. The revised criteria have now unified the diagnostic pathway for clinical presentations typical of MS with attack or progressive onset, and established a new pathway for patients without symptoms or with nonspecific clinical presentations accompanied by MRI findings typical of MS. The 2024 revisions continue to rely on recognition of typical clinical and MRI findings of MS, and additionally recommend specific approaches to pediatric patients, patients with vascular comorbidities, and older patients to further reduce the risk of misdiagnosis. Previous data suggest barriers to implementation, and misunderstanding and misapplication of prior revisions to MS diagnostic criteria that may be associated with misdiagnosis. Implementation of the revised 2024 McDonald criteria globally, particularly in low and low-middle income countries, will require educational outreach, leveraging and maximizing existing resources, and engagement of health care systems to improve access to new technology. This review contextualizes the implications of key revisions in the 2024 criteria for routine clinical care, while providing accessible guidance for its appropriate application with a lens toward nonspecialist clinicians and trainees globally, to ensure early and accurate MS diagnosis.

Introduction

Diagnostic criteria for multiple sclerosis (MS) continue to evolve. Revisions over the past 2 decades have helped reduce time to diagnosis and consequentially improved clinical outcomes by facilitating earlier initiation of disease-modifying treatment (DMT).[1-3] Recent data supporting new diagnostic algorithms tested in MS research cohorts[4-6] have motivated additional revisions to the criteria. The

[1]Department of Neurological Sciences, Larner College of Medicine at the University of Vermont, Burlington; [2]Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, London, United Kingdom; [3]NIHR University College London Hospitals Biomedical Research Centre, United Kingdom; [4]Department of Neurology, Tunku Abdul Rahman Neuroscience Institute, Kuala Lumpur Hospital, Malaysia; [5]Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ontario, Canada; [6]National Multiple Sclerosis Society, New York, NY; [7]Clínica Alemana De Santiago, Clínica Dávila, Universidad del Desarrollo, Chile; [8]Division of Public Health, Larner College of Medicine at the University of Vermont, Burlington; [9]Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Iran; [10]Department of Neurology, University of North Carolina-Chapel Hill School of Medicine; [11]Department of Medicine, University Teaching Hospital, Lusaka, Zambia; [12]Section of Neuroradiology, Department of Radiology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain; [13]Departments of Neurology and Laboratory Medicine, and Pathology and Centre for Multiple Sclersois and Autoimmune Neurology, Mayo Clinic, Rochester, MN; [14]Translational Neuroimmunology Group, Kids Neuroscience Centre and ANZAC Research Institute, Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Australia; and [15]Department of Neurology, Concord Hospital and Concord Clinical School, Sydney, Australia.

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Glossary

ADEM = acute disseminated encephalomyelitis; **AQP4** = aquaporin-4; **CVS** = central vein sign; **DIS** = dissemination in space; **DIT** = dissemination in time; **DMT** = disease-modifying treatment; **kFLC** = kappa free light chain; **LMIC** = lower-middle income country; **MOGAD** = myelin oligodendrocyte glycoprotein antibody-associated disease; **MOG-IgG** = myelin oligodendrocyte glycoprotein immunoglobulin G; **MS** = multiple sclerosis; **OCB** = oligoclonal band; **OCT** = optical coherence tomography; **PPMS** = primary progressive MS; **PRL** = paramagnetic rim lesion; **RIS** = radiologically isolated syndrome; **VEP** = visual evoked potential.

resulting 2024 McDonald criteria reflect substantive changes that deliver new pathways to the diagnosis of MS.[7]

Despite the potential for McDonald criteria revisions to result in earlier diagnosis over time, several studies suggest barriers to implementation in routine care. Surveys of British and Scottish neurologists[8,9] found that prior revised criteria were not widely used. Recent data collected from 107 countries several years after the publication of the 2017 McDonald criteria identified numerous regions where the criteria were either not commonly used or where there was persistent use of earlier less sensitive criteria.[10] Lack of awareness or training by clinicians was identified as the most frequent reason why contemporary MS diagnostic criteria were not used as intended.[10]

Although lack of implementation of updated MS diagnostic revisions may hinder early diagnosis of MS, on the other hand, misunderstanding and misapplication of the criteria can result in misdiagnosis.[11-13] Clinician surveys have indicated that neurologists found previous MS diagnostic criteria confusing or difficult to apply correctly.[8,9] Studies published in the past 4 years cumulatively surveying approximately 800 clinicians in the United States, Canada, France, and Germany comprised of residents, nonspecialist neurologists, MS specialist neurologists, and radiologists demonstrated concerning misunderstanding of key elements of MS diagnostic criteria, as well as their misapplication in clinical vignettes that could have implications for diagnostic accuracy in routine care.[14-17]

The 2024 McDonald criteria hold potential for both earlier and more accurate diagnosis of MS. However, they also introduce new challenges for global implementation and require expertise in their application in clinical practice to prevent misdiagnosis. The 2024 criteria necessarily detail data motivating revisions and the methodology used to reach consensus.[7] By contrast, this review contextualizes the implications of key revisions in the 2024 criteria for routine clinical care, while providing accessible guidance for its appropriate application with a lens toward nonspecialist clinicians and trainees, to ensure early and accurate MS diagnosis.

What Has Changed in the 2024 McDonald Criteria?

As in previous criteria, diagnosis of MS by the 2024 criteria requires thoughtful and rigorous evaluation, and exclusion of a "better explanation" than MS. Knowledge of disorders that may mimic MS and their diagnostic features has expanded markedly since the publication of 2017 McDonald criteria. Consideration of alternative diagnoses requires clinical expertise and judgement. Although the differential diagnosis of MS is broad, simply recognizing that a clinical presentation or MRI finding is atypical for MS,[18-21] even if an alternate diagnosis is not immediately apparent, can avert preventable misdiagnoses by prompting further investigation and an open mind. Despite pressure from compelling data to start treatment as early as possible in suspected MS, in such situations, further evaluation and monitoring is a preferred approach. Recent international collaborative consensus efforts led by the Americas Committee for Treatment and Research in MS Differential Diagnosis Consortium produced 4 accessible publications that define presentations typical of MS, and comprehensively review clinical and paraclinical "red flags" that can suggest alternative diagnoses to MS.[18-21]

Table 1 summarizes the key differences between the 2017 and 2024 MS diagnostic criteria. Radiologic features typical of MS, and those that are not suggestive of MS, which are critical for accurate implementation of the 2024 McDonald criteria are demonstrated in Figures 1 and 2.

Changes to Dissemination in Space

Previous MS diagnostic criteria required lesions in at least 2 of the 4 CNS regions typically affected by MS (periventricular, cortical/juxtacortical, infratentorial, and spinal cord) for fulfilment of dissemination in space (DIS) (Table 2). Recent studies have highlighted that both symptomatic optic nerve lesions in patients with acute optic neuritis, and asymptomatic lesions in patients with suspected relapsing or progressive MS, may allow for earlier diagnosis in some patients.[22] The 2024 McDonald criteria incorporate the optic nerve as an additional region for DIS, expanding the number of typical CNS sites involved in MS from 4 to 5 (Table 1).[7] Several tools are available for evaluating the optic nerve for objective evidence of a lesion as detailed in a recent review,[22] including (1) orbital MRI demonstrating a T2-hyperintense optic nerve lesion, (2) abnormal visual evoked potentials (VEPs) with prolonged P100 latency, and (3) optical coherence tomography (OCT) with intereye differences in peripapillary retinal nerve fiber layer and/or macular ganglion cell-inner plexiform layer thickness of ≥6 and ≥4 μm, respectively.

Table 1 Differences Between 2017 and 2024 MS Diagnostic Criteria

MS Diagnostic Criteria	2017 Criteria	2024 Criteria
MRI DIS anatomical locations	• Periventricular • Cortical/juxtacortical • Infratentorial • Spinal cord	• Periventricular • Cortical/juxtacortical • Infratentorial • Spinal cord • Optic nerve[a] • Two spinal cord lesions can substitute for DIS in progressive presentations[a]
Paraclinical testing to aid diagnosis	MRI T2 hyperintense brain and spinal cord lesions Gd-enhancing lesions ≥2 CSF-restricted OCBs Visual evoked potentials	MRI T2 hyperintense brain, spinal cord, orbit lesions,[a] Gd-enhancing lesions Central vein sign[a] Paramagnetic rim lesions[a] ≥2 CSF-restricted OCBs Intrathecal kappa free light chains index ≥6.1[a] Visual evoked potentials Optical coherence tomography[a]
MRI DIT **Substitutes for DIT (DIT not required)**	Gd-enhancing and nonenhancing lesions New T2-hyperintense lesions at follow-up ≥2 CSF-restricted OCBs	Gd-enhancing and nonenhancing lesions New T2-hyperintense lesions at follow-up ≥2 CSF-restricted OCBs DIS in ≥4/5 anatomical locations[a] Select 6 CVS[a] Intrathecal kappa free light chains index ≥6.1[a]
Clinical presentations incorporated in criteria that allow for the diagnosis of MS	Clinical attack (i.e., relapse) Progressive disability	Clinical attack (i.e., relapse) Progressive disability Nonspecific symptoms[a] Paroxysmal symptoms[a] Asymptomatic[a]
Paraclinical testing to aid diagnosis	MRI T2 hyperintense brain and spinal cord lesions; Gd-enhancing lesions ≥2 CSF-restricted OCBs Visual evoked potentials	MRI T2 hyperintense brain, spinal cord, orbit lesions,[a] Gd-enhancing lesions, central vein sign,[a] paramagnetic rim lesions[a] ≥2 CSF-restricted OCBs Intrathecal kappa free light chains index ≥6.1[a] Visual evoked potentials Optical coherence tomography[a]
Pediatric presentation	Diagnostic criteria identical to adults with caveats: • Criteria should not be applied in patients with ADEM	Diagnostic criteria identical to adults with caveats: • Criteria should not be applied in patients with ADEM • MOG-IgG testing is strongly recommended in children <12 y of age[a] • CVS is defined as when ≥50% of lesions demonstrate CVS[a]
Age >50, vascular comorbidities, vascular risk factors, or migraine	≥3 periventricular lesions recommended for DIS	CSF-restricted OCBs >2[a] or Intrathecal kappa free light chains index ≥6.1[a] or Select 6 CVS or ≥1 spinal cord lesion[a]

Abbreviations: ADEM = acute disseminated encephalomyelitis; CVS = central vein sign; DIS = dissemination in space; DIT = dissemination in time; MOG-IgG = myelin oligodendrocyte glycoprotein immunoglobulin G; MS = multiple sclerosis; OCB = oligoclonal band.
[a]Key differences between the 2017 and 2024 MS diagnostic criteria.

In an additional change, in patients with ≥12 months of steadily increasing neurologic disability independent of relapses, ≥2 spinal cord lesions can substitute for fulfillment of DIS for the diagnosis of primary progressive MS (PPMS).[7]

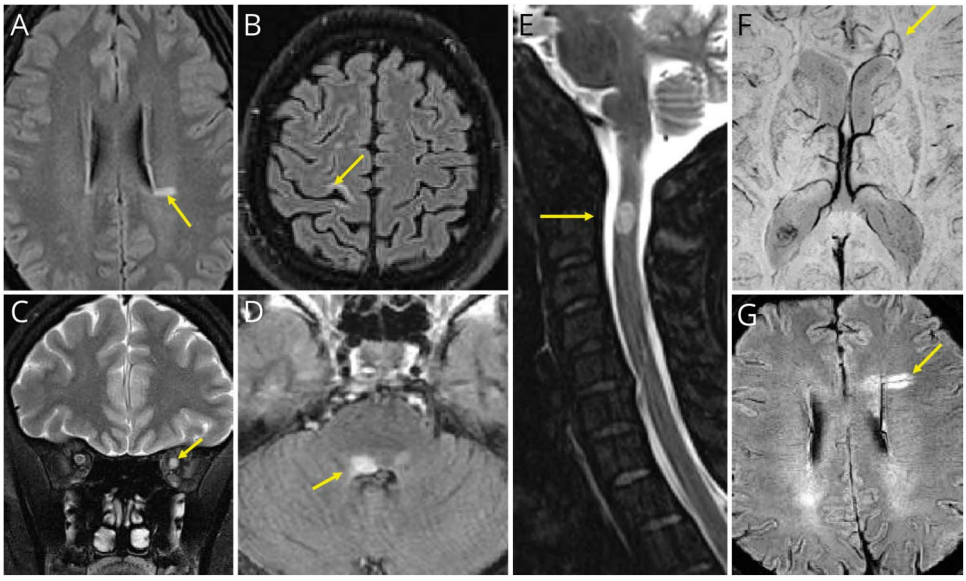
Changes to and Substitutes for Dissemination in Time

MS diagnosis has historically required evidence of both DIS and dissemination in time (DIT) (Table 2). However, waiting for DIT may delay diagnosis in some patients, and considerable research has focused on how to predict which patients will later fulfill DIT, to facilitate earlier diagnosis. As a result, the 2017 McDonald criteria incorporated CSF-restricted oligoclonal bands (OCBs) as a substitute for clinical or MRI evidence of DIT. The 2024 McDonald criteria allow for additional clinical scenarios where DIT is no longer required.

Fulfillment of multiple CNS regions by nongadolinium enhancing T2-hyperintense MRI lesions predicts DIT.[7] Data have demonstrated that removing DIT in this scenario maintains diagnostic accuracy for relapsing and progressive MS.[6,7] As a result, the 2024 criteria permit diagnosis of MS in patients with a typical clinical presentation (i.e., an attack or clinical progression) and lesions in 4 or 5 CNS regions fulfilling DIS.[7]

In patients with typical clinical presentations and lesions in 2 or 3 CNS regions, the 2024 MS diagnostic criteria also newly incorporate the MRI biomarker central vein sign (CVS) as an additional substitute for DIT to expedite diagnosis of MS (Tables 1 and 2, Figures 1 and 3). Although training in CVS assessment is necessary to ensure accuracy, incorporation of CVS in the criteria can also expedite diagnosis in clinical practice in patients who do not fulfil MRI DIT, and before CSF evaluation.[23,24] The CVS reflects the perivenous distribution of MS lesions and can be detected on susceptibility-

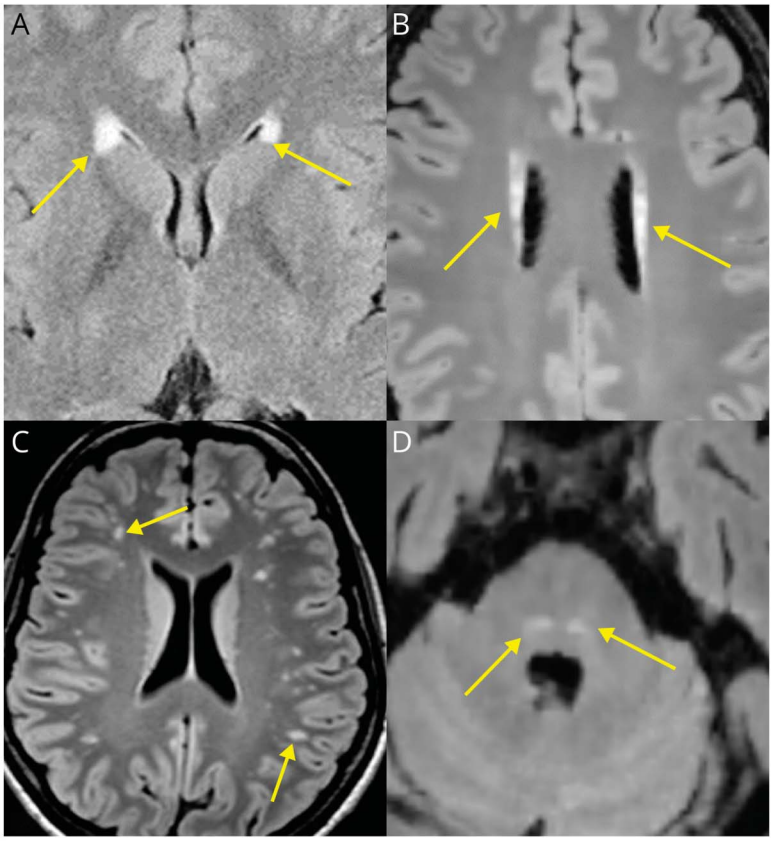
Figure 1 Typical MRI Appearance and Anatomical Locations of Multiple Sclerosis Lesions



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). Reprinted from *The Lancet Neurology*, 24, Montalban X, Lebrun-Frenay C, Oh J, et al., Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria, 850-865,2025, with permission from Elsevier.[7]

sensitive MRI sequences as a thin (<2 mm) hypointense line or dot running through the center of a lesion (Figure 1F) in 2 perpendicular planes.[25] The "Select 6" CVS rule (≥6 white matter lesions with CVS; or in cases with <10 white matter lesions, lesions with CVS outnumbering lesions without CVS) has demonstrated high specificity for MS,[23] with similar

Figure 2 Brain MRI Findings Not Suggestive of Multiple Sclerosis Lesions



(A) Periventricular caps (arrows) and (B) periventricular bands (arrows) reflecting disruption of the ependymal lining likely (nonvascular origin). (C) Subcortical and deep white matter lesions (note the thin band of normal white matter interposed between the lesion and the cortical gray matter, preventing its classification as juxtacortical, arrows). (D) Lesions involving the central pontine white matter (medial lemniscus) highly suggestive of vascular-related origin (arrows).

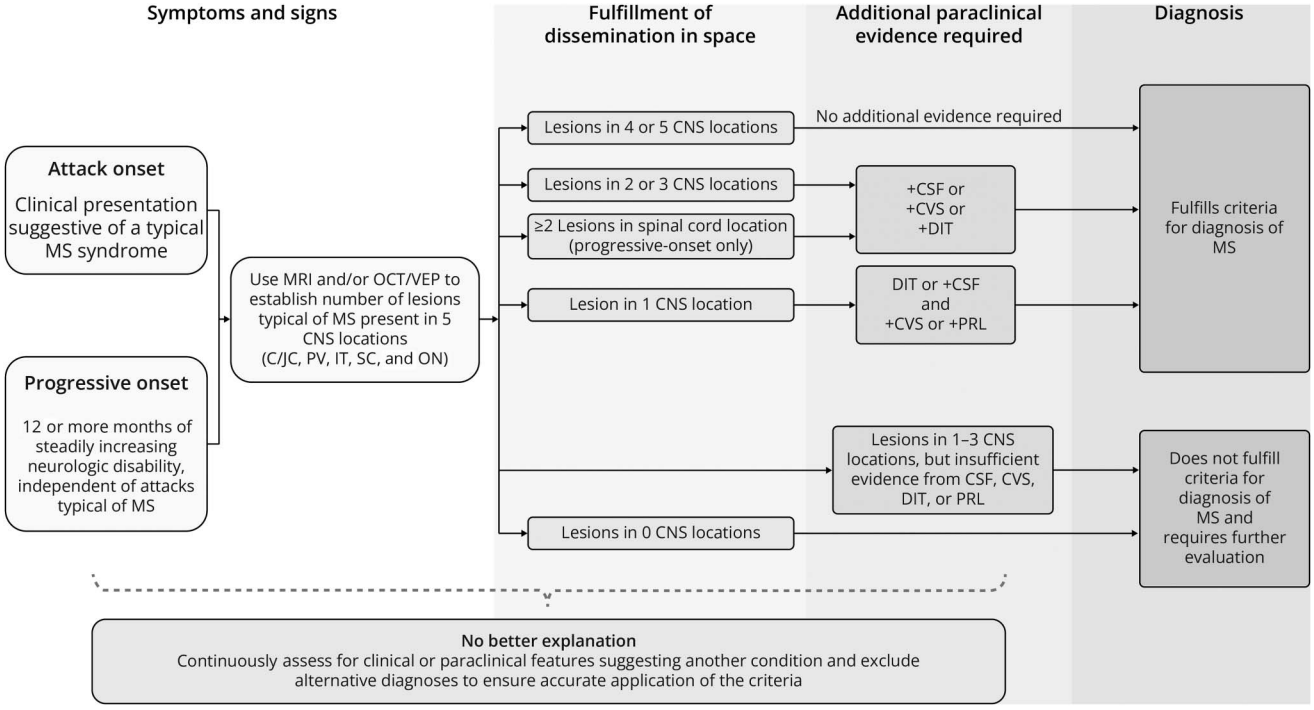
Table 2 Glossary of Key Terms for Application of 2024 McDonald Criteria Revisions[7,22-24]

Attack ("relapse" or "exacerbation"): Patient-reported symptoms and corroborating objective findings on neurologic examination or paraclinical testing (i.e., MRI) reflecting an inflammatory demyelinating event in the CNS typical of multiple sclerosis (MS). Attacks develop acutely or subacutely with a duration of at least 24 h, with or without recovery and in the absence of fever or infection.
Central vein sign (CVS): An MRI biomarker where central veins within white matter lesions are visualized as a thin hypointense line or small hypointense dot in the center of lesions on susceptibility-sensitive sequences. CVS identification should follow established guidelines.[1]
Central vein sign Select 6 rating method: The presence of ≥6 white matter lesions demonstrating CVS. In cases with <10 white matter lesions, a majority should demonstrate CVS.[1]
Clinically isolated syndrome (CIS): A first demyelinating event suggestive of MS (see "attack" definition above).
CSF-restricted oligoclonal bands (OCBs): The presence of ≥2 OCBs found in the CSF but not serum, indicating intrathecal antibody production. OCB evaluation should follow recommended methodology.[2]
CSF kappa free light chains (kFLC): Immunoglobulin-G kappa light chains secreted by plasma cells are detectable in serum and CSF using nephelometry or turbidimetry. Elevated CSF kFLC expressed as an index with serum indicates intrathecal antibody production. kFLC evaluation should follow recommended methodology.[2]
Dissemination in space (DIS): T2-hyperintense lesions on MRI in at least 2 of 5 CNS anatomical locations (juxtacortical/cortical, periventricular, infratentorial, spinal cord, and optic nerve) typically affected in MS. An optic nerve lesion can also be identified using visual evoked potentials (VEPs) or optical coherence tomography (OCT). A second clinical attack in a different anatomical location than the first can also be considered DIS.
Dissemination in time (DIT): New T2-hyperintense lesions on MRI over time, or the simultaneous presence of gadolinium contrast-enhancing and nonenhancing lesions on a single MRI. A second clinical attack can also be considered DIT. DIT is no longer required for MS diagnosis in all patients.
Infratentorial lesion: A T2-hyperintense lesion on MRI in the brainstem (typically near the surface), cerebellar peduncles, or cerebellum.
Cortical lesions: MRI lesions within the cerebral cortex. Special MRI techniques, such as 3D double-inversion recovery, phase-sensitive inversion recovery, and magnetization-prepared rapid acquisition with gradient echo sequences, are often required to visualize these lesions.
Juxtacortical lesion: A T2-hyperintense lesion on MRI touching the cortex without evidence of white matter between the lesion and the cortex.
Lesion: An area of hyperintensity on T2-weighted or proton-density weighted MRI scan.
Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): A monophasic or relapsing demyelinating disease of the CNS affecting the optic nerve, brain, or spinal cord that is distinct from MS, and associated with MOG-IgG antibodies. MOGAD diagnostic criteria should be applied to confirm diagnosis.[3]
MS typical syndromes: A clinical attack typical of MS (e.g., supratentorial syndromes, optic neuritis, specific brainstem or cerebellar syndromes, or partial myelitis).[4]
No better explanation: Patient's presentation is typical of MS, and there is an absence of clinical or paraclinical findings suggestive for an alternative diagnosis, or negative pertinent workup for such alternative diagnoses.[4]
Objective evidence: Findings on neurologic examination or paraclinical testing (i.e., MRI, visual evoked potential (VEP), and OCT) that localize symptoms to evidence of a CNS lesion.
Optic nerve lesion: An optic nerve lesion can be demonstrated on neurologic examination, MRI, VEP, or OCT.[5]
Paramagnetic rim lesions (PRLs): An MRI where a paramagnetic rim (which can be either hypointense or hyperintense compared with the lesion core, depending on the sequence used) along the edge of chronic MRI lesions is identified on susceptibility-sensitive sequences. PRL identification should follow established guidelines.[1]
Periventricular lesion: A T2-hyperintense white matter lesion on MRI touching the lateral ventricles without evidence of white matter in between the lesion and the ventricle.
Progressive course: An MS course characterized by steadily increasing, objective neurologic worsening independent of relapses for at least a year. Fluctuations, periods of stability, and superimposed relapses might occur.
Radiologically isolated syndrome: Incidental MRI findings in the brain or spinal cord suggestive of multiple sclerosis in an individual without symptoms of an attack or progressive neurologic worsening.[1]
Relapsing course: An MS course characterized by attacks (relapses) with or without residual neurologic disability between episodes.
Spinal cord lesion: A spinal cord lesion on T2-weighted MRI, short tau inversion recovery, proton-density images, or other appropriate image in 2 sagittal and 1 axial planes.

diagnostic performance to OCBs supporting its use as an alternative to CSF analysis. As a result, in the 2024 criteria, Select 6 CVS can substitute for DIT to allow for diagnosis in patients with a typical presentation for MS (Figures 1 and 3).[7,23] The 2024 MAGNIMS-CMSC-NAIMS consensus recommendations detail requirements for CVS identification to facilitate diagnosis of MS.[23]

In the 2024 criteria, much like the 2017 criteria, "positive CSF" can substitute for DIT in patients presenting with

Figure 3 Pathways to Diagnosis of MS in Patients With Attack-Onset or Progressive-Onset Presentations



CNS locations: C/JC = cortical/juxtacortical; PV = periventricular; IT = infratentorial; SC = spinal cord; ON = optic nerve. Paraclinical evidence: +CSF = positive CSF—the presence of ≥2 or more CSF restricted oligoclonal bands or kappa free light chain index ≥6.1 according to recommended laboratory techniques. +CVS = positive central vein sign—the presence of ≥6 lesions with CVS per NAIMS criteria. If <10 white matter lesions present, CVS-positive lesions must exceed CVS-negative lesions. +DIT = fulfillment of dissemination in time by second clinical attack, simultaneous gadolinium-enhancing (Gd+) and nonenhancing lesions, or a new T2-hyperintense or Gd+ lesion. +PRL = positive paramagnetic rim—presence of ≥1 PRLs according to NAIMS criteria. CVS = central vein sign; DIT = dissemination in time; MS = multiple sclerosis; OCT = optical coherence tomography; PRL = paramagnetic rim lesion; VEP = visual evoked potential.

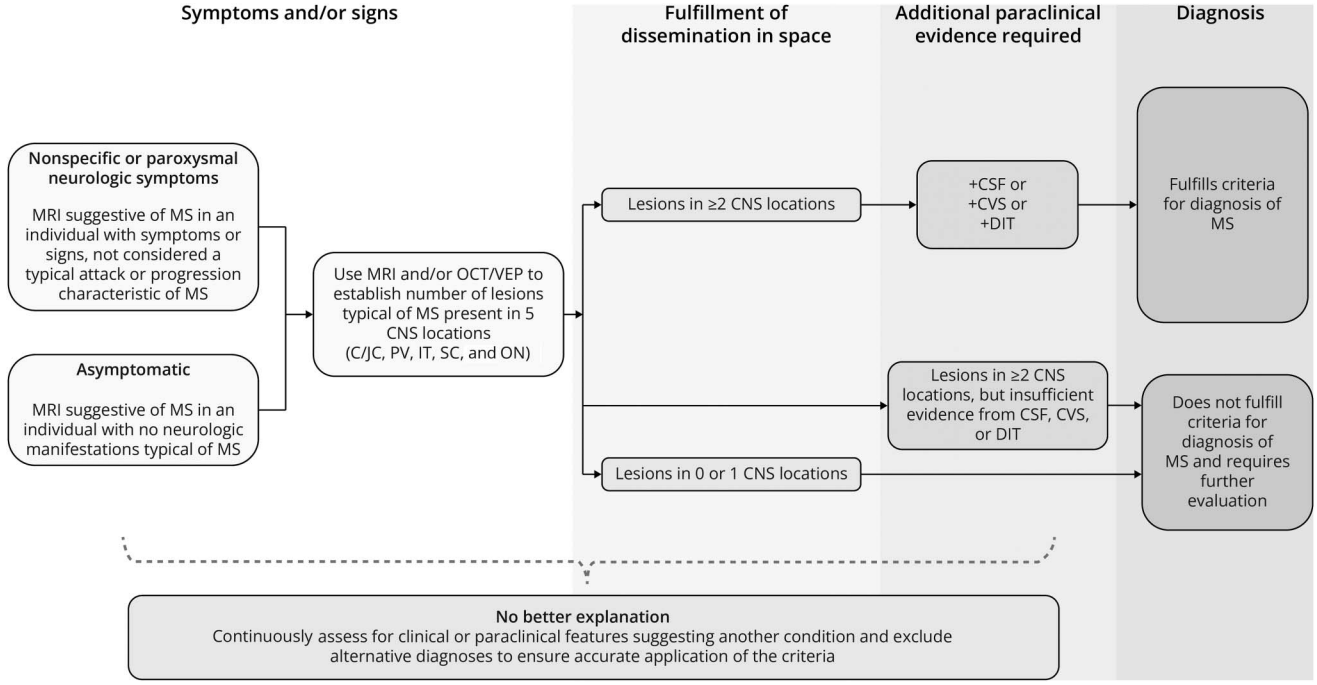
typical clinical presentations and lesions in 2 or 3 CNS regions. However, "positive CSF" is now expanded from the presence of 2 or more CSF-restricted OCBs to also include increased intrathecal kappa free light chains (kFLCs) (Table 2).[7,24] Much like OCBs, intrathecal production of kFLCs is associated with neuroinflammation. The measurement of kFLCs offer a quantitative and rapid assessment which can be fully automated, compared with the more labor intensive and time-consuming and expertise-dependent methodology required to provide a visual inspection for CSF-restricted OCBs.[24,26] Recent studies indicate that intrathecal kFLCs provide comparable diagnostic sensitivity and specificity for MS with CSF-restricted OCBs,[24,26] and increased intrathecal kFLCs are used interchangeably with CSF-restricted OCBs to substitute for DIT in the 2024 criteria. The 2024 criteria suggest a kFLC index of ≥6.1, calculated by comparing kFLCs in CSF with kFLCs in the serum (similar to OCB testing), is considered positive. Although performance of kFLCs and OCBs for the diagnosis of MS has been comparable, concordance between positive CSF OCBs and kFLCs have been approximately 90%, suggesting that in some clinical situations ordering both tests simultaneously could improve sensitivity.[24] A practical and resource efficient approach might be to first complete kFLC index testing while storing additional CSF and serum samples to allow for subsequent OCB testing in patients with negative or borderline kFLC index values where MS is highly suspected.[24,27] Recently reported global data indicated that OCB testing was unavailable in 13% of 122 countries,[28] often due to lack of expertise, suggesting that implementation of kFLC testing could aid MS diagnosis particularly in such regions. Consensus recommendations concerning "positive CSF" in the evaluation of MS published in tandem with the 2024 criteria further detail methodology for kFLC assessment.[24]

Expansion of Presentations Where MS Can Be Diagnosed

Previous MS diagnostic criteria limited diagnosis to patients presenting with an attack or disability progression typical of MS and involvement of at least 2 CNS regions. Mounting data support expanding diagnosis of MS to patients with MRI evidence of MS, regardless of their symptoms at the time of presentation; and to patients with presentations typical of MS, but involvement of only a single CNS region without DIS.[7]

Patients with a clinical attack or progression, and MRI findings highly suggestive of MS may rarely present with involvement of a single CNS region. The 2024 criteria newly permit diagnosis of MS in patients with MRI evidence limited to a single CNS region, with additional evidence of DIT or

Figure 4 Pathways to Diagnosis of MS in Patients With Nonspecific or Paroxysmal Neurologic Symptoms or Asymptomatic Presentations



CNS locations: C/JC = cortical/juxtacortical; PV = periventricular; IT = infratentorial; SC = spinal cord; ON = optic nerve. Paraclinical evidence: +CSF = positive CSF—the presence of ≥2 or more CSF restricted oligoclonal bands or kappa free light chain index ≥6.1 according to recommended laboratory techniques. +CVS = positive central vein sign—the presence of ≥6 lesions with CVS per NAIMS criteria. If <10 white matter lesions present, CVS-positive lesions must exceed CVS-negative lesions. +DIT = fulfillment of dissemination in time by second clinical attack, simultaneous gadolinium-enhancing (Gd+) and nonenhancing lesions, or a new T2-hyperintense or Gd+ lesion. +PRL = positive paramagnetic rim—presence of ≥1 PRLs according to NAIMS criteria. CVS = central vein sign; DIT = dissemination in time; MS = multiple sclerosis; OCT = optical coherence tomography; VEP = visual evoked potential.

positive CSF, in combination with either Select 6 CVS or at least 1 paramagnetic rim lesion (PRL) (Table 1, Figure 3).[7] A PRL is surrounded by iron-laden activated microglia encircling a core that may seem hypointense or hyperintense on susceptibility-based MRI sequences depending on the vendor's polarity settings (Figure 1G) and is highly specific for MS.[7,23] PRL identification requires expertise, and 2024 MAGNIMS-CMSC-NAIMS consensus recommendations[23] detail requirements for accurate PRL identification.

Radiologically isolated syndrome (RIS) has been defined by the incidental identification of CNS T2 hyperintense lesions on MRI typical of MS, in the absence of a clinical attack or progressive disability.[29] Although many patients with RIS are asymptomatic at presentation, observational studies have demonstrated that approximately 50% develop an attack or progression within 10 years.[29] Patients with MRI findings typical of MS may also present with nonspecific neurologic symptoms (i.e., sensory symptoms that do not clearly localize to a lesion) or paroxysmal syndromes of less than 24 hours that would not meet the definition of a typical MS attack (i.e., Uthoff phenomenon, Lhermitte phenomenon, tonic spasms, trigeminal neuralgia, or uncommonly, seizures).[30,31] For the first time, the 2024 MS diagnostic criteria incorporate a pathway to diagnosis for asymptomatic patients and those with nonspecific or paroxysmal symptoms who demonstrate MRI findings typical of MS.[7] In these patients, involvement of at least 2 CNS regions and either positive CSF, Select 6 CVS, or DIT is required for the diagnosis of MS (Figure 4).

Changes to Diagnostic Approaches for Specific Patient Populations

The 2024 McDonald criteria are applicable across the lifespan, with a consensus that pediatric and adult-onset MS represents the same underlying disease process.[7] However, the criteria contain important caveats for the diagnosis of MS in children, older adults, and patients with specific comorbid conditions to improve accuracy and prevent misdiagnoses.

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) accounts for more than half the presentations of demyelination in children younger than 12 years of age,[32] and can present with phenotypes that overlap with MS including optic neuritis or myelitis, thereby potentially being misdiagnosed as MS.[33] The 2024 McDonald criteria specify that testing for serum myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) with a cell-based assay[34] should be considered in all children younger than 12 years of age, and in older children or adults with clinical and/or MRI features suggestive of MOGAD.[7,34] Furthermore, the 2024 McDonald criteria should not be applied in children with acute

disseminated encephalomyelitis (ADEM), a common pediatric presentation of MOGAD, unless subsequent clinical attacks or MRI lesions are typical of MS.[7] Owing to a lack of data evaluating Select 6 CVS in patients younger than 18, the criteria also recommend a more conservative approach to CVS assessment in this younger cohort, requiring that more than 50% of lesions demonstrate CVS for incorporation in the diagnostic pathway for pediatric onset of MS.[7,23]

Ageing and/or comorbidities such as migraine or small vessel cerebrovascular disease due to hypertension, diabetes, dyslipidemia, or tobacco use may be associated with nonspecific MRI multifocal white matter changes that increase the risk of MS misdiagnosis, particularly in patients without a clinical presentation typical of MS.[20] Therefore, in patients older than 50 years of age or in patients with vascular comorbidities, the 2024 McDonald criteria recommend clinicians seek specific evidence to support a diagnosis of MS that includes either a spinal cord lesion, positive CSF, or Select 6 CVS.[20] These findings would not be expected in the context of healthy ageing, headache disorders, or vascular disease and would therefore increase specificity for MS beyond fulfillment of DIS and DIT alone, thus reducing the risk of MS misdiagnosis in this patient population.

Diagnosis of PPMS has also changed in the 2024 criteria to more closely align with relapsing-remitting MS and to ensure diagnostic accuracy (Figure 3). Although a patient presenting with progressive disability for greater than a year, with 2 spinal cord lesions and brain lesions in 1 or more CNS regions would fulfil 2017 criteria for PPMS,[35] the 2024 criteria additionally require DIT, CVS, or positive CSF.[7]

Pathways to the Diagnosis of MS

Through substantial revisions noted above, the 2024 McDonald provides multiple new pathways to the diagnosis of MS, which are visualized in Figures 3 and 4. These figures highlight flexibility—not every paraclinical assessment is required to confirm a diagnosis of MS in every patient. Except for specific cases of patients with PPMS who do not have multiple spinal cord lesions, all patients meeting 2017 criteria would also fulfill the revised 2024 McDonald criteria. Clinical findings in combination with routine MRI and CSF evaluation remain sufficient for diagnosis in most patients, and in some, incorporation of 2024 revisions to DIS would permit earlier diagnosis. In some clinical scenarios—such as patients in whom MRI DIT is not fulfilled, where CSF testing is unavailable, or who present with lesions in a single CNS anatomical location—pathways incorporating new paraclinical testing may expedite a diagnosis of MS which would not have been possible by prior criteria.

For instance, in a patient presenting with optic neuritis with an MRI of the orbits and brain demonstrating a contrast-enhancing optic nerve lesion, and a lesion in 1 additional anatomical location (i.e., periventricular), DIS and DIT are fulfilled by 2024 criteria and the patient can be diagnosed with MS earlier than in prior criteria. Similarly, if a patient presented with optic neuritis, received a noncontrast brain MRI that revealed lesions in 4 anatomical locations (i.e., optic nerve, periventricular, juxtcortical, and infratentorial), they would fulfill 2024 criteria for MS without positive CSF or DIT required by prior criteria. Finally, in a patient presenting with a progressive myelopathy and MRI evidence of 2 spinal cord lesions, DIS is considered fulfilled, and the finding of positive CSF would allow a diagnosis of PPMS.

Implementation of new paraclinical tools incorporated in the 2024 criteria can also facilitate earlier diagnosis. For example, in a patient presenting with internuclear ophthalmoplegia with a single non contrast-enhanced brain MRI that demonstrates lesions fulfilling 2 DIS anatomical locations (i.e., infratentorial and periventricular) and additional subcortical and deep white matter lesions, the finding of 6 CVS positive lesions on the same MRI would fulfill 2024 criteria for the diagnosis of MS without further testing. In a patient with myelitis, and brain and spinal cord MRI findings that satisfy 1 DIS anatomical location (i.e., spinal cord), a prior episode of vision loss described by the patient suggestive of optic neuritis can be now confirmed by OCT to fulfill both DIS and DIT and allow for the diagnosis of MS. Finally, in a patient first presenting with optic neuritis with an MRI demonstrating an enhancing optic nerve lesion fulfilling DIT and only 1 DIS anatomical location (optic nerve), the presence of a single nonenhancing brain MRI lesion demonstrating a PRL in a non-DIS anatomical location (i.e., deep white matter) would permit the diagnosis of MS.

In each of these examples, the diagnosis of MS can only be confirmed if clinical, MRI, and other paraclinical findings are typical of MS and there is no better explanation than MS.

2024 McDonald Criteria Revisions and Avoiding Risk of MS Misdiagnosis

MS misdiagnosis, an incorrect assignment of a diagnosis of MS to a person without MS, is a frequent contemporary problem that results in harm to patients, as well as unnecessary costs to healthcare systems.[12] A recent systematic review and metanalysis found that 15% of patients presenting to subspeciality centers with a preexisting diagnosis of MS were misdiagnosed.[13] As detailed above, the 2024 criteria recommend diagnostic approaches that incorporate specific paraclinical testing in patients older than 50 years of age, patients with vascular comorbidities and in pediatric patients, in order to reduce the risk of MS misdiagnosis. Common neurologic disorders such as migraine, functional neurologic disorder, and cerebrovascular disease are frequently referred for MS evaluation and misdiagnosed as MS despite clinical and MRI findings atypical of MS,[11,12,36,37] indicating a widespread problem in diagnostic approaches. Recent studies demonstrating a lack of understanding of key elements of MS

diagnostic criteria and their correct application by clinicians in practice suggest a likely explanation for pervasive misdiagnosis of MS.[14-17] Clinical expertise for the correct application of the 2024 criteria informed by a thorough understanding of its terminology (Table 2) is critical to prevent misdiagnoses.

Avoiding misdiagnosis requires accurate recognition of clinical and paraclinical features atypical for MS, and at times, these findings may not initially point to specific diagnoses but should prompt further evaluation.[18] Such clinical "red flags" include hyperacute (minutes to hours) symptom presentation, severe neurologic deficits (i.e., complete blindness or paraplegia), symmetric CNS involvement, and encephalopathy. A CSF white cell count of greater than 50 per microliter, protein concentrations above 100 mg/dL, or CSF glucose below 60% of serum glucose should all prompt consideration of disorders other than MS. The 2024 inclusion of a diagnostic pathway for patients with MRI findings typical of MS, without a clinical presentation typical of MS, elevates the importance of discriminating MS MRI findings to avoid misdiagnoses. Clinicians should be adept at identifying CNS lesions and lesion locations characteristic of MS (Figure 1) while guarding against nonspecific white matter changes, which may be more suggestive of vascular or other etiologies (Figure 2). In some circumstances, findings from longitudinal MRI monitoring, such as complete resolution of T2 lesions or persistent T1 contrast enhancement, can also point towards a diagnosis other than MS.

Presentations with nonspecific or paroxysmal symptoms now included in the 2024 criteria likely have lower specificity for MS. Extra scrutiny for alternative disorders where, for example, seizures occur with higher frequency is required (e.g., MOGAD, seizure disorder with concomitant small vessel disease, or autoimmune encephalitis).[38,39] Although asymptomatic patients or those with nonspecific neurologic symptoms that do not localize to a CNS lesion who also have MRI abnormalitiesfulfilling DIS may now be diagnosed with MS; the requirement of DIT, positive CSF, or CVS Select 6 in such patients to fulfill 2024 criteria increases specificity for MS with the intention of preventing misdiagnosis (Figure 4).

MOGAD presents with clinical phenotypes that overlap with MS, and the 2024 criteria revisions attempt to address potential misdiagnosis of MOGAD as MS, particularly in children.[18,33] A clear positive MOG serum antibody result by live cell-based assay, as determined by rigorously validated laboratory thresholds, can help distinguish MOGAD from MS.[34] However, MOG-IgG seropositivity with low titers, or results obtained using fixed rather than live cell-based assays, require cautious interpretation, particularly when ordered in patients with low probability of MOGAD, such as patients with clinical and MRI findings typical of MS.[34,40] Low-titer MOG-IgG has been reported in 1%–2% of patients with MS and has been reported in other neurologic disorders, highlighting the risk of misdiagnosis when MOG-IgG testing is applied indiscriminately.[41-43] Compared with MS, patients with MOGAD have MRI lesions that are typically poorly defined, involve long segments of the spinal cord and optic nerves, often resolve radiologically over time, and rarely demonstrate subclinical MRI activity.[40,44,45] Longitudinally extensive optic nerve involvement, often bilateral, with moderate-severe optic disc swelling and optic nerve sheath enhancement is typical for MOGAD,[40,46] as is encephalopathy in a child with ADEM. Despite these distinguishing features, at times clinical and radiologic overlap between MS and MOGAD can cause diagnostic uncertainty, particularly in patients with low lesion burden such as isolated short-segment myelitis, or optic nerve involvement with a concurrent single white matter brain lesion, or when specific and sensitive live cell-based antibody testing for MOG-IgG is unavailable. In such scenarios, repeat antibody testing using optimized live cell-based assays, longitudinal clinical and MRI follow-up, and consultation with specialists are essential to ensure diagnostic accuracy.

Identification of spinal cord lesions can increase specificity for MS; however, small lesions can be challenging to identify, and erroneous identification of spinal cord lesions can lead to misdiagnosis. The 2024 McDonald criteria[7] and accompanying 2024 MAGNIMS-CMCS-NAIMS imaging guidelines[23] now recommend confirmation of an MRI spinal cord lesion in 2 sagittal and 1 axial sequence to distinguish small MS lesions from artifact, thereby preventing false-positive findings and risk of misdiagnoses.[23,47] Identification of a single MRI spinal cord lesion typical of MS in conjunction with brain white matter lesions aids exclusion of common syndromes associated with brain lesions often referred for MS evaluation (e.g., migraine and small vessel ischemic disease) that largely lack spinal cord involvement. The presence of 2 MRI spinal cord lesions typical of MS in patients with progressive disability increases specificity for MS such that this finding can substitute for DIS according to the 2024 criteria.

Practical Approaches to Implementing the 2024 McDonald Criteria in Underresourced Regions

The Multiple Sclerosis International Federation 2023 Atlas of MS reported that more than 90% of low- and middle-income countries (LMICs) face major barriers to early diagnosis of MS[10]due to lack of awareness and education concerning MS among both the general population and health care workers, as well as limited access to neurologists, neuroradiologists, MS specialists, MRIs, and CSF diagnostics. Social determinants of health influencing therapeutic access, economic constraints, and lack of prioritization further delay MS diagnosis.[48-51] Implementation efforts surrounding the 2024 McDonald criteria in LMICs should focus on improving the understanding of criteria through education, maximizing existing resources,

and engaging health care systems to improve access to new technology.

Necessary infrastructure and expertise in interpretation of MRIs may be barriers to global adoption of CVS and PRL evaluation. Some regions are unlikely to have access to susceptibility-based sequences, 3T MRI machines, and/or neuroradiologists. Although these paraclinical tools may help facilitate early diagnosis of MS in some patients, they are not mandatory, and parallel pathways to diagnosis may be more accessible in some regions (Figures 3 and 4). It is important to note that CVS and PRLs can be identified on susceptibility-based imaging and 1.5T MRIs, which are more globally available. Data indicate that even at 1.5T, the proportion of MS lesions exhibiting CVS remains above the established 40% threshold, and a comparative analysis of 1.5T and 3.0T MRI found that 82% of PRLs identified at 3.0T were also visible at 1.5T.[52] Visibility of CVS at 1.5T could be improved by acquiring the sequence during or immediately after injection of contrast.[7,53] Despite the potential availability of MRI capabilities and awareness of the updated MAGNIMS-CMSC-NAIMS consensus recommendations[23] for MRI in MS, implementing CVS and PRL detection in many regions, including well-resourced regions, will require extensive education of not just neurologists, but also of radiologists to ensure CVS and PRL detection is performed with high accuracy.[54] Collaboration with radiologists and local health care systems will be needed to ensure proper implementation of optimal MRI protocols for CVS and PRL detection.[23]

Although access to kFLCs may be limited in some regions, many laboratories in resource-limited settings are already performing this assay in serum for the diagnosis of other disorders, such as multiple myeloma. kFLCs may provide a quantitative assessment of intrathecal Ig synthesis with a rapid turn-around of results, in settings where CSF-restricted OCB assessment may be prohibitively expensive and/or unavailable due to lack of expertise. As such, efforts to raise awareness about kFLC and its equivalent importance to CSF-restricted OCBs may conceivably increase uptake and accessibility of CSF evaluation for MS in these settings.

Availability of OCT and/or VEPs, and expertise for their interpretation may also be limited in some regions. However, their incorporation in the 2024 criteria for visual pathway assessment may avoid the need for CSF analysis, which may be challenging or unavailable in some settings. For example, in patients with lesions in 3 CNS anatomical locations, evidence of an optic nerve lesion as a fourth location by OCT could reduce a barrier to diagnosis. The 2024 McDonald criteria may additionally provide an avenue for engaging local governments for improved access to these tools and training to gain expertise for their interpretation.

The differentiation of MS from MOGAD and other disorders can be accomplished by careful assessment of clinical and neuroimaging and laboratory findings. Barriers to access MRI and laboratory testing, including cost to patients, can hinder differential diagnosis assessment.[10,28] Furthermore, lack of access to optimal assays for aquaporin-4 (AQP4)-IgG and MOG-IgG testing can make diagnosis of antibody-mediated demyelination challenging in resource-limited regions.[19,55] The reduced sensitivity of fixed cell-based assays compared with live cell-based assays, and reduced access to live cell-based assays in the detection of AQP4 antibodies and in particular, MOG antibodies, remains a critical issue.[56] Misdiagnosis of MOGAD or neuromyelitis optica spectrum disorder as MS commits patients to divergent treatment pathways, and treatment with MS DMT in such patients can result not only in a lack of benefit but also ongoing relapses and accumulating disability. Clinical acumen in differentiating these disorders remains critical.

Implementation of the 2024 McDonald criteria will require a multifaceted, intersectoral response in underresourced regions (Table 3). Regional investment in acquiring paraclinical tests, and training of medical staff and specialists in the conduct and interpretation of these tests will require education and investment. In regions with neurologists, targeted education programs contextualizing the criteria to the resources available in the local setting will be essential, as will advocacy work by patient and physician groups to improve access to diagnostic tests which are currently not available. In some regions, when MS is highly suspected yet barriers to implementation of paraclinical tools incorporated in the 2024 criteria persist, development of new referral networks to subspeciality centers that provide access to such testing may be needed. In regions without neurologists, neuroradiologists, or MS specialists, collaboration with international experts, utilization of telemedicine consultations, and engagement at a national level to improve access to important biomarkers, specialists and neuroimaging tools will be needed. In the future, data from underresourced regions that report barriers to implementation of the 2024 McDonald criteria and/or how it has been successfully operationalized would be a valuable contribution to the literature to aid regional advocacy efforts, guide providers in comparably underresourced settings, and inform future revisions of MS diagnostic criteria.

Conversations With Patients Surrounding 2024 McDonald Criteria Revisions

Patients with an established MS diagnosis and those undergoing diagnostic evaluation may question how the changes to the McDonald criteria will affect them. Although revisions to the criteria give health care professionals additional tools to diagnose MS more quickly and accurately, it is important to emphasize that the updates to the criteria would not change their patients' diagnoses of MS made under earlier criteria. By

Table 3 Practical Approach to Accessibility and Implementation of 2024 McDonald Criteria

Changes	Intervention: education and capacity building	Implementation
Optic nerve as fifth anatomical location	Educate on use and interpretation of VEP, OCT, and MRI optic nerve Target audience: Neurologists, ophthalmologists, radiologists	Acquisition of VEP, OCT, and MRI technology/tools; training of paramedical staff to run services
DIS	Educate on recognition and interpretation of DIS in 2 of the 5 anatomical location Investing in local and sustainable training of radiologists, neurologists and ophthalmologists	Acquisition of MRI machines with stronger fields strengths and improved availability of necessary MRI brain sequences
CVS and PRLs	Educate on identifying CVS Select 6 and PRLs, including its use in supporting a diagnosis of MS in specific situations Training of neuroradiologists or improving neurology training for general radiologists	Improving access to MRI susceptibility-based sequences sensitive for CVS and PRLs on 1.5T and 3T MRI
CSF kFLC: Diagnosis by turbidimetry or nephelometry	Educate pathologists on the identification, validation, and use of CSF kappa light chain Train laboratory technicians on performing the assay Educate neurologists on the indications and interpretation of CSF kFLC	Acquiring necessary laboratory equipment and/or reagents
MRI findings typical of MS without a typical clinical presentation	Education on the concept and identification of true RIS and approach to ruling out mimic disorders, when taking into account the local epidemiology and regional differential diagnosis	Acquisition of MRI machines with stronger fields strengths and improved availability of necessary MRI brain sequences, improved access to paraclinical testing to enable diagnosis of MS

Abbreviations: CVS = central vein sign; DIS = dissemination in space; kFLC = kappa free light chain; MS = multiple sclerosis; OCT = optical coherence tomography; PRL = paramagnetic rim lesion; RIS = radiologically isolated syndrome; VEP = visual evoked potential.

contrast, some patients who were previously diagnosed with clinically isolated syndrome or RIS may now fulfill diagnostic criteria for MS. Diagnostic certainty associated with the label "MS" may provide relief in some patients. This change may also have implications for improved access to DMT in some regions. The diagnosis of MS in patients previously labelled RIS will require thoughtful counselling and shared decision-making, given that data surrounding prognostication and treatment of RIS differ from clinically isolated syndrome or MS. Referral to patient advocacy organizations for additional education, psychosocial support, and peer connections may benefit patients newly diagnosed with MS because of changes to the 2024 criteria.

Conclusions

The 2024 revisions to the McDonald criteria present multiple new pathways to the diagnosis of MS. Like prior criteria, accurate diagnosis relies upon detailed knowledge of the criteria's framework, and clinical acumen for its application. Recent studies from Egypt, Croatia, Spain, and the United Kingdom that have compared the performance of the 2024 with 2017 criteria suggest that the 2024 revisions will yield improved sensitivity and thus earlier diagnosis in many patients.[57-60] Prospective validation studies in patients presenting for evaluation for MS in diverse regions with varied access to paraclinical testing incorporated in the 2024 criteria will be required to better understand the effect of these revisions. Ultimately, implementation efforts by researchers, clinicians, educators, and policy makers in the global MS community will be critical to fully achieve the promise of the 2024 McDonald criteria for patients with MS.

Author Contributions

A.J. Solomon: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. W.J. Brownlee: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. S. Viswanathan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. G. Fadda: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J. Fiol: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. L.M. Galleguillos Goiry: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. T. Griffin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M.A. Sahraian: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. D.R. Saylor: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. À. Rovira: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. E.P. Flanagan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. S. Ramanathan: drafting/revision of the manuscript for

content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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