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Overview of McDonald Criteria: History and Updates

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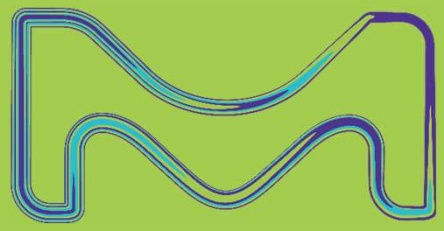


EMD SERONO

MS is an immune-mediated disorder of the CNS[1]

MS is a chronic demyelinating disease of the CNS with an autoimmune etiology, characterized by localized areas of inflammation, demyelination, axonal loss, and gliosis in the brain and spinal cord[1]

The chronic accumulation of physical and cognitive disability among people with MS has substantial effects on social, economic, and individual well-being[2]

CNS, central nervous system; MS, multiple sclerosis.

1. Milo R, et al. *Autoimmun Rev*. 2014;13(4-5):518-24; 2. Jakimovski D, et al. *The Lancet*. 2024;403:183-202.

MS in the US: Prevalence, demographics, and regional distribution

- Approximately 1 million people in the US live with MS; most people are diagnosed between **20** and **40 years of age**[1,2]
- Affects up to **3** times as many **women** as men[3]
- MS prevalence is the highest among the white population,[4] with increasing rates observed among African Americans[5]
- Patients typically receive a confirmed diagnosis of MS within 1 year once they are under a neurologist's care[b,6]

In general, MS is commonly observed in areas farthest from the equator[7]

Region	Prevalence of MS[8]
West	272.7[a]
Midwest	353.1[a]
South	272.6[a]
Northeast	377.4[a]

[a]Per 100,000 US Residents; 2010 US Census[8]

[b]Retrospective study based on claims data for patients diagnosed with MS between October 1, 2010 and May 31, 2014.

CNS, central nervous system; MS, multiple sclerosis; US, United States.

1. Bebo B, et al. *Neurology*. 2022;98(18):e1810-e1817; 2. Habbestad A, et al. *J Neurol*. 2023;271(4):1610–1617; 3. Dunn SE, et al, *Curr Top Behav Neurosci*. 2015:26:29-56; 4. Hittle M, et al. *JAMA Neurol*. 2023;80:693-701; 5. Amezcua L, McCauley JL. *Mult Scler*. 2020;26:561-567; 6. Visaria J, et al. *Clin Ther.* 2018;40:926-939; 7. National Multiple Sclerosis Society. Who Gets Multiple Sclerosis? Factors of MS. https://www.nationalmssociety.org/understanding-ms/what-is-ms/who-gets-ms. Accessed June 18, 2025; 8. Wallin MT, et al. *Neurology*. 2019;92:e1029-e104.

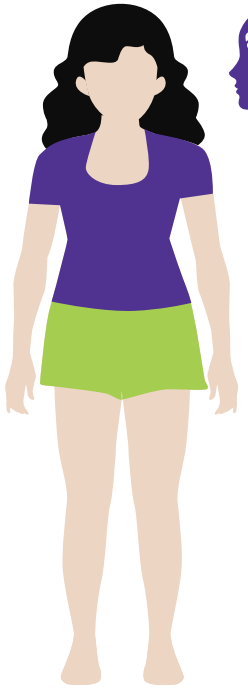
Clinical symptoms of MS

General

- Fatigue[1,2]
- Pain[1,2]
- Altered sensation (e.g., numbness or tingling)[1,2]

Muscle and movement

- Weakness/involuntary muscle spasms[1,2]
- Loss of movement[1,2]



Neurologic

- Cognitive changes, emotional changes, or mood disorders[1,2]
- Sleep issues[2]
- Visual disorders[1,2]

Urinary and genital

- Sexual dysfunction[1,2]
- Bladder/bowel problems[1,2]

- MS symptoms may present with one dominant symptom or a cluster of symptom[2]
- Early and accurate diagnosis of MS is essential for enhancing disease management strategies and improving patient outcomes[3]

MS, multiple sclerosis.

1. Correia I et al. *J Clin Med*. 2024;13(19):5687; 2. National Multiple Sclerosis Society. MS Signs & Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed June 18, 2025; 3. Thompson AJ, et al. *Lancet Neurol*. 2018;17:162-173.

Overview of McDonald criteria

- The McDonald criteria are a set of diagnostic guidelines used to determine whether a patient has MS, based on an evaluation of clinical symptoms, MRI findings, and biomarkers, which can be adapted as necessary for use in clinical trials.[1-4] These criteria integrate DIS, and DIT to facilitate an early and accurate diagnosis in patients in whom MS is likely[1-7]

2001

McDonald criteria introduced[1]

Outcomes of diagnostic evaluation could be MS, possible MS[a] or not MS; core criteria: dissemination in space and time

2005

McDonald criteria updated[2]

Incorporated new evidence, clarified and further supported existing evidence concepts

2010

McDonald criteria updated[3]

Further simplified and MRI criteria revisited

2017

McDonald criteria updated[4-6]

Inclusion of OCB as determining factors for the diagnosis of RMS

2024

Proposed updates to the McDonald criteria[7]

RIS can be diagnosed as MS if certain biomarkers are present; κFLCs can be used as a diagnostic marker to help identify MS

[a]For those at risk for MS, but for whom diagnostic evaluation is equivocal.

DIS, dissemination in space; DIT, dissemination in time; κFLCs, kappa free light chains; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal band; RIS, radiologically isolated syndrome; RMS, relapsing multiple sclerosis.

1. McDonald WI, et al. *Ann Neurol*. 2001;50:121-127; 2. Polman CH, et al. *Ann Neurol.* 2005;58:840-846; 3. Polman CH, et al. *Ann Neurol*. 2011;69:292-302; 4. Thompson AJ, et al. *Lancet Neurol*. 2018;17:162-173; 5. van der Vuurst de Vries RM, et al. *JAMA Neurol.* 2018;75(11):1392-1398; 6. Schwenkenbecher P, et al. *Front Neurol.* 2019;10:188; 7. Montalban X, et al. ECTRIMS 2024.

Components of the McDonald criteria

DIS, DIT, relapses, neurological deficits

Dissemination in Space (DIS)[1]

DIS can be demonstrated by one or more T2-hyperintense lesions[a] that are characteristic of MS in two or more of four areas of the CNS:

- Periventricular[b]
- Cortical or juxtacortical
- Infratentorial brain regions
- Spinal cord

Dissemination in Time (DIT)[1]

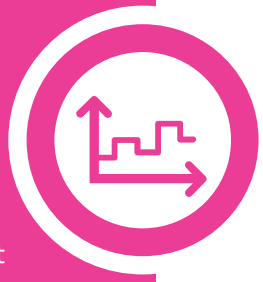
- Demonstrated by the simultaneous presence of Gd enhancing and/or non-enhancing T1 lesions[a] at any time

OR

- By a new T2-hyperintense or Gd enhancing T1 lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

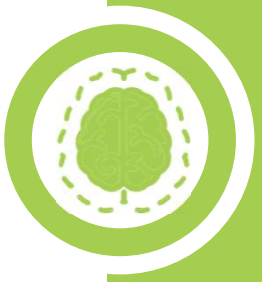
Clinical attacks (relapses)[1]

- Relapses are demonstrated by a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of ≥24 hours, with or without recovery, and in the absence of fever or infection
- Attack, relapse, exacerbation, and (when it is the first episode) CIS are synonyms



Neurological deficits[1-3]

- Neurological deficits refer to the observable impairments in neurological function that result from MS (e.g., weakness, sensory disturbances, visual problems, balance and coordination difficulties, and cognitive changes)
- The presence of neurological deficits helps to establish the diagnosis, especially when combined with evidence of lesions in the CNS seen on MRI



[a]Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. [b]For some patients, individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.[1]

CIS, clinically isolated syndrome; CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; MRI, magnetic resonance imaging; MS, multiple sclerosis.

1. Thompson AJ, et al. *Lancet Neurol*. 2018;17(2):162-173; 2. Polman CH, et al. *Ann Neurol*. 2011;69:292-302; 3. Polman CH, et al. *Ann Neurol*. 2005;58:840-846.

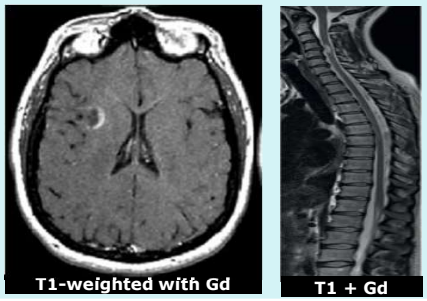
Proposed components of the 2024 McDonald criteria

MRI measures commonly used in MS

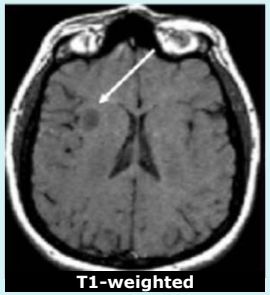
- MRI has been increasingly used to support the diagnosis of MS and to identify atypical radiological features suggestive of alternative diagnoses[1]
- Brain and spinal cord MRI remain the most useful paraclinical tests for MS diagnosis and can substitute for clinical findings in the determination of DIS or DIT in patients with a typical CIS[1]

MRI types used to diagnose and/or monitor MS[2-5]

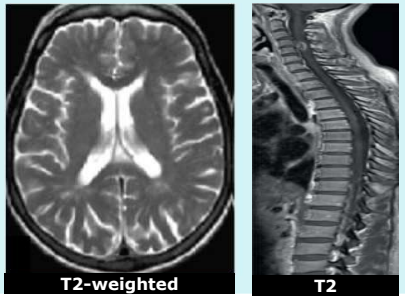
T-1 weighted (with Gd)
Identifies bright areas that indicate early active inflammation and disruption of BBB



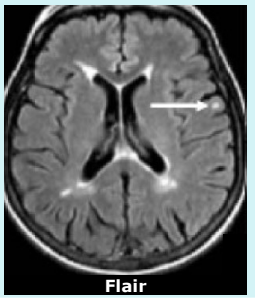
T-1 weighted (No Gd)
Identifies dark areas that indicate possible permanent nerve damage



T-2 weighted
Captures overall disease burden or lesion load (total number of lesions, both old and new)



FLAIR
Shows MS activity by reducing interference from the spinal fluid



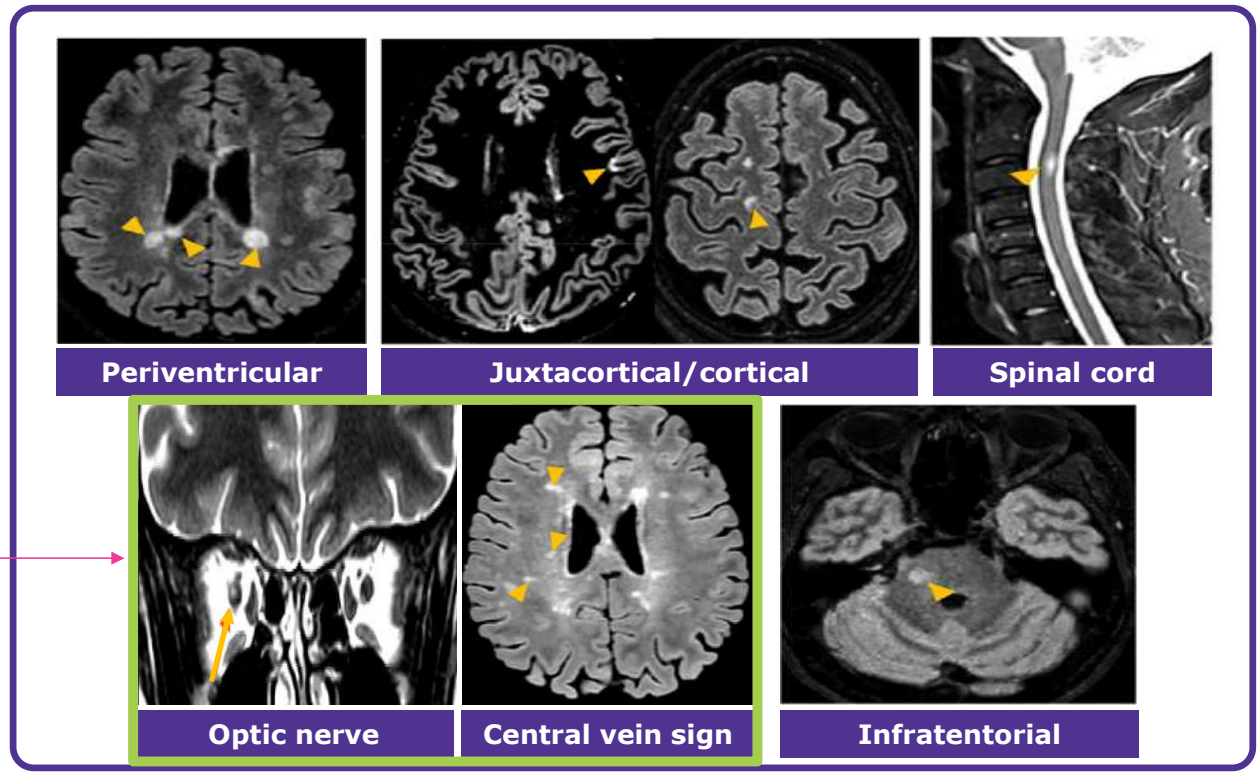
Adapted from Bakshi R, et al. *NeuroRx* 2005.[3]; Wattjes MP, et al. *Lancet Neurol.* 2021.[5]

BBB, blood-brain barrier; CIS, clinically isolated syndrome; DIS, dissemination in space; DIT, dissemination in time; FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis.

1. Thompson AJ, et al. *Lancet Neurol* 2018;17:162–73; 2. National Multiple Sclerosis Society. Magnetic Resonance Imaging (MRI). https://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools/MRI. Accessed June 18, 2025; 3. Bakshi R, et al. *NeuroRx* 2005;2(2):277-303; 4. Magnetic Resonance Imaging (MRI) of the Brain and Spine: Basics. https://case.edu/med/neurology/NR/MRI%20Basics.htm. Accessed June 18, 2025; 5. Wattjes MP, et al. *Lancet Neurol.* 2021;20(8):653-670.

Proposed components of the 2024 McDonald criteria

Types of MRI lesions seen in MS



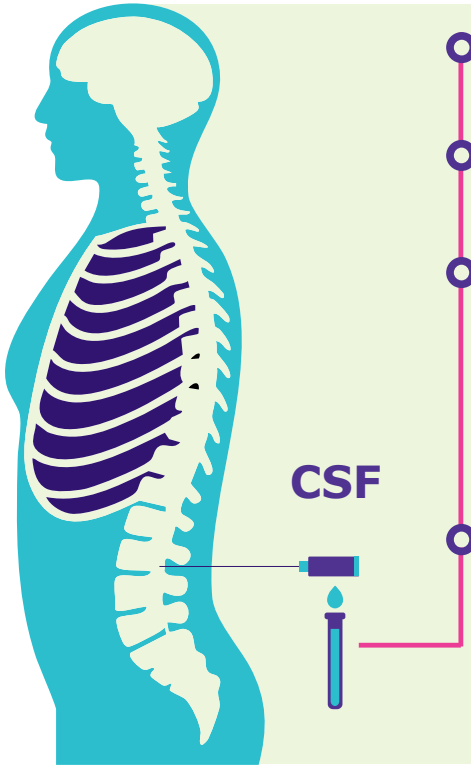
Adapted from Rocca MA, et al. *Lancet Reg Health Eur.* 2024.

Rocca MA, et al. *Lancet Reg Health Eur*. 2024;22:44:100978.

MRI, magnetic resonance imaging; MS, multiple sclerosis.

Proposed components of the 2024 McDonald criteria

CSF, oligoclonal bands, and κFLC: Significance in MS diagnosis



- CSF analysis enables the assessment of inflammatory processes confined to the CNS and indicates immunological changes associated with MS progression[1]
- IgG OCBs are present in the CSF of most patients with MS, and are considered to be the immunological hallmark of MS.[2] Higher OCB counts may suggest greater disease severity and sensory system involvement as the initial clinical presentation[3]
- κFLC is emerging as a promising biomarker for MS diagnosis.[4] Elevated κFLC levels (κFLC index) can help differentiate MS from other neurological conditions.[5] Intrathecal κFLC synthesis, determined by an increased κFLC index, has similar diagnostic accuracy to CSF OCBs[6]

- CSF examination is strongly recommended in the following situations[7]:
  - When clinical and MRI evidence is insufficient to support MS diagnosis, particularly if DMT initiation is considered
  - When there is a presentation other than a typical CIS, including PPMS
  - When clinical, imaging, or laboratory features are atypical of MS, and in populations in which MS is less common such as children, older individuals, or non-white populations

- The 2017 McDonald criteria updates state that MS can be diagnosed based on[7]:
  - A typical CIS
  - Clinical or MRI evidence of DIS
  - No better explanation for symptoms
  - CSF OCBs (without atypical findings)
- Diagnosis can be made even without:
  - MRI criteria for DIT on baseline scan
  - A second attack
  - New/active lesions on follow-up MRI

- The proposed 2024 McDonald criteria updates suggest κFLC as an appropriate paraclinical test for MS[8]
- As κFLC are interchangeable with OCB, it can substitute for OCBs in MS diagnosis[8]

CIS, clinically isolated syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; DMT, disease-modifying therapy; IgG, immunoglobulin G; κFLCs, kappa free light chains; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal band; PPMS, primary progressive multiple sclerosis.

1. Sasso B, et al. *Medicina (Kaunas).* 2019;55(6):245; 2. Garner M, et al. *PLoS One.* 2020;15(2):e0228883; 3. Khedr EM, et al. *Mult Scler Relat Disord* 2025;95:106336; 4. Konen FF, et al. *Cells. 2021*;10(11):3056; 5. Vecchio D, et al, *Sci Rep.* 2020;10:20329; 6. Arneth B, et al. *Medicina (Kaunas).* 2022;58(11):1512; 7. Thompson AJ, et al. *Lancet Neurol* 2018;17:162–73; 8. Montalban X, et al. ECTRIMS 2024.

Diagnostic process using McDonald criteria

The diagnosis of MS is made based on information gathered from:

Integration of findings to meet criteria[1]:

- MS
- Possible MS (when criteria are partially met)
- Not MS (when another diagnosis is established)

Medical and family history[2,3]

- Evaluation of past and present symptoms and family medical history

Neurological examination[2,3]

- Walking/balance
- Strength
- Vision/eye movement
- Speech or reflexes
- Hearing

MRI[2-4]

- Evaluation of the brain and/or spinal cord for demyelinating lesions

Laboratory testing[2,3,5]

- Blood tests that help rule out other diseases
- CSF analysis or spinal tap: analyses of the spinal fluid for abnormal immune responses within the CNS such as oligoclonal bands
- Evoked potential: measurement of the CNS electrical activity

CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MS, multiple sclerosis.

1. McDonald WI, et al. *Ann Neurol*. 2001;50:121-127; 2. National Multiple Sclerosis Society. How MS is Diagnosed. https://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-MS. Accessed June 18, 2025; 3. MS Society. How is MS diagnosed. https://www.mssociety.org.uk/about-ms/diagnosis/the-tests-for-ms. Accessed June 18, 2025. 4. National Multiple Sclerosis Society. Magnetic Resonance Imaging (MRI) for diagnosing multiple sclerosis. https://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools/MRI. Accessed June 18, 2025; 5. Šoda J, et al. *Sensors (Basel)*. 2023;23(1):497.

Proposed McDonald criteria 2024: Overview

The latest McDonald updates introduced several key changes with the goal of making the diagnostic process more accurate and allowing for earlier diagnosis, which could lead to better treatment outcomes for patients[1,2]

RIS: Can be diagnosed as MS if certain biomarkers are present[1]

Optic nerve: Added as a diagnostic anatomical location[1]

CVS: A new diagnostic marker that can help differentiate MS from other inflammatory CNS lesions[1]

PRL: MRI marker with high (≥95%) specificity for MS[1]

κFLCs: A diagnostic marker that can help identify MS[1]

DIT: No longer mandatory to diagnose MS[a]

Special population: More strict features for confirming diagnosis in individuals >50 years, headache disorders (including migraine), or with vascular disorders. MOG-IgG Ab could be used for confirming MS diagnosis in children and adolescents[1]

[a]The role of DIT in MS diagnosis is important, and it may still be considered to diagnose MS in addition to the other diagnostic criteria.[3] The combination of both DIS and DIT improves MS diagnostic criteria performance by enhancing specificity.[4]

Ab, antibody; CNS, central nervous system; CVS, central vein sign; DIT, dissemination in time; IgG, immunoglobulin G; κFLCs, kappa free light chains; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; PRL, paramagnetic rim lesions; RIS, radiologically isolated syndrome.

1. Montalban X, et al. ECTRIMS 2024; 2. McDonald diagnostic criteria, 2024. https://ectrims.eu/mcdonald-diagnostic-criteria. Accessed June 18, 2025; 3. Thompson AJ, et al. *Lancet Neurol*. 2018;17(2):162-173; 4. Brownlee WJ et al. *Neurology*. 2025;104(7):e210274.

Key details of the proposed 2024 updates to the McDonald criteria[1] (1/2)

The proposed 2024 recommended updates

RIS	In patients with RIS, meeting the following is sufficient for diagnosing MS[1]: • DIS and DIT • DIS and OCB • DIS ≥6 CVS
Optic nerve as a 5th topography	Findings which may serve as evidence of optic nerve involvement[1]: • MRI: ≥1 typical short segment intrinsic optic nerve lesions with no better explanation identified • VEP: Abnormal peak time using a full field pattern reversal • OCT: Abnormal
DIT is no longer mandatory to diagnose MS[a]	However, DIT may still be considered to diagnose MS in addition to the other diagnostic criteria[2]
Updated DIS criteria	• DIS is met when 2 out of 5 topographies (ON, JC/IC, PV, IT, spinal cord) show typical lesions, regardless of whether these lesions are symptomatic[1] • In patients with progressive disease, 2 spinal cord lesions are sufficient to demonstrate DIS[1] • Meeting the criteria of DIS and DIT[b] is sufficient to diagnose MS[1] • Meeting the criteria of DIS plus OCB and/or κFLCs[b] is sufficient to diagnose MS[1] • In patients with typical symptoms, the presence of typical lesions in ≥4 topographies is sufficient to diagnose MS[1] • In patients with typical symptoms and typical lesions in 1 topography, the presence of 6 CVS or PRLs plus DIT or CSF positive is sufficient to diagnose MS[1]

NOTE: The information provided is based on an oral presentation at ECTRIMS 2024 and may still be undergoing updates. Finalized criteria will be available upon manuscript publication. Please refer to the published work for the most accurate information.

[a]Except in cases of RIS. [b]This is as per 2017 McDonald criteria.[2]

CSF, cerebrospinal fluid; CVS, central vein sign; DIS, dissemination in space; DIT, dissemination in time; IC, intracortical; IT, infratentorial; JC, juxtacortical; κFLC, kappa free light chain; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal band; OCT, optical coherence tomography; ON, optic nerve; PRL, paramagnetic rim lesions; PV, periventricular; RIS, radiologically isolated syndrome; VEP, visual evoked potential.

1. Montalban X, et al. ECTRIMS 2024; 2. Thompson AJ, et al. *Lancet Neurol*. 2018;17(2):162-173.

Key details of the proposed 2024 updates to the McDonald criteria[1] (2/2)

The proposed 2024 recommended updates

κFLCs as a tool for diagnosis of MS	• κFLCs are interchangeable with OCB[1]
Same criteria for PPMS and RMS diagnosis	• PPMS: ≥2 spinal cords lesions is evidence for DIS in the diagnosis of PPMS[1]
Need of paraclinical evidence to diagnose MS	• Paraclinical evidence includes changes in visual evoked potentials, MRI findings, blood and CSF analysis, and OCT results[2]
Stricter features for confirming diagnosis in individuals over 50 years, or with headache disorders (including migraine), or with vascular disorders	• A spinal cord lesion, positive CSF or CVS can serve as an additional feature[1]
Addition of CVS and PRLs as optional tools for diagnosis in certain situations	• In patients with typical symptoms and typical lesions in 1 topography: presence of 6 CVS or ≥1 PRL plus DIT or CSF positive[1] • Presence of 6 CVS can serve as an additional feature for confirming diagnosis of MS[1] Additionally, CVS is detectable at 1.5T MRI scans, with improved visibility particularly on Gd-enhanced susceptibility-weighted images[3]
Pediatric MS	• Presence of CVS in ~50% of T2 lesions strongly suggests MS[1] • MOG-IgG Ab cell-based assay testing strongly recommended in children with initial demyelinating incident <12 years of age[1] • ≥12 years of age with demyelinating event: MOG-IgG Ab[1] cell-based assay testing is recommended for for atypical presentation of MS[1]

NOTE: The information provided is based on an oral presentation at ECTRIMS 2024 and may still be undergoing updates. Finalized criteria will be available upon manuscript publication. Please refer to the published work for the most accurate information.

Ab, antibody; CSF, cerebrospinal fluid; CVS, central vein sign; DIT, dissemination in time; Gd, gadolinium; IgG, immunoglobulin G; κFLCs, kappa free light chain; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal band; OCT, optical coherence tomography; PPMS, primary progressive MS; PRL, paramagnetic rim lesions; RMS, relapsing MS.

1. Montalban X, et al. ECTRIMS 2024; 2. Thompson AJ, et al. *Lancet Neurol*. 2018;17(2):162-173; 3. Sparacia G, et al. *Neuroradiol J.* 2021;34(5):470–475..

Significance of the proposed 2024 updates for the diagnosis of MS

- The recommendations for updating the McDonald diagnostic criteria consider new understanding of how MS appears and progresses in individuals. These recommendations demonstrate a shift toward considering the biologic basis of MS at diagnosis
- The proposed 2024 updates to the McDonald criteria include tests that target what's happening under the surface and the damage that is being caused by MS, in addition to the symptoms the person experiences
- The new updates introduce several key changes aimed at making the diagnostic process more accurate and enabling earlier diagnosis, which may lead to earlier treatment and improved patient outcomes

MS, multiple sclerosis.

McDonald diagnostic criteria, 2024. https://ectrims.eu/mcdonald-diagnostic-criteria. Accessed June 18, 2025.

Summary

- MS is a chronic demyelinating disease of the CNS with an autoimmune etiology[1]
- Common MS symptoms include fatigue, pain, and altered sensation (such as numbness or tingling).[2] Approximately 1 million people in the US live with MS[3]
- In MS, time is brain.[4] Early and accurate diagnosis of MS is essential for enhancing disease management strategies and improving patient outcomes[5]

- The McDonald criteria are clinical guidelines used to diagnose MS. These criteria integrate DIS, DIT including relapses, lesions, and biomarkers to facilitate early and accurate diagnosis. The criteria have been updated several times since their introduction in 2001[6-11]

The proposed 2024 updates introduced several key changes to improve diagnostic accuracy and allow for earlier diagnosis. Key updates include[11]:

- RIS can now be diagnosed as MS if certain biomarkers are present (DIS and DIT, DIS and OCB, DIS ≥6 CVS)
- The optic nerve is added as a 5th topography for DIS
- New diagnostic markers to identify MS with high specificity were introduced such as CVS, PRL, and κFLCs
- DIT is no longer needed for MS diagnosis
- Stricter features for confirming diagnosis in specific populations such as pediatric patients and individuals >50 years

CNS, central nervous system; CVS, central vein sign; DIS, dissemination in space; DIT, dissemination in time; κFLCs, kappa free light chains; MS, multiple sclerosis; OCB, oligoclonal band; PRL, paramagnetic rim lesions; RIS, radiologically isolated syndrome; US, United States.

1. Milo R, et al. *Autoimmun Rev*. 2014;13(4-5):518-24; 2. Correia I et al. *J Clin Med*. 2024;13(19):5687; 3. Bebo B, et al. *Neurology*. 2022;98(18):e1810-e1817; 4. Longbrake E, et al. *Neurology*. 2023;101(13):549-550; 5. Thompson AJ, et al. *Lancet Neurol*. 2018;17:162-173; 6. McDonald WI, et al. *Ann Neurol*. 2001;50:121-127; 7. Polman CH, et al. *Ann Neurol*. 2005;58:840-846; 8. Polman CH, et al. *Ann Neurol*. 2011;69:292-302; 9. van der Vuurst de Vries RM, et al. *JAMA Neurol.* 2018;75(11):1392-1398; 10. Schwenkenbecher P, et al. *Front Neurol.* 2019; 10:188; 11. Montalban X, et al. ECTRIMS 2024.