International Advisory Committee on Clinical Trials in MS | ECTRIMS EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS | MS National Multiple Sclerosis Society

Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria

An Initiative of the International Advisory Committee on Clinical Trials in MS

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Xavier Montalban, Christine Lebrun-Frénay, Jiwon Oh, Georgina Arrambide, Marcello Moccia, Maria Pia Amato, Lilyana Amezcua, Brenda Banwell, Amit Bar-Or, Frederik Barkhof, Helmut Butzkueven, Olga Ciccarelli, Jeremy Chataway, Jeffrey A Cohen, Giancarlo Comi*, Jorge Correale, Florian Deisenhammer, Massimo Filippi, Julie Fiol, Mark S Freedman, Kazuo Fujihara, Cristina Granziera, Ari J Green, Hans-Peter Hartung, Kerstin Hellwig, Ludwig Kappos, Dorlan Kimbrough, Joep Killestein, Fred Lublin, Romain Marignier, Ruth Ann Marrie, Aaron Miller, Susana Otero-Romero, Daniel Ontaneda, Sudarshini Ramanathan, Daniel Reich, Maria A Rocca, Àlex Rovira, Shiv Saidha, Amber Salter, Jaume Sastre-Garriga, Deanna Saylor, Andrew J Solomon, Maria Pia Sormani, Bruno Stankoff, Mar Tintore, Helen Tremlett, Anneke Van der Walt, Shanthi Viswanathan, Heinz Wiendl, Brigitte Wildemann, Bassem Yamout, Paola Zaratin, Peter A Calabresi, Timothy Coetzee, Alan J Thompson

Lancet Neurology 2025

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Introduction

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29 Nov-2 Dec 2023 Barcelona

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Dx criteria have an impact on:

- Patient-Doctor dialogue[1]
- Treatment decisions[2]
- Clinical trials[3,4]
- Prognosis of MS[2]

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[1]DOI:10.1034/j.1600-0404.2003.00086.x
[2] DOI: 10.1212/WNL.0000000000012726
[3] DOI: 10.1177/00220345705600303011
[4] DOI: 10.1002/mus.27392

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Philosophy underlying changes to 2024 McDonald Criteria for MS Diagnosis

AN ATTEMPT TO INCORPORATE ***ACCUMULATING SCIENTIFIC EVIDENCE*** INTO DIAGNOSTIC CRITERIA

EARLIER DIAGNOSIS (AND APPROPRIATE MANAGEMENT) IN THOSE WHO ***BIOLOGICALLY*** HAVE MS

MECHANISMS TO PREVENT ***MISDIAGNOSIS***

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The two fundamental principles for the diagnosis of multiple sclerosis

- Worldwide applicability of diagnostic criteria

- Essential role of paraclinical diagnostic tests

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Methodology

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Convening Body

The International Advisory Committee on Clinical Trials in Multiple Sclerosis is a global body sponsored by **European Committee for Treatment and Research in MS (ECTRIMS)** and the **National MS Society (US)**. The Committee has existed for over 40 years and is composed of experts in clinical trials and clinical research in MS.

- The Committee provides perspective and guidance in planning and implementing clinical trials for new agents for multiple sclerosis treatment. It is well known for its work in developing all previous versions of the McDonald Diagnostic Criteria and the 1996 and 2013 clinical course descriptors for MS.

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2024 Revision Contributors

- Scientific Steering Committee Chairs
  - Xavier Montalban (ES)
  - Peter Calabresi (US)
  - Tim Coetzee (US)
  - Christine Lebrun Frenay (FR)
  - Jiwon Oh (CA)
  - Alan Thompson (UK)
- 56 international experts with expertise in clinical management, radiology, methodology, epidemiology, and patient perspective
- Included more first-time contributors to McDonald Criteria revision process
  - 17 Previous contributors
  - 39 New contributors
- Global representation
  - 16 countries
  - Africa, Asia, Europe, Middle East, Latin America, North America, and Oceania represented
    - Included representatives from low resource settings
- Gender Balance – 32 M/24 F

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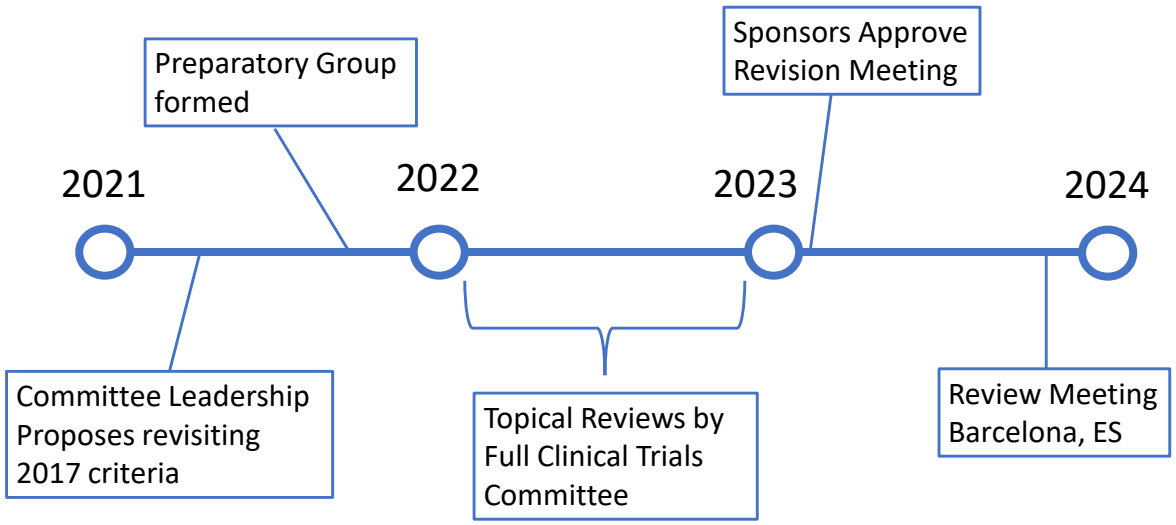
Timeline



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Consensus Methodology

- Consensus recommendations were developed using a modified Nominal Group Technique
  - Presentation of proposed revisions and supporting evidence
  - Group discussion of proposals
  - Presentation of general statements and recommendations
  - Voting on statements and recommendations
- Voting criteria
  - 90% of meeting participants vote must on a statement
  - Statements and recommendations must receive 80% agreement to be accepted
  - Statements receiving 70-80% may be reconsidered with an additional round of voting

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General Updates

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2024 revisions of the McDonald criteria

General Principles for an MS Diagnosis

- The clinical presentation of MS is similar throughout diverse geographical regions and all races and ethnicities.
- MS is a diagnosis of exclusion (i.e., no better explanation).
- Paraclinical tests are essential for the diagnosis of MS.
- Brain and spinal cord MRI remain the most useful paraclinical tests to aid the diagnosis of MS.
- Misdiagnosis and underdiagnosis have harmful consequences for patients.
- MS diagnosis should be reassessed periodically.
- Statements applied to CIS may also be applied to patients with a previous history of relapses but who have yet to have an MS diagnosis.

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Major Changes to the 2017 McDonald criteria in the 2024 McDonald Criteria

- The optic nerve may serve as a fifth anatomical location to demonstrate DIS if no better explanation exists for optic nerve pathology as detected by MRI, OCT, or VEP.
- DIS is fulfilled when 2 out of 5 anatomical locations (optic nerve juxtacortical/intracortical, periventricular, infratentorial, spinal cord) show typical lesions, regardless of whether these lesions are symptomatic.
- DIT is not mandatory for a diagnosis of MS in specific situations
- The demonstration of CVS+ by MRI may be used to diagnose MS in specific situations.
- The demonstration of PRLs by MRI may be used to diagnose MS in specific situations.
- kFLC-Index is interchangeable with OCB and consequently can substitute for OCBs for diagnosing MS.
- RIS and other presentations with non-specific symptoms are MS when certain criteria are fulfilled.
- Paediatric-onset and adult-onset MS can be diagnosed using a single diagnostic criteria framework.
- Progressive and relapsing MS represent a unified diagnosis and require unified diagnostic criteria.
- Additional recommendations should be considered for confirming the diagnosis of MS in individuals at age ≥50 years or with vascular comorbidities.

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Novelties of the revised McDonald criteria

Yellow for sensitivity
Grey for specificity

~~CLINICAL ATTACK~~ → Radiologically Isolated Syndrome can be classified as MS in specific situations

Dissemination in space (DIS) → The optic nerve is a 5th lesion site; MS can be diagnosed on DIS alone if high fulfilment; No distinction between RRMS and PPMS

Dissemination in time (DIT) → Use of imaging (CVS and PRL) and OCB/KFLC as tools to improve specificity and replace DIT

…and no better explanation → Extra safeguards for children and patients over 50

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Goals of these changes

- Diagnosis is faster
- Diagnosis is easier
- Diagnosis is more accessible
- Prevent Misdiagnosis
- Increase Specificity

To lead to…

Diagnosis of one disease (MS) with a variety of clinical presentations through the life span

TO IMPROVE OUTCOMES

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Optic Nerve

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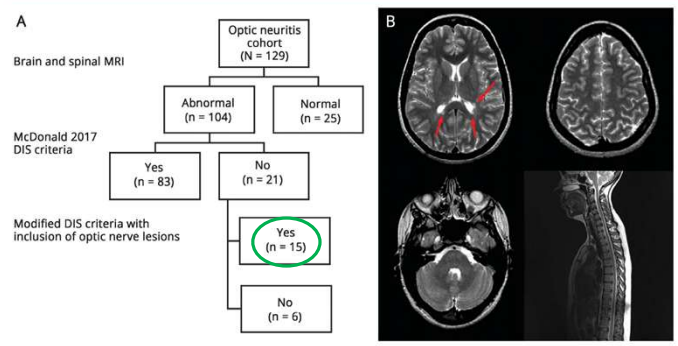
Including the optic nerve lesion in dissemination in space

160 CIS patients (129 ON, 31 non-ON) – FU 15y

Figure Effect of including symptomatic optic nerve involvement in dissemination in space (DIS)



	Sensitivity (95% CI), %	Specificity (95% CI), %	Accuracy (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
DIS alone					
McDonald 2017 criteria	83 (73–90)	68 (53–81)	78 (69–84)	82 (72–90)	70 (54–82)
Modified DIS criteria including optic nerve involvement	95 (88–99)	57 (42–72)	81 (74–88)	80 (70–87)	87 (70–96)

Brownlee, Neurology 2018

Inclusion of optic nerve lesion increased sensitivity, and accuracy for DIS criteria

*157 CIS – shorter FU 3y - MRI optic nerve, OCT, VEP (**all modalities have similar sensitivity**)*

Vidal-Jordana & MAGNIMS, Neurology 2024

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Optic nerve as a fifth topography

- **Optic neuritis** represents the first manifestation of MS in **25-35% of CIS patients**
- **Different rates** of **optic nerve involvement** have been reported in established MS patients, **based on** the **sequence** used, and MS **disease duration** (ranging from **72.7%** to **100%** in eyes with **prior history of ON**, and from **8.8%** **to** **72%** in **asymptomatic** eyes)
- Involvement of the optic nerve can be assesed by **MRI, VEP** and **OCT**
- Considerable evidence supports the minimal threshold of at least **one lesion in at least 2 out of the 5 topographies after including the optic nerve** (Brownlee WJ et al. Neurology. 2018; Vidal-Jordana A et al. Neurology. 2021; Bsteh G et al. Neurology. 2023; Vidal-Jordana A et al. Neurology. 2024.

Table 1. Optic nerve lesion detection by test.

	Study population	Technique for optic nerve evaluation	Main results
Optic nerve MRI			
Acute/subacute ON			
Berg et al.[29]	First ON episode (CIS), $n=104$ (73% with abnormal brain MRI; median time since ON: 5 days)	Coronal fat-saturated T2 turbo and T1 post-Gd spin echo (1.5 T or 3.0 T)	T2 lesion: 79.8% T1 Gd+ lesion: 74% Both (T2 and T1-Gd+): 69.2%
Soelberg et al.[30]	First ON episode (CIS), $n=31$ (80.6% with abnormal brain MRI; median time since ON: 21 days)	3D FLAIR, or 2D FLAIR, or 2D STIR (1.5 T)	T2 lesion: 80.6% in first MRI
Cellina et al.[31]	First ON episode (CIS), $n=37$ (51.4% with abnormal brain MRI; time since ON: 7 days; corticosteroids allowed)	3D transversal STIR, and transversal T1 spin echo fat-saturated post-Gd (1.5 T)	T2 lesions: 65.8% T1 Gd+ lesion: 34.1%
Bursztyn et al.[32]	First ON episode (CIS), $n=92$ (median time since ON: 11.5 days)	Coronal fat-saturated T2 turbo and coronal and axial fat-saturated T1 post-Gd (1.5 T or 3.0 T)	T2 lesion: 73.9% T1 Gd+ lesion: 78.3% Any (T2 and/or T1-Gd+): 83.7% Both (T2 and T1-Gd+): 69.6%
MS patients			
Hodel et al.[23]	ON confirmed clinically and with VEP, can include MS patients, $n=31$ (no clinical information provided)	2D coronal STIR FLAIR, 3D DIR sequence: 2D coronal and multi planar reconstruction, axial and coronal T1 post-Gd (3.0 T)	2D STIR FLAIR: 84% 2D DIR coronal: 88% 3D DIR multiplanar: 95%
Sartoretti et al.[26]	MS patients with no ON history, $n=95$ (disease duration : 8.9 years); control group with other diseases, $n=50$	3D sagittal DIR with coronal reconstruction (3.0 T)	Asymptomatic ON lesion detection: 72% in MS patients; 0% in control group
Riederer et al.[24]	CIS/RRMS/SPMS patients, $n=39$ (53.8% with ON; might be acute); control group, $n=17$	3D-DIR sequence	Whole cohort: 58.9% Patients with ON history: 100% Patients without ON history: 9.5%
London et al.[25]	CIS patients, $n=66$ (33.3% with ON; 92.4% DIS fulfilment)	Multiplanar 3D DIR reconstruction (3.0 T)	T2 lesion in ON-CIS: 100% T2 lesion in non-ON-CIS: 22.7%
Davion et al.[27]	MS patients, $n=98$ (median disease duration: 11.6 years); analysis conducted at an eye level	3D DIR and 3D FLAIR (3.0 T)	Whole cohort: 61.2% T2 lesion in ON eyes: 82.2% T2 lesion in non-ON eyes: 48.8%

Vidal-Jordana et al. Mult Scler J 2024

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Optic nerve may serve as the fifth topography

The Visual System

General Principles and Recommendations

- The optic nerve may serve as a **fifth anatomical location to demonstrate DIS** if no better explanation exists for optic nerve pathology.
- One or more intrinsic optic nerve lesions with no better explanation (e.g., without prominent chiasmal involvement, optic perineuritis, or longitudinally extensive lesion) identified by **MRI** may serve as evidence of optic nerve involvement to demonstrate DIS
- An abnormal peak time using a full field pattern reversal **visual evoked potential** (significant interocular asymmetry or p100 peak time above upper limit of normal with no better explanation) may serve as evidence of optic nerve involvement to demonstrate DIS
- Provided rigorous quality control is applied, optical coherence tomography-derived peripapillary retinal nerve fiber layer or macular ganglion cell inner plexiform layer (GCIPL) inter-eye differences of 6 µm or more and 4 µm or more, respectively, support unilateral optic nerve involvement to demonstrate DIS

Refer to: Recommendations on the use of optical coherence tomography and visual evoked potentials for fulfilling dissemination in space as part of the 2024 Revised McDonald Diagnostic Criteria for multiple sclerosis. (Saidha et al., Lancet Neurology 2025)

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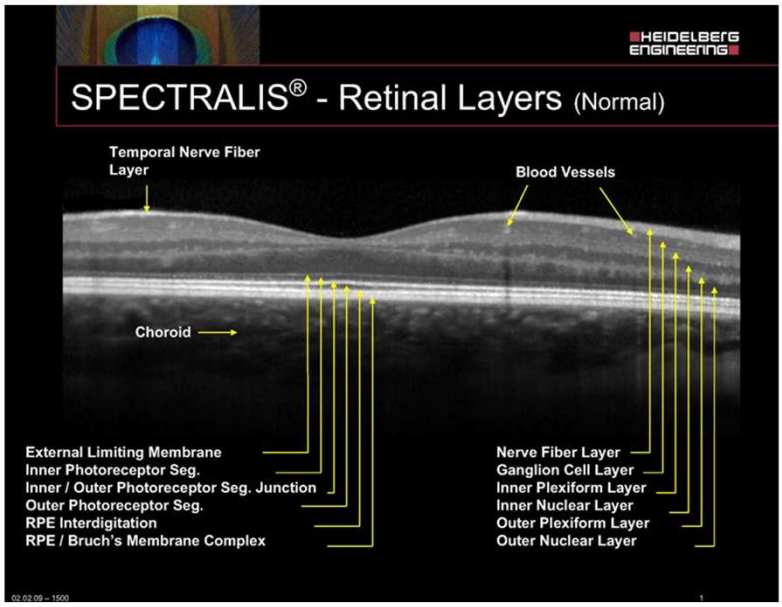

https://eyewiki.org/File:Oct_SpectralisLayers_reduced.jpg#file

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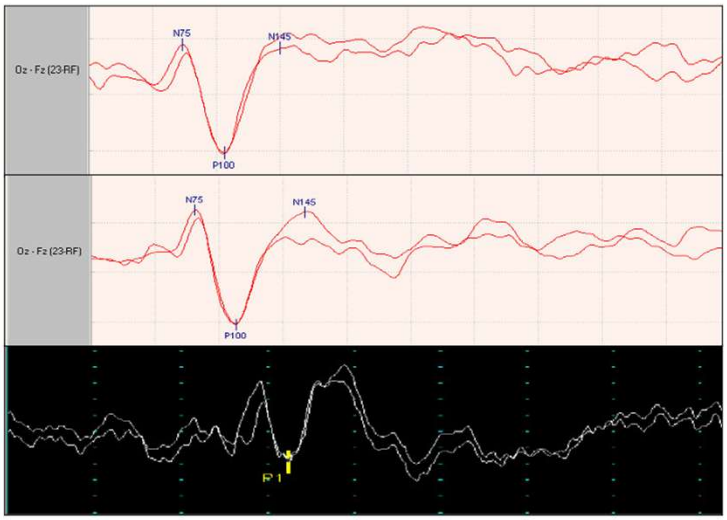
Pattern and flash visual evoked potentials (VEPs)



Baiano C, Zeppieri M. Visual Evoked Potential. [Updated 2023 May 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK582128/

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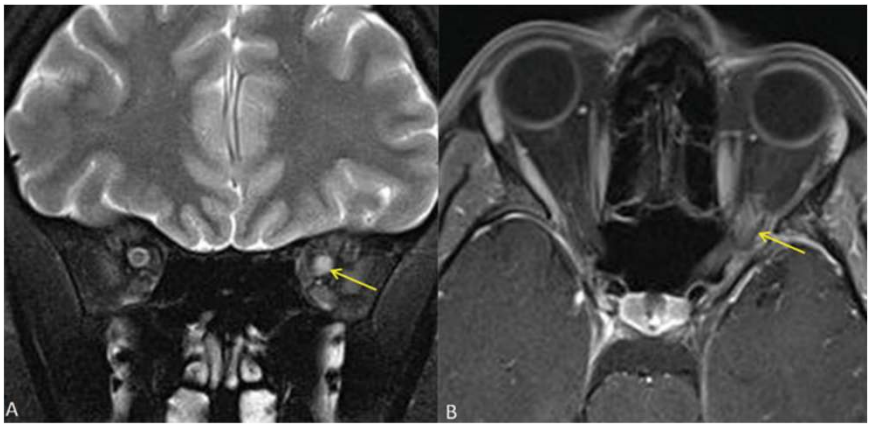
Optic nerve MRI – fat saturation



STIR: short tau inversion recovery

Gad T1-FS: spectral fat-saturation

Rovira & Barkhof. Clinical Neuroradiology – the ESNR textbook. Springer 2019

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kFLCs

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Kappa free light chains (KFLC) as a tool for diagnosis

Besides OCB, an excess of kappa and lambda free light chains (KFLC, LFLC) can be produced during chronic intrathecal inflammation

They can be measured rapidly and quantitatively, and **KFLC in particular** have diagnostic properties that seem similar to those of OCB in MS

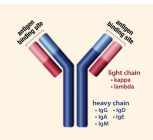

Table 3. Sensitivity, specificity, positive and negative predictive value for elevated KFLC, MRI parameters and OCB regarding conversion of clinically isolate syndrome to definite multiple sclerosis.

	N	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Q KFLC	77	86.8 (71.9–95.6)	38.5 (23.4–55.4)	57.9 (44.1–70.9)	75.0 (50.9–91.3)
OCB	77	92.1 (78.6–98.3)	33.3 (19.1–50.2)	57.4 (44.1–70.0)	81.3 (54.4–96.0)
Intrathecal IgG-Synthesis	76	43.2 (27.1–60.5)	64.1 (47.2–78.8)	53.3 (34.3–71.7)	54.3 (39.0–69.1)
IgG-Index >0.70	76	43.2 (27.1–60.5)	64.1 (47.2–78.8)	53.3 (34.3–71.7)	54.3 (39.0–69.1)
Barkhof	66	12.5 (3.5–29.0)	88.2 (72.5–96.7)	50.0 (15.7–84.3)	51.7 (38.2–65.0)

- KFLC differentiate CIS/MS from other neurological diseases/controls
- The diagnostic properties of kFLC are also similar to those of OCB when assessed in CIS cohorts and, importantly, the concordance between OCB and kFLC is about 87.0%
- KFLC could represent a valid, easier and rater-independent alternative to OB detection. It might provide results within 24 hrs
- An international panel of experts in CSF analysis recommended including intrathecal kFLC synthesis as an additional tool to diagnose MS besides OCB determination, after considering the pros and cons of each technique

Senel M et al. PLoS One. 2014, Presslauer S et al. Mult Scler. 2016, Passerini G et al. Mult Scler Int. 2016; Voortman MM et al. Mult Scler. 2017; Arrambide G et al. Brain 2018, Hegen H MSJ 2023, Levraut et al, 2024

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kFLCs can be used as a tool for diagnosis

Kappa free light chains

General Principle

- kFLC is an appropriate paraclinical test for the diagnosis of MS.

Recommendation

- kFLC are interchangeable with OCB and consequently can substitute for OCBs for diagnosis of MS (cut-off of 6.1).

Refer to: the accompanying paper on the CSF examination (Deisenhammer et al., eBioMedicine 2025)

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DIS

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Updated DIS criteria

CNS topographies in the MS Diagnosis – Dissemination in Space

General Principles and recommendations

- DIS is fulfilled when 2 out of 5 topographies (ON, JC/IC, PV, IT, SC) show typical lesions, regardless of whether these lesions are symptomatic.
- Fulfillment of DIS and DIT is sufficient to diagnose MS as stated in 2017 McDonald Criteria.
- Fulfillment of DIS plus positive CSF (e.g., OCB and/or kFLC) is sufficient to diagnose MS
- In patients with typical clinical presentations the presence of typical lesions in at least 4 locations is sufficient to diagnose MS.
- 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 positive is sufficient to diagnose MS
- In patients with progressive disease, two spinal cords lesions are enough to demonstrate DIS

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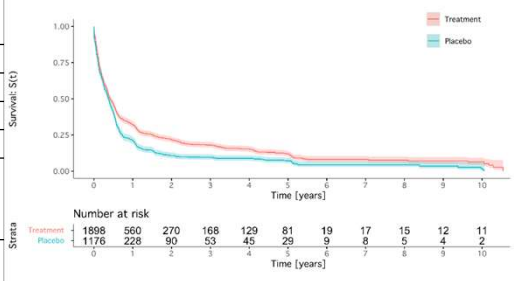
DIT is no longer needed for diagnosis

Demographical data and survival estimates to DIT

CIS TRIALS
BENEFIT (Bayer)
CHAMPS (Biogen)
TOPIC (Sanofi)
PreCISe (Teva)
REFLEX (Merck)
ORACLE MS (Merck)

Characteristic	n
Sex, n (%) Female Male	 2,092 (68%) 987 (32%)
Age at CIS, years (SD)	31.56 (7.88)
Baseline number of T2 lesions, n (%) > 8 1-3 4-8	 2,242 (73%) 266 (8.7%) 545 (18%)
Presence of CSF-restricted OB, n (%)*	290 (78%)
Baseline EDSS, median (IQR)	1.50 (1.00, 2.00)
Last EDSS, median (IQR)	1.50 (1.00, 2.00)
Follow-up years, median (IQR)	2.66 (1.58, 5.05)
Dissemination in time, n (%) By CDMS By New T2 or Gd-enhancing lesions Combined	 1,080 (35%) 2,456 (80%) 2,586 (84%)
Dissemination in space¥, n (%) At baseline† During follow-up‡	 840 (77%) 494 (80%)

Survival estimates for DIT Combined (by arm)



* Partial information for BENEFIT study
¥ Calculated for cerebral topographies (juxtacortical, periventricular and infratentorial)
† Calculated for BENEFIT and ORACLE MS studies
‡ Calculated for ORACLE MS study

Papolla A , Arrambide G ,..., Montalban X. In preparation

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CVS/PRLs

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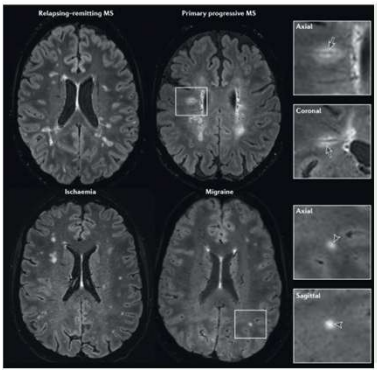
Learn how to assess CVS and PRL and appropriate MRI protocols to utilize



Box 2 | **Radiological definition of a central vein**

A central vein exhibits the following properties on T2*-weighted images:

- Appears as a thin hypointense line or small hypointense dot
- Can be visualized in at least two perpendicular MRI planes, and appears as a thin line in at least one plane
- Has a small apparent diameter (<2 mm)
- Runs partially or entirely through the lesion
- Is positioned centrally in the lesion (that is, located approximately equidistant from the lesion's edges and passing through the edge at no more than two places), regardless of the lesion's shape

Exclusion criteria for lesions:

- Lesion is <3 mm in diameter in any plane
- Lesion merges with another lesion (confluent lesions)
- Lesion has multiple distinct veins
- Lesion is poorly visible (owing to motion or other MRI-related artefacts)

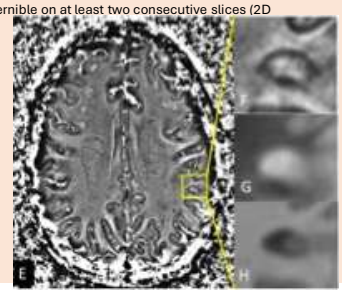
Sati, Nature Rev Neurol 2016

Definition of paramagnetic rim lesion

- Detected using phase susceptibility weighted images
- A discrete rim with paramagnetic properties that is continuous around at least two-thirds of the outer edge of the white matter portion of the lesion
- The rim (or part of it) is discernible on at least two consecutive slices (2D acquisition) or in two orthogonal planes
- The core of the lesion colocalizes with all or part of a T2-hyperintense lesion that does not enhance on T1- weighted post-gad scans

Exclusion criteria:

- Veins running alongside the rim that may resemble a rim



Bagnato, Brain J Neurol 2024

- Refer to: 2024 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI for the diagnosis of MS accompanying paper (Barkhof et al., Lancet Neurology 2025)

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Sati, P., Oh, J., Constable, R. T., Evangelou, N., Guttmann, C. R., Henry, R. G., ... & NAIMS Cooperative. (2016). The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. Nature Reviews Neurology, 12(12), 714-722.

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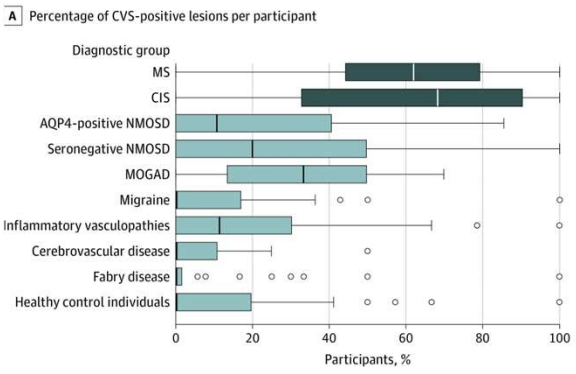
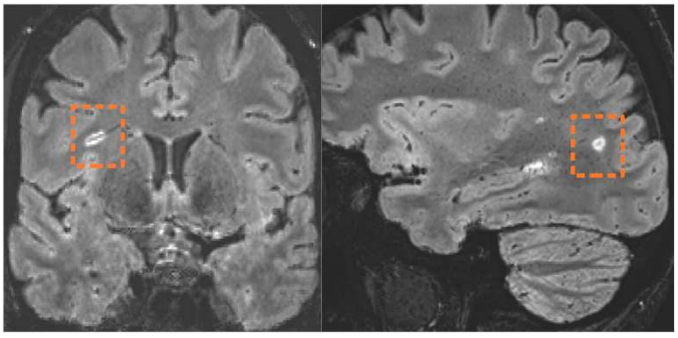
Central Vein Sign

- CVS is seen in ~65% of MS patients
- A higher proportion of lesions in MS have CVS compared to migraine, SVD, NMOSD
- CVS-6 + MRI DIS has similar diagnostic performance to OCBs + MRI DIS

≥6 white matter lesions have the CVS. In cases with <6 white matter lesions, the number of CVS+ lesions must outnumber CVS- lesions





Toljan MSJ 2024; Cagol & MAGNIMS, JAMA Neurol 2024

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General principles and recommendations related to the central vein sign

Central vein sign

- 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 (DIS), the presence of CVS is defined using select 6, or >50% if the number of lesions is <10, is sufficient for diagnosis
- In patients with typical clinical presentations and typical lesions in one region, the presence of the select 6 CVS, or >50% if the number of lesions is <10, plus DIT or positive CSF is sufficient for diagnosis

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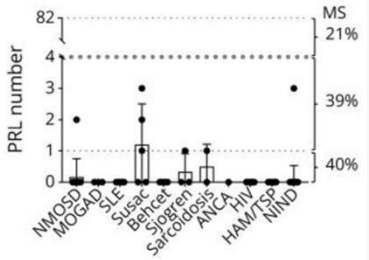
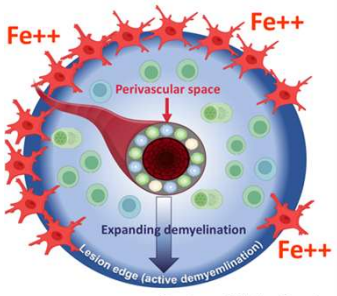
Borelli Neurol Neuroimmunol Neuroinflamm 2024

Paramagnetic Rim Lesions

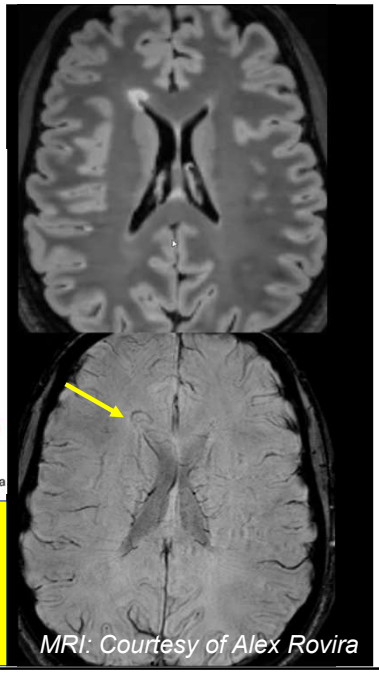
- Present in ~50% MS cases, i.e., **not very sensitive**
- **Highly specific for MS**

100 pts with other neurological conditions





Courtesy of Cristina Granziera



MRI: Courtesy of Alex Rovira

1 PRL and CSF OCB/kFLC or
1 PRL and MRI DIT
can be used in patients with the first event & lesions present in 1 CNS site

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Paramagnetic Rim Lesion (PRL)

- Discrete rim with paramagnetic properties on susceptibility-sensitive sequences at ≥1.5 T
- Continuous through ≥2/3 of outer edge of a white matter lesion on slice of maximal visibility
- Co-localization with edge of all or part of a lesion core, hyperintense on T2 weighted images
- Co-localization with all or part of a T2 hyperintense non-enhancing lesion

Bagnato et al Brain 2024 PMID: 38226694

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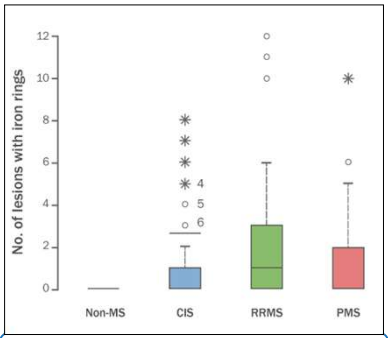
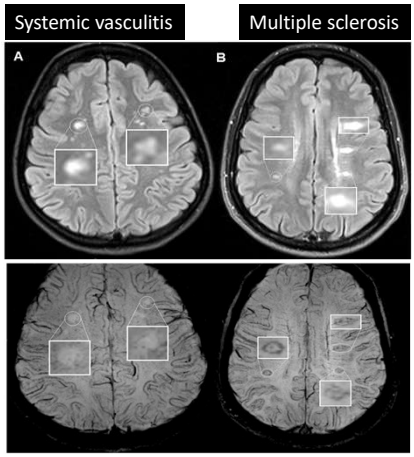
Paramagnetic rim lesions (PRLs): MS versus other CNS disorders

Iron Microglia, Macrophages



48% of CIS, 59% of RRMS and 39% of PMS patients had at least one lesion with an iron rim**

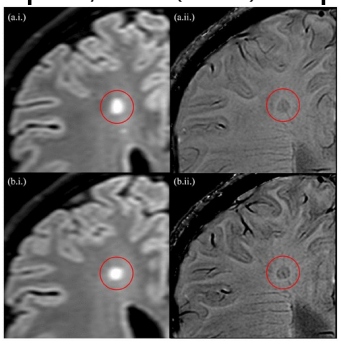
Calvi et al. Mult Scler J 2020



Clarke MA et al. AJNR Am J Neuroradiol. 2020

≥ 1 PRL in SWI has **high specificity (99.7%)/low sensitivity (24%)** when distinguishing MS/CIS vs mimics/healthy controls

(7 MAGNIMS Centers, 3T, various protocols, MS (n = 254), MS mimics (n = 91), older healthy controls (n = 217)



Meaton I et al., Mult Scler. 2022

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PRLs can be used to increase specificity

Paramagnetic Rim Lesions

General Principles and Recommendations

- Demonstration of PRLs by MRI may be used in the diagnosis of MS in specific situations.
- Demonstration one or more PRL by MRI can increase the specificity of the diagnosis
- Demonstration of PRLs is not required for diagnosis of MS.
- In patients with typical symptoms and typical lesions in one region, the presence of ≥1 PRL plus DIT or positive CSF is sufficient to diagnose MS

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Population Specific Recommendations

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Additional lab tests should confirm diagnosis in children

Pediatric MS

General Principles

- Pediatric and adult-onset MS 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 MS attacks and/or new T2 lesions in typical MS topography >90 days post-ADEM onset, is required before the MS diagnostic criteria can be applied.

Recommendations

- In children and adolescents (<18 years) the presence of CVS in more than 50% of T2 lesions strongly supports a diagnosis of MS.
- MOG-IgG testing using a cell-based assay is strongly recommended in children with an incident CNS demyelination under age 12 years.
- In persons ages >=12 with an incident demyelinating event, MOG IgG testing using a cell-based assay is recommended for presentations with symptoms not specific to multiple sclerosis or suggestive for myelin oligodendrocyte glycoprotein antibody-associated disease, but not of all people being investigated for MS.

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Increasing specificity in older patients

Confirming Diagnosis in Patients ≥50

In patients who are being considered for a diagnosis of MS presenting at age ≥50 years and/or significant vascular risk factors (including hypertension, smoking, diabetes, hyperlipidemia) or known vascular disease and/or headache disorders, **additional features are strongly recommended** to confirm diagnosis of MS.

- 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

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RIS

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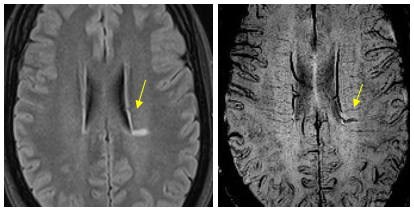
Radiologically Isolated Syndrome (RIS)

The radiologically isolated syndrome (RIS) is identified by the incidental discovery of CNS **white matter T2-weighted hyperintense foci** on MRI that demonstrate morphological and spatial characteristics **highly typical of multiple sclerosis (MS)** but without clinical symptomatology related to inflammatory demyelination[1-3]



1. Okuda DT, Mowry EM, Beheshtian A, *et al*. Incidental MRI anomalies suggestive of multiple sclerosis: The radiologically isolated syndrome. *Neurology*. 2009;72:800-805.
2. Lebrun C, Bensa C, Debouverie M, *et al*. Association between clinical conversion to multiple sclerosis in radiologically isolated syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential: Follow-up of 70 patients. *Arch Neurol*. 2009;66:841-846.
3. Siva A, Saip S, Altintas A, Jacob A, Keegan BM, Kantarci OH. Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. *Mult Scler*. 2009;15:918-927.

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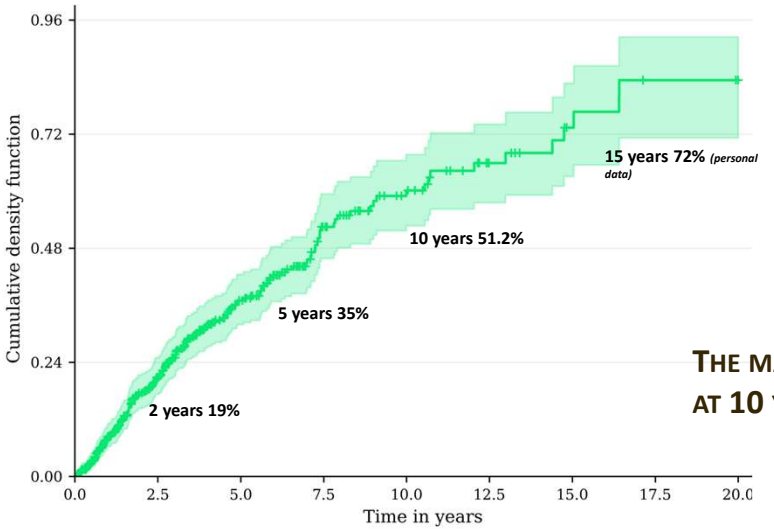
From RIS to clinical MS



THE MAJORITY OF PATIENTS WILL HAVE MS AT 10 YEARS

Christine Lebrun Frenay, International Advisory Committee on Clinical Trial in MS, Barcelona 2023

Lebrun et al 2020, 2021
Okuda et al, 2009, 2014
Kantarci et al, 2016

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RIS is MS in specific situations

Radiologically Isolated Syndrome

General Principle

- RIS is identified by the incidental discovery of CNS white matter T2-weighted hyperintense foci on MRI, highly typical of MS but without clinical symptomatology related to inflammatory demyelination or findings on clinical examination.

Recommendations

- In patients with RIS, fulfilling:
  - DIS and DIT
  - DIS and positive CSF
  - DIS and the presence of the select 6 CVS

is sufficient for diagnosing MS.

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PPMS

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A single framework should be used to diagnose MS

Primary Progressive MS

General Principles

- PPMS requires evidence of clinical progression over at least 12 months
- **A single, unified framework of diagnostic criteria should be used to diagnose relapsing and primary progressive MS.**

Recommendations

- ≥2 spinal cord lesions is evidence for DIS for a diagnosis of PPMS.

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Diagnosing MS

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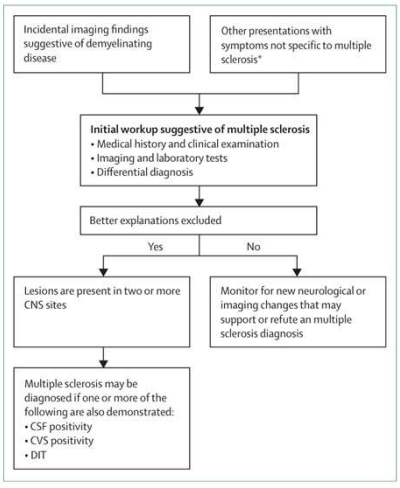

Figure 2: **Diagnostic algorithm for radiologically isolated syndrome and other non-specific presentations**
CVS=central vein sign. DIT=dissemination in time. *Presentations might include: (1) symptoms or signs overlapping those of multiple sclerosis but with no characteristic attack; or (2) paroxysmal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

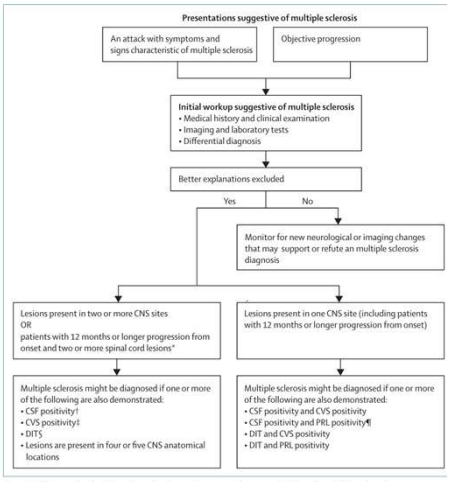

Figure 3: **Diagnostic algorithm for relapsing and progressive presentations of multiple sclerosis**
CVS=central vein sign. DIT=dissemination in time. PRL=paramagnetic rim lesion. *In patients presenting with 12 months or longer disease progression from symptom onset, the presence of two or more spinal 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.

Montalban et al.
Lancet Neurol 2025

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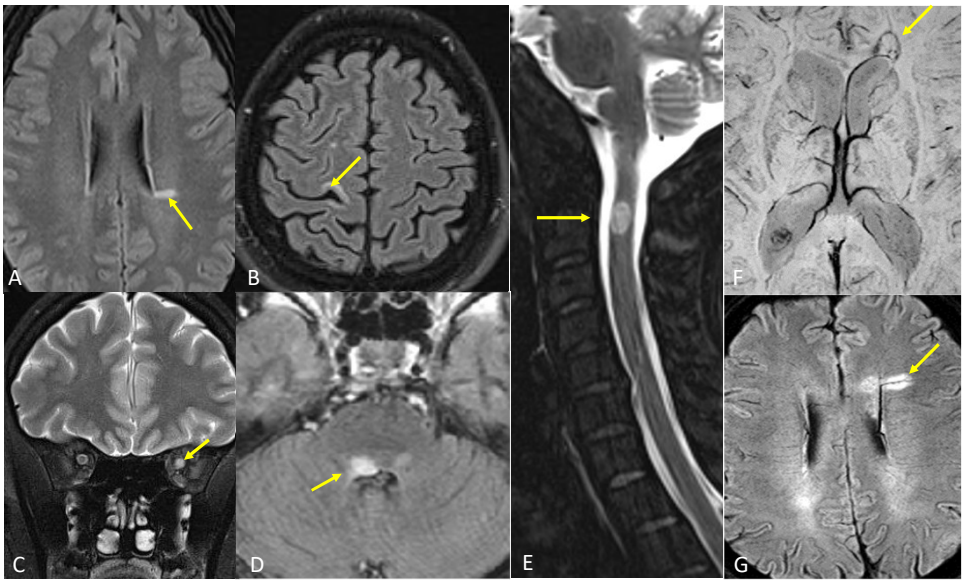

Typical MRI Appearance of MS Lesions

Courtesy of Àlex Rovira

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Challenges of the revised McDonald criteria

(1) Further demand on Radiology: new MRI features (CVS, PRL) may require additional scanning and reporting times

(2) Many new elements: when to do what?

(3) They require clinical and radiological expertise in MS

(4) Treatment algorithms will need to 'catch up' with diagnostic criteria

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Summary

- Unified approach for diagnosing multiple sclerosis
- The optic nerve can now serve as a fifth anatomical location
- CVS, PRLS, and kFLC in CSF can be used, when available, to provide supportive evidence
- In certain cases, radiologically isolated syndrome can fulfil the criteria for a MS diagnosis
- Updated guidance for the diagnosis of MS in older individuals and those with comorbidities
- **The 2024 revised criteria should expedite the diagnosis of multiple sclerosis, while maintaining specificity.**

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Thank you to our Contributors

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The Magnetic Resonance Imaging in Multiple Sclerosis study group, the Consortium of Multiple Sclerosis Centers, and North American Imaging in Multiple Sclerosis Cooperative MRI guidelines working group, the IMSVISUAL consortium, National MS Society, European Committee for Treatment and Research in Multiple Sclerosis

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