Updates in Multiple Sclerosis: Diagnostic Criteria and Emerging Therapies

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Clinical Neurological Society of America

Disclosures

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Objectives

- **Review** updates to 2024 McDonald Criteria.
- **Examine** the clinical impact of the new criteria on diagnosis and management
- **Review** emerging therapies for MS

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Introduction

- MS is difficult to diagnose, as it is mimicked by many common conditions.
- There has been recent interest in understanding the incidence and causes of MS misdiagnosis in recent years
- Recent studies have found a range of MS misdiagnosis among new patients with established MS diagnoses referred to academic centers to be between 17-19%
- The 2024 Updates to the McDonald Criteria take into account the emerging biological evidence needed to diagnose MS early while de-emphasizing the need for dissemination in time

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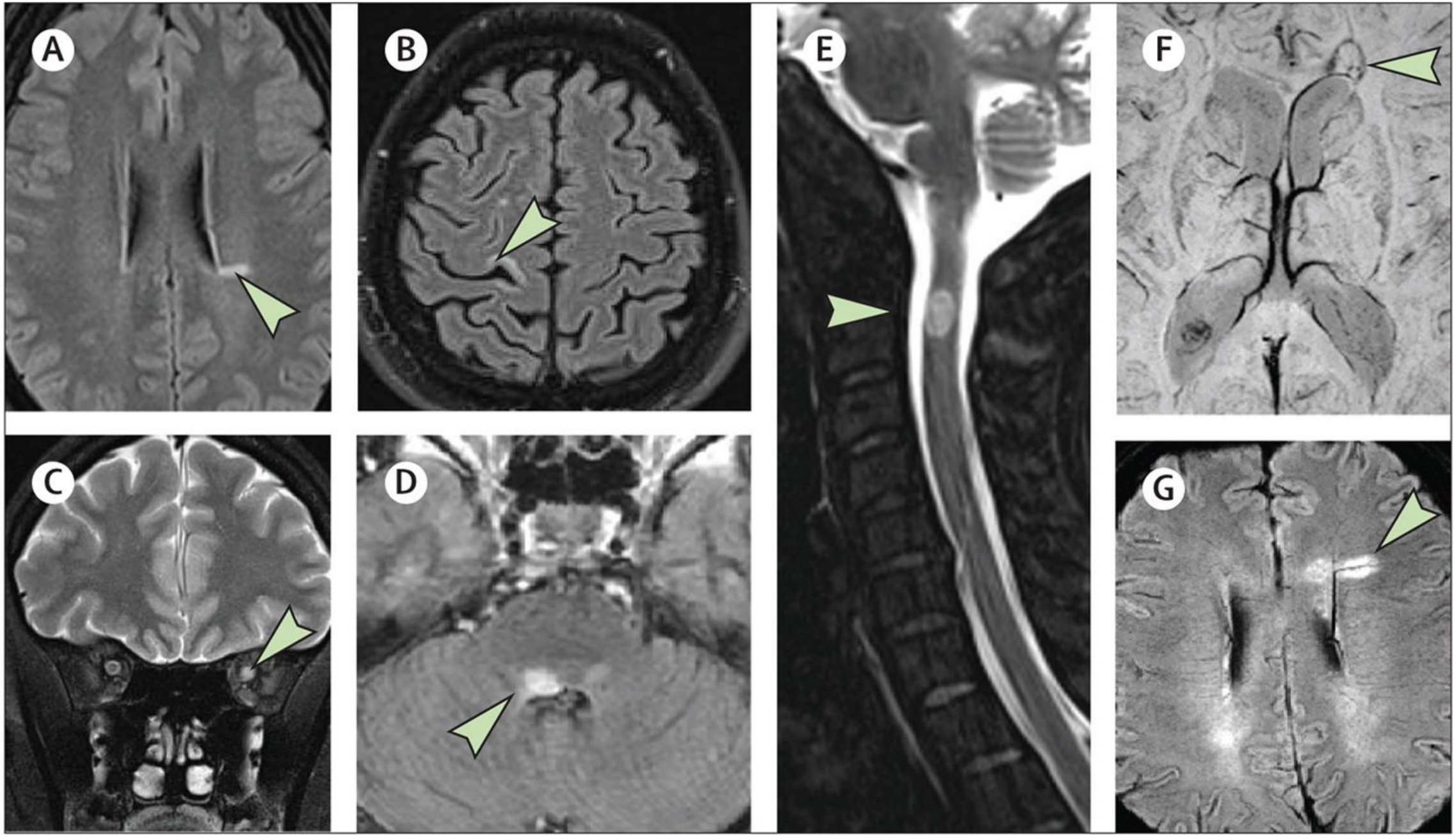
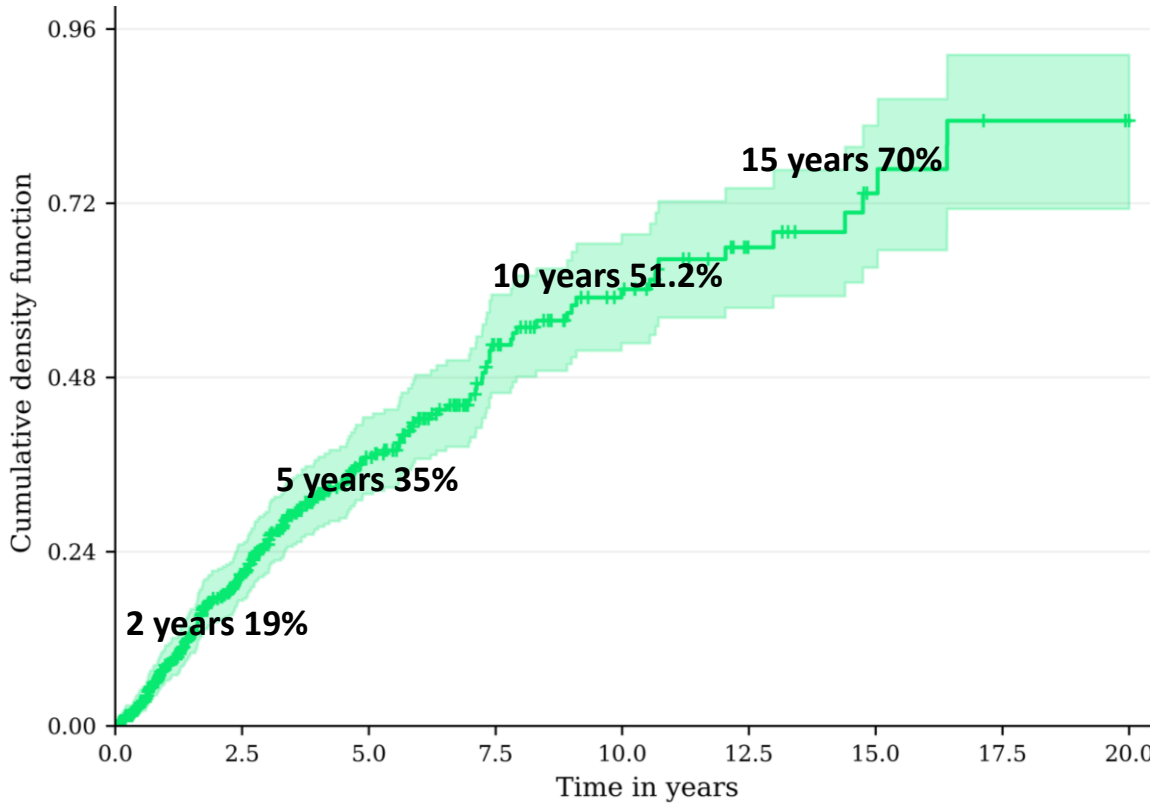


Montalban, X., et al. (2025). *Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria.* Lancet Neurology, 24(10), 850-865. https://doi.org/10.1016/S1474-4422(25)00270-4

Radiologically Isolated Syndrome

- **Increasing recognition that RIS → MS at higher proportions over 5 years**
- **Updates to Criteria:**
  - In patients with RIS, fulfilling DIS and DIT is sufficient for diagnosing MS.
  - In patients with RIS, fulfilling DIS and OCB is sufficient for diagnosing MS.
  - In patients with RIS fulfilling DIS, the presence of ≥6 CVS is sufficient for diagnosing MS.



Montalban, X et al. 2024 Revisions of the McDonald Criteria. *ECTRIMS 2024*

Lebrun-Frenay C, Kantarci O, Siva A, Sormani MP, Pelletier D, Okuda DT, et al. Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event. *Ann Neurol* (2020) 88(2):407–17. doi: 10.1002/ana.25799

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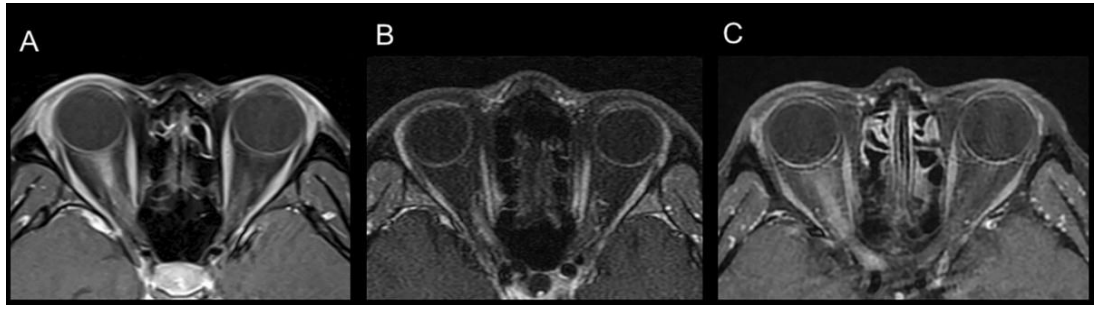
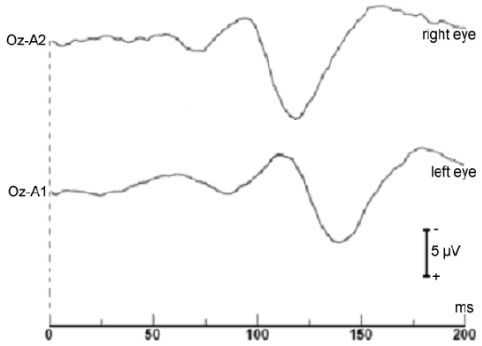
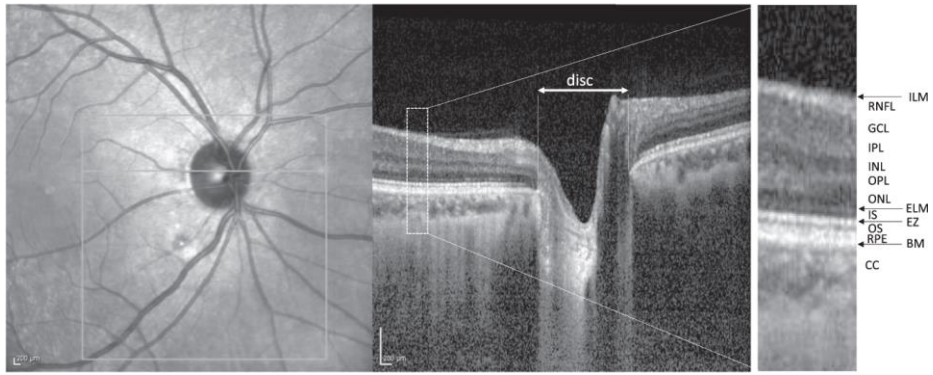
Optic Nerve Changes

- **Traditional topographies for DIS:**
  - **Periventricular**
  - **Juxtacortical/Cortical**
  - **Infratentorial**
  - **Spinal Cord**
- **Optic neuritis is the presenting symptom in 25-35% of MS patients**
- **CIS cohort followed for 10 years showed increase in sensitivity, same specificity with ON as a topography**
- **Multiple ways to assess ON involvement**
  - **MRI, VEP, OCT**







(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.

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From the Committee:

General Principles and Recommendations

- The optic nerve may serve as a fifth anatomical location to demonstrate DIS
  - If there is no better explanation for the findings than MS
- One or more typical short segment intrinsic optic nerve lesions with no better explanation (including no prominent chiasmal involvement, 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.
- An abnormal OCT may serve as evidence of optic nerve involvement to demonstrate DIS.

Montalban, X et al. 2024 Revisions of the McDonald Criteria. *ECTRIMS 2024*

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DIT is not Always Needed

- Fulfillment of DIS and DIT is sufficient to diagnose MS as noted in 2017 criteria
- When you don’t need DIT:
  - Fulfilling DIS with (+) CSF (OCBs or kFLC) is enough to diagnose MS
  - Patients with typical lesions and 4 of 5 topographies impacted
  - Typical symptoms, typical lesions in one topography
    - Presence of six CVS lesions or PRLs plus DIT or (+) CSF
  - Progressive Disease
    - Two spinal cord lesions is enough for DIS

Montalban, X et al. 2024 Revisions of the McDonald Criteria. *ECTRIMS 2024*

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CSF Kappa Free Light Chains

- Chronic intrathecal inflammation can lead to excess of both kappa and lambda free light chains
- Kappa free light chains have similar diagnostic utility to oligoclonal banding
- Similar properties when assessed in CIS populations with good concordance (87%) to OCBs.
- KFLC can be measured more affordably, not rater-dependent
- **Bottom line: CSF KFLCs are interchangeable with OCBs and will become part of the "MS Profile"**

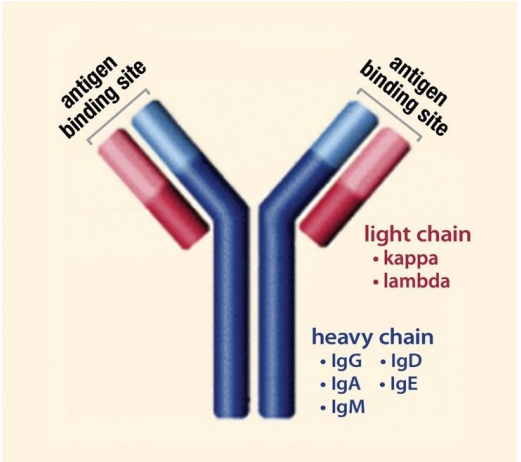

Table 3. Sensitivity, specificity, positive and negative predictive value for elevated KFLC, MRI parameters and OCB regarding conversion of clinically isolate syndrome to definite multiple sclerosis.

	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)

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

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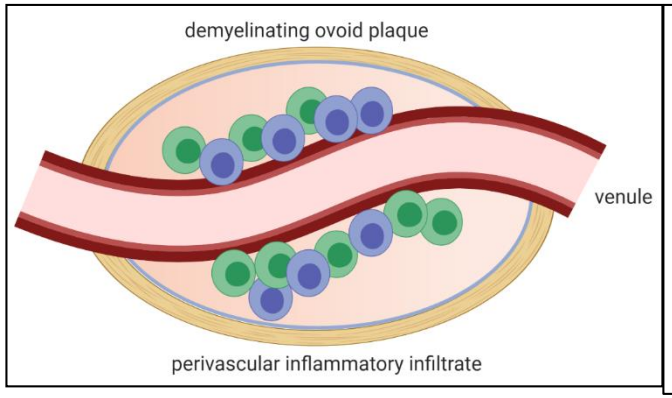
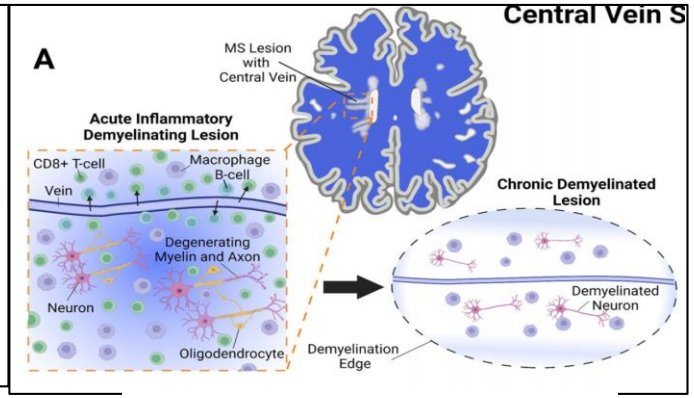
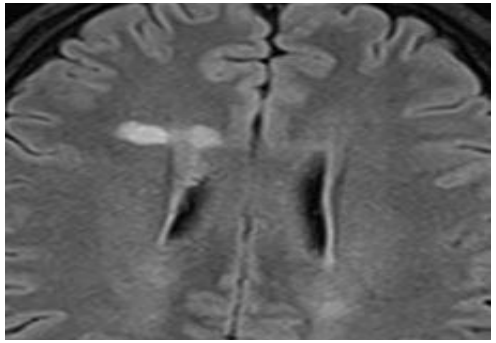
Central Vein Sign (CVS)



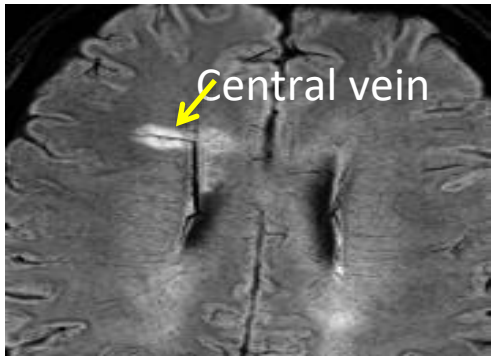
Sati et al. Nat Rev Neurol 2016



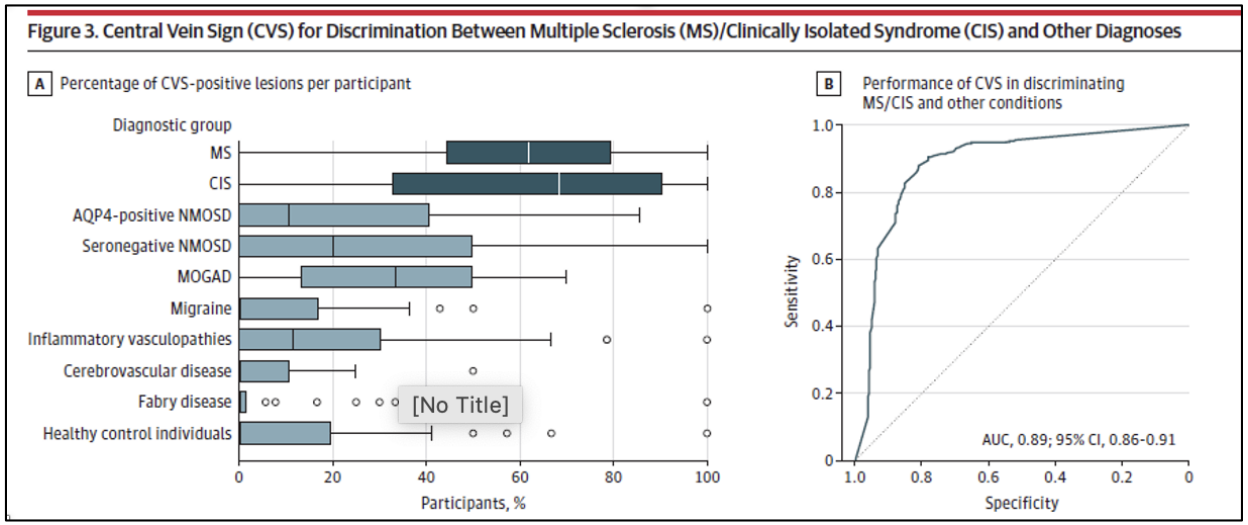
Gill et al., Eur J Immunol 2023



SWI (3T)



Dawson J. Trans Roy Soc Edinb 1916;
Horowitz et al. Am J Neuroradiol 1989



Cagol et al. JAMA Neurol 2024

Montalban, X et al. 2024 Revisions of the McDonald Criteria. *ECTRIMS 2024*

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Central Vein Sign

General Principles and Recommendations

- Demonstration of CVS by MRI *may* be used in the diagnosis of MS.
- Demonstration of CVS by MRI can increase specificity of diagnosis in MS.
- Demonstration of CVS is ***not required*** for diagnosis of MS.
- In patients with typical symptoms and DIS, the presence of **6 CVS lesions** is sufficient for diagnosis of MS.
- In patients with typical symptoms and typical lesions in one topography, the presence of 6 CVS plus DIT or positive CSF is sufficient to diagnose MS

Montalban, X et al. 2024 Revisions of the McDonald Criteria. *ECTRIMS 2024*

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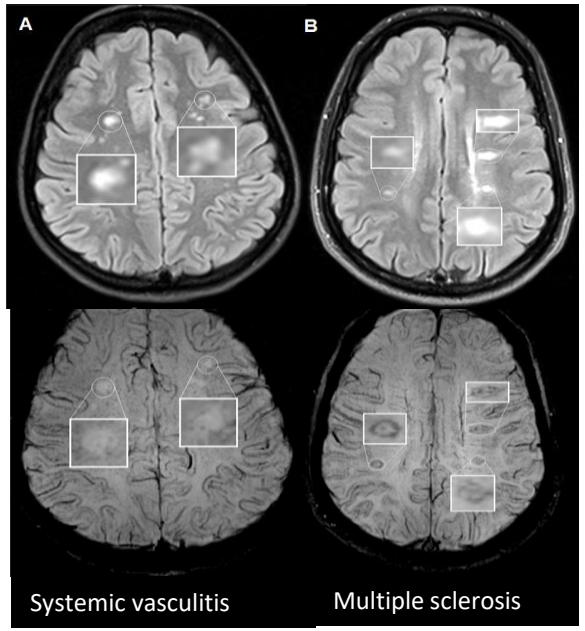
Paramagnetic Rim Lesions are Highly Specific for MS

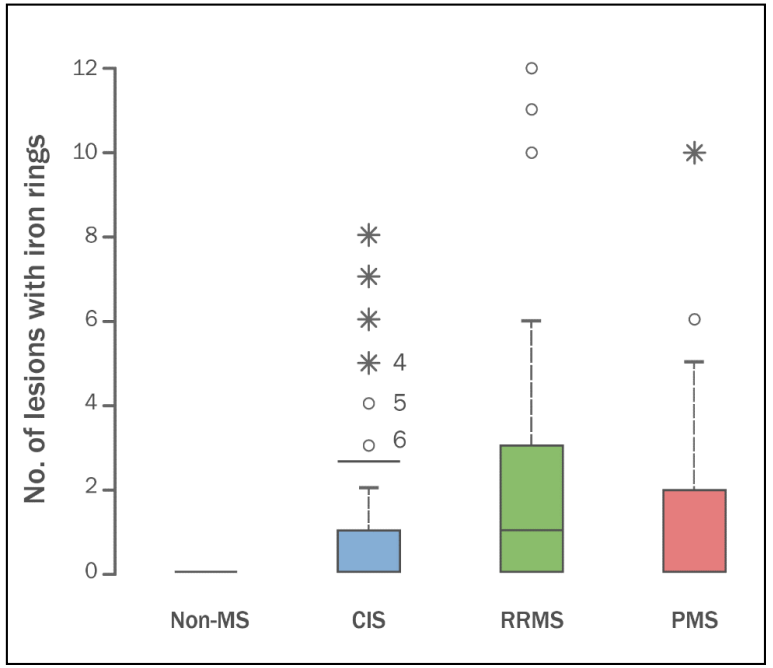
Iron | Microglia, Macrophages

≥ 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





Calvi et al. Mult Scler J 2020

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

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Montalban, X et al. 2024 Revisions of the McDonald Criteria. *ECTRIMS 2024*

What are PRLs?

- MS lesions with a thin rim of *paramagnetic* signal on MRI
- Proposed markers of ongoing, chronic inflammatory disease activity
  - "smoldering inflammation"
- PRLs are believed to be areas of persistent inflammation where microglia and macrophages are active at the edge of lesions
- Slowly expanding over time rather than "one-time" inflammatory events
  - "Slowly enlarging lesions"
- Potential treatment target in clinical trials given their high specificity for MS and increasing interest in "smoldering inflammation" or progression independent of relapse activity (PIRA)

Absinta M, Sati P, Schindler M, et al. *Persistent 7-Tesla phase rim predicts poor outcome in new multiple sclerosis patient lesions.* **Journal of Clinical Investigation.** 2016;126(7):2597-2609.

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PRL Criteria

General Principles and Recommendations

- Demonstration of PRLs may be used in the diagnosis of MS
- Demonstration of PRLs by MRI increases the specificity of diagnosis in MS
- Demonstrating PRLs is not required to diagnose MS
- In patients with typical symptoms, typical lesion(s) in one topography, ≥1 PRL plus DIT or CSF positive is sufficient to diagnose MS

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Patients over 50 or with Comorbidities

Practice Point: Age-related comorbidities can present diagnostic challenges in interpreting the possibility of a demyelinating process in adults over 50 years of age. Late-onset MS (>50 years) is increasingly recognized, and >50% of patients living with MS are >50 years old.

•Patients older than 50 or with significant vascular risk factors should be considered with additional features to support the diagnosis of MS

- Spinal cord involvement
- Positive CSF
- (+) CVS or PRLs

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Pediatric MS

Aim: Pediatric and adult onset MS should share the same diagnostic framework

Recommendations

- In children and adolescents (<18 years) the **presence of CVS in approximately 50% of T2 lesions strongly suggests 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 advocated in the context of an atypical presentation for MS** but is not advocated for all persons being investigated for MS.

Montalban, X et al. 2024 Revisions of the McDonald Criteria. *ECTRIMS 2024*

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Primary Progressive MS

Aim: PPMS requires evidence of clinical progression over >12 months. PPMS and RMS should share a single diagnostic framework

Recommendations

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

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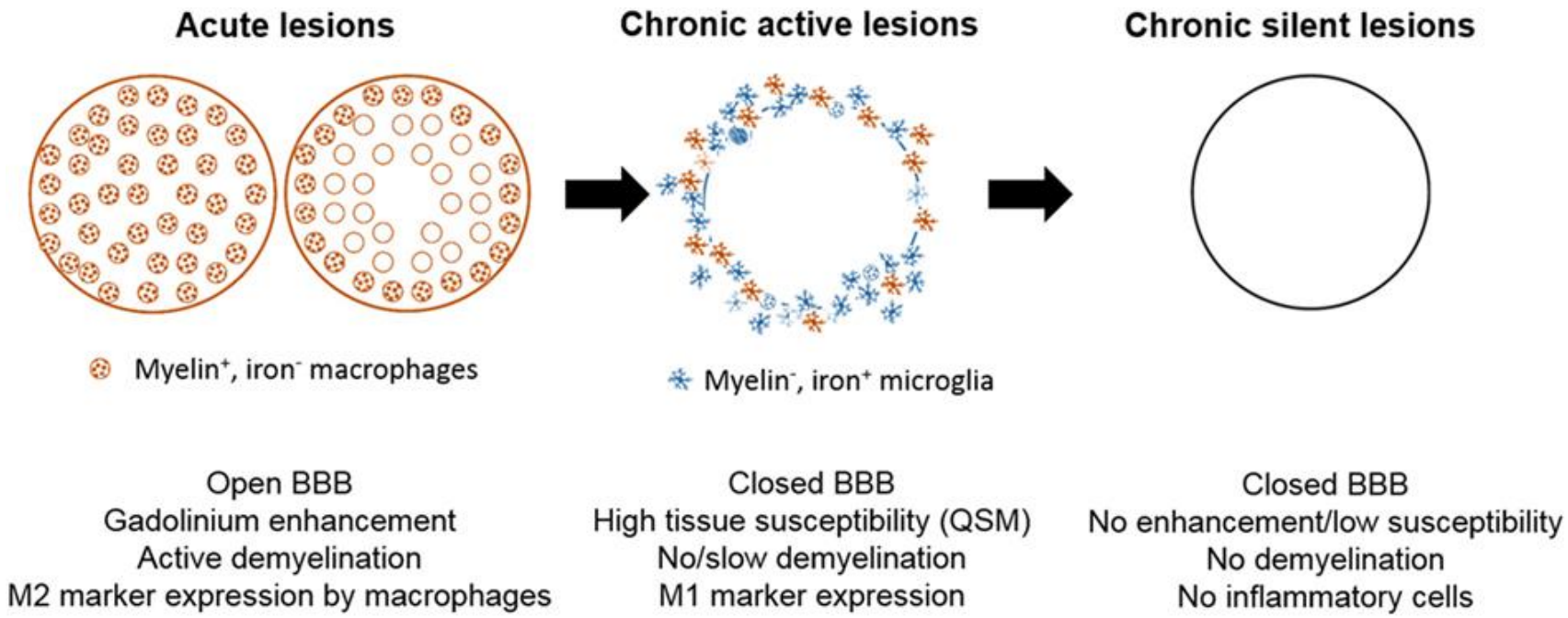
Emerging Treatments for MS



Front. Immunol., 18 February 2018
Sec. Multiple Sclerosis and Neuroimmunology
Volume 9 - 2018 | https://doi.org/10.3389/fimmu.2018.00255

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BTK Inhibitors

BTK Inhibitors in Development

- Evobrutinib
  - Phase 3 evolution RMS1 and evolution RMS2
    - Failed to meet endpoints in RRMS v. teriflunomide. No longer in development
- Tolebrutinib
  - Failed endpoints in RRMS v. teriflunomide
  - Inactive SPMS:
    - reduced new, enlarging T2 lesions by 38% v. placebo
    - 31% reduction in 6 month CDP v. placebo
    - 10% of patients with 6 month CDI

Naydovich, L. R., Orthmann-Murphy, J. L., & Markowitz, C. E. (2025). Beyond relapses: How BTK inhibitors are shaping the future of progressive MS treatment. *Neurotherapeutics, 22*(4), e00602. https://doi.org/10.1016/j.neurot.2025.e00602

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BTK Inhibitors

- Fenebrutinib
  - Phase II FENopta trial:
    - ARR of 0.06 in RRMS patients over 96 weeks
    - No disability progression observed over 96 week OLE study
    - No Gd(+) lesions noted at 96 weeks
  - Phase III
    - PPMS FENtrepid versus ocrelizumab
    - RMS FENhance 1 & 2
  - Recent Announcements:
    - Fenebrutinib met endpoints in RMS study (FENhance 2).
      - Companion trial FENhance 1 still pending
    - Fenebrutinib was *noninferior* to ocrelizumab

Naydovich, L. R., Orthmann-Murphy, J. L., & Markowitz, C. E. (2025). Beyond relapses: How BTK inhibitors are shaping the future of progressive MS treatment. *Neurotherapeutics, 22*(4), e00602. https://doi.org/10.1016/j.neurot.2025.e00602

https://www.roche.com/investors/updates/inv-update-2025-11-10

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BTK Inhibitors

BTK Inhibitors in Development

- Remibrutinib
  - Still in Phase III studies.
    - *REMODEL-1 (NCT05147220) and 2 (NCT05156281)*
  - Demonstrated safety in other autoimmune diseases in phase II trials
- Orelabrutinib
  - Phase II study showed statistically significant reduction in Gd (+) lesions at 24 weeks with 80mg/day dose
  - Advancing to Phase III studies in progressive MS; trial planned for SPMS
- BIIB091
  - Still in Phase II RMS trial versus diroximel fumarate

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Other Emerging Therapies

- **Frexalimab**
  - Anti-CD40 ligand
  - Patients with MS have elevated levels of activated T-cells expressing CD40-L
  - Promising option for both relapsing MS and PIRA
- **Autologous Hematopoeitic Stem Cell Transplant (HSCT)**
  - In Clinical trials right now (BEAT-MS)
- **Chimeric Antigen Receptor T-Cell Therapy (CAR-T)**
  - Very early in trials
  - Custom engineered T-cell infusion (anti-CD19 most commonly) infused into patient after immune ablation, leading to expansion of CAR-T cell population and a “living” therapy. May lead to deeper, longer-term B-cell depletion
  - Common approach in solid-tumor oncology, emerging in autoimmune diseases

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Take Home Points

- The optic nerve now counts as a 5th imaging topography in MS Dissemination in Space
- Dissemination in Time is no longer strictly required to diagnose MS
- The central vein sign and paramagnetic rim lesions may be used to support a diagnosis of MS
- CSF Kappa free light chains are considered an equivalent metric to CSF OCBs.
- RIS is now considered to be MS
- BTK inhibitors are an emerging therapeutic option in both relapsing and progressive forms of MS

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Questions