DIAGNOSTIC CRITERIA OF MULTIPLE SCLEROSIS: CLINICAL SIGNIFICANCE AND INNOVATIONS IN THE 2024 MCDONALD REVISIONS

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Abstract. Background: *Multiple Sclerosis (MS) is a chronic, immune-mediated demyelinating and neurodegenerative disorder of the central nervous system (CNS), characterized by multifocal lesions disseminated in both time and space. Early and accurate diagnosis is essential to initiate disease-modifying therapy (DMT), reduce long-term disability, and ensure reliable patient stratification in research and clinical trials.*

Objective: *To critically examine the **2024 McDonald Criteria**, the most recent and comprehensive revision of the globally endorsed MS diagnostic framework, emphasizing its integration of novel biomarkers and advanced imaging technologies within a pathophysiological context.*

Methods: *A narrative synthesis of recent literature (2018–2025) was performed, encompassing major consensus statements from ECTRIMS, The Lancet Neurology, and related peer-reviewed studies. The review focuses on the evolution of diagnostic criteria, incorporation of immunological and radiological markers, and their implications for real-world clinical practice.*

Results: *The 2024 McDonald revision introduces major innovations: recognition of **optic nerve involvement** as a fifth anatomical domain for dissemination in space (DIS); inclusion of **kappa free light chain (κ-FLC) index** as an alternative to oligoclonal bands (OCBs) for dissemination in time (DIT); and the use of **advanced MRI markers**—notably, the **central vein sign (CVS)** and **paramagnetic rim lesions (PRLs)**—as supportive features to enhance diagnostic specificity. These refinements reflect a broader paradigm shift toward **biomarker-based precision diagnosis**, aligning clinical, radiological, and molecular data into a unified algorithm.*

Conclusion: *The 2024 McDonald Criteria represent a significant evolution in the diagnostic landscape of multiple sclerosis. By integrating **molecular immunopathology** and **microstructural imaging**, the new framework enhances diagnostic precision while mitigating the risk of overdiagnosis. Its successful implementation, however, depends on multidisciplinary expertise and access to standardized imaging and biomarker assays across clinical settings.*

Keywords: *Multiple Sclerosis, McDonald Criteria 2024, κ-FLC, MRI biomarkers, central vein sign, optic nerve, paramagnetic rim lesions, diagnostic specificity.*

1. Introduction

Multiple Sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disease of the central nervous system (CNS) that represents one of the most intricate disorders in modern neuroimmunology. It arises from an aberrant autoimmune response directed against CNS myelin and oligodendrocytes, resulting in multifocal lesions disseminated in time and space**.**

Globally, MS affects an estimated **2.8 million individuals**, with its prevalence steadily increasing due to improved diagnostic capabilities and extended survival. The disease disproportionately impacts **young adults**, typically manifesting between **20 and 40 years of age**, and demonstrates a clear **female predominance** with a female-to-male ratio approaching **3:1**.

These demographic patterns emphasize hormonal, genetic, and environmental influences in disease pathogenesis.

Despite significant progress in diagnostic and therapeutic strategies, multiple sclerosis remains a diagnostic challenge**.** Its clinical spectrum overlaps with a wide range of other inflammatory and vascular conditions of the CNS, notably **neuromyelitis optica spectrum disorders (NMOSD)**, **myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)**, and **small-vessel ischemic leukoencephalopathy**. Distinguishing MS from these mimicking entities is essential, as their underlying pathophysiological mechanisms and therapeutic responses differ substantially.

The diagnostic framework of MS has evolved considerably over the past two decades.

The **McDonald Criteria**, first established in 2001 and subsequently revised in 2005, 2010, 2017, and 2024, have progressively refined the operational definition of disease dissemination in both **space (DIS)** and **time (DIT)**. These revisions reflect an ongoing effort to balance diagnostic sensitivity—facilitating earlier recognition—with specificity**,** minimizing the risk of misdiagnosis.

Timely and accurate diagnosis is paramount. Early identification of true MS allows for prompt initiation of disease-modifying therapy **(DMT)**, which can significantly reduce relapse frequency, delay disability progression, and preserve long-term neurological function.

Conversely, misdiagnosis may expose patients to unnecessary immunosuppression and psychological distress.

The 2024 McDonald revision represents the most comprehensive refinement yet, integrating biomarkers of intrathecal immunoglobulin synthesis (κ-FLC index) and advanced MRI markers (central vein sign, paramagnetic rim lesions) alongside traditional clinical criteria.

This approach embodies a shift toward precision neuroimmunology**,** emphasizing the interplay between clinical assessment, molecular biomarkers, and imaging-based pathology**.**

Ultimately, the diagnostic journey in MS mirrors the evolution of neuroscience itself—bridging immunology, imaging, and molecular biology to define a disease whose complexity continues to challenge and inspire modern medicine.

2. Immunopathogenesis of Multiple Sclerosis

The immunopathogenesis of Multiple Sclerosis (MS) represents a complex interplay between genetic susceptibility**,** environmental triggers**,** and autoimmune dysregulation culminating in demyelination and neuroaxonal injury within the central nervous system (CNS).

The hallmark pathological feature is the immune-mediated destruction of oligodendrocytes and secondary axonal degeneration**,** which occur through a series of tightly orchestrated immunological events.

2.1 Peripheral Immune Activation

MS begins peripherally, where **autoreactive CD4⁺ T helper cells**—predominantly Th1 and Th17 subsets—escape central tolerance mechanisms in the thymus. Environmental and viral exposures, particularly **Epstein–Barr Virus (EBV)** infection, are strongly implicated in initiating this autoreactive state through molecular mimicry**.** EBV-infected B cells express latent membrane protein 1 (LMP1) and nuclear antigens (EBNA1) that share epitopes with myelin components such as myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG)**,** leading to cross-reactive T-cell activation.

Activated Th1 cells release **interferon-γ (IFN-γ)** and **tumor necrosis factor-α (TNF-α)**, promoting macrophage activation, while Th17 cells secrete **interleukin-17 (IL-17)** and **IL-22**,

which disrupt endothelial tight junctions of the **blood–brain barrier (BBB)**. This cytokine storm primes the CNS for immune infiltration.

2.2 Blood–Brain Barrier Breakdown and CNS Entry

The BBB, normally an immunologically privileged interface, becomes permeable under the influence of matrix metalloproteinases (MMP-2 and MMP-9) and inflammatory cytokines.

These molecules degrade the basement membrane, allowing activated lymphocytes and monocytes to transmigrate into the CNS parenchyma via integrin-mediated adhesion (particularly VLA-4/VCAM-1 interactions).

This breach marks the transition from a peripheral to a central immune response, establishing a chronic inflammatory milieu within the CNS.

2.3 Intrathecal Inflammation and Demyelination

Once inside the CNS, T cells, B cells, and macrophages orchestrate multifocal inflammatory lesions:

- **$CD4^+$ T cells** amplify inflammation through IFN-γ and IL-2 signaling, sustaining macrophage recruitment.
- **$CD8^+$ cytotoxic T cells** directly lyse oligodendrocytes and neurons via perforin and granzyme pathways.
- **B cells** differentiate into plasma cells that produce **oligoclonal IgG bands (OCBs)** and **kappa free light chains (κ-FLCs)**—the principal CSF biomarkers now embedded in diagnostic criteria.
- **Microglia and macrophages** engulf myelin debris, releasing reactive oxygen species (ROS) and nitric oxide, further exacerbating demyelination and axonal transection.

Histologically, these processes yield the characteristic **plaques** seen on MRI: areas of demyelination surrounded by lipid-laden macrophages and astroglial scarring.

2.4 Chronic Neurodegeneration

Chronic MS lesions exhibit microglial activation**,** astrocytic gliosis, and axonal loss**,** even in the absence of overt inflammation. Mitochondrial dysfunction and persistent oxidative injury drive energy failure within demyelinated axons, leading to irreversible neuronal loss. The accumulation of paramagnetic rim lesions (PRLs) on MRI corresponds to these sites of chronic active inflammation, reflecting the ongoing smoldering pathology that underlies progressive MS phenotypes.

2.5 Integrated Schematic (Figure 1 Suggestion)

Figure 1. Immunopathogenic Cascade in Multiple Sclerosis

[Genetic Predisposition + EBV Infection]
↓
Autoreactive Th1 / Th17 Activation
↓
Cytokine Release (IFN-γ, TNF-α, IL-17)
↓
BBB Breakdown via MMPs and VLA-4
↓
Lymphocyte & Monocyte CNS Infiltration
↓
Intrathecal B-cell Activation → OCBs & κ-FLC
↓

Demyelination → Axonal Loss → Gliosis

This schematic visually represents the multi-step immunopathogenic sequence from peripheral activation to chronic CNS degeneration.

2.6 Summary

The immunopathogenesis of MS is thus a multistage autoimmune cascade involving peripheral T- and B-cell dysregulation, BBB compromise, and compartmentalized intrathecal inflammation. These insights form the biological rationale for modern diagnostic biomarkers—particularly CSF oligoclonal IgG and κ-FLC—and underpin therapeutic strategies targeting lymphocyte trafficking (e.g., natalizumab), B-cell depletion (e.g., ocrelizumab), and cytokine modulation

Figure 1: Immunopathogenic Cascade of MS → Peripheral activation → BBB disruption → CNS infiltration → Demyelination → Axonal degeneration.

3. Evolution of Diagnostic Criteria

Year	Criteria	Core Diagnostic Elements	Limitation
1965	Schumacher	Clinical relapses and anatomical dissemination	No imaging; late diagnosis
1983	Poser	Clinical + CSF IgG + evoked potentials	Complex, non-quantitative
2001	McDonald (Original)	MRI substitutes for clinical attacks (DIS, DIT)	Low specificity
2017	McDonald (Revised)	OCB allowed as substitute for DIT	Over-sensitivity; misdiagnosis risk
2024	McDonald (Latest)	Optic nerve, κ-FLC, CVS, PRLs included	More complex, requires expertise

4. The 2024 McDonald Criteria: Core Updates

4.1 The 2024 McDonald Criteria: Dissemination in Space and Time

The 2024 McDonald revision refines the conceptual framework of lesion dissemination by explicitly defining five anatomical domains for dissemination in space (DIS)**:**

1. Periventricular**,**
2. Cortical or juxtacortical**,**
3. Infratentorial**,**
4. Spinal cord**,** and
5. Optic nerve *(newly integrated domain)*.

The addition of the optic nerve reflects a pivotal shift in diagnostic philosophy, recognizing optic neuritis not merely as an isolated syndrome but as a core manifestation of central demyelination. Optic nerve involvement is now formally acknowledged to carry equivalent diagnostic weight to other CNS regions, supported by abundant evidence from optical coherence tomography (OCT) and high-resolution orbital MRI**,** which demonstrate characteristic demyelinating lesions and axonal thinning in early MS.

Dissemination in time (DIT) continues to serve as the marker of disease chronicity and recurrence**,** reflecting ongoing immune activation within the CNS. Evidence of DIT can be established through:

• **Magnetic Resonance Imaging (MRI):** identification of simultaneous gadolinium-enhancing and non-enhancing lesions on a single scan, or the emergence of new T2 or gadolinium-enhancing lesions on follow-up imaging;

• **Cerebrospinal Fluid (CSF) Biomarkers:** detection of **oligoclonal IgG bands (OCBs)** or an elevated **kappa free light chain (κ-FLC) index >5.9**, either of which now serves as a valid surrogate marker of temporal dissemination.

The inclusion of κ-FLC index as a quantitative, automated biomarker marks a major methodological advancement. Compared to traditional OCB analysis, κ-FLC offers greater reproducibility, objectivity, and cost-efficiency, making it particularly valuable in laboratories lacking specialized electrophoresis equipment. Its adoption aligns MS diagnostics with the growing emphasis on standardized, quantifiable, and technology-driven biomarkers**.**

Overall, the 2024 revision transforms the McDonald Criteria into a biologically anchored diagnostic model**,** merging spatial lesion distribution with immunological evidence of chronic CNS autoimmunity—an integration that enhances both early diagnostic sensitivity and long-term specificity**.**

Figure 2: Diagnostic Algorithm → Clinical syndrome → MRI DIS/DIT → CSF biomarkers → Exclusion of mimics → MS confirmation.

5. Biomarker Correlation

Biomarker	Mechanism	Diagnostic Role	Strength
OCBs	Intrathecal IgG synthesis	DIT substitute	Sensitive but non-specific
κ-FLC	Free light chain production	DIT substitute	Quantitative, automated
NfL	Axonal injury marker	Disease activity	Prognostic value
GFAP	Astroglial activation	Neurodegeneration	Experimental

6. MRI Features and Differential Diagnostic Considerations

Magnetic Resonance Imaging (MRI) remains the cornerstone of Multiple Sclerosis (MS) diagnosis, providing the most objective evidence for lesion dissemination in both space and time.

The typical MRI phenotype of MS encompasses a set of characteristic lesion morphologies and distributions that reflect perivenular inflammation and demyelination.

Periventricular lesions are among the most distinctive findings, manifesting as **"**Dawson's fingers**"**—elongated, flame-shaped plaques radiating perpendicular to the lateral ventricles along medullary veins. This perivenular orientation underscores the vascular component of lesion formation, now further supported by the central vein sign (CVS)**,** in which a small venule traverses the lesion center. CVS is currently regarded as a high-specificity imaging biomarker distinguishing MS from other inflammatory or vascular white-matter diseases.

Juxtacortical and cortical lesions involve U-fibers adjacent to the gray–white matter junction and are strongly correlated with cognitive impairment and cortical demyelination.

Advanced imaging sequences, such as double inversion recovery (DIR) and phase-sensitive inversion recovery (PSIR), markedly enhance detection of these cortical plaques.

Infratentorial lesions typically affect the pons, cerebellar peduncles, and midbrain**,** often correlating clinically with internuclear ophthalmoplegia, ataxia, and dysarthria.

Their presence is particularly useful for diagnostic specificity, as infratentorial plaques are uncommon in vascular leukoencephalopathies.

Spinal cord lesions in MS are classically short-segment (less than three vertebral segments), asymmetric, and peripheral, frequently located in the lateral and posterior columns.

This sharply contrasts with neuromyelitis optica spectrum disorder (NMOSD)**,** in which lesions are longitudinally extensive and centrally positioned.

The optic nerve**,** now formally included as the fifth anatomical domain for dissemination in space (DIS), typically demonstrates focal gadolinium enhancement during acute optic neuritis and chronic axonal thinning on optical coherence tomography (OCT). High-resolution orbital MRI using fat-suppressed T2-weighted and STIR sequences improves detection of subtle demyelinating lesions in this region.

Emerging MRI features, such as **paramagnetic rim lesions (PRLs)**—chronic, iron-laden plaques with peripheral susceptibility signals—serve as markers of ongoing microglial activation and correlate with progressive disease forms. Together, CVS and PRLs represent a new generation of imaging biomarkers bridging pathophysiology with diagnostic imaging.

Differential diagnostic considerations are crucial in avoiding misinterpretation of MRI findings:

- **NMOSD**: Characterized by longitudinally extensive spinal cord lesions (>3 vertebral segments) and area postrema involvement.
- **MOGAD**: Shows bilateral optic neuritis, fluffy brainstem lesions, and frequent cortical encephalitis.
- Vascular small-vessel disease: Produces punctate deep white-matter hyperintensities that spare the corpus callosum and U-fibers, lack enhancement, and exhibit a distinct age-related distribution pattern.

When interpreted systematically and correlated with clinical and CSF findings, MRI enables precise differentiation between MS and its mimics, supporting the integration of radiological evidence into the 2024 McDonald diagnostic algorithm**.**

7. Conclusion

The 2024 McDonald Criteria represent a pivotal advancement in the diagnostic framework of Multiple Sclerosis (MS)**,** uniting clinical, radiological, and immunological dimensions into a single, evidence-based model. By incorporating optic nerve involvement as a recognized anatomical domain, integrating the **kappa free light chain (κ-FLC) index** as a quantitative biomarker of intrathecal immunoglobulin synthesis, and adopting microstructural MRI markers such as the central vein sign (CVS**)** and paramagnetic rim lesions (PRLs**)**, the revised criteria achieve a delicate yet powerful balance between early diagnostic sensitivity and pathological specificity**.**

This paradigm shift moves MS diagnostics beyond reliance on static imaging and clinical observation, toward a biologically anchored, biomarker-driven approach**.** The integration of molecular immunopathology and high-resolution neuroimaging not only enhances diagnostic precision but also deepens our understanding of disease mechanisms, facilitating earlier intervention and improved long-term outcomes.

Nevertheless, the successful application of these criteria requires standardization across imaging platforms**,** training in advanced neuroimaging interpretation**, and** broader laboratory access to κ-FLC assays**,** particularly in low-resource settings.

As such, the 2024 McDonald framework should be viewed as both a diagnostic milestone and a call to harmonize global practice in neuroimmunology.

In essence, this revision does not merely redefine how MS is diagnosed—it redefines how MS is conceptualized**,** signaling a transition from descriptive neurology to precision neuroimmunology**,** where diagnosis, pathogenesis, and therapy converge within a unified scientific paradigm.

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