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# Update in Multiple Sclerosis

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## Relevant Disclosures

- Clinical trial site PI for Sanofi and Novartis
- Paid consultant for Can Do MS

## Objectives

- Background / Pathogenesis
- Diagnostic Work-up
- Diagnostic Criteria Updates
- New and Emerging Treatments

## Multiple Sclerosis Background

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- ~ 1 million patients in US
- One of the leading causes of atraumatic disability in young adults
- Age of onset 20-40
- Females > males
- Determinants of more severe long-term disability – male sex, non-Caucasian populations, older age at onset, spinal cord syndrome at onset, high early relapse rate

## Pathogenesis

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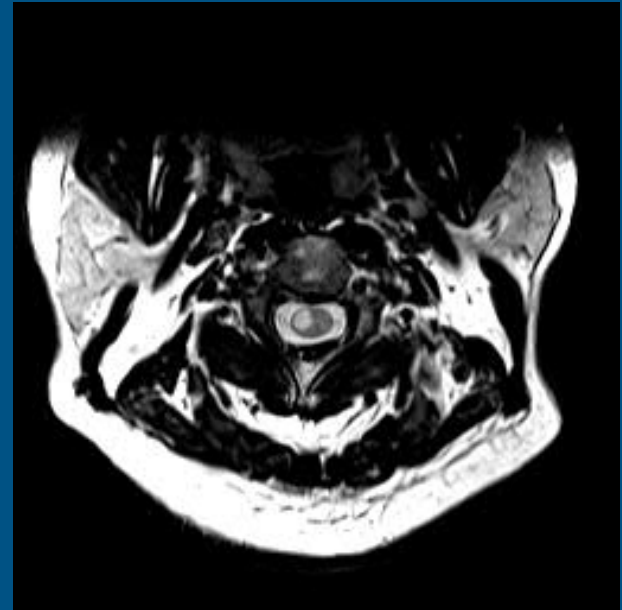
- General population risk 0.1%
- Genetic susceptibility
  - 1<sup>st</sup> degree 2-5%; Monozygotic twins – 20-30% risk
  - HLA-DRB1\*1501 – 3 fold increased odds
- Environmental Factors
  - EBV
  - UV exposure and Vitamin D
  - Obesity
  - Smoking – dose dependent

# MS Diagnosis

## Typical Presenting Syndromes

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- Optic neuritis
  - Unilateral, pain with eye movement, central blurring
- Brainstem syndromes
  - Trigeminal neuralgia
  - INO
- Cerebellar syndromes
  - Ataxia, nystagmus
- Transverse Myelitis
  - Partial myelitis, Lhermitte's sign, sensory loss > motor loss



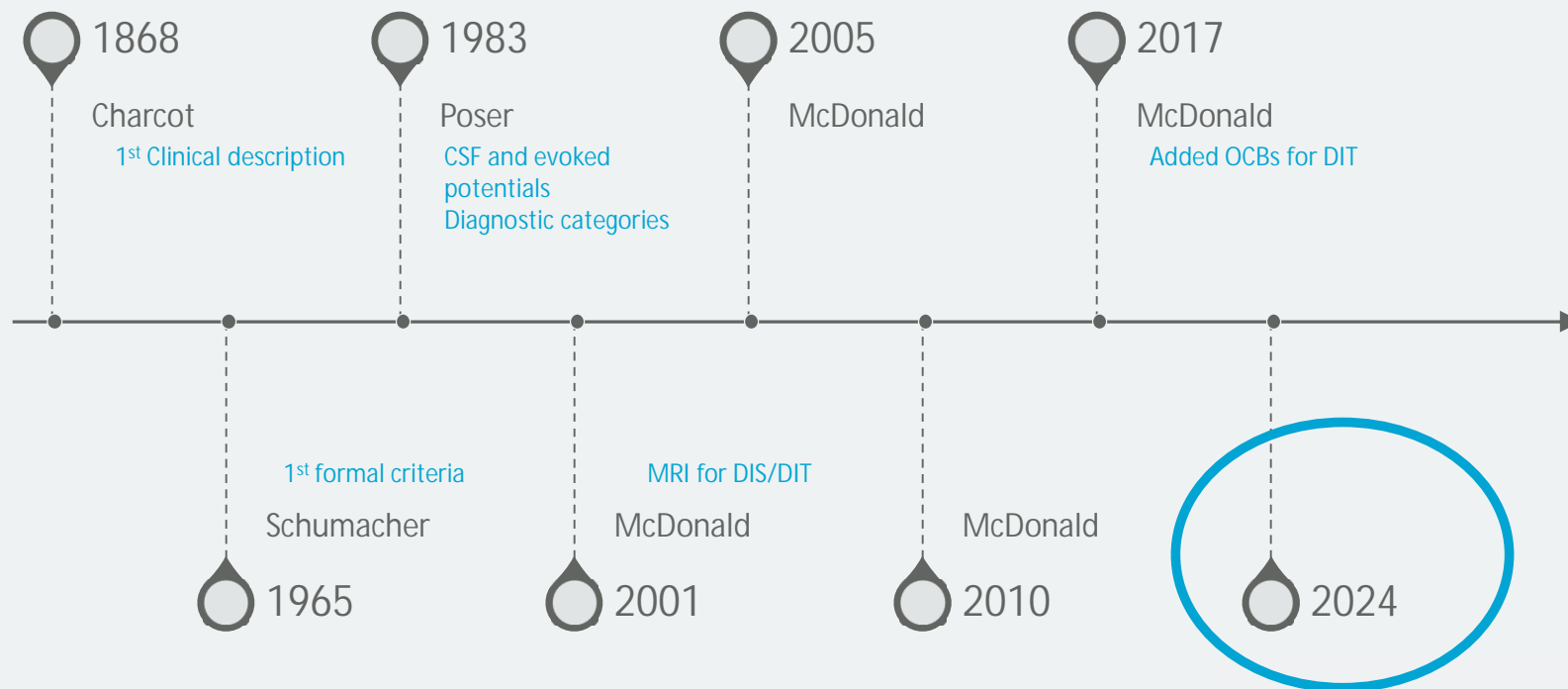
## Differential Diagnosis

- Small vessel disease
- NMOSD
- MOGAD
- Acute Demyelinating Encephalomyelitis (ADEM)
- Neurosarcoidosis
- Idiopathic Intracranial Hypertension (IIH)
- Behcet's
- Other CNS manifestations of Rheumatologic disease
- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephlaopathy (CADASIL)
- Neoplasm
- Migraines

## Diagnostic Evaluation

- MRI brain, cervical and thoracic spine with and without contrast
- +/- CSF for oligoclonal bands
- Mimic testing
  - MOG and NMO testing
  - +/- more systemic autoimmune work-up
- Vitamin D levels

# Diagnostic Criteria Over Time



## MS Diagnosis – 2017 Criteria

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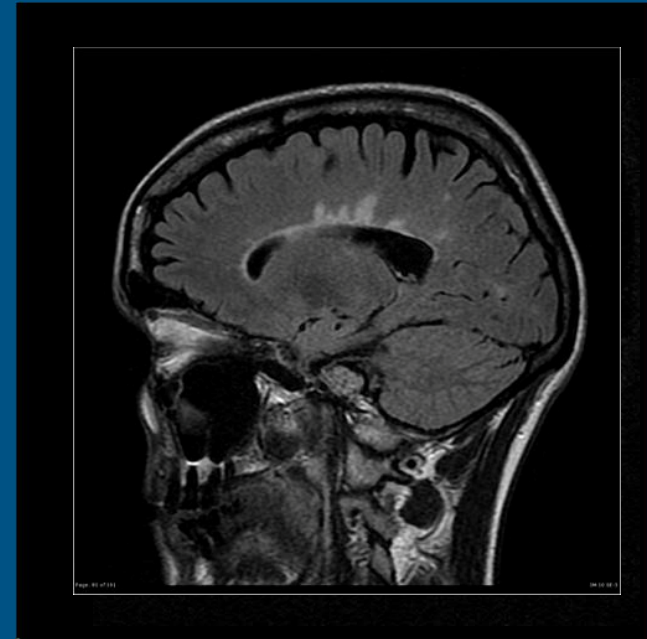
- Dissemination of a central demyelination syndrome in TIME and SPACE
  - ~85% sensitivity and specificity

## MS Diagnosis – 2017 Criteria

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### Space (Dissemination in Space – DIS)

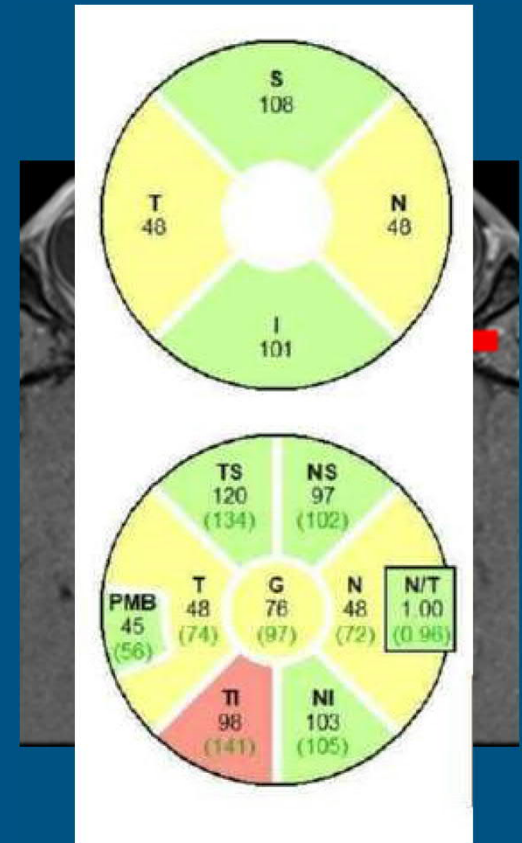
- Detection of lesions in at-least two of these distinct anatomic locations
  - Juxtacortical/Cortical
  - Periventricular
  - Infratentorial
  - Spinal Cord



## MS Diagnosis – 2024 Criteria

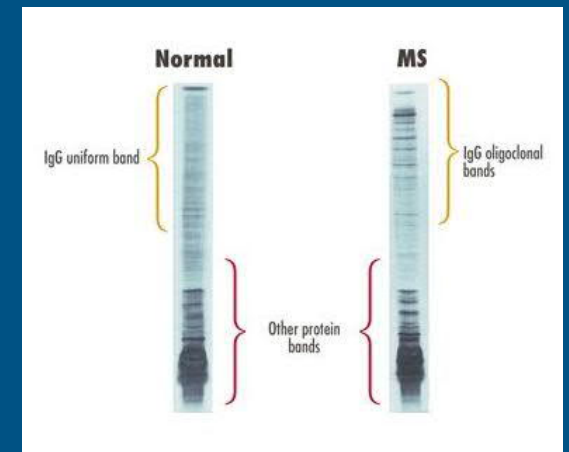
### Space (DIS)

- Detection of lesions in at-least two of these distinct anatomic locations
  - Juxtacortical/Cortical
  - Periventricular
  - Infratentorial
  - Spinal Cord
  - **Optic nerve**
    - **MRI, OCT, VEP**



## MS Diagnosis – 2017 Criteria

- **Time (Dissemination in Time - DIT)**
  - Discrete events separated in time
  - Gd+ and Gd- lesions on MRI
  - MRI changes over time
  - Oligoclonal bands



## MS Diagnosis – 2024 Criteria

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- **Time (Dissemination in Time - DIT)**
  - Discrete events separated in time
  - Gd+ and Gd- lesions on MRI
  - MRI changes over time
  - Oligoclonal bands

**Dissemination in time no longer  
necessary**

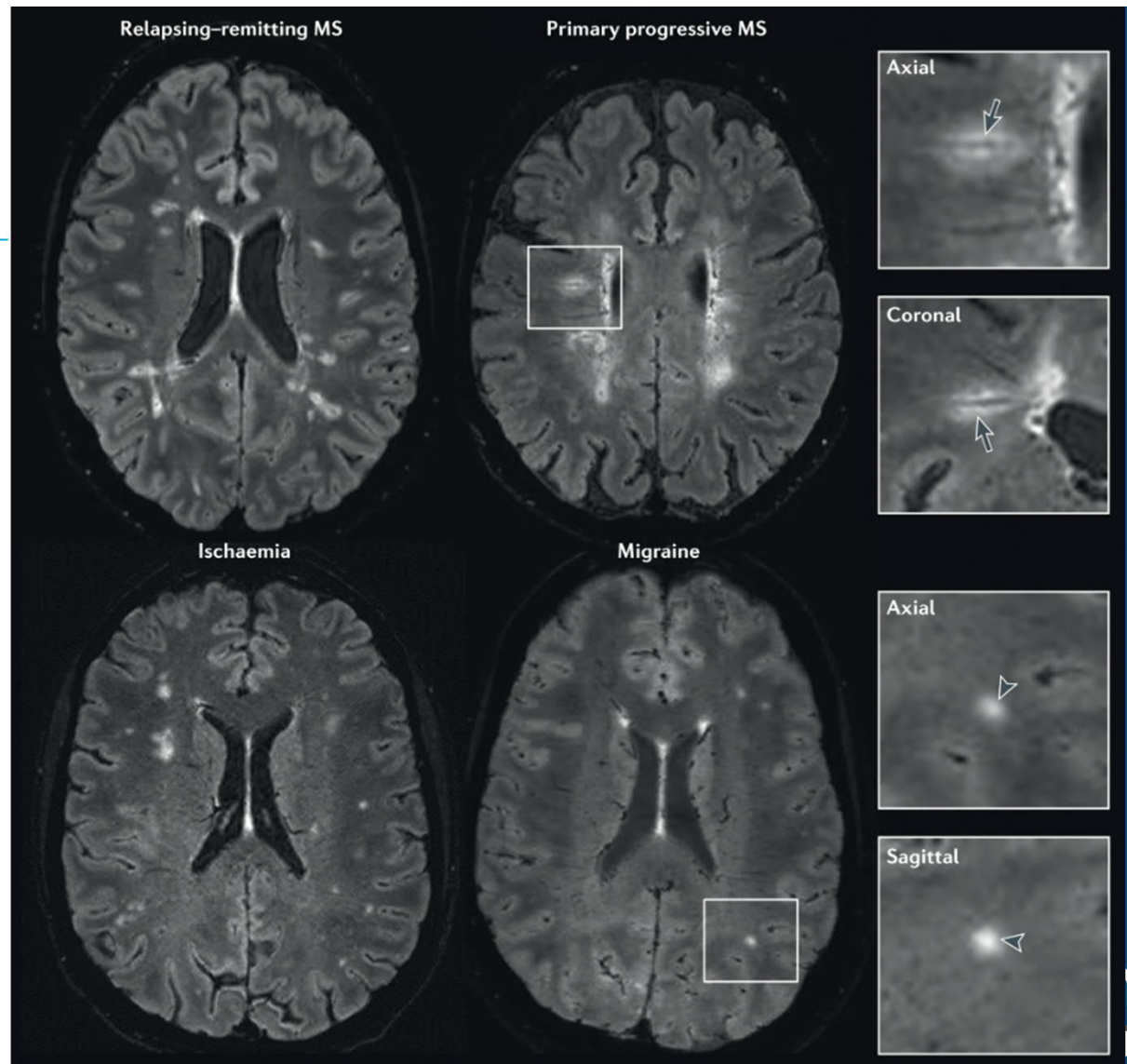
## MS Diagnosis – 2024 Criteria – New Supportive Evidence

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- Central Vein Sign
- Paramagnetic Rim Lesions
- Kappa Free Light Chain

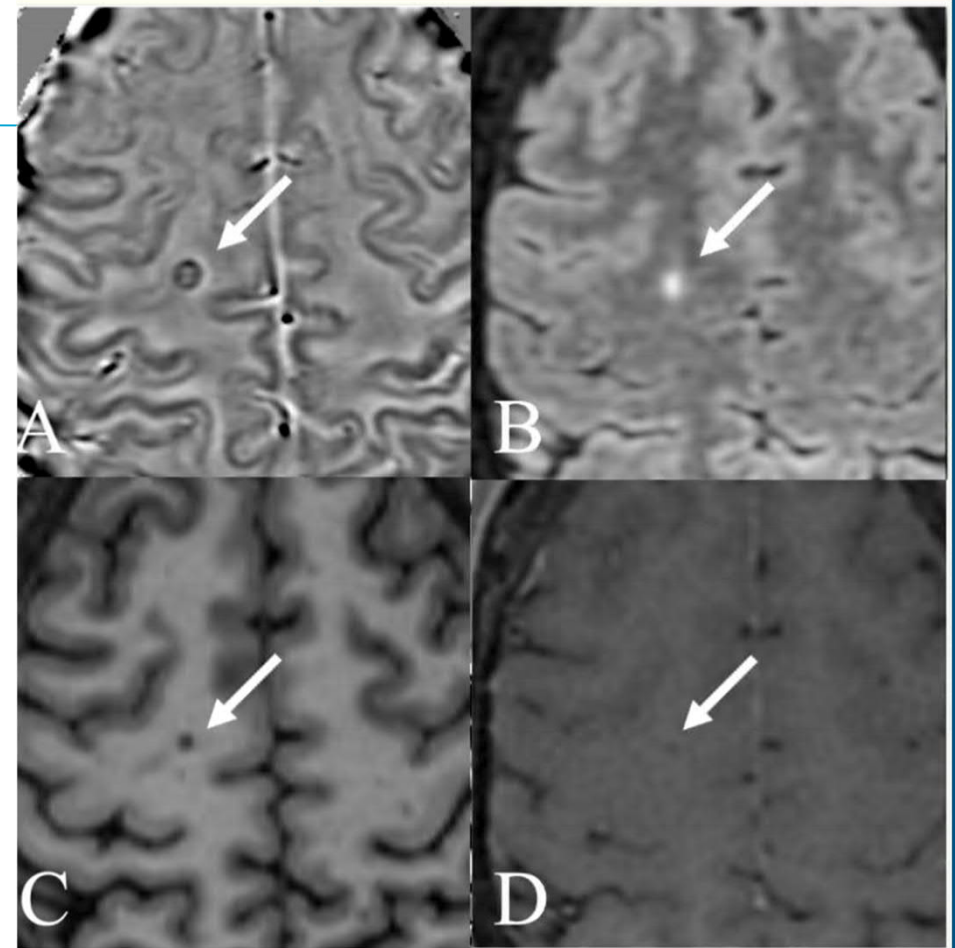
## Central Vein Sign

- Highly sensitive and specific for MS
- Best seen with iron sequences – T2\*



## Paramagnetic Rim Lesions

- Susceptibility weighted sequences
- Iron accumulation in microglia

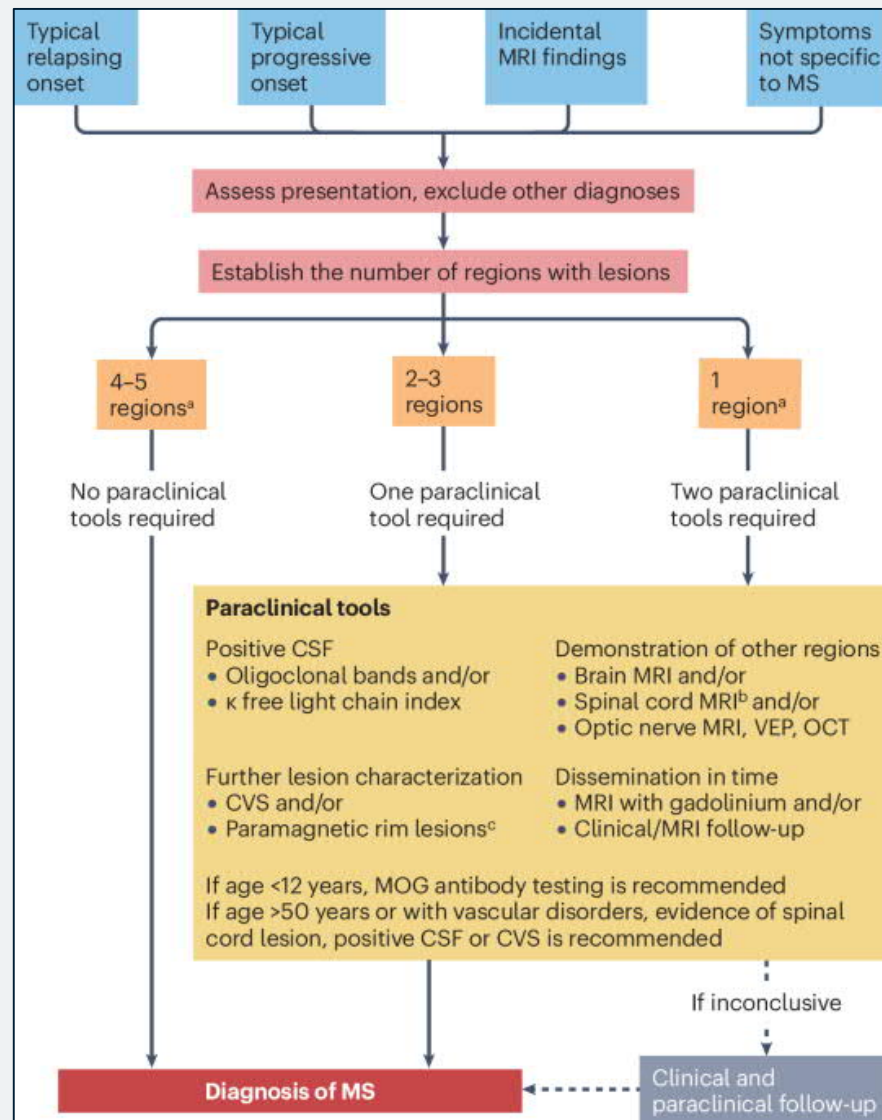


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## Kappa Free Light Chains

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- Indicates intrathecal immunoglobulin production
- More accessible than oligoclonal bands
- More cost effective than oligoclonal bands



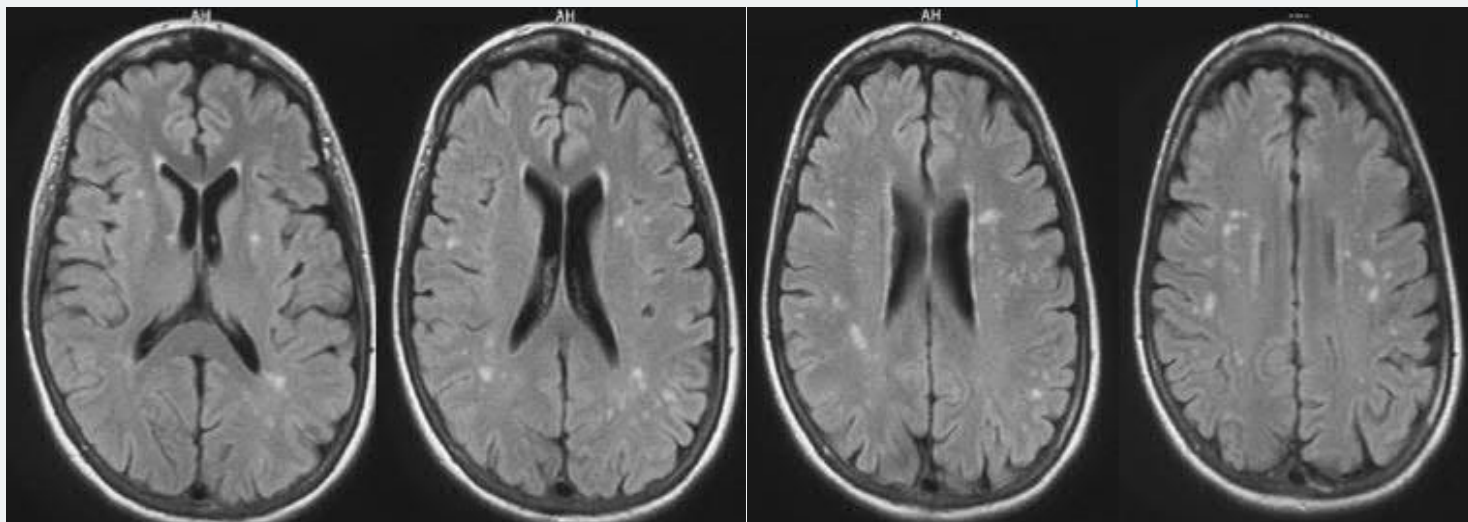
## And no better explanation!

### Red Flags

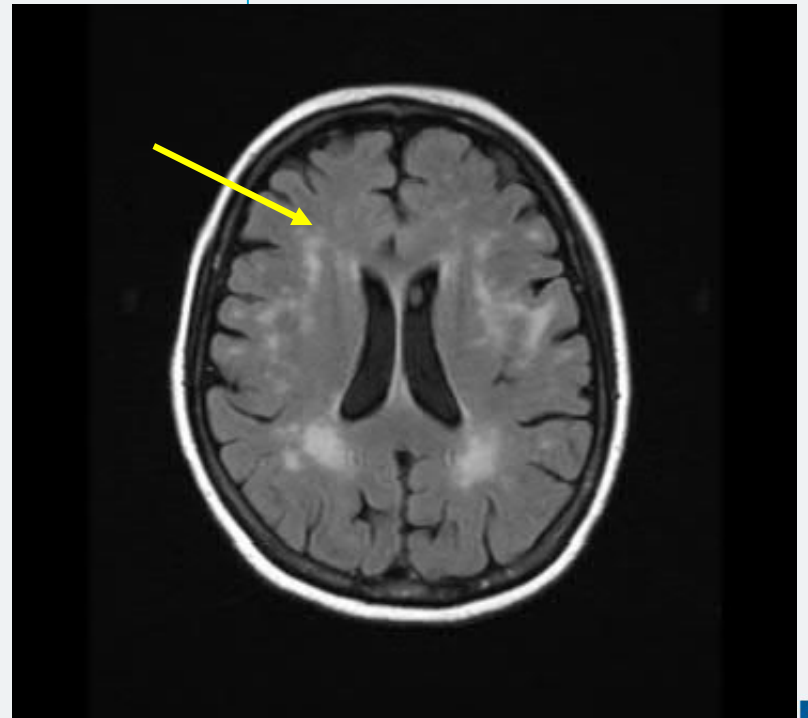
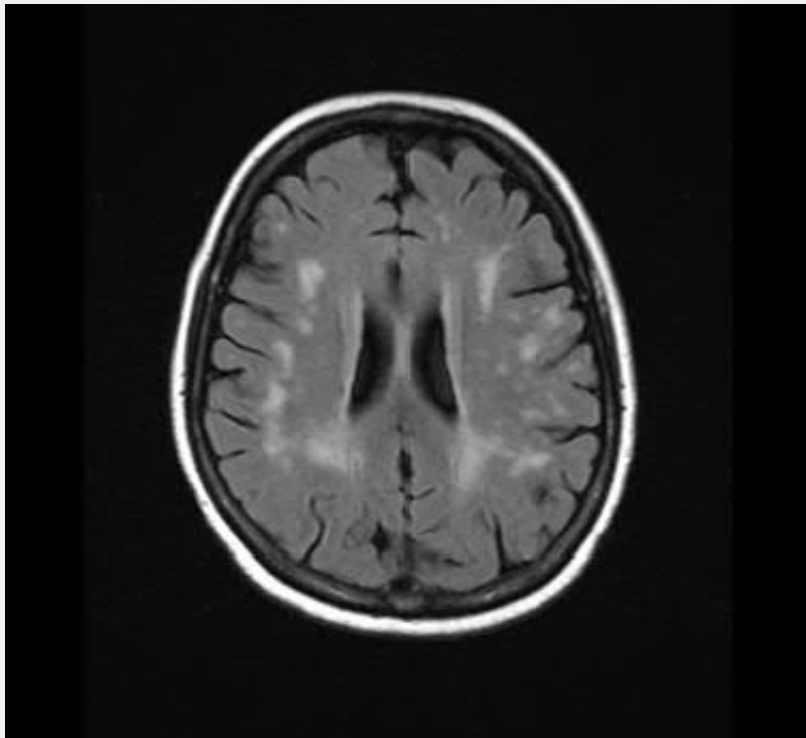
- Severe optic neuritis
- Bilateral optic neuritis
- LETM
- Complete spinal cord lesions / LETM
- Encephalopathy
- Cranial nerve involvement
- CSF pleocytosis
- Systemic symptoms

## Case

- A 35-year-old woman with a history of hypertension and prior diagnosis of MS was seen to establish care in a specialty MS center
- History of frequent falls, fatigue, and visual difficulties described as pain involving both eyes beginning 10 years ago



## Small vessel ischemic disease



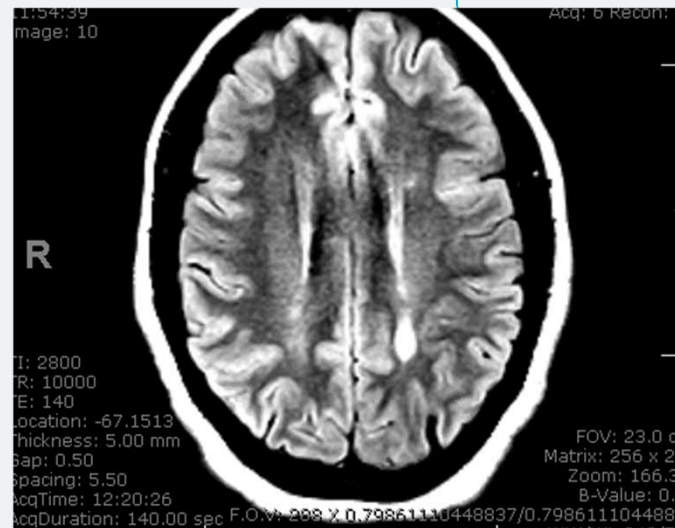
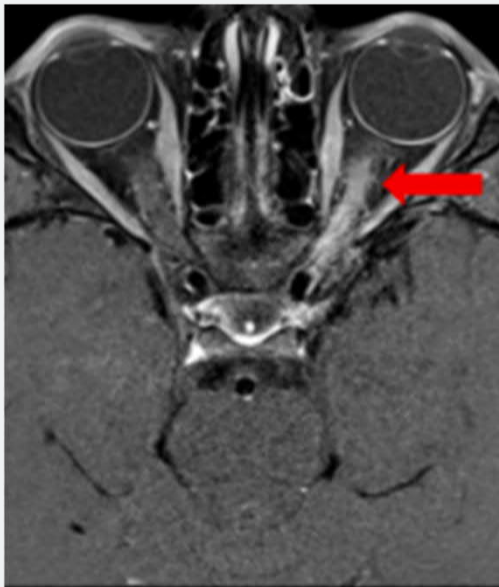
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## Special Considerations Based on Age and Comorbidity

- Higher risk for misdiagnosis
  - Age 50 years and older
  - Comorbidity – HTN, smoking, diabetes, HLD
- MRI changes seen in migraine, small vessel disease
- Additional tests or further evidence strongly recommended
  - Spinal cord lesions
  - Positive CSF
  - Central vein sign

## Case

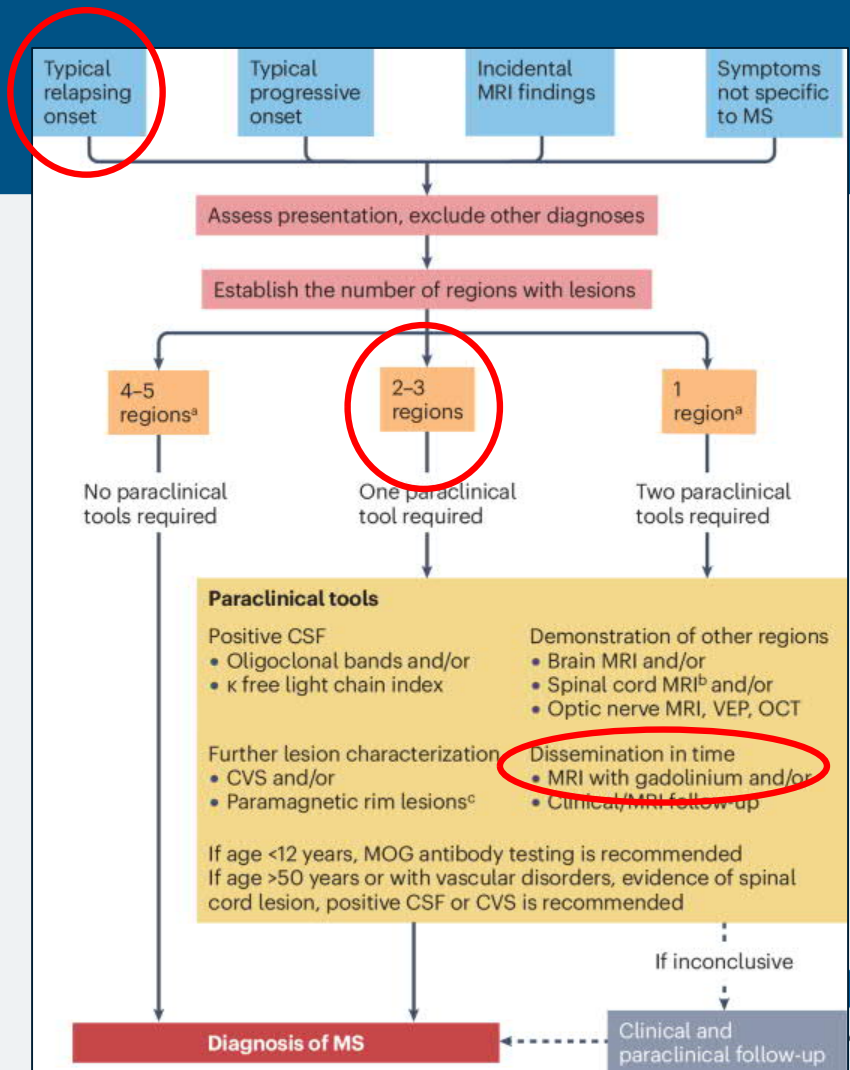
- 27 yo female presents with blurry vision, OS. Symptoms preceded by pain with eye movement
- Diagnosed with optic neuritis and treated with IVMP



# Case

- Does she fulfill criteria?

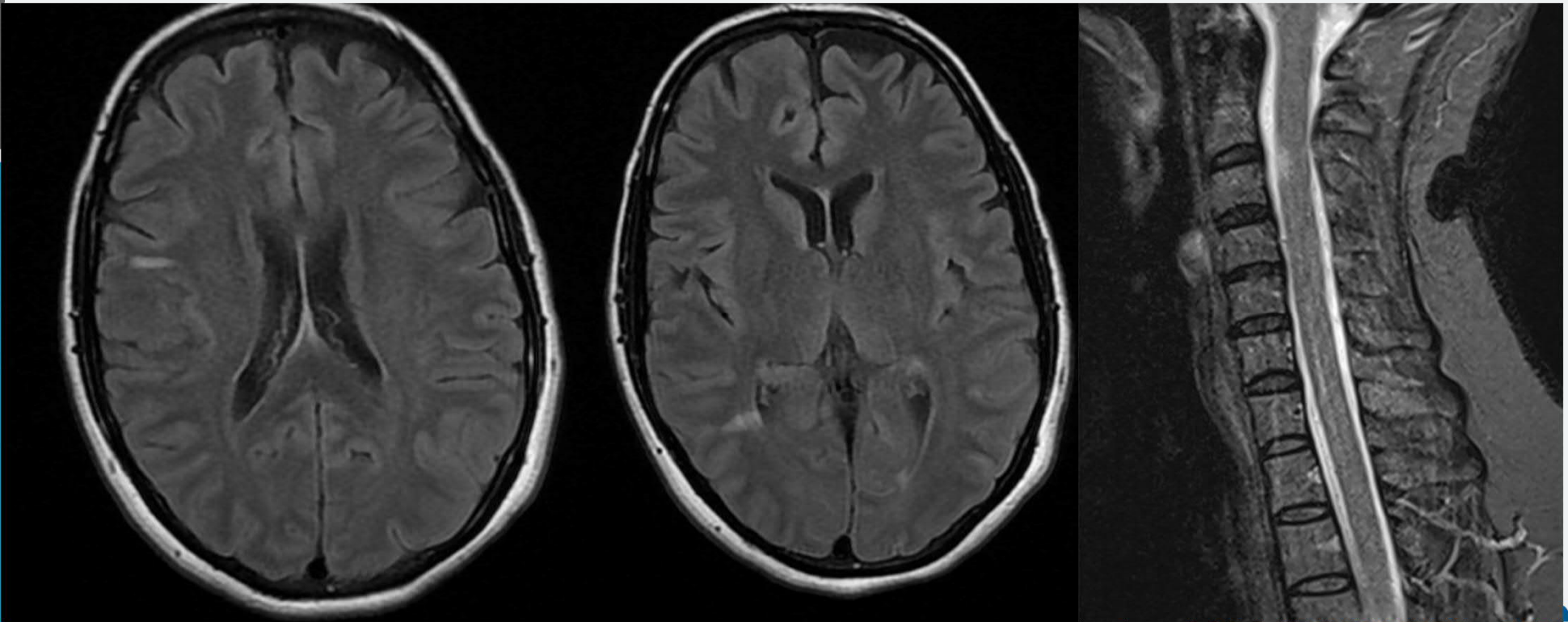
Yes



## Case

- 26 year-old woman with persistent headaches and neck pain after a car accident
- Otherwise healthy, no other past medical history
- Neurological exam normal
- PCP orders MRIs for further evaluation

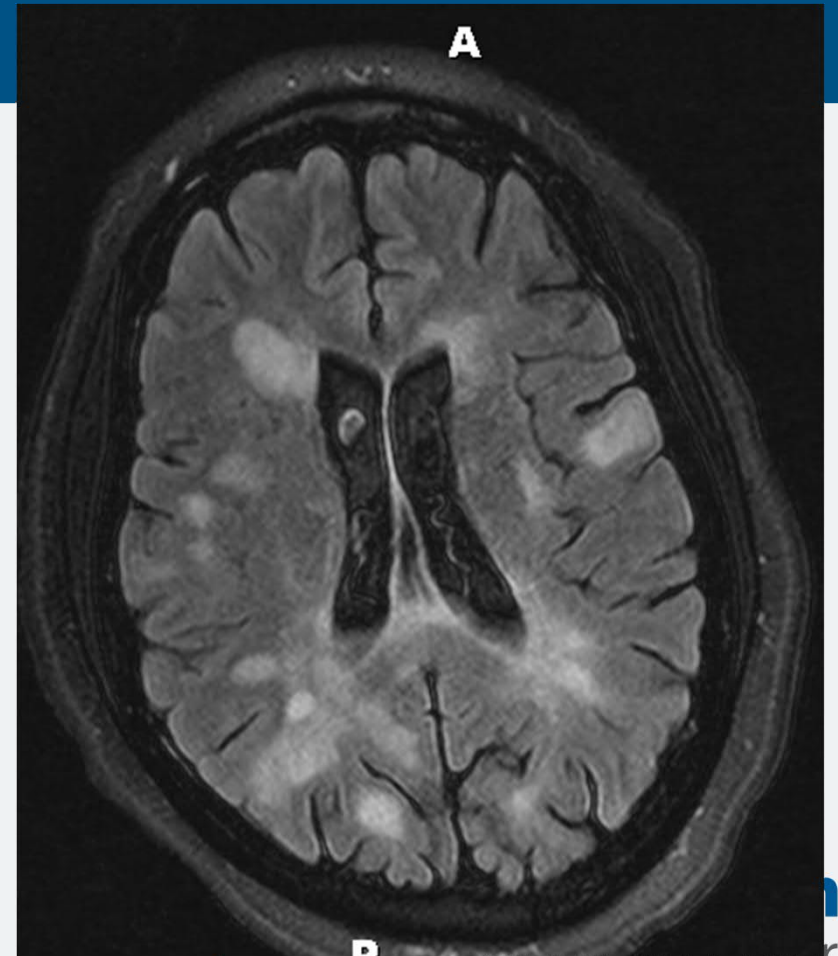
## Case



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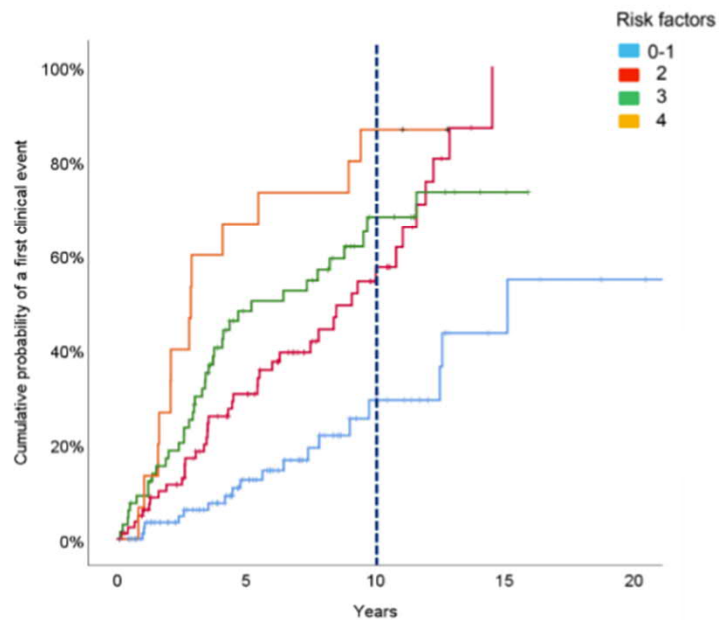
# Radiologically Isolated Syndrome

- Presence of demyelinating changes on MRI of brain or spinal cord done for evaluation of a condition other than MS or typical demyelinating symptoms
- Lesions should be T2 hyperintense, ovoid, and well circumscribed located in typical regions
- Risk high for RRMS if:
  - Younger age
  - Male sex
  - Cord or infratentorial lesion
  - +Gd
  - OCBs



# Radiologically Isolated Syndrome

## Risk stratification



**4 factors: 87% converted**

**3 factors: 68% converted**

**2 factors: 54% converted**

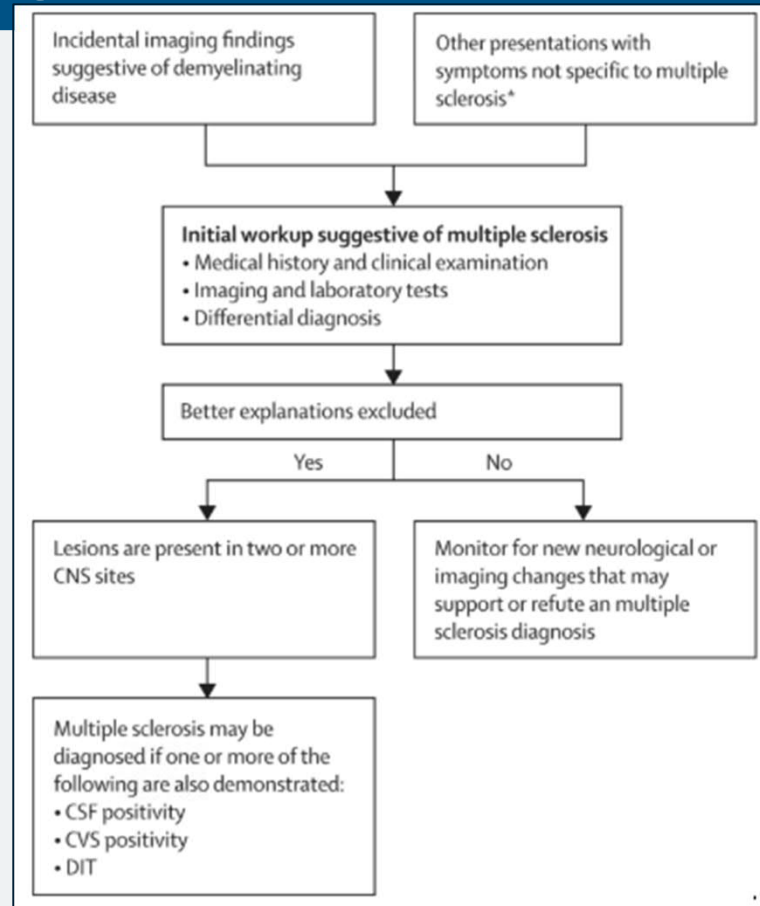
**0-1 factor: 29% converted**

Christine Lebrun Frenay, International Advisory Committee 2022

Lebrun-Frenay et al, 2020

Lebrun-Frenay C, Kantarci O, Siva A, Sormani MP, Pelletier D, Okuda DT; 10-year RISC study group on behalf of SFSEP, OFSEP. Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event. Ann Neurol. 2020 Aug;88(2):407-417. doi: 10.1002/ana.25799. Epub 2020 Jun 29. PMID: 32500558.

## 2024 – RIS to RRMS

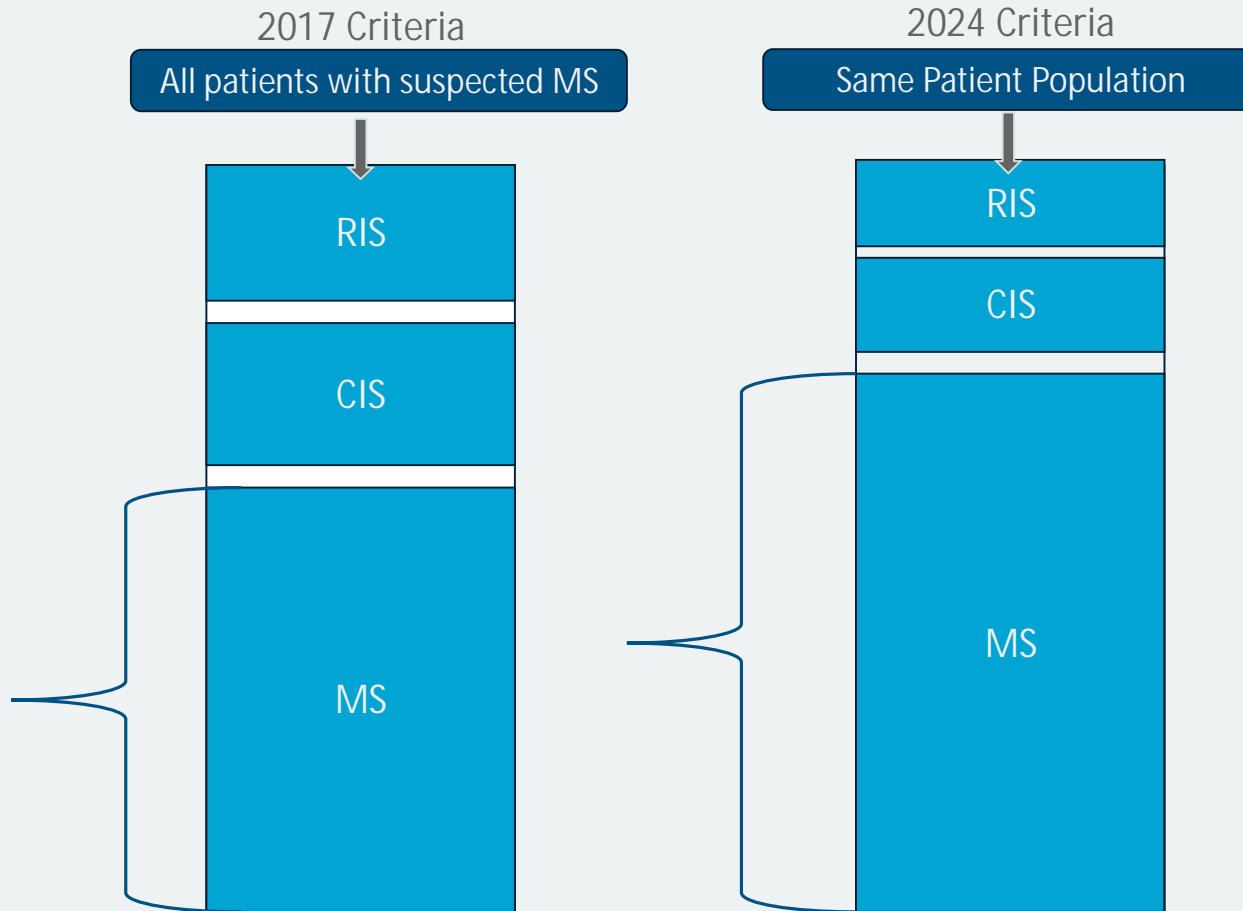


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## Summary

- Optic nerve is new 5<sup>th</sup> anatomical location
- Central vein sign and paramagnetic rim lesions added as supportive evidence on imaging
- Kappa free light chain in CSF added as supportive evidence
- Easier for RIS to be called RRMS

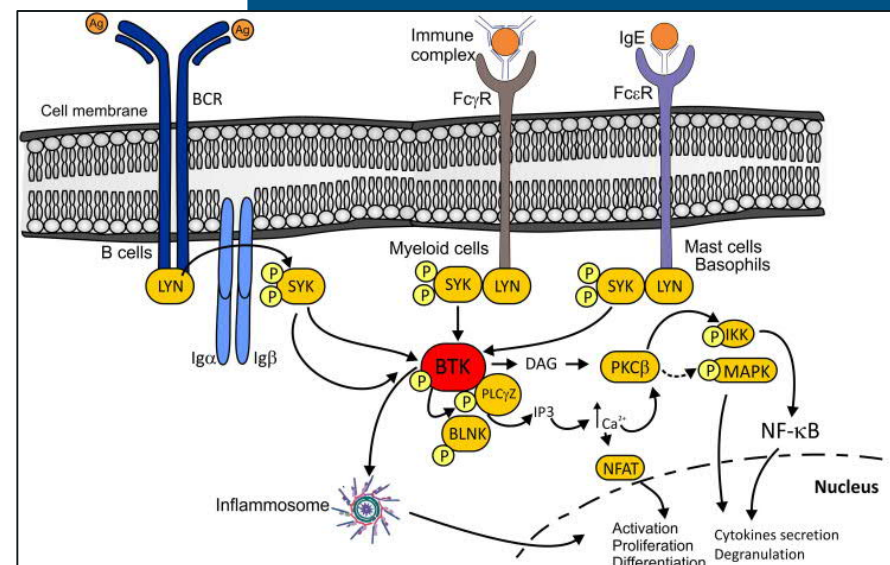
# Increased Diagnosis Rates



# Treatment Updates

# Bruton Tyrosine Kinase Inhibitors

- **Tolebrutinib (Sanofi)**
  - HERCULES – non-relapsing SPMS confirmed disability progression reduced by 31%
  - GEMINI – relapsing – no significant change compared to comparator
- **Fenebrutinib (Roche)**
- **Remibrutinib (Novartis)**



## Other Emerging Treatments

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- **Frexalimab** – Anti-CD40 Ligand
- **Forulumab** – Anti-CD3 monoclonal antibody
  - SPMS
  - Intranasal
- **CNM-AU8** – Gold nanoparticles – remyelination
- **Stem Cell Therapies**

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