Updates in Multiple Sclerosis

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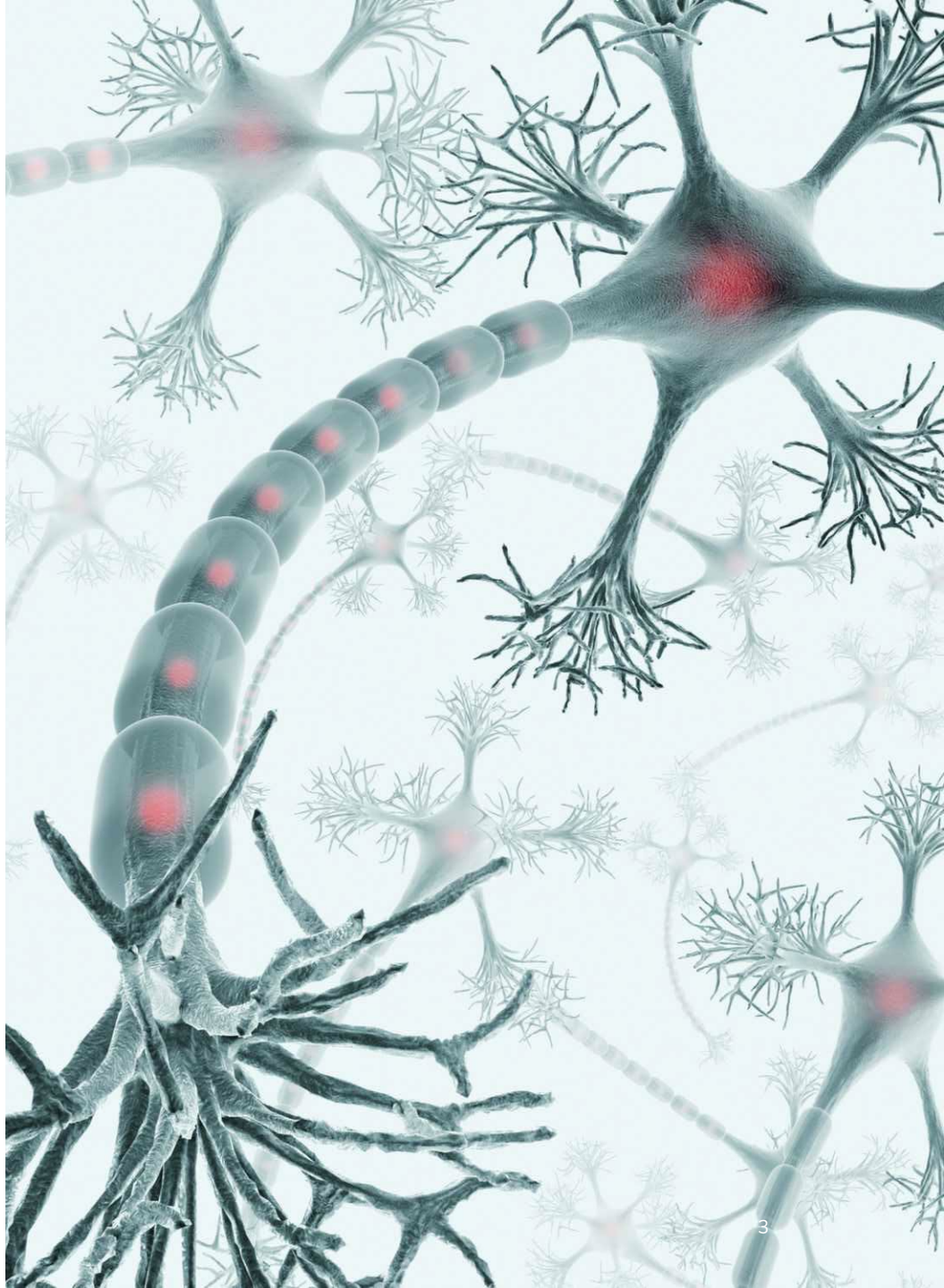
Disclosures

- Dr. Gyang has served as consultant with Genentech, Sanofi, Horizon, EMD Serono and Greenwich Biosciences
- Clinical recommendations are evidence based and free of commercial bias

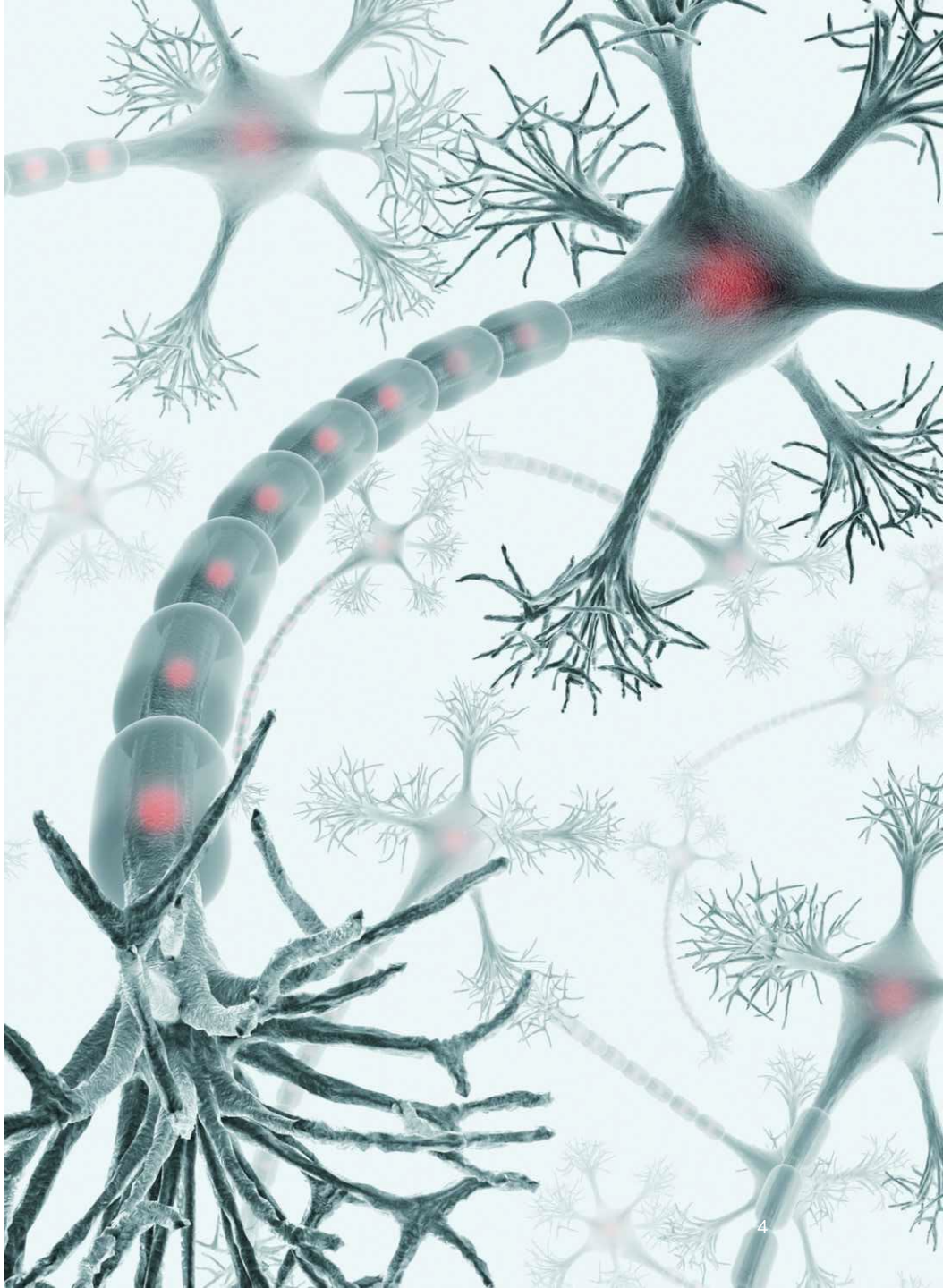
Outline

- Multiple Sclerosis (MS) – overview
  - Epidemiology, etiology, demographic distribution, pathogenesis, phenotypes
- Diagnosis of MS
  - Evolution of diagnostic criteria
  - McDonald's 2017 diagnostic criteria
  - MRI criteria and novel MRI techniques
  - Diagnostic challenges and differential diagnosis
- Disease modifying therapies (DMTs)
  - Current DMTs
  - Treatment paradigms
  - Notable clinical trials



Multiple Sclerosis

- Most common inflammatory demyelinating disorder of the central nervous system (CNS)
- Characterized by multifocal areas of demyelination within the CNS
- Second leading cause of disability in young adults
- Diverse clinical presentation and disease phenotypes
- Affects about 1 million people in the US



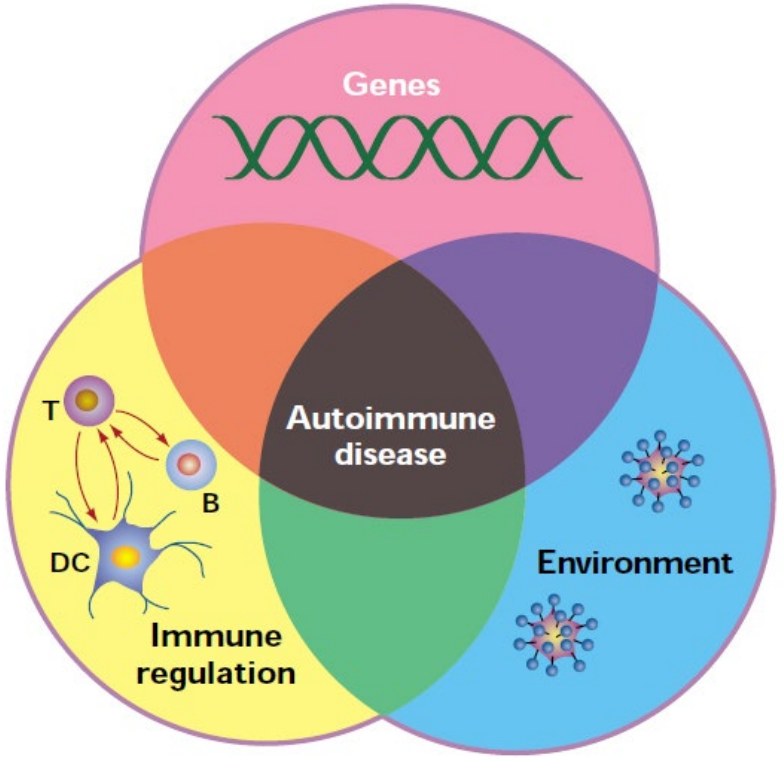
Etiology of MS

Over 200 immune gene SNPs are implicated in the risk of MS

- HLA-DR1, IL-2 receptor, IL-7 receptor, OAS1 polymorphism, AA genotype, CBLB in Sardinia, KIF 1B, GPC5 etc.

Immune dysregulation

- Adaptive immune response
  - T and B lymphocytes.
- Innate immune response
  - microglia and macrophage

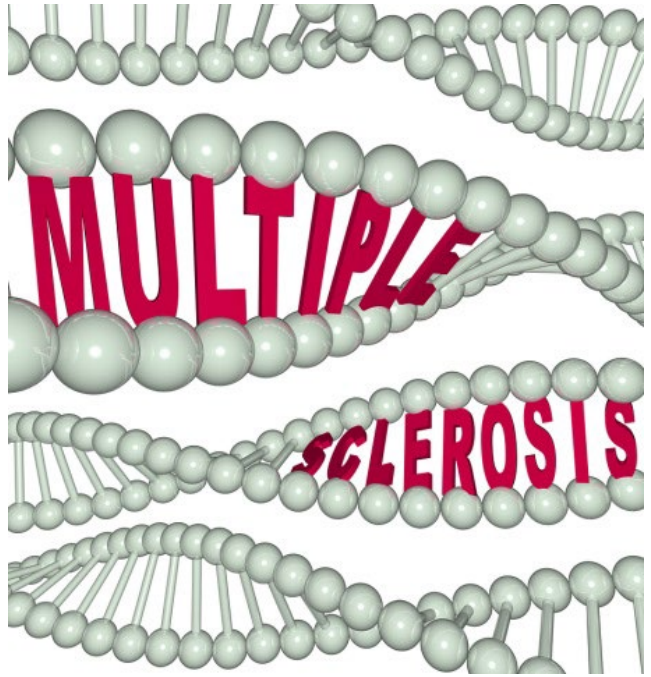


Latitude
Obesity
Microbial Agents
Viruses - EBV
Gut microbiome
Vitamin D
Smoking
Diet

Ermann J, Fathman G. Nat Immunol 2001 Sep;2(9):759-61

Epidemiology of MS

- Female to Male ratio (F:M)
  - Relapsing remitting MS – 3:1
  - Primary progressive MS – 1.2:1
- Mean age of MS onset
  - Relapsing remitting MS ~ 30 years
  - Primary progressive MS ~40 years
- Genetic susceptibility
  - HLA-DRB1*1501 haplotype
  - Concordance: monozygotic twins -30%, dizygotic twins - 5%
  - 20- to 40-fold increased risk of MS in first-degree relatives of patients with MS



MS prevalence

- Utilized a validated algorithm applied to private, military, and public administrative health claims datasets
- Identified adult cases of MS between 2008 and 2010
- Estimated 2010 prevalence - 309.2 per 100,000
- Female:Male ratio 2.8
- North-south decreasing prevalence gradient

The prevalence of MS in the United States

A population-based estimate using health claims data

Mitchell T. Wallin, MD, MPH, William J. Culpepper, PhD, Jonathan D. Campbell, PhD, Lorene M. Nelson, PhD, Annette Langer-Gould, MD, PhD, Ruth Ann Marrie, MD, PhD, Gary R. Cutter, PhD, Wendy E. Kaye, PhD, Laurie Wagner, MPH, Helen Tremlett, PhD, Stephen L. Buka, ScD, Piyameth Dilokthornsakul, PharmD, PhD, Barbara Topol, MS, Lie H. Chen, DrPH, and Nicholas G. LaRocca, PhD, on behalf of the US Multiple Sclerosis Prevalence Workgroup

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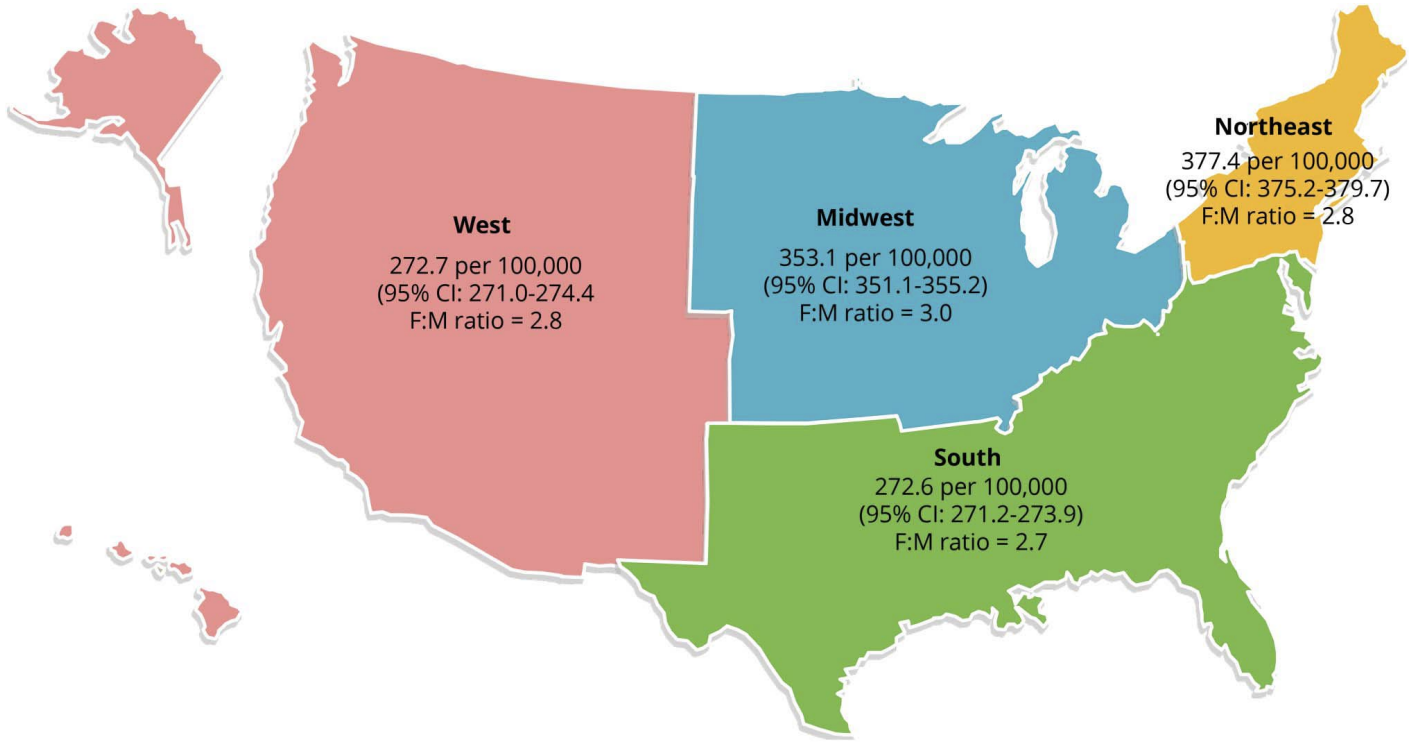
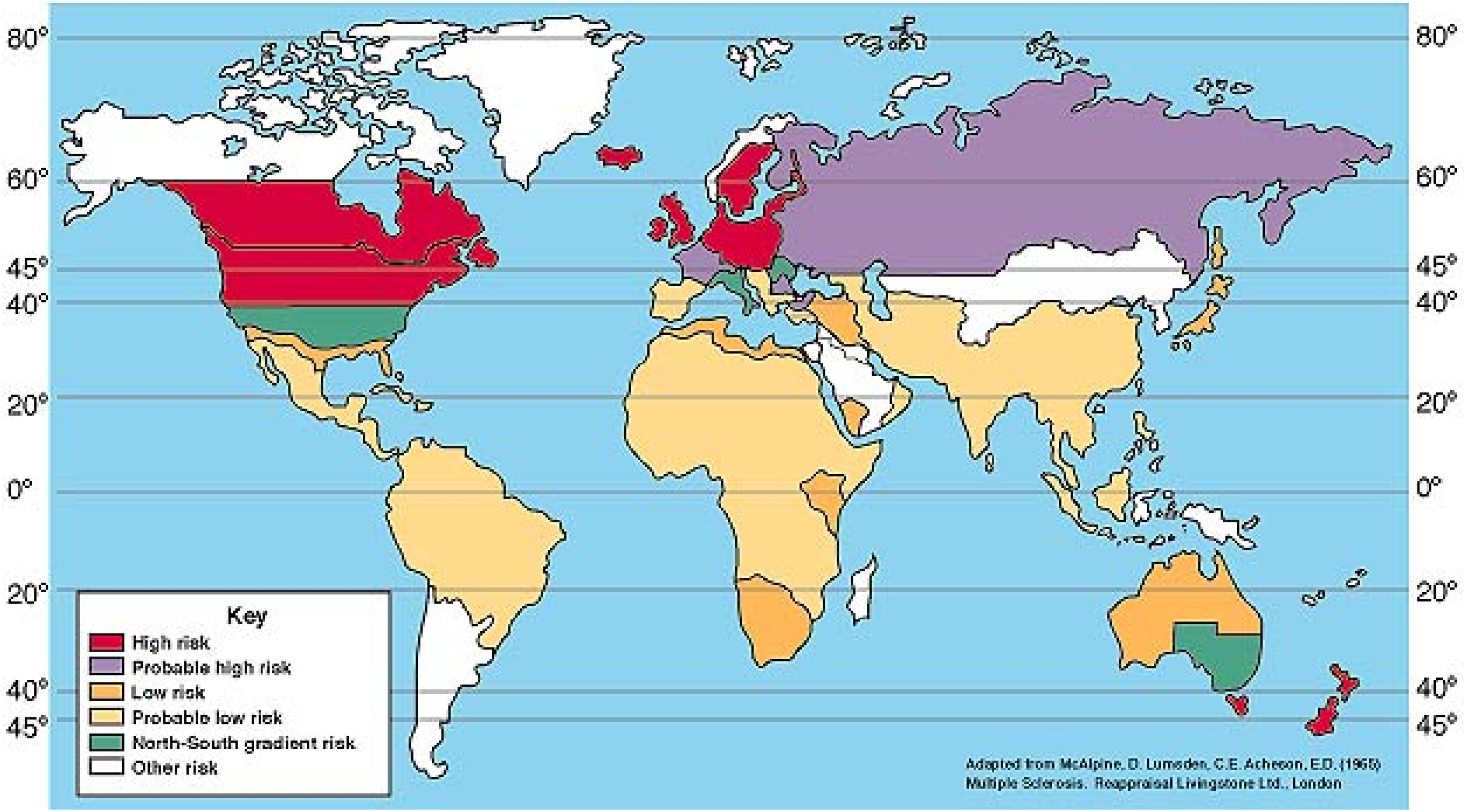
Neurology® 2019;92:e1029-e1040. doi:10.1212/WNL.0000000000007035



Wallin MT. Neurology. 2019 Mar 5;92(10)

World Distribution of Multiple Sclerosis



Adapted from McAlpine, et al. 1966. Multiple Sclerosis. Reappraisal Livingstone Ltd. London.

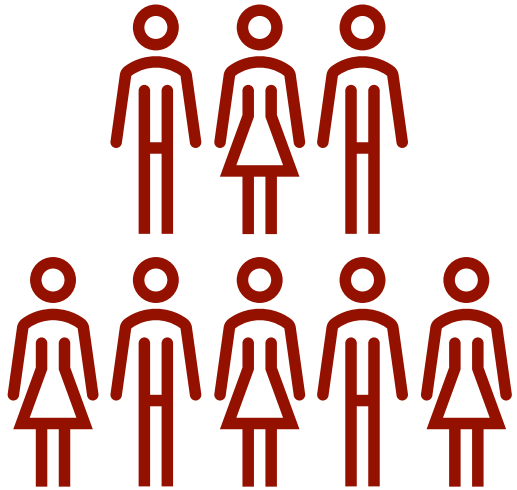
Migration studies

- Place of residence at 0-15 years determines lifelong risk of MS
  - Migration modifies risk only among those who migrate early, before adolescence.
    - Migration before the age of 15 →acquisition of the risk for the new place of residence
  - ?Environmental exposure/immune priming that occurs in childhood
    - ?Viral/microbial exposure, ?toxin, ?sunlight, ?UV radiation
    - Hygiene hypothesis – early childhood exposure to microbial organisms protects against allergic and autoimmune disorders

Alter M, et al. Neurology. 1978;28(11):1089-1093.
Stiemsma LT, et al. Immunotargets Ther. 2015 Jul 27;4:143-57.

Demographic distribution

- MS has been reported in most ethnic/racial groups
- Prevalence is highest in White individuals of northern European ancestry
- There is a growing incidence of MS in ethnic minority groups
  - Increasing rate of MS among African Americans (AAs) compared to whites
  - Minority populations in the US have a higher incidence of MS compared with their ancestral countries of origin.
  - Recent studies have shown highest incidence in AA women

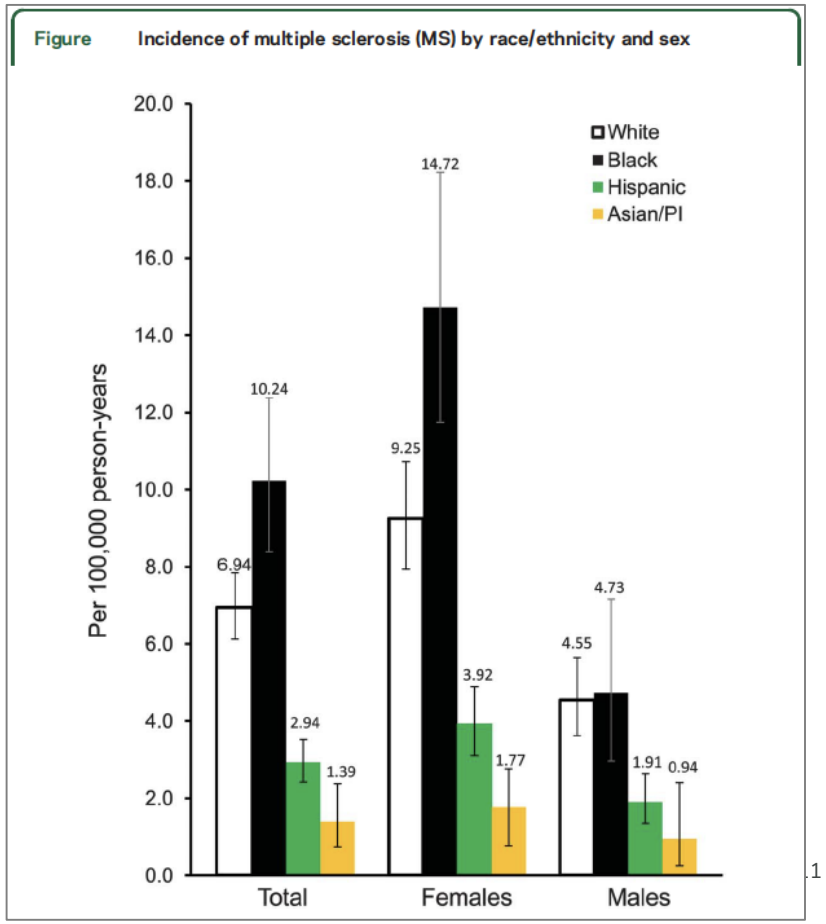


Demographic incidence of MS

Table 1
Incidence of multiple sclerosis in diverse minority populations

Incidence of MS	Cohort	Period	Whites	African American	Hispanic	Asian	Native American
Langer-Gould	Kaiser Permanente Southern California	2008–2010	6.9	10.2	2.9	1.4	n/a
Wallin	US military-Veteran population	1990–2007, 2000–2007 for Hispanics	9.3	12.1	8.2	3.3	3.1

Rivas-Rodríguez E. Neurol Clin. 2018 Feb;36(1):151-162

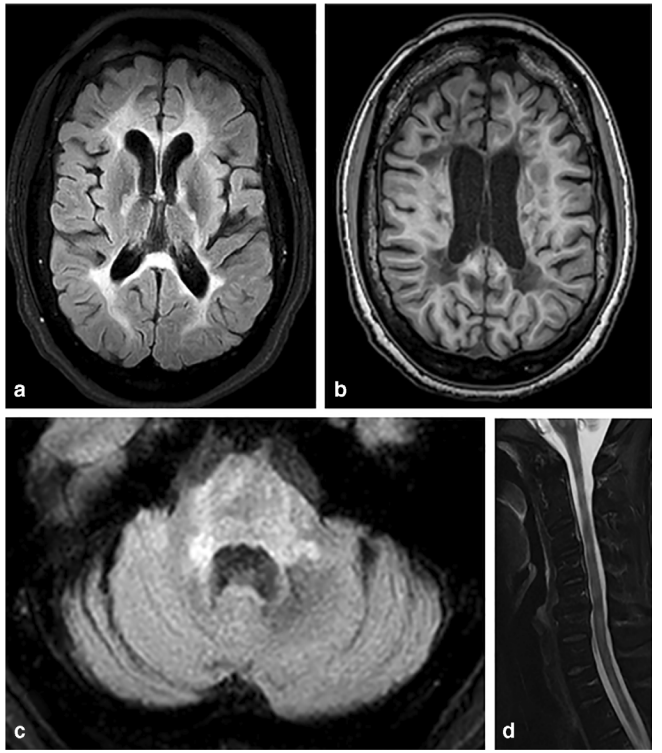


Langer-Gould A, et al. Neurology 2013;80(19):1734–9.

Racial minorities with MS have distinct disease characteristics

Compared to whites, racial minorities with MS have distinct disease characteristics

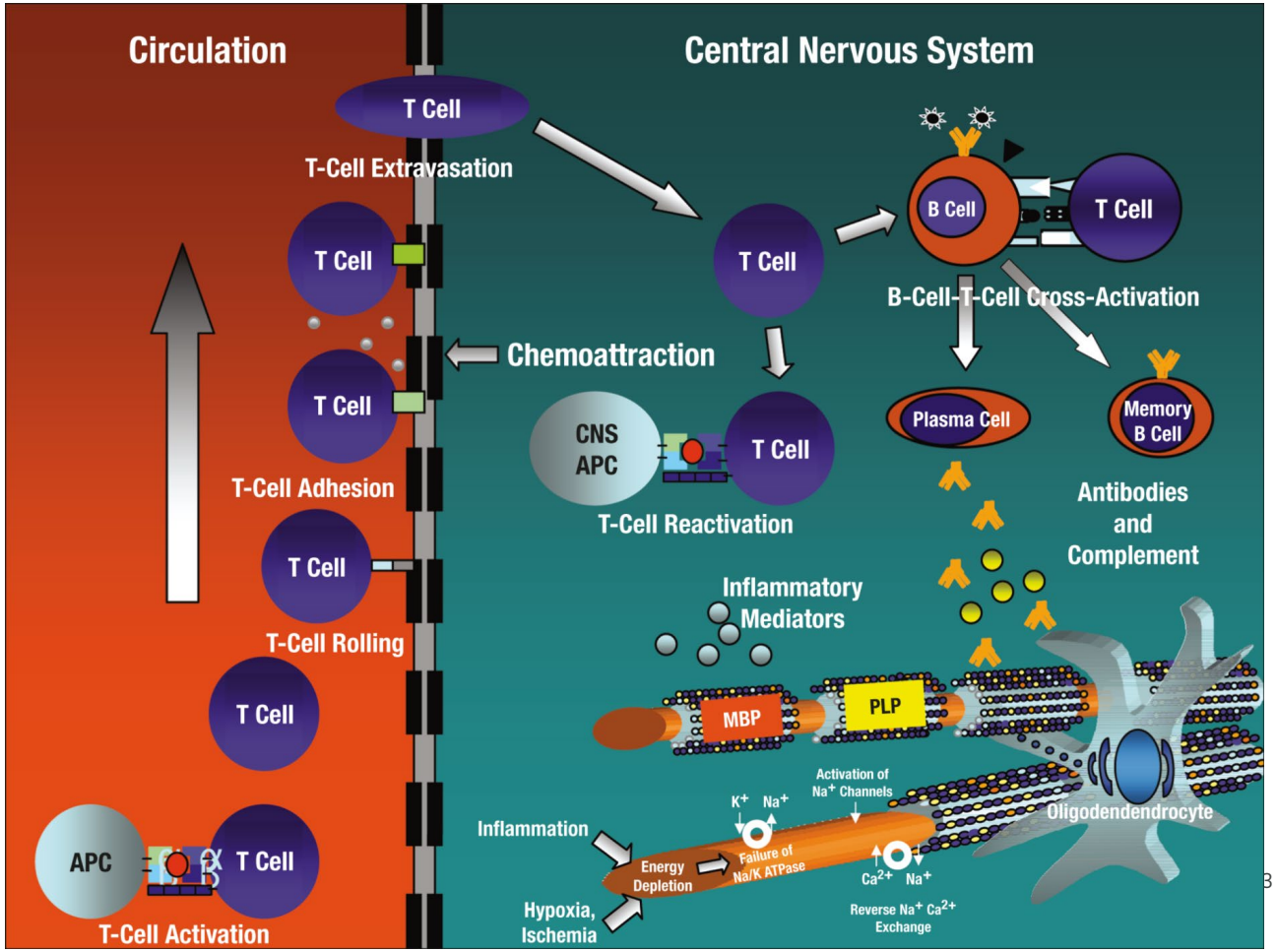
- Hispanics and African Americans (AAs) have been reported to develop MS at a younger age compared to whites
- Hispanic Americans have a high frequency of optic neuritis and transverse myelitis than White Americans
- AAs are more likely to have higher lesion volumes and more rapid brain and retinal tissue loss than whites
- AAs were more likely to exhibit rapid neurodegeneration as measured by the MRI and OCT compared to whites



Cipriani VP, Klein S. Curr Neurol Neurosci Rep. 2019 Nov 13;19(11):87

Pathogenesis of MS

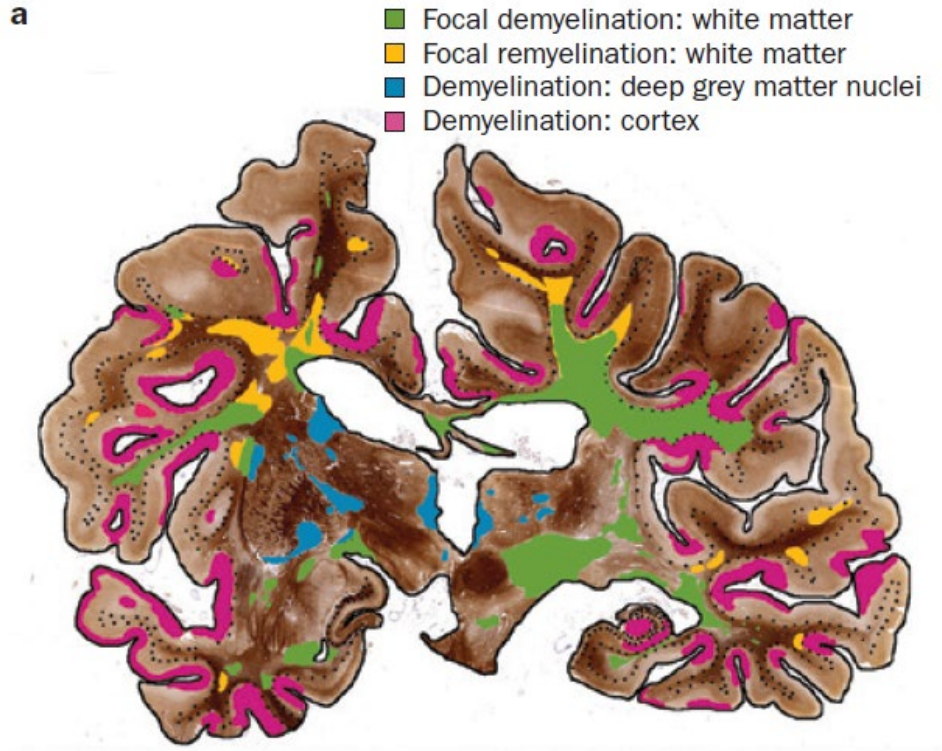
- Antigen presentation to CD4 T cell
  - By dendritic or B cells in lymph nodes
  - Antigen recognized as non-self by T cell
  - Antigen remains unknown – ?Viral
- Activation of T cells
  - Pro-inflammatory (T1, T17)
  - Clonal expansion
- CD4 released into peripheral circulation and migrates into CNS
- T cell "sees" antigen in CNS similar to antigen previously recognized
  - Re-activation of CD4 T cell (autoimmune T cell)
  - Recruits other immune cells
  - Secretion of inflammatory molecules



Frohman EM, et al. *Arch Neurol.* 2005;62(9):1345-1356

Hallmarks of MS pathology

1. Inflammation
   - Present at all stages of MS
   - There is a break in BBB
     - Perivascular and parenchymal infiltrates
     - Meningeal lymphatic follicles
2. Focal plaques of demyelination (and remyelination)
   - Present in gray and white matter at all stages of the disease
   - Remyelination – shadow plaques
3. Diffuse global tissue injury (neurodegeneration)
   - More pronounced in progressive MS
   - Normal appearing white and grey matter also shows widespread inflammation

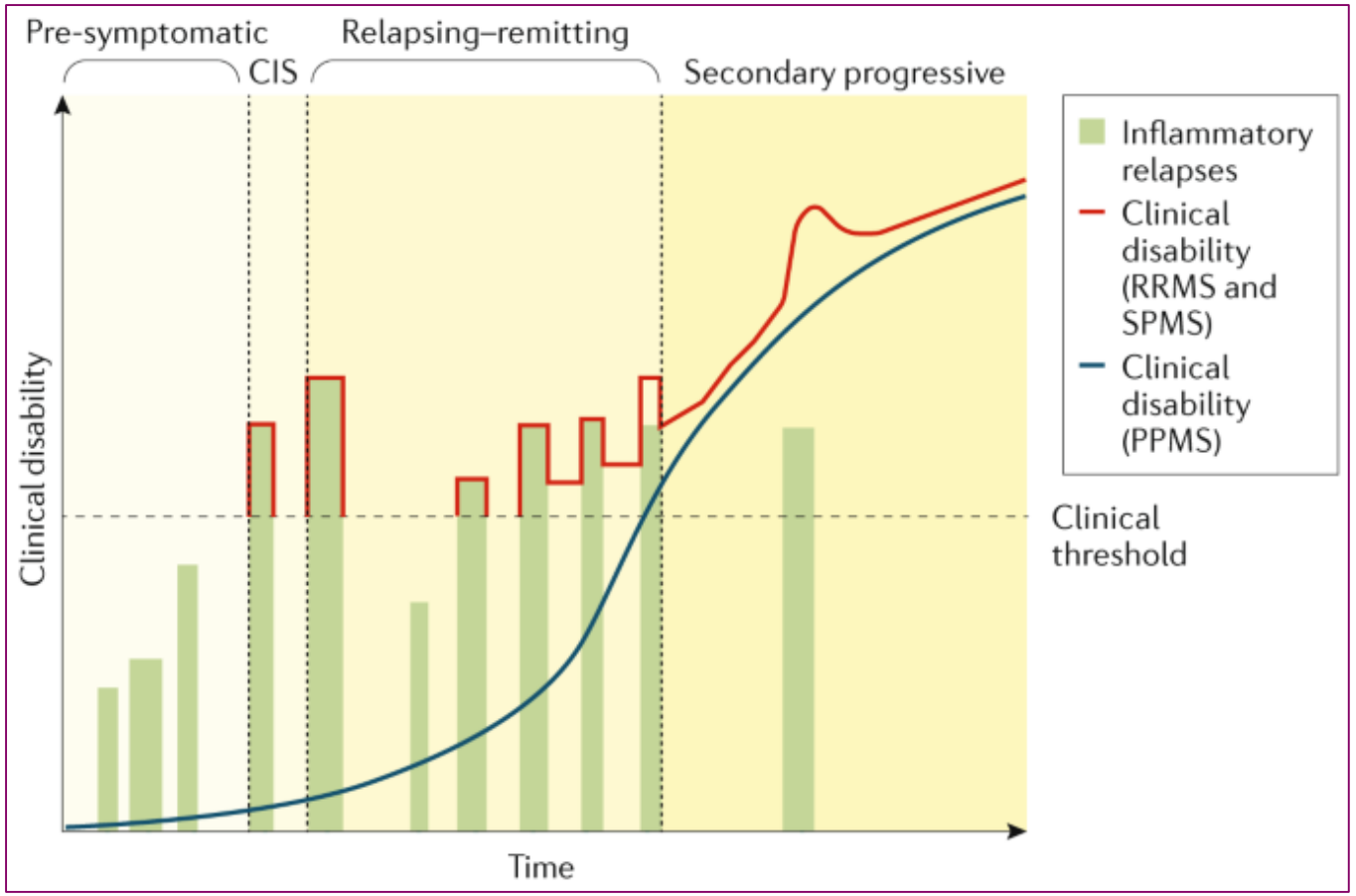


Lassmann, H. *et al. Nat. Rev. Neurol.* 8, 647–656 (2012)

MS Phenotypes

- **Clinically isolated syndrome (CIS)**
  - First clinical presentation
  - Not yet fulfilled criteria for DIT and/or DIS
- **Relapsing remitting MS**
- **Secondary progressive MS**
- **Primary progressive MS**

- **Radiologically isolated syndrome (RIS)**
  - Incidental imaging findings suggesting CNS inflammatory demyelination
  - Absence of clinical signs or symptoms
  - Could be pre-clinical MS or not MS
  - 34% will develop MS in 5 years



Filippi M, et al. *Nat Rev Dis Primers*. 2018;4(1):43.

Diagnosis of MS

- No single test or clinical feature is sufficient to establish an MS diagnosis
- Most criteria are based on clinical presentation plus paraclinical studies
- Criteria are designed to capture – CNS lesions with
  - Dissemination in time (DIT)
  - Dissemination in space (DIS)
  - Exclusion of alternative diagnoses
    - Concept of ‘no better explanation’

Evolution of diagnostic criteria

- 1868, Charcot's triad
  - Nystagmus, intention tremor, and scanning speech (dysarthria)
- 1906, Marburg criteria
  - Uhtoff's sign, absent abdominal reflexes and pyramidal tract signs
- 1965, Schumacher criteria (established for clinical trial enrollment)
  - ≥2 CNS lesions occurring in ≥2 episodes within >1 month
- 1983, Poser criteria
  - Included paraclinical studies to supplement clinical findings
    - CSF, evoked potential, urological studies, CT and later MRI

Gafson A, et al. Mult Scler Rel Disord 2012;1:9–14.

McDonald's criteria 2001, revised 2005, 2010, 2017

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

Thompson AJ, Banwell BL, Barkhof F, et al. Lancet Neurol. 2018

2017 revision
- Inclusion of cortical lesions
- Symptomatic lesion can count for DIS
- + CSF can count for DIT in CIS

McDonald's criteria 2001, revised 2005, 2010, 2017

Panel 6: 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with a disease course characterised by progression from onset (primary progressive multiple sclerosis)

Primary progressive multiple sclerosis can be diagnosed in patients with:

- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus two of the following criteria:

- One or more T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions* in the spinal cord
- Presence of CSF-specific oligoclonal bands

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

Thompson AJ, Banwell BL, Barkhof F, et al. Lancet Neurol. 2018

MRI in MS

Novel MRI techniques
- **Central Vein Sign (CVS)**
- **Paramagnetic Rim Lesion (PRL)**

- MRI criteria are based on the presence of focal CNS white matter lesions with typical MS morphology
  - Dissemination in time and space (DIS and DIT)
  - Protocol – CMSC MRI protocol for MS diagnosis and follow up – ideally 3T

- MRI findings
  - T2/FLAIR or STIR (spine): focal hyperintense lesions – demyelination
  - T1: hypointense lesions (T1 black holes) – axonal degeneration
  - Volume loss

  Active lesions
  - Gadolinium uptake on T1 sequence
  - T2/FLAIR- acute lesions often have surrounding edema
  - May demonstrate DWI/ADC signal change

Filippi M, Lancet Neurol. 2016 Mar;15(3):292-303.

MRI criteria

Distribution

2 of 4 required for DIS

1. Periventricular
2. Juxtacortical/cortical
3. Infratentorial
4. Spinal cord

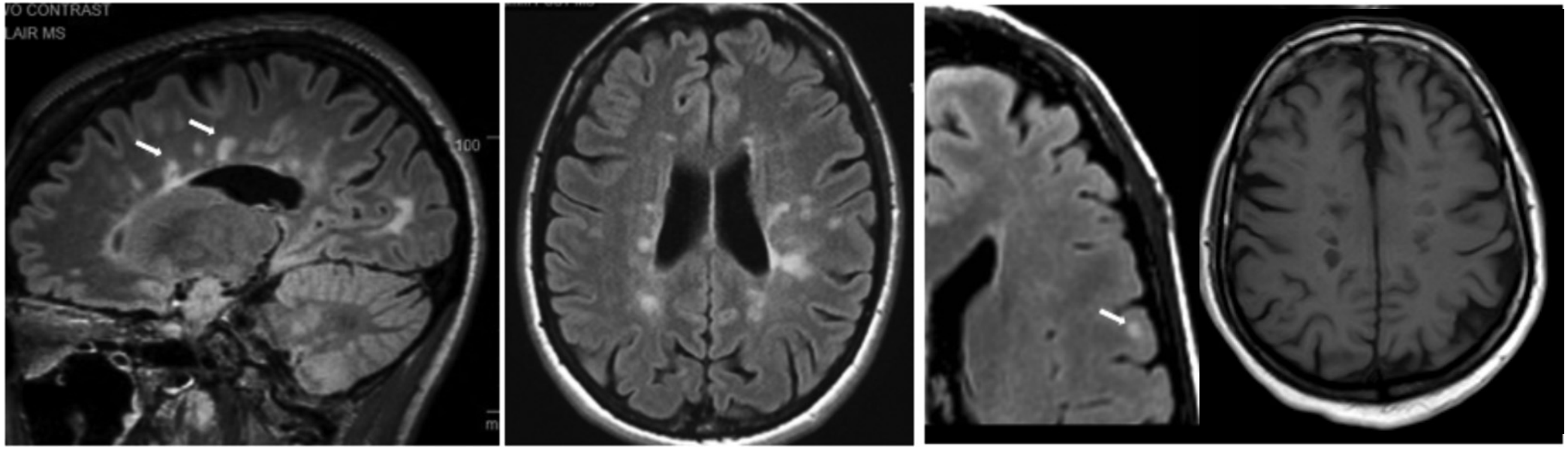
Morphology

- Ovoid/oval
- Dawson fingers
- Perivenular
- Open ring enhancement
- Homogenous enhancement

Evolution in time

- New or enlarging T2/FLAIR lesions
- New T1 Gadolinium enhancing lesions
- Brain volume loss
- Spine volume loss

Brain MRI

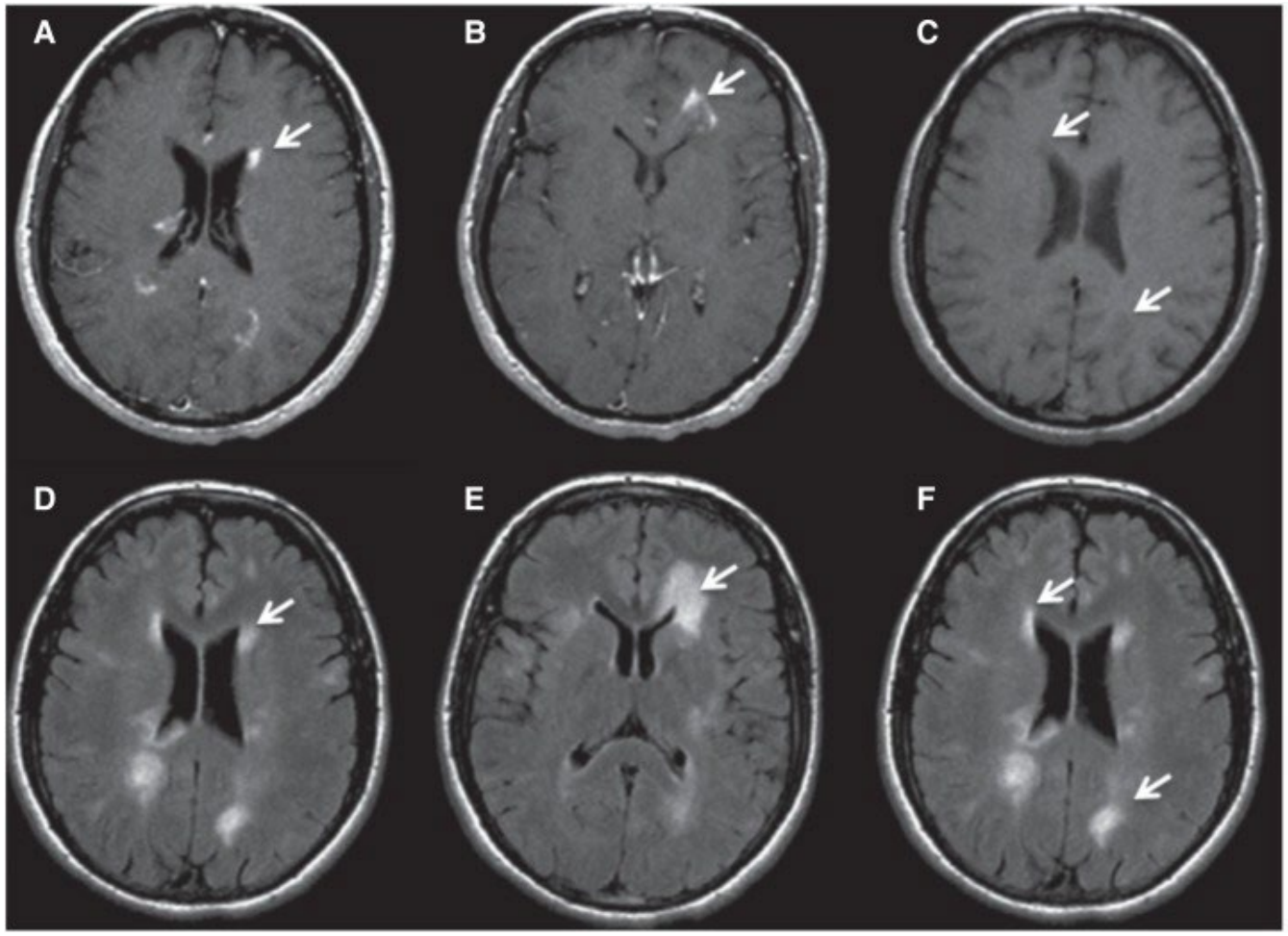


- Periventricular, Dawson fingers
- Ovoid/oval, perpendicular to ventricles
- Juxtacortical/cortical
- T1 black holes

Hemond CC. *Cold Spring Harb Perspect Med.* 2018;8(5):a028969
Radiopedia.com

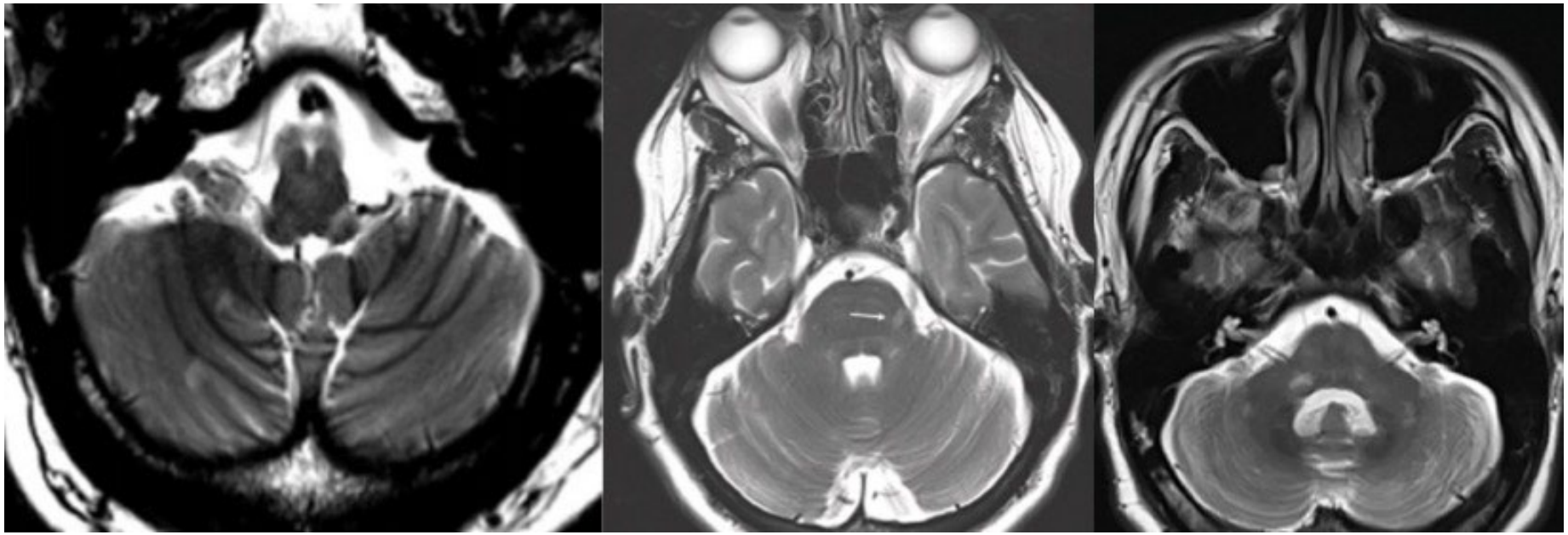
Brain MRI

- T1- post contrast imaging
  - Homogeneous enhancement
  - Open-ring enhancement
- T1 sequence
  - T1 black holes



Hemond CC. *Cold Spring Harb Perspect Med.* 2018;8(5):a028969

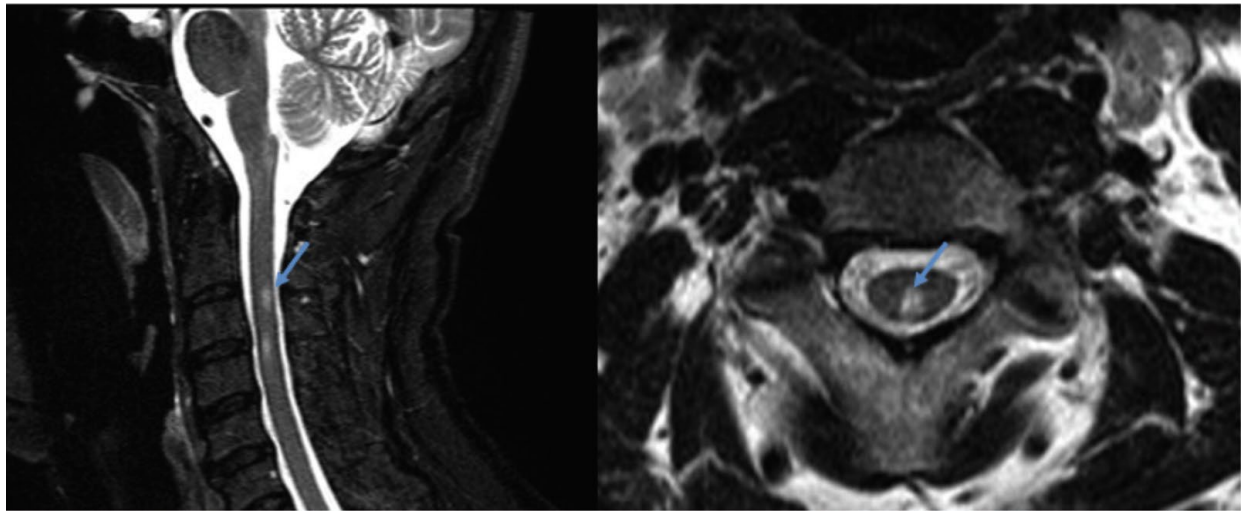
Infratentorial lesions



- Cerebellar hemispheres
- Brainstem
- Cerebellar peduncles

Spinal cord MRI

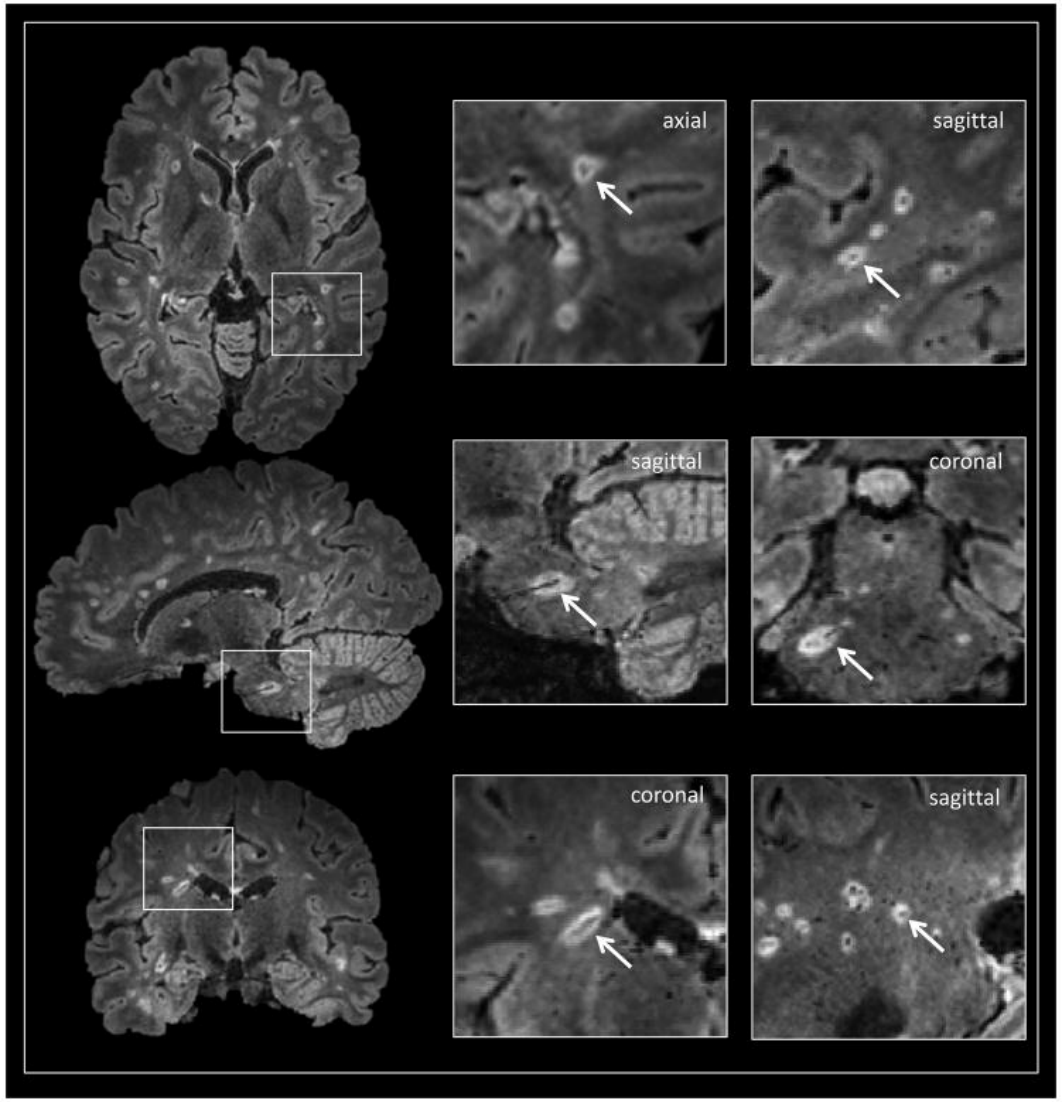
- Fast spin-echo T2-weighted and STIR, post gad-T1
- T2 lesions are more common in the c-spine than T-spine
- Short segment (1-2), posterior and lateral areas of the cord
- Acute gadolinium-positive lesions tend to be more-likely symptomatic compared to brain



Hemond CC. *Cold Spring Harb Perspect Med.* 2018;8(5):a028969

Central Vein Sign (CVS

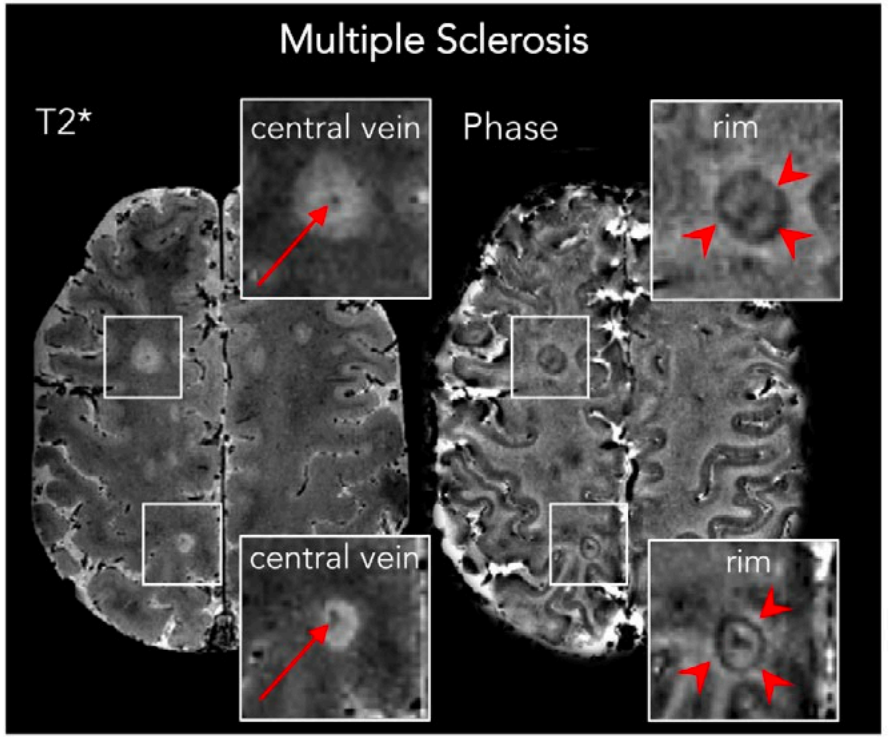
- Central Vein sign on T2, SWI
  - Proposed to have high specificity for MS lesions compared with other diagnostic considerations, including small vessel disease, migraine or other inflammatory condition
  - Arise due to tissue remodeling after disruption of the blood–brain barrier in postcapillary venules at the time of lesion onset



Hemond CC. *Cold Spring Harb Perspect Med.* 2018;8(5):a028969

Paramagnetic Rim Lesions (PRLs)

- PRLs – usually demonstrated on 7T and 3T, SWI MRI sequences
  - Perilesional chronic inflammation and iron accumulation in microglia
  - A marker of **compartmentalized smoldering disease**
  - Residual and detrimental iron-laden microglia/macrophage accumulation at the lesion edge after acute inflammation subsides
  - High prevalence in MS with high specificity



Maggi P, et al. *Ann Neurol*. 2020;88(5):1034-1042.

MS – Differential diagnosis

Inflammatory	Infectious	Metabolic	Vascular
SLE	Lyme disease	Vitamin B12 deficiency	Migraine variants
Sjogren syndrome	Neurosyphilis	Adrenoleukodystrophy	CADASIL
Behcet disease	PML	Adrenomyeloneuropathy	Moyamoya
Neurosarcoidosis	HIV	Mitochondrial disease	Binswanger's disease
ADEM	HTLV-1 myelopathy	Fabry disease	Small vessel disease
NMO	Toxoplasmosis	Krabbe disease	Cerebroretinal vasculopathy
APLS		Leukoencephalopathy with neuroaxonal spheroids	Degos disease
CNS vasculitis	**Neoplastic**		
Other vasculitides	CNS lymphoma	Adult polyglucosan body disorder	
Paraneoplastic disease	Glioma		

Ratchford J. *Neurology* 2008;70:1071–1072
Singhal D, Berger J. Future Neurology. Vol. 7, No. 5,

MS Diagnostic challenges

- Many other disorders can exhibit DIT and DIS
- Non-specific white-matter abnormalities on MRI can be seen in a variety of disorders
- Importance of identifying clinical and radiological red flags or atypical features
- Applying the concept of ‘no better explanation’

Red flags

Clinical red flags

- Onset after age 50 or prior to adolescence
- Family history of a similar disease
- Presence of gray matter features
  - Seizures, aphasia, dementia
- PNS or multi-systemic involvement
  - Multiple neuropathies, cardiac or pulmonary symptoms, bone lesions
- Systemic features that are unexplained by MS
  - Fever/ night sweats, weight loss, arthropathy, rash, ulcers, dry mouth and eyes, ocular disease
- Continually progressive course

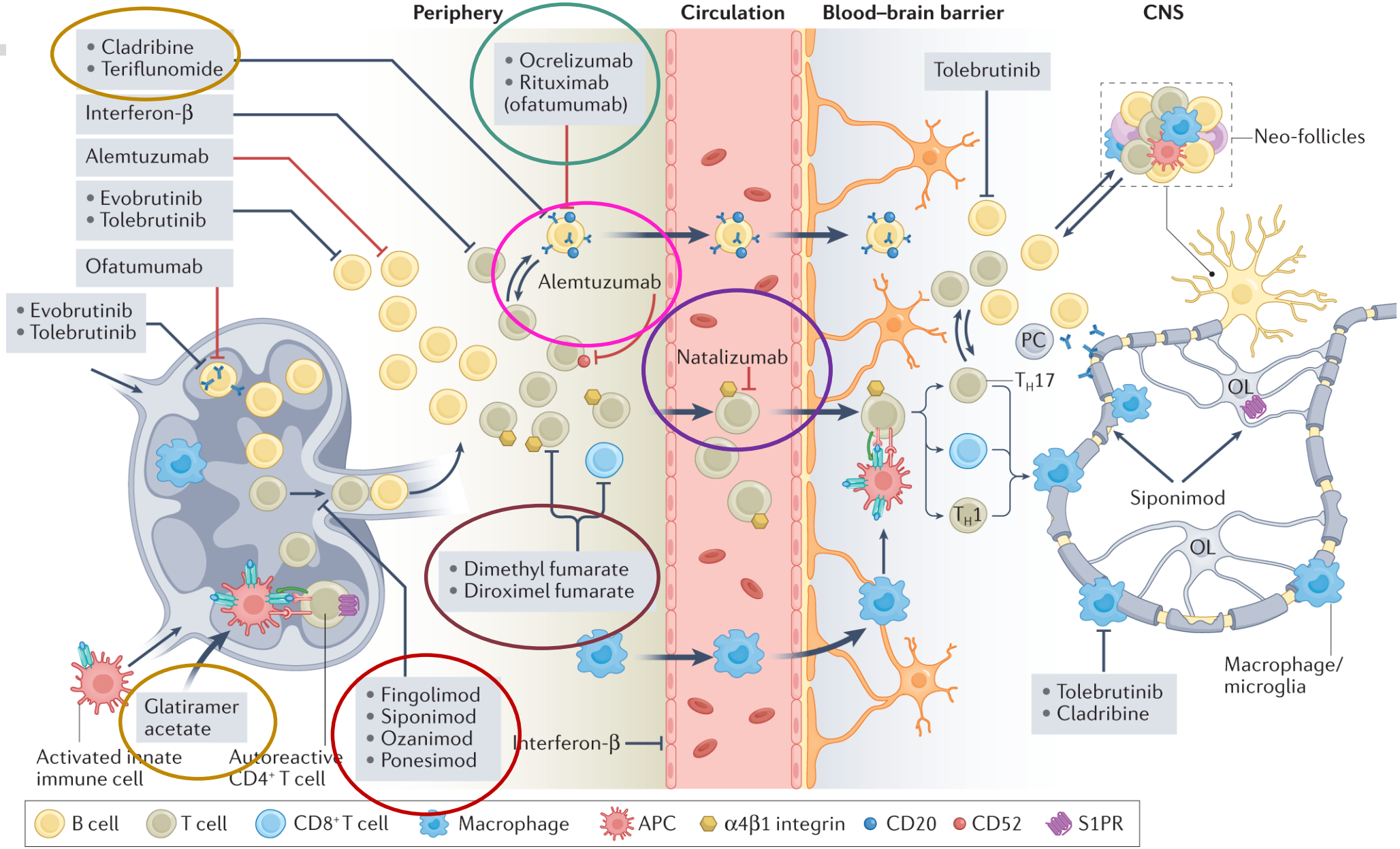
Radiological (MRI) red flags

- Symmetric lesions
- Peripheral white matter lesions (as opposed to periventricular)
- Lack of ovoid lesions, T1 “black holes” or corpus callosum involvement
- Gray matter involvement
- Longitudinally extensive cord lesions
- Persistently enhancing lesions
- Simultaneous enhancement of all lesions
- Microhemorrhagic foci
- Mass effect with vasogenic edema
- Normal MRI brain and spine

Disease modifying therapies (DMTs)

Interferon Beta	Glatiramer Acetate	Teriflunomide	Fumarates
• Rebif • Betaseron • Avonex • Plegridy	• Copaxone • Glatopa	• Aubagio	• Tecfidera (DMF) • Vumerity • Bafietram

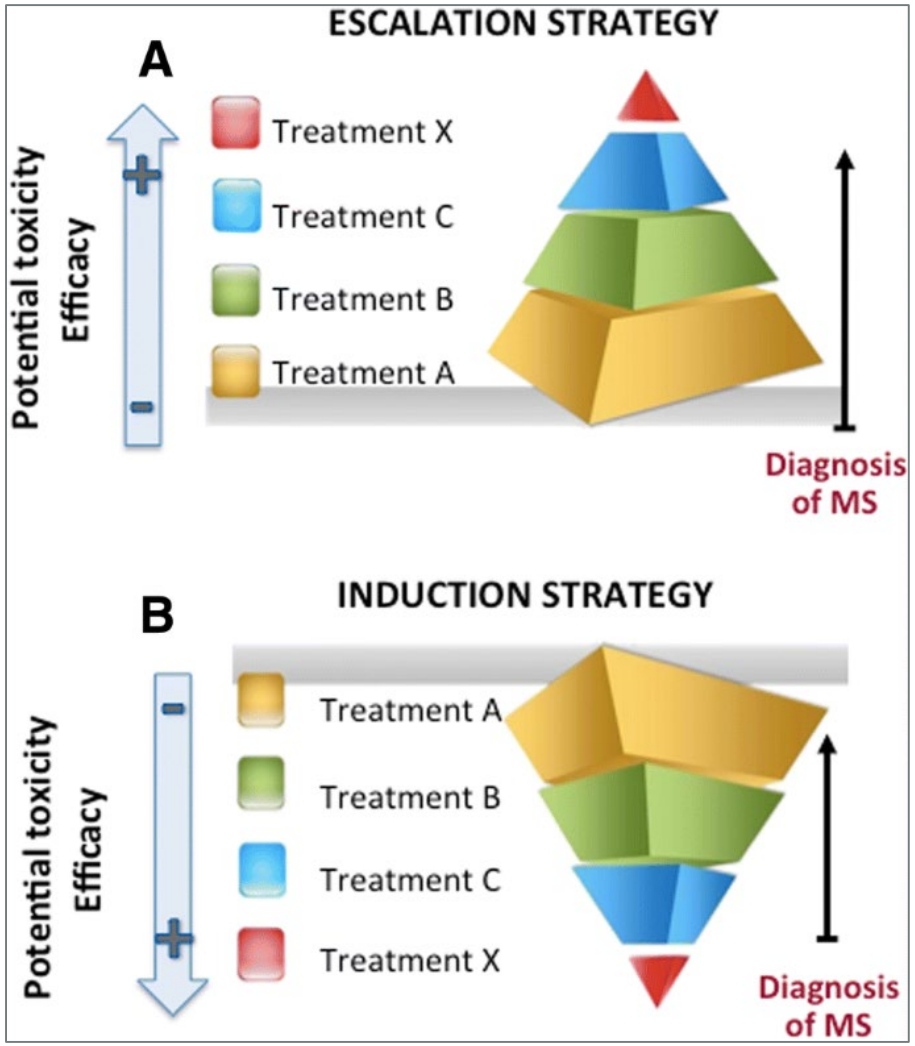
S1P1 modulators	B cell depleting therapies	Natalizumab	Others
• Fingolimod • Siponimod • Ozanimod • Ponesimod	• Ocrelizumab • Rituximab • Ofatumumab	• Tysabri	• Alemtuzumab • Cladribine



Bierhansl, L. *Nat Rev Drug Discov* **21**, 578–600 (2022)

Treatment paradigms

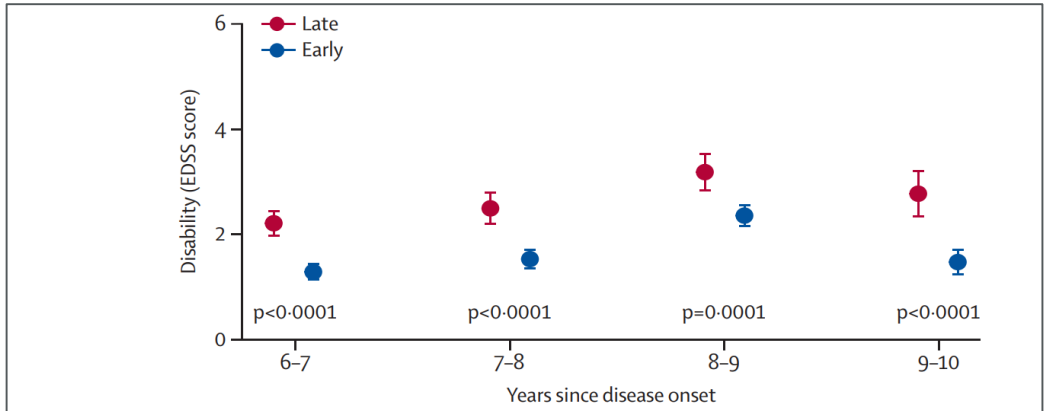
- Escalation vs. Induction (early aggressive therapy)
- Maintenance vs. reconstitution
  - Reconstitution therapies – alemtuzumab and cladribine
- Autologous Hematopoietic Stem Cell Transplant
  - In studies demonstrated high efficacy and a durable outcome in active relapsing MS



Ruggieri et al. Multiple Sclerosis and Demyelinating Disorders (2018) 3:5

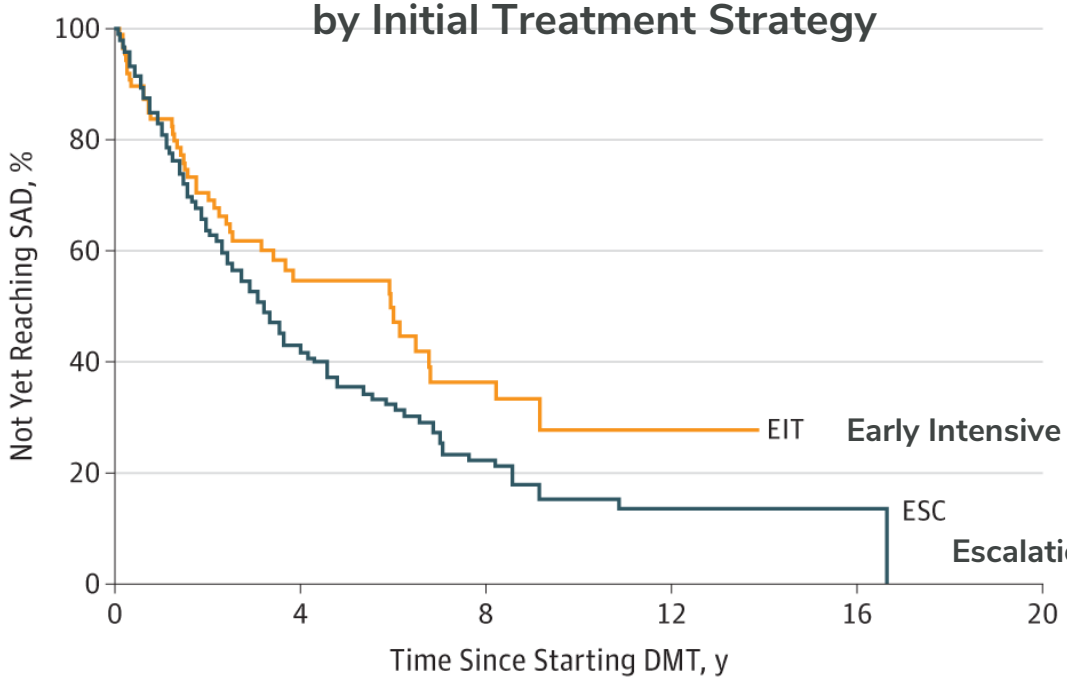
Escalation vs. induction – which is better?

Disability Trajectory 6–10 Years After Disease Onset: Early vs Late Treatment with High-Efficacy DMT



Number of patients				
Late	233	192	168	135
Early	189	140	126	89
Proportion of patients above EDSS 6 score				
Late	14 (6·0%)	16 (8·2%)	17 (9·9%)	15 (11·0%)
Early	5 (2·6%)	3 (2·1%)	4 (3·2%)	3 (3·4%)

Time to Sustained Accumulation of Disability by Initial Treatment Strategy



No. at risk					
ESC	316	75	21	6	1
EIT	89	29	12	1	0

Harding K, et al. *JAMA Neurol*. 2019:76(5):536-541;
He A, et al. *Lancet Neurol*. 2020;19(4):307-316.

Notable clinical trials – BTK inhibitors

- Bruton's tyrosine kinase (BTK) inhibitors
  - BTK – an enzyme found in B cells, myeloid cells and CNS microglial cells
  - Promising phase II studies in RRMS
  - Multiple phase III trials in both relapsing and progressive MS phenotypes

BTK-inhibitors
- Tolebrutinib
- Evobrutinib
- Fenebrutinib

- Potential advantages of BTK-i in MS
  - Effects on both adaptive and innate immune cells
  - Ability to penetrate the blood brain barrier
  - Direct effect on microglia cells in the CNS
  - May have neuroprotective effects
  - Potential benefit in both relapsing and progressive MS

Notable clinical trials - aHSCT

Autologous hematopoietic stem cell transplant (aHSCT)

- BEAT-MS clinical trial
  - Multi-center, randomized, blinded and controlled study
  - High dose immunosuppression followed by aHSCT vs. best available therapy (BAT) for MS
  - Individuals with relapsing forms of MS who demonstrate substantial breakthrough disease activity
  - Sponsor – National Institute of Allergy and Infectious Diseases (NIAID)

Areas of need/research

- Progressive MS therapies
- Remyelinating therapies
- Neuroprotective therapies
- Neuro-restorative therapies

OSU MS Center

- Team
  - Six fellowship-trained MS specialists
  - One advance practice provider
  - MS nurse, clinical pharmacists, psychologists, social worker, rehab- PT, OT, speech
  - Collaborators – urology, psychiatry, ophthalmology
- Basic and translation science research
- Clinical research and clinical trials

Exceptional clinical care

- Quality of life (QOL) clinic
- MS fatigue/sleep clinic
- MS psychotherapy clinic
- Unique multidisciplinary clinics
  - MS symptom management multidisciplinary clinic
  - Aging in MS multidisciplinary clinic
  - Neurosarcoidosis multidisciplinary clinic
  - Neuro-rheuamatology multidisciplinary clinic

Thank you

- Questions