THE 12TH ANNUAL LINDA MORGANTE

Multiple Sclerosis Nurse Leadership Program

2021

# MULTIPLE SCLEROSIS OVERVIEW AND DIAGNOSIS

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ACHL ACADEMY for CONTINUED HEALTHCARE LEARNING

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER

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# MS Overview and Diagnosis

THE 12TH ANNUAL LINDA MORGANTE MS Nurse Leadership Program

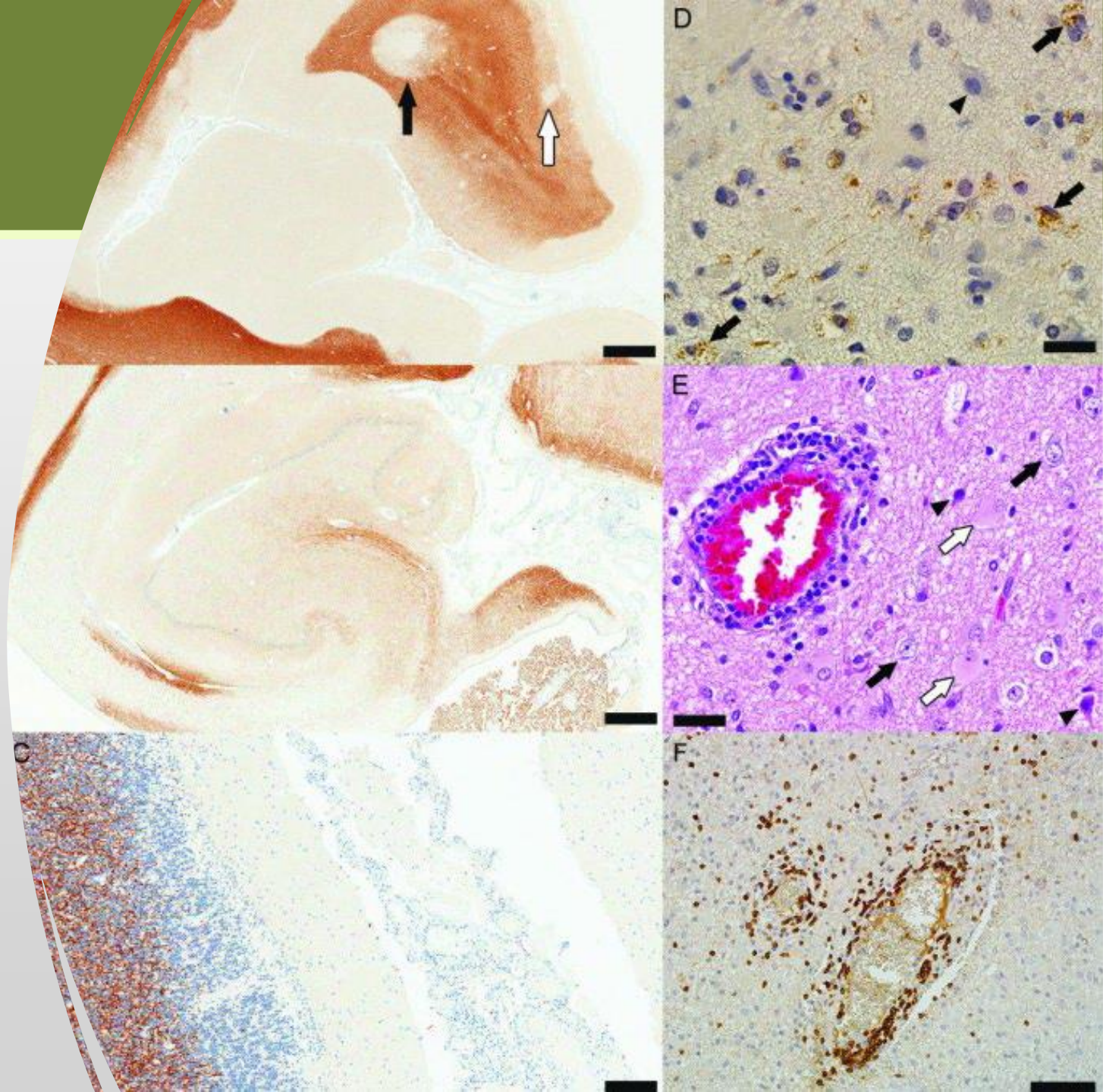
# Multiple Sclerosis

- Immune mediated disease of the CNS
- Affects an estimated 900,000 people in the US
- Leading cause of nontraumatic neurological disability in young adult
- Mean age of onset 20-30 years
- Female : Male ratio 3:1
- Can lead to physical disability, cognitive impairment, and decreased quality of life
- Reduces life expectancy by 7 to 14 years

Magyari M, et al. *Curr Opin Neurol*. 2019;32(3):320-326.; Vaughn CB, et al. *Nat Rev Neurol*. 2019;15(6):329-342.

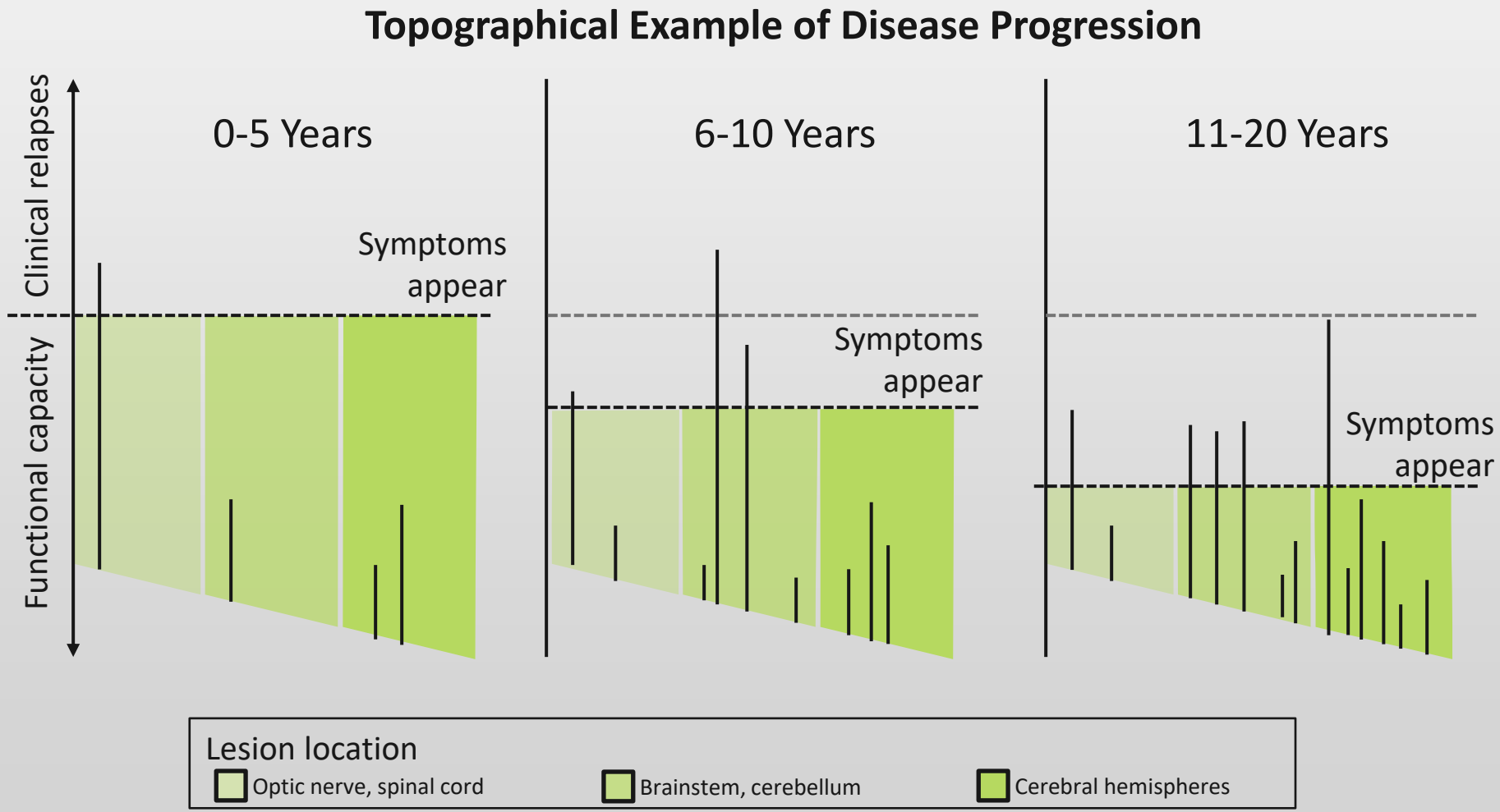
# Multiple Sclerosis

- Inflammation with demyelination
- Astroglial proliferation (gliosis) and neurodegeneration
- Meningeal and cortical grey matter pathology in multiple sclerosis



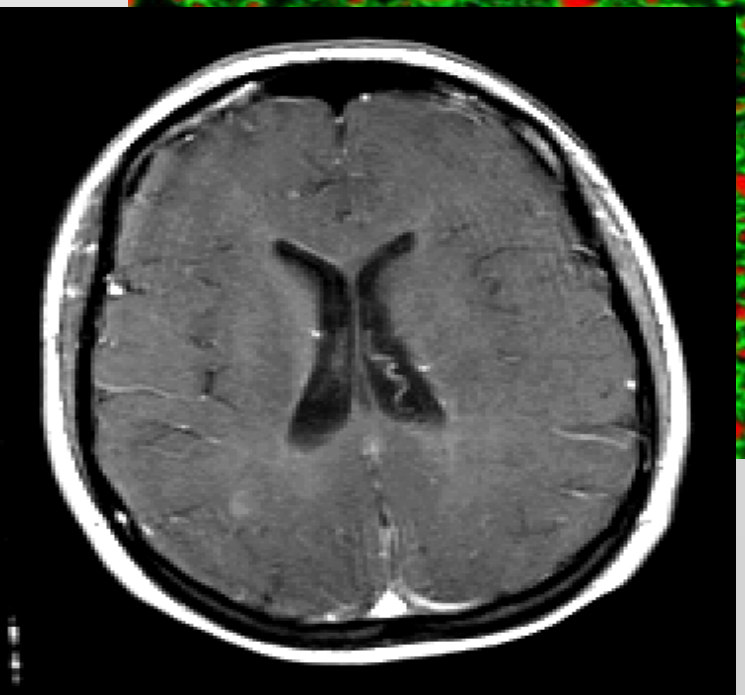

Popescu BFG et al. *BMC Neurology*. 2012;12:11.

# MS as a Silent Disease: Topographical Model



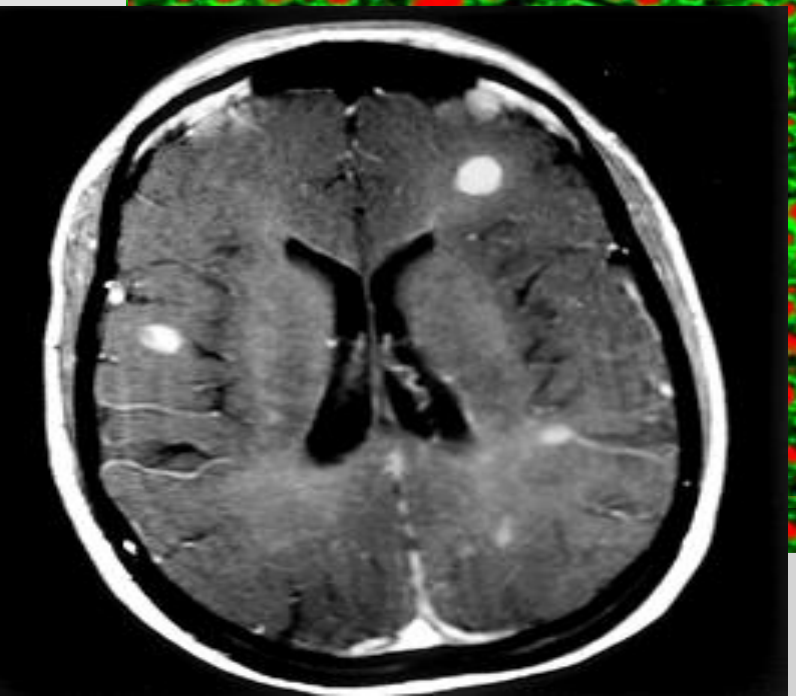

Krieger SC. Poster presented at: 2015 Meeting of the CMSC; May 29, 2015; Indianapolis, IN. Poster DX47.

# Normal White Matter



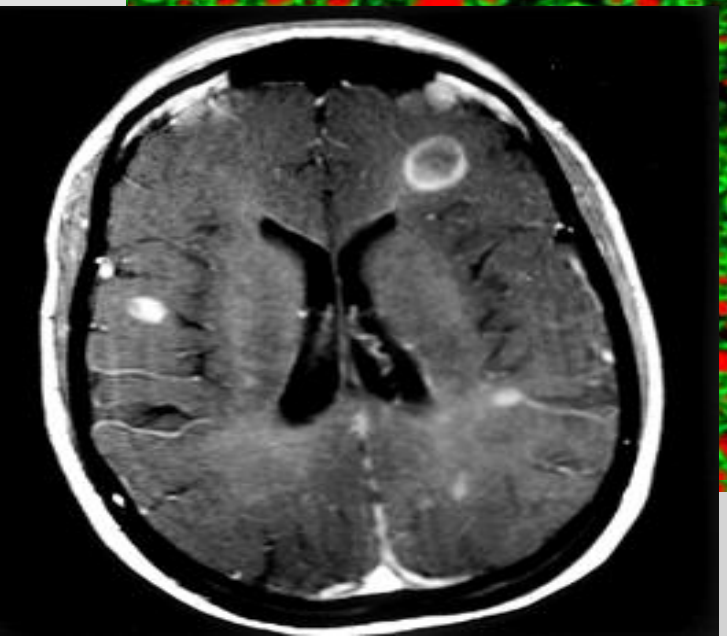
Images courtesy of Bruce D. Trapp.

# Active Lesion



Images courtesy of Bruce D. Trapp.

# Chronic Active Lesion



Images courtesy of Bruce D. Trapp.

# Chronic Inactive Lesion

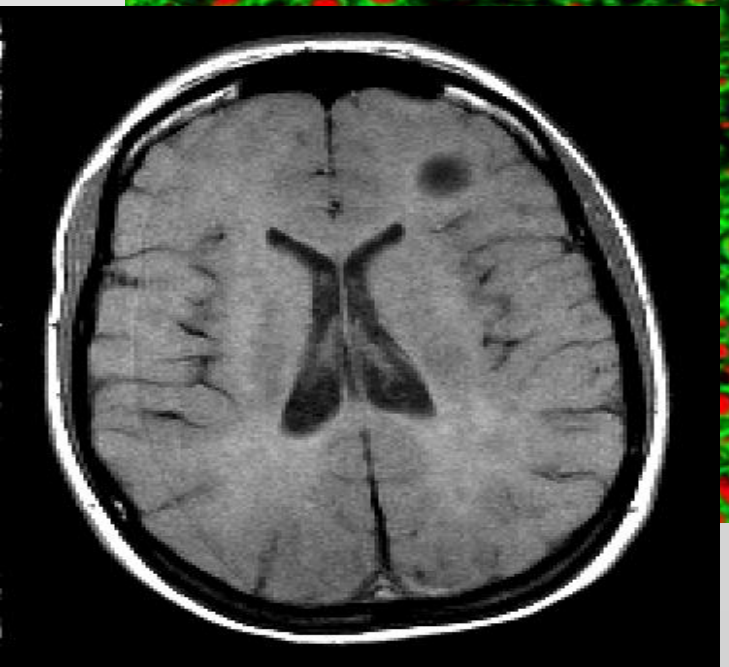
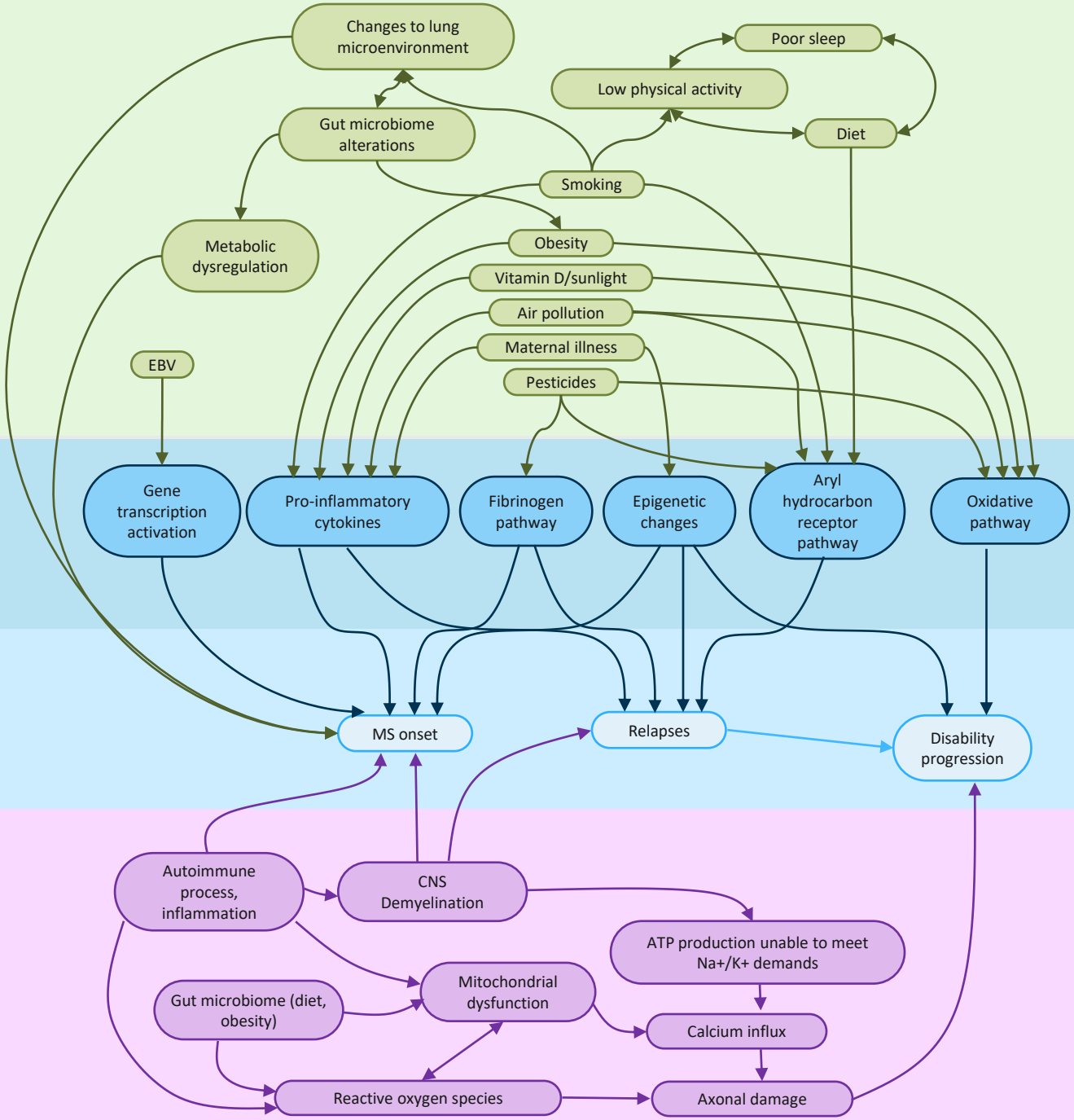


Image courtesy of Bruce D. Trapp.

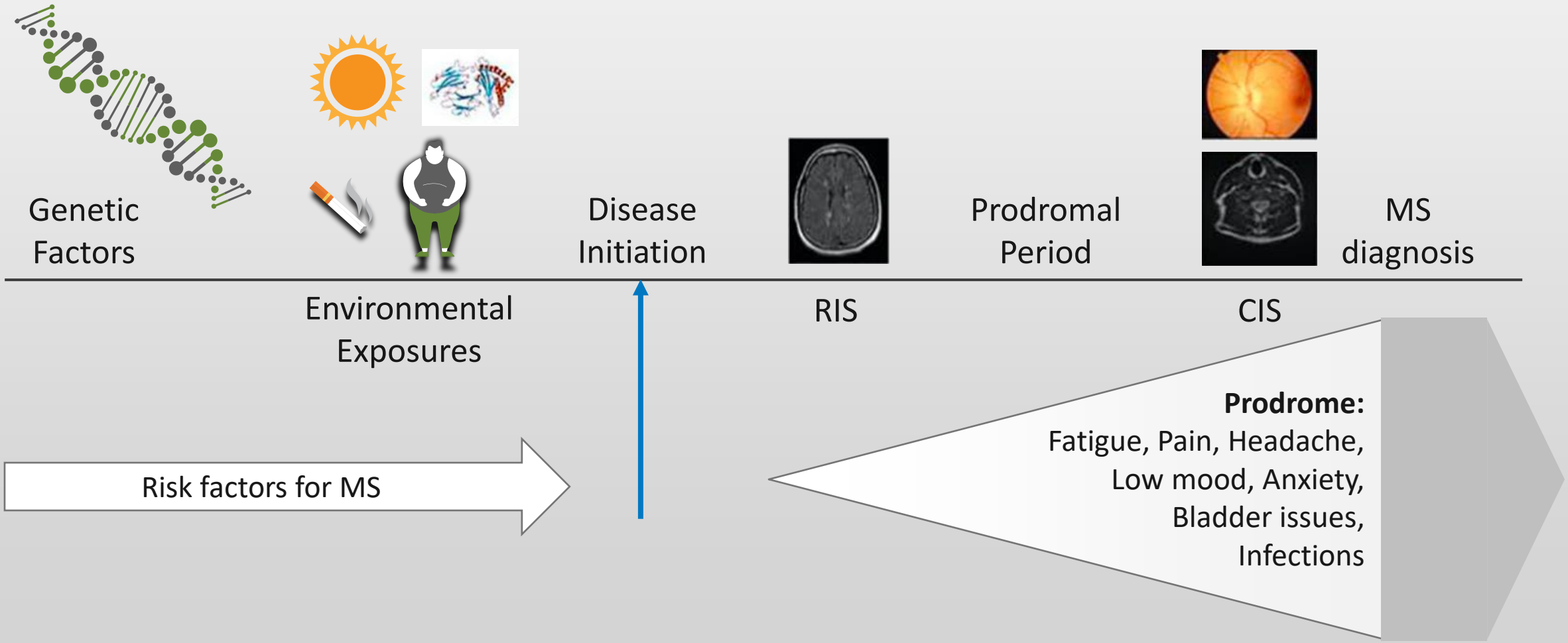
# Environmental and Genetic Factors

- Around 20% of the heritability risk is attributable to common genetic variants
  - HLA DRB15:01 haplotype (odds ratio (OR) of ~3)
- Smoking
- Obesity
- Low sun exposure
  - Vitamin D deficiency




Waubant E et al. *Ann Clin Transl Neurol*. 2019;6(9):1905-1922.

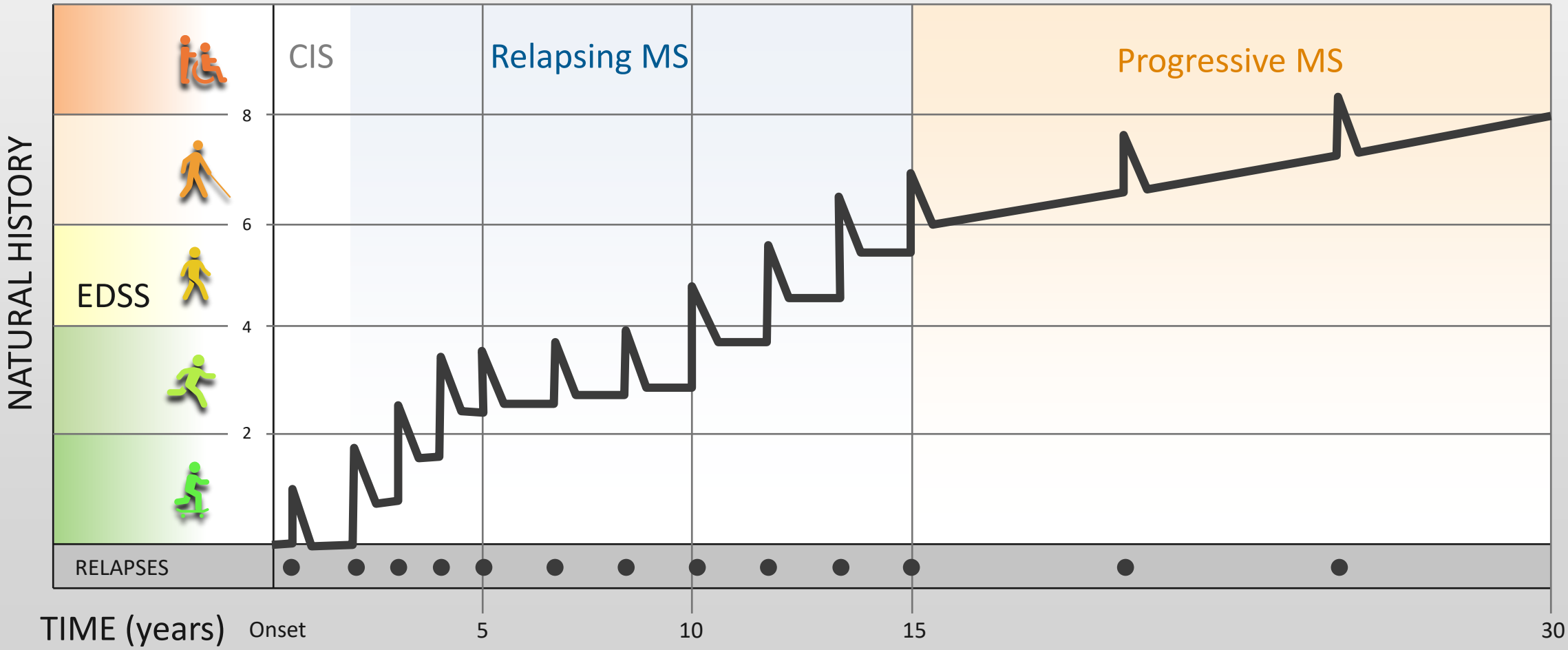
# Prodromal MS




Adapted from: Tremlett H et al. *Mult Scler*. 2021;27(1):6-12.

# Natural History of MS Pre-treatment Era

Hauser and Cree American Journal of Medicine 2020




CIS – Clinically Isolated Syndrome; EDSS - Expanded Disability Status Scale

Hauser SL et al. *Am J Med*. 2020;133(12):1380-1390.

# MS Diagnosis

- MS is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests
- Magnetic resonance imaging: The imaging procedure of choice for confirming MS and monitoring disease progression in the CNS
- Evoked potentials: Used to identify subclinical lesions; results are not specific for MS
- Lumbar puncture: May be useful to support DIT; CSF is evaluated for oligoclonal bands and intrathecal immunoglobulin G (IgG) production

DIT – dissemination in time

https://cdn.ymaws.com/mscare.site-ym.com/resource/collection/9C5F19B9-3489-48B0-A54B-623A1ECEE07B/2018MRIGuidelines_booklet_with_final_changes_0522.pdf. Accessed May 14, 2021.

# Difficulty in Diagnosing MS

- There is no single pathognomonic clinical feature or diagnostic test for MS
- Other conditions can mimic MS in:
  - MRI appearance
  - Clinical presentation
  - Clinical course
  - CSF findings
- Increased risk for more than 1 autoimmune condition
- Great variability in MS
  - Age of onset
  - Clinical course
  - Symptoms and signs
  - Paraclinical evidence
- Misdiagnosis of MS remains a problem in clinical practice

Gaitán MI et al. *Front Neurol*. 2019;10:466.

# Typical Presenting Syndromes of MS

- Optic Neuritis
  - Unilateral
  - Retrobulbar pain &/or with movement
  - Recovery expected
  - No retinal exudates or disc hemorrhages
- Myelitis
  - Partial sensory or motor
  - Bowel and bladder dysfunction
  - Thoracic band-like sensation
  - L'hermitte's sign
- Brainstem/Cerebrum
  - Ocular motor syndromes
  - Hemisensory, crossed sensory
  - Hemiparesis
  - Trigeminal neuralgia
  - Hemifacial spasms
- Cerebellum
  - Cerebellar tremor
  - Acute ataxia

Frohman EM et al. *Neurology*. 2003;61:602-611.; Solomon AJ et al. *Neurology*. 2019;92(1):26-33.; Brownlee WJ, et al. *Mult Scler*. 2021;27(6):805-806.

# Atypical Presenting Syndromes of MS

- Isolated 4th CN palsy
- Complete 3rd CN palsy
- Hearing loss
- Homonymous hemianopsia
- Aphasia
- Seizures
- Depressed LOC
- Progressive motor deficit
- Extrapyramidal features
- Loss of reflexes

CN – cranial nerve; LOC – locus of control

Solomon AJ et al. *Neurology*. 2019;92(1):26-33.; Brownlee WJ, et al. *Mult Scler*. 2021;27(6):805-806.

# Disorders That Can Mimic MS

- Vascular
  - Migraine; CNS vasculitis; antiphospholipid syndrome; CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
- Inflammatory autoimmune diseases
  - Systemic lupus erythematosus (SLE); neuro-Behçet disease; Sjögren syndrome; sarcoidosis; Susac's syndrome
- Inflammatory demyelinating disorders
  - Neuromyelitis Optica Spectrum Disorders (NMOSD's); Anti-MOG; acute disseminated encephalomyelitis (ADEM); tumefactive MS
- Infectious disorders
  - Neuroborreliosis (Lyme disease); syphilis; West Nile virus; progressive multifocal leukoencephalopathy (PML); cysticercosis; HTLVI/II; HIV or herpes encephalitis

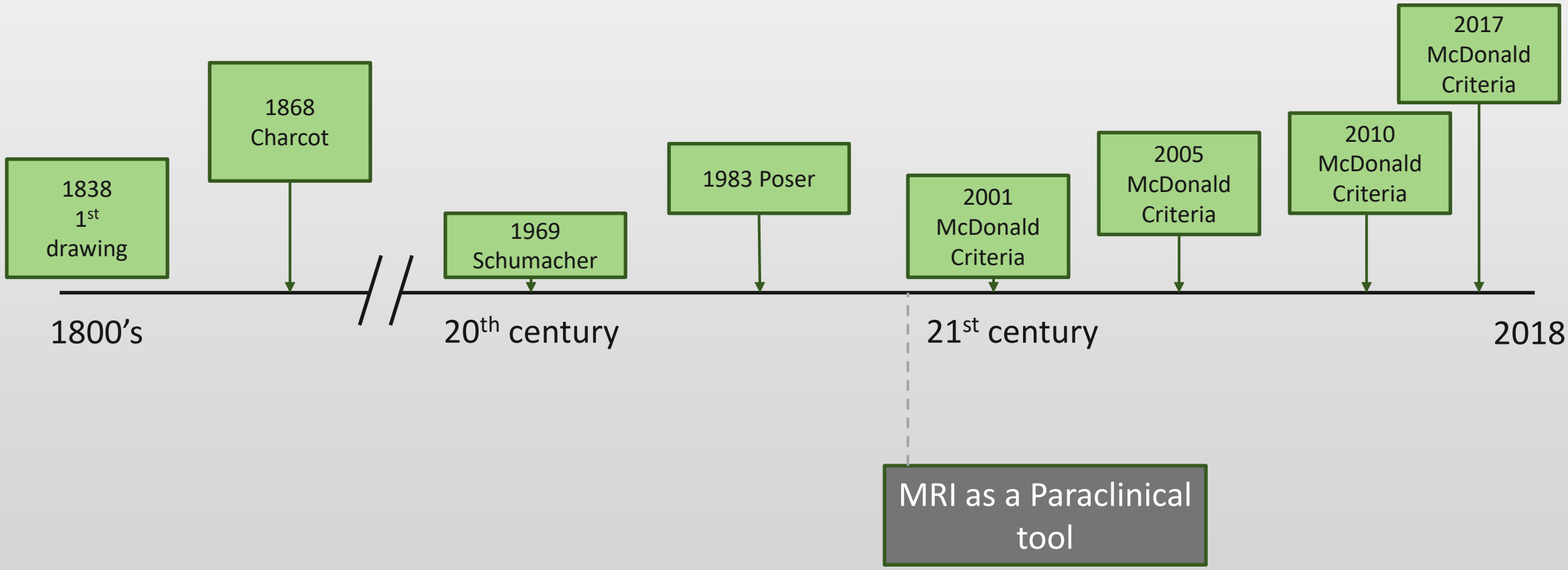
https://www.nationalmssociety.org/Symptoms-Diagnosis/Other-Conditions-to-Rule-Out. Accessed May 14, 2021.

# Disorders That Can Mimic MS (cont.)

- Metabolic disorders
  - Mitochondrial disorders (MELAS, MERRF, LHON); B12 deficiency; Wilson's disease
- Leukodystrophies
  - Adrenoleukodystrophy
  - Metachromatic leukodystrophy
- Multifocal CNS neoplasms
  - Lymphoma; gliomastosis cerebri
  - Metastases
- Other
  - Spinal stenosis; central pontine myelinolysis; radiation therapy
  - Medications: adalimumab

https://www.nationalmssociety.org/Symptoms-Diagnosis/Other-Conditions-to-Rule-Out. Accessed May 14, 2021.

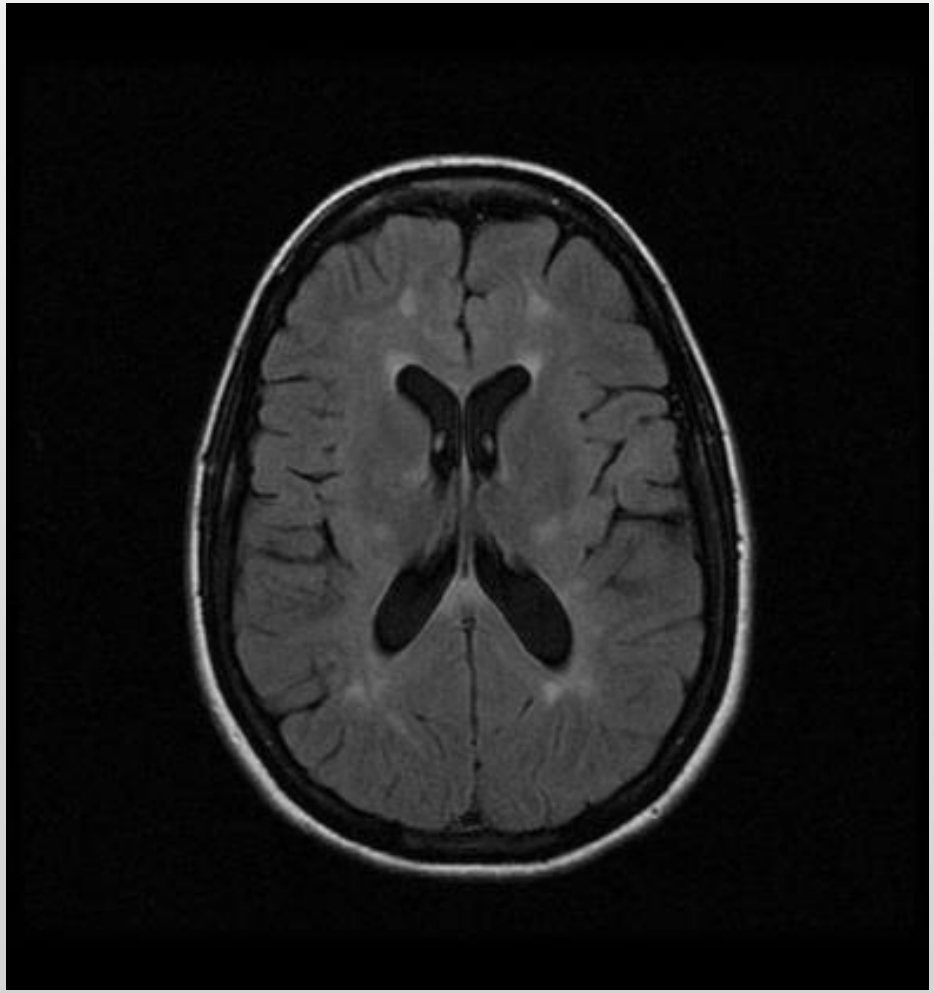
# Multiple Sclerosis Criteria




Thompson AJ. *Lancet*. 2018;391(10130):1622-1636.; Partucco L. *Mult Scler J Exp Transl Clin*. 2017;3(3):2055217317721943.

# 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis

| No. of Clinical attacks | No. of MRI lesions with objective clinical evidence | Additional data needed for diagnosis of multiple sclerosis |
|---|---|---|
| **Relapsing-remitting multiple sclerosis** | | |
| ≥2 | ≥2 | None |
| ≥2 | 1 | None |
| ≥2 | 1 | DIS demonstrated by an additional clinical attack implicating a different CNS Site or by MRI |
| 1 | ≥2 | DIT demonstrated by additional clinical attack, MRI, or CSF-specific oligoclonal bands |
| 1 | 1 | DIS demonstrated by additional clinical attack implicating a different CNS site or by MRI *and* DIT demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands |
| **Primary progressive multiple sclerosis** | | |
| Required: 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse<br>Plus 2 of the following: 1 or more T2-hyperintense lesions characteristic of multiple sclerosis in 1 or more of the following brain regions: periventricular cortical or juxtacortical, or infratentorial; 2 or more T2-hyperintense lesions in the spinal cord; presence of CSF-specific oligoclonal bands | | |



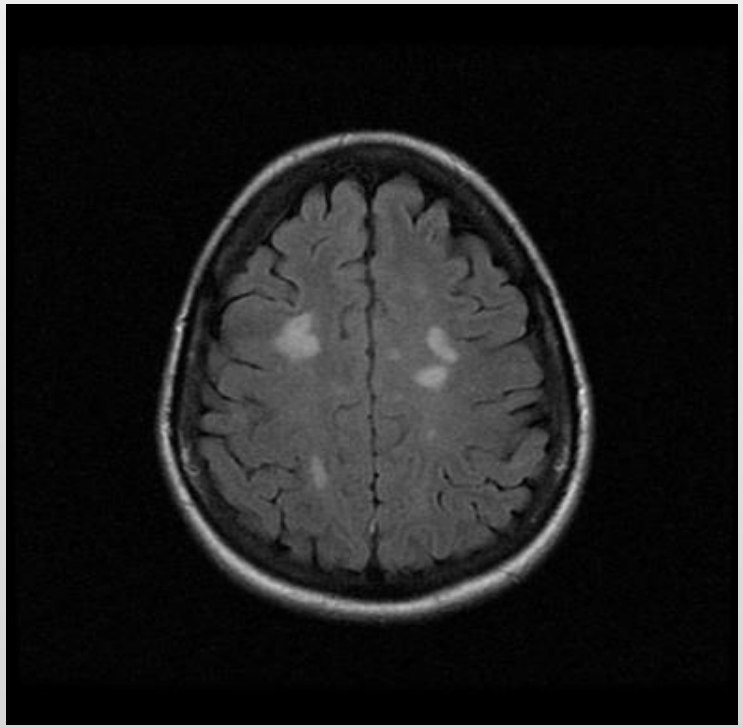
Thompson AJ et al. *Lancet Neurol*. 2018;17(2):162-173.; Image courtesy of Aliza Ben-Zacharia PhD, DNP, ANP-BC, FAAN.

# Key changes made to the McDonald Criteria in 2017

- Brain stem and cord lesions can now be counted among the 2 lesions disseminated in space and time
- CSF oligoclonal bands can now be used to substitute for demonstration of dissemination in time in some settings
- Both asymptomatic and now symptomatic MRI lesions can be considered in determining dissemination in space (optic nerve lesions are still excluded).
- Cortical lesions have been added to juxtacortical lesions as determinant for dissemination in space

Thompson AJ et al. *Lancet Neurol*. 2018;17(2):162-173.

# The MS Lesion Checklist



https://practicalneurology.com/articles/2018-july-aug/the-multiple-sclerosis-lesion-checklist. Accessed May 14, 2021.; Image courtesy of Aliza Ben-Zacharia PhD, DNP, ANP-BC, FAAN.

| Description of Lesion Types | Present = yes Absent = no (Circle) | Note Number of Lesions |
|---|---|---|
| **Nerve root entry zone**. The lesions that track along nerve roots, especially the trigeminal nerve root, favor an inflammatory over vascular etiology. In an active MS lesion, enhancement may extend from parenchyma into nerve proper. | **Yes No** | |
| **Middle cerebellar peduncle.** Middle cerebellar peduncle (MCP) involvement in MS is seen frequently, but less than in the body of the pons. | **Yes No** | |
| **Medial longitudinal fasciculus.** This tract is commonly affected in MS both clinically (inter-nuclear ophthalmoplegia [INO]) and on MRI, however, vascular etiology is more common. Bilateral internuclear ophthalmoplegia may be somewhat more common in MS compared to stroke but is seen in many conditions. | **Yes No** | |
| **Other brainstem lesions adjacent to cerebrospinal fluid border.** "With remarkable regularity the brainstem lesions [are] contiguous with the inner and outer cerebrospinal fluid (CSF) borders." | **Yes No** | |
| **Cerebellar hemisphere.** Demyelinating cerebellar lesions are not contiguous with the CSF border, but appear within the deep cerebellar white matter. The cerebellum is often spared in vascular disease, but is commonly affected in MS, especially when the brainstem is involved. | **Yes No** | |
| **Inferior temporal lobe.** Another area of white matter that is preferentially affected in MS compared to vascular disease. | **Yes No** | |
| **Lesions adjacent to lateral ventricle—***Dawson's fingers*. "Wedge-shaped areas with broad base to the [lateral] ventricle, and extensions into adjoining tissue in the form of finger-like processes or ampullae, in each of which a central vessel could usually be found"[3] Frontal caps and bands along ventricular surface are normal signs of aging and should be not be confused with periventricular demyelinating lesions. | **Yes No** | |
| **Corpus callosum.** Demyelination at the callosal-septal interface may take the form of discrete lesions or more diffuse lumpy-bumpy appearance (ie, dot-dash sign), which is seen on multiple sagittal FLAIR images, in contrast to the smooth appearance of the subcallosal vein that is usually only seen on a single sagittal image. | **Yes No** | |
| **U-fibers (arcuate fibers).** U-fiber lesions that track along arcuate fibers are particularly characteristic of demyelination and are not seen in normal aging or vascular disease. | **Yes No** | |
| **Other cortical/juxtacortical lesions.** Plaques in cortex and at junction of cortex and white matter are very common in MS. A recent study recommended combining cortical and juxtacortical lesions for purposes of MS diagnosis. Cortical lesions may be better appreciated on double inversion recovery (DIR) sequence, which is not routinely available. | **Yes No** | |

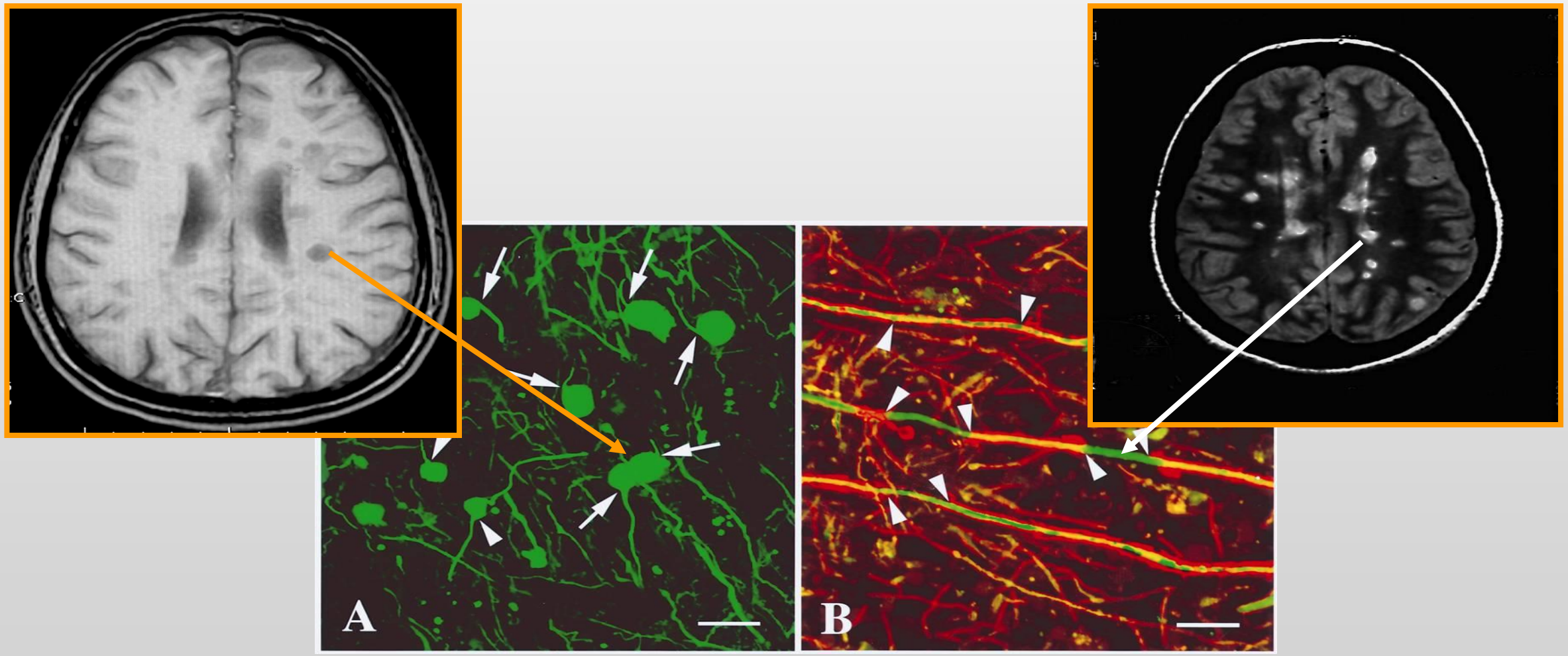
# Typical MS Lesions

- Key Locations
  - Periventricular
  - Corpus callosum
  - Cortical juxtacortical
  - Cerebellar peduncle
  - Cervical spine
- Shape
  - Oval/ovoid/>3-5mm
  - Dawson's fingers
- Well-demarcated
- No mass effect

- Spinal cord lesions
  - <3 vertebral segments
  - Only part of cross-section of the cord
  - No extensive cord swelling
- Gad enhancement
  - Initially nodular
  - Can evolve to a ring or an arc
    - T1 hypointense center
    - Opening of ring points toward the cortex

Neema M et al. *Neurother*. 2007;4 (4): 602-617.

# Demyelination and Axonal Transection on MRI




Courtesy of Bruce D. Trapp.

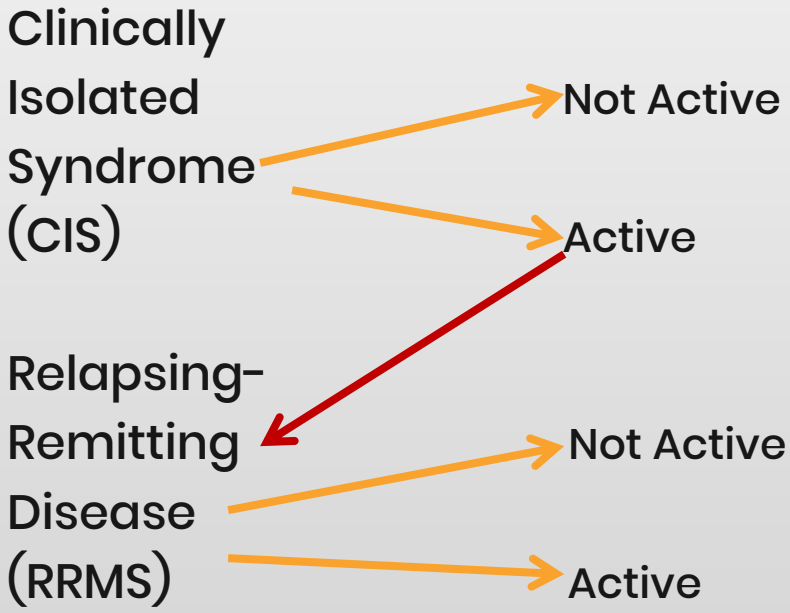
# Oligoclonal Bands in CSF

- Presence independent predictor of CIS to RRMS and RIS to CIS or disability accumulation (HR 2.0, 95% CI 1.2–3.6) in CIS
- Patients with CIS who had 8–12 OCBs had a 2.5-fold greater risk of conversion to CD MS than patients with fewer OCBs

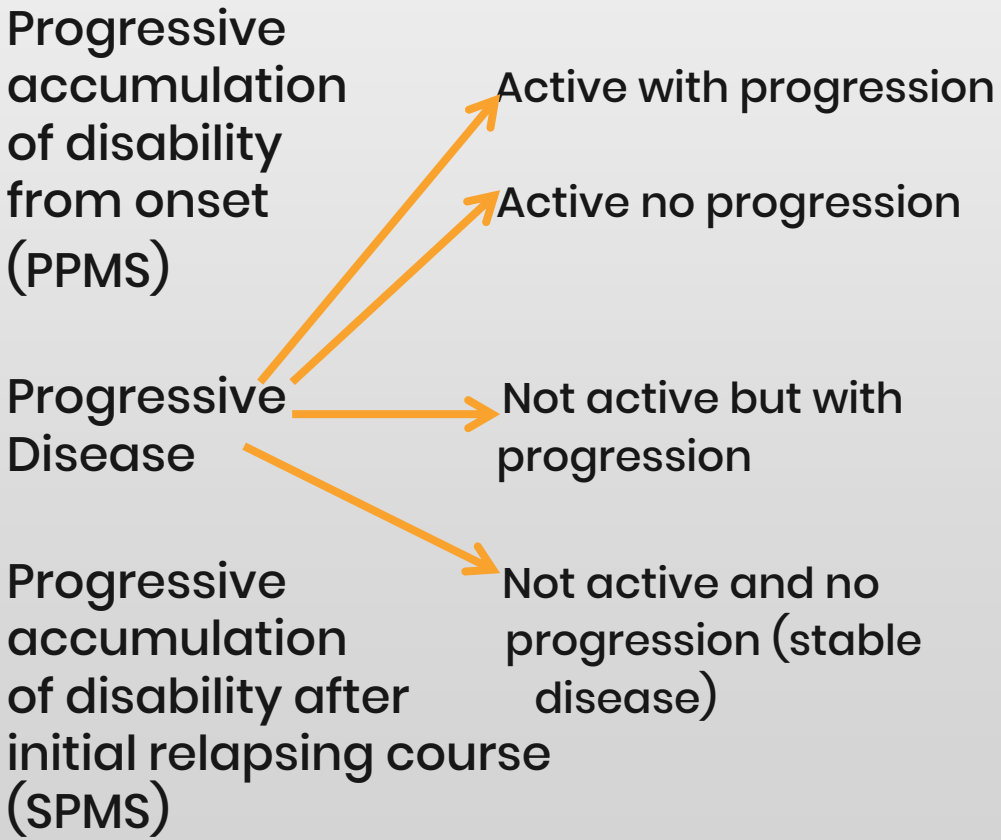
Deisenhammer F et al. *Front Immunol*. 2019;10:726.

# Revised Clinical Phenotypes

## Relapsing-Remitting Disease




## Progressive Disease




Adapted from: Lublin F et al. *Neurology*. 2014;83:278-86.

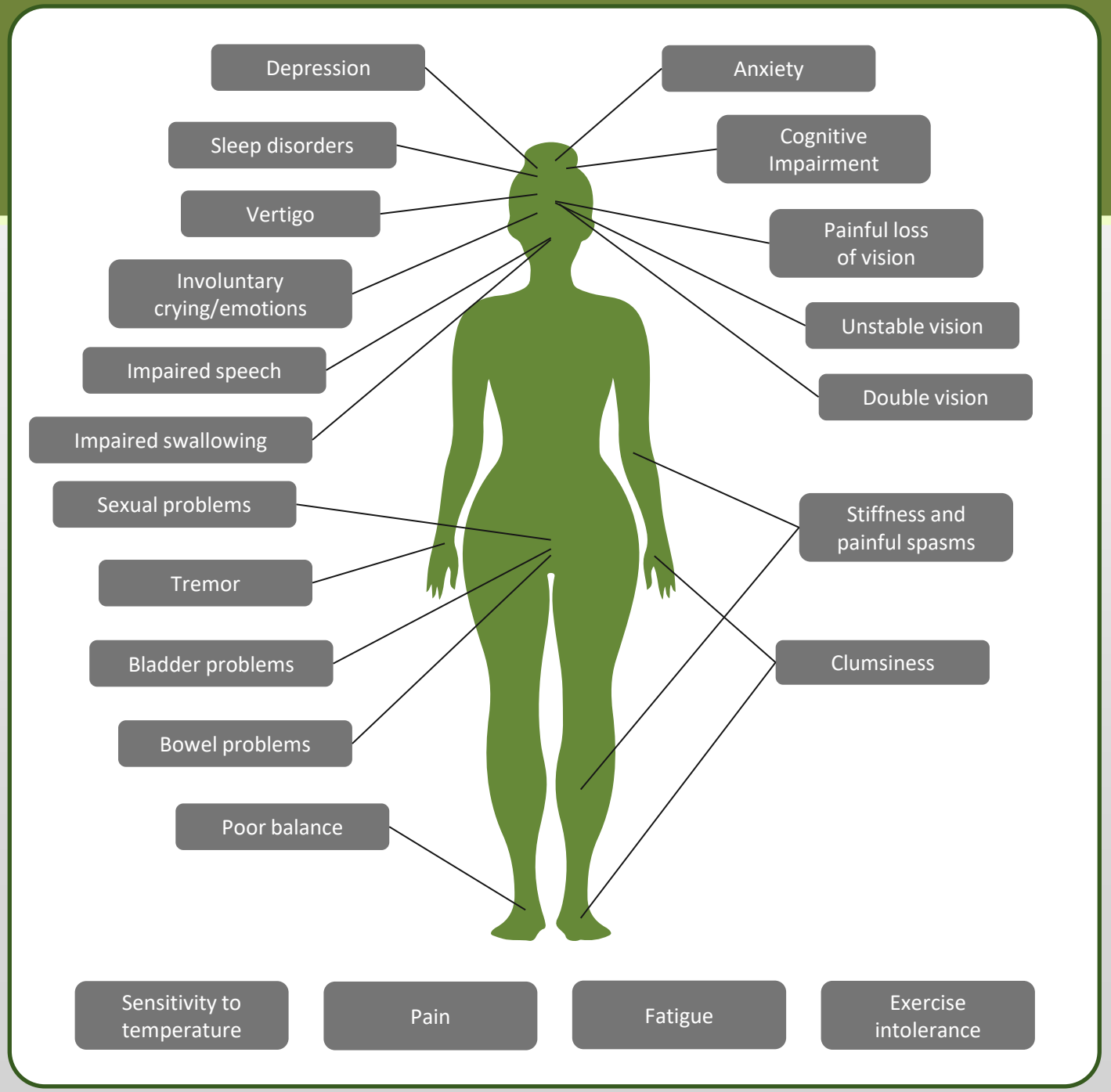
# Relapse vs. Pseudo Relapse

| Characteristic | Relapse | Pseudo Relapse |
|---|---|---|
| Nature | New or worsened symptoms, which are due to new inflammatory MS activity in the brain or spinal cord | Worsened neurologic symptoms; the underlying cause of the worsening is not from new immune system activity or inflammation |
| Timing | New symptoms manifest over a few hours or days and then plateau over a few days to weeks and then slowly improve over weeks to months | Worsened symptoms fluctuate, and especially if they resolve completely and then return |
| Recurrence | MS does not often result in repeated inflammation in the exact same part of the brain | The recurrence of old symptoms is more common in a pseudo relapse |
| Localization | Symptoms that can be explained by anew active MS lesion in the CNS | No place that a lesion in the CNS cause the symptoms/Another process: infection, medication, stress |
| Type of Symptoms | Vision loss, numbness, weakness are typical symptoms of a relapse | Sudden worsening of spasticity and pain are rarely due to an acute relapse |

https://www.imsmp.org/education/ms-relapse-vs-pseudorelapse. Accessed May 19, 2021.

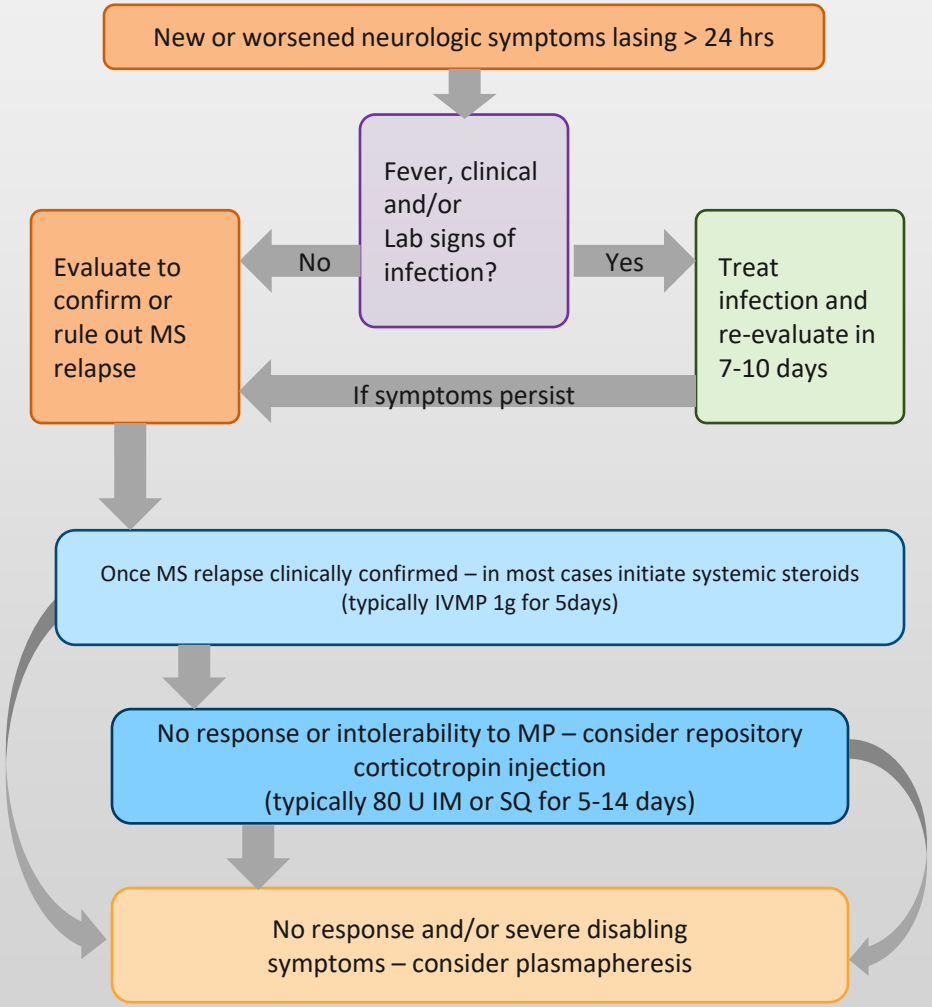
# Signs and Symptoms of MS

A common misconception is that any attack of CNS demyelination means a diagnosis of acute MS

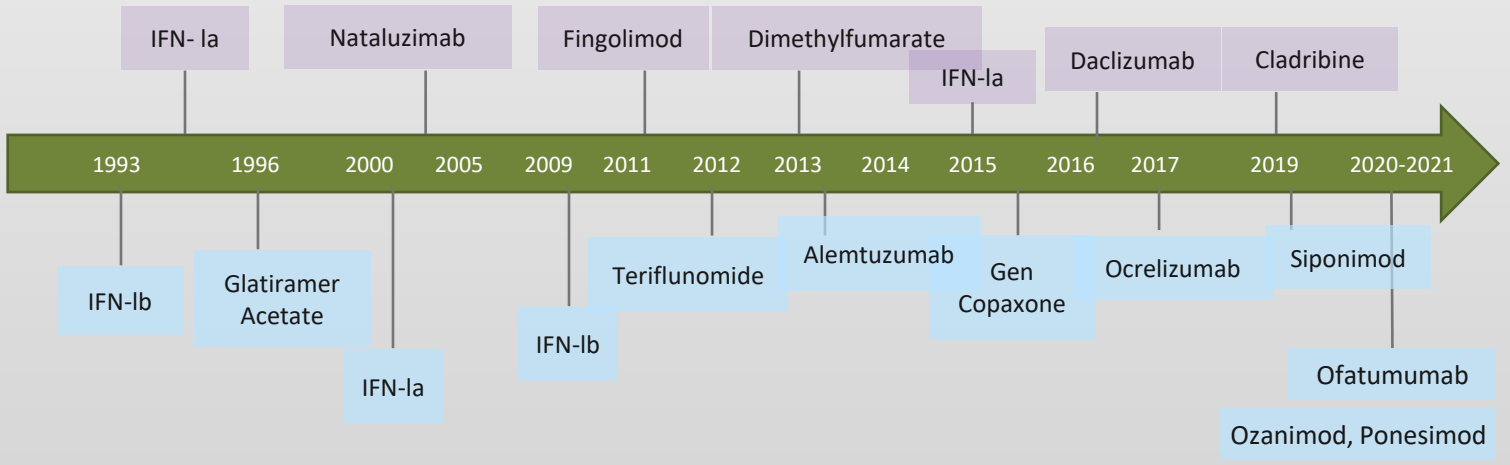



https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed May 14, 2021.

# Confirmed MS Diagnosis



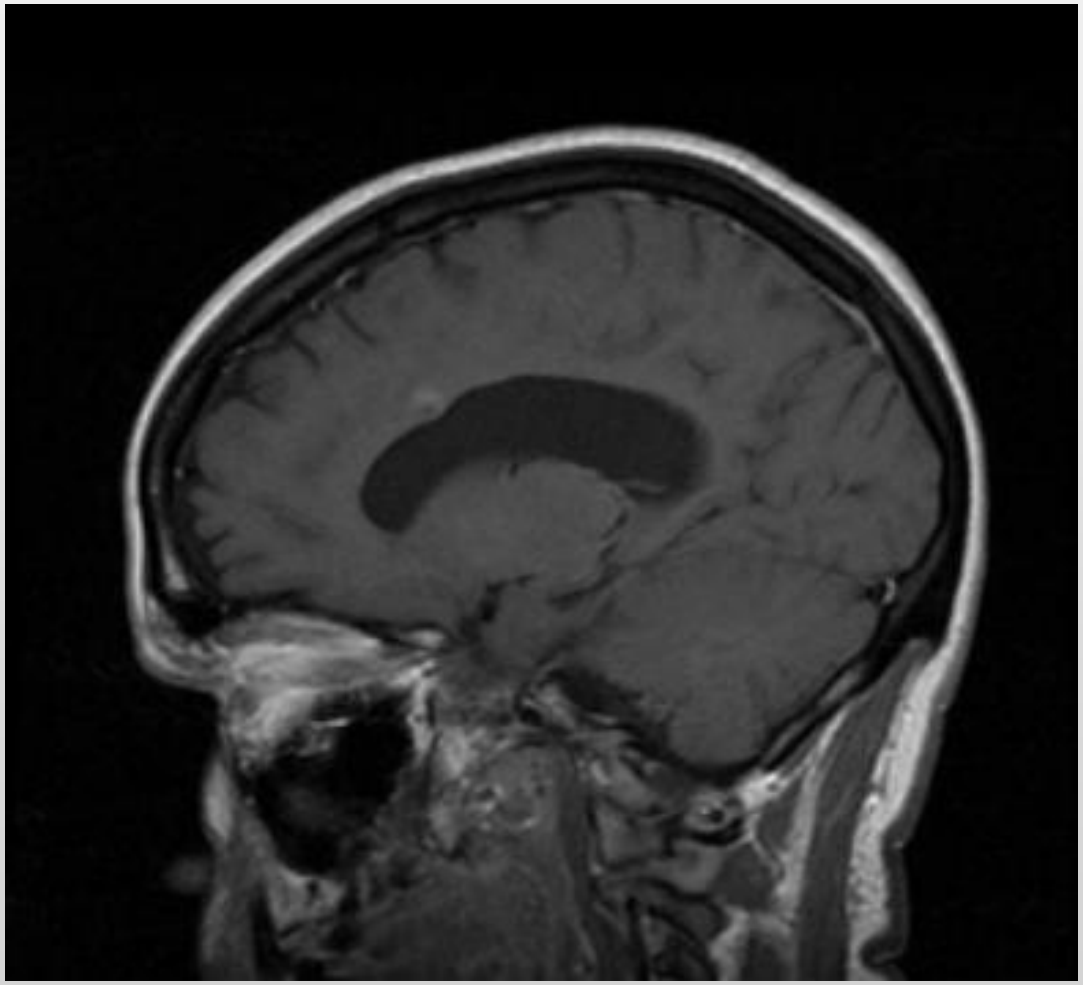

## Initiate DMT




https://cdn.ymaws.com/mscare.site-ym.com/resource/collection/9C5F19B9-3489-48B0-A54B-623A1ECEE07B/2018MRIGuidelines_booklet_with_final_changes_0522.pdf. Accessed May 14, 2021.

# Radiological Isolated Syndrome

- Diagnosis of RIS occurs during diagnosis of another unrelated condition, such as migraine headaches or trauma to the area
- Typical MRI MS lesions without clinical presentation
- Two-year period, one third of patients with RIS develop a neurological event and are diagnosed with MS, one third develop a new finding on MRI without any symptoms, and one third show no change



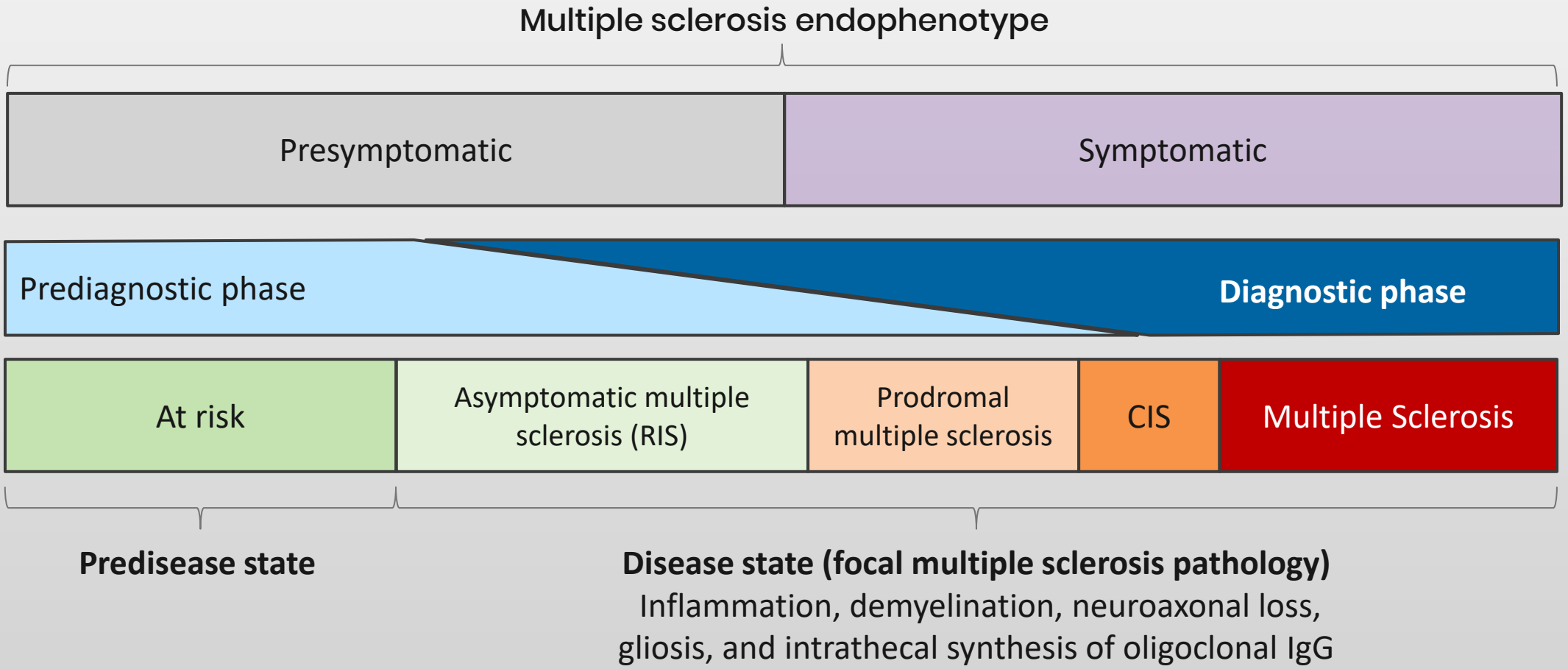
Okuda, DT et al. *PloS one*. 2014;9(3):e905.; Image courtesy of Aliza Ben-Zacharia, PhD, DNP, ANP-BC, FAAN.

# Clinically Isolated Syndrome

- CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the CNS
- The episode, must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a MS diagnosis because people who experience a CIS may or may not go on to develop MS
- The 2017 McDonald criteria make it possible to diagnose MS in a person with CIS who also has specific findings on brain MRI

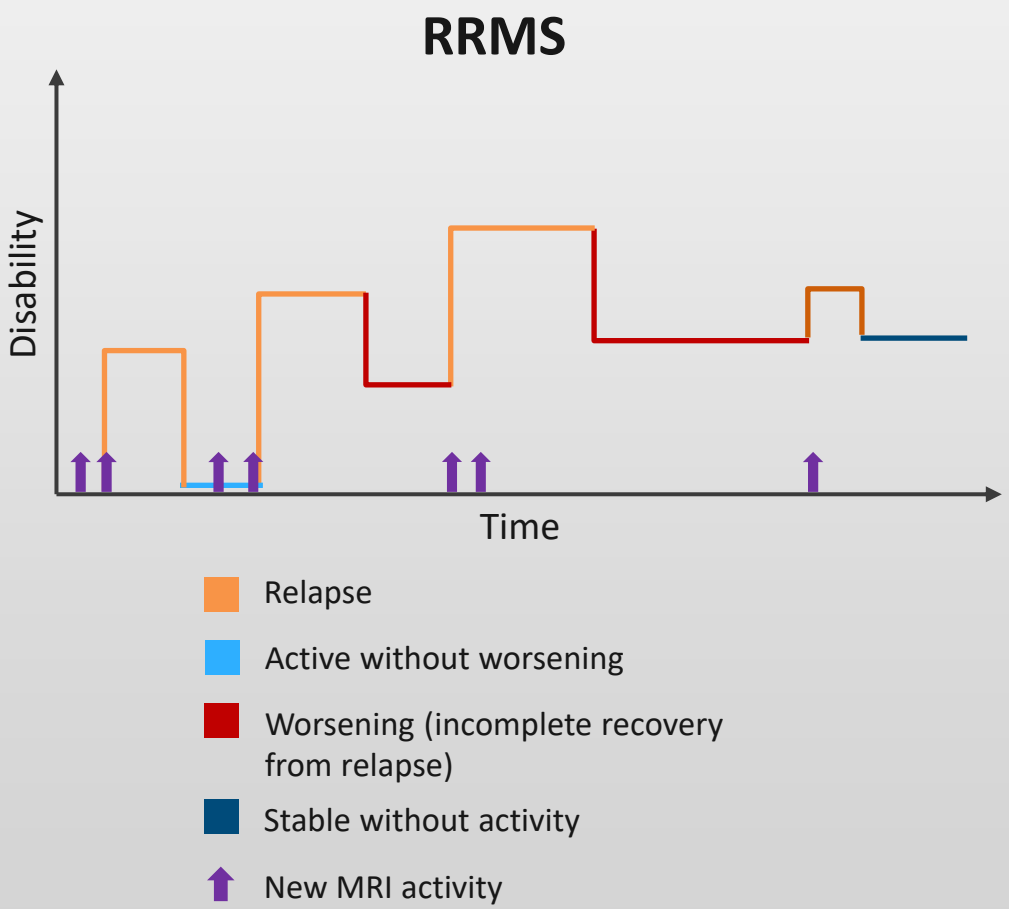
https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Clinically-Isolated-Syndrome-(CIS). Accessed May 14, 2021.

# MS Endophenotypes




Giovannoni G. *Lancet Neurol*. 2017;16(6):413-414.

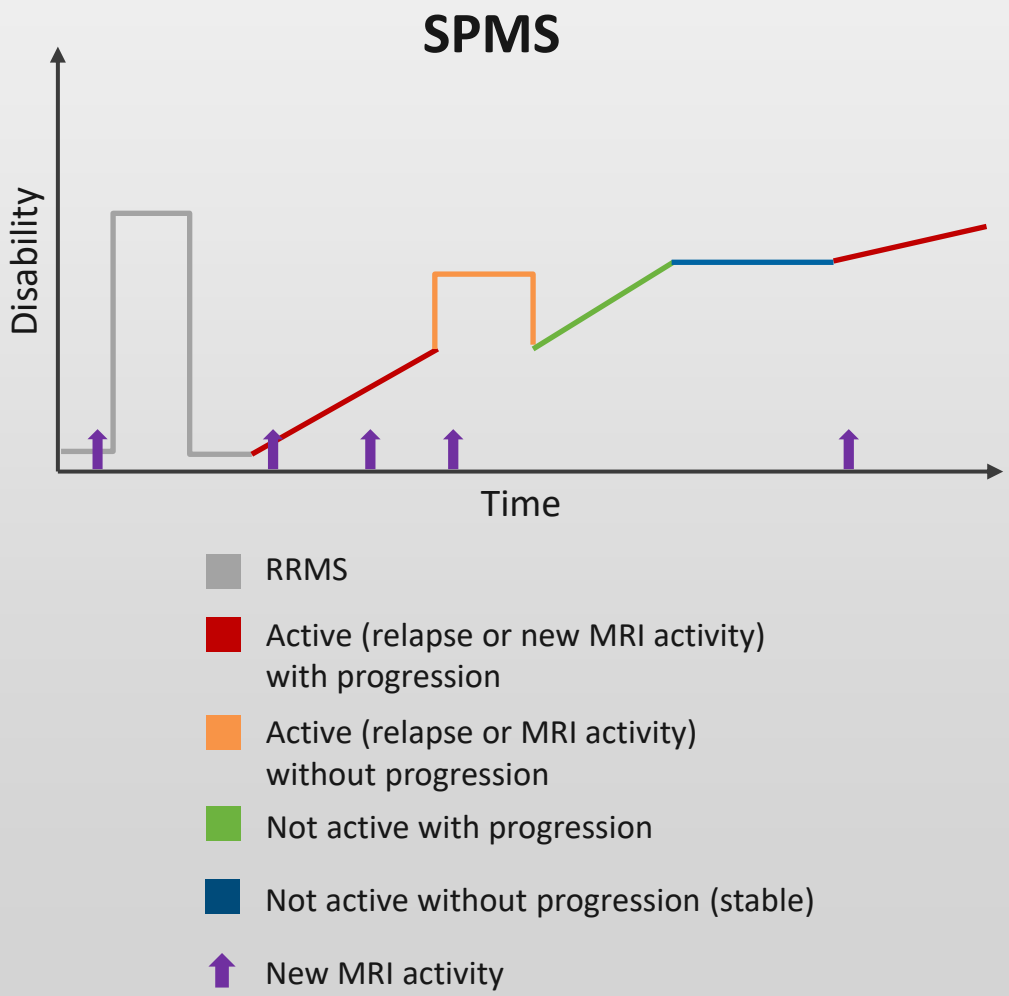
# Relapsing Remitting Multiple Sclerosis




- Relapses and remissions
- Transforms into SPMS
- Attacks of new or increasing neurologic symptoms
- Relapses lead to disability accumulation/EDSS
- RRMS active (with relapses and/or evidence of new MRI activity)
- RRMS not active, worsening (a confirmed increase in disability following a relapse) or not worsening

https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS. Accessed May 14, 2021.

# Secondary Progressive MS

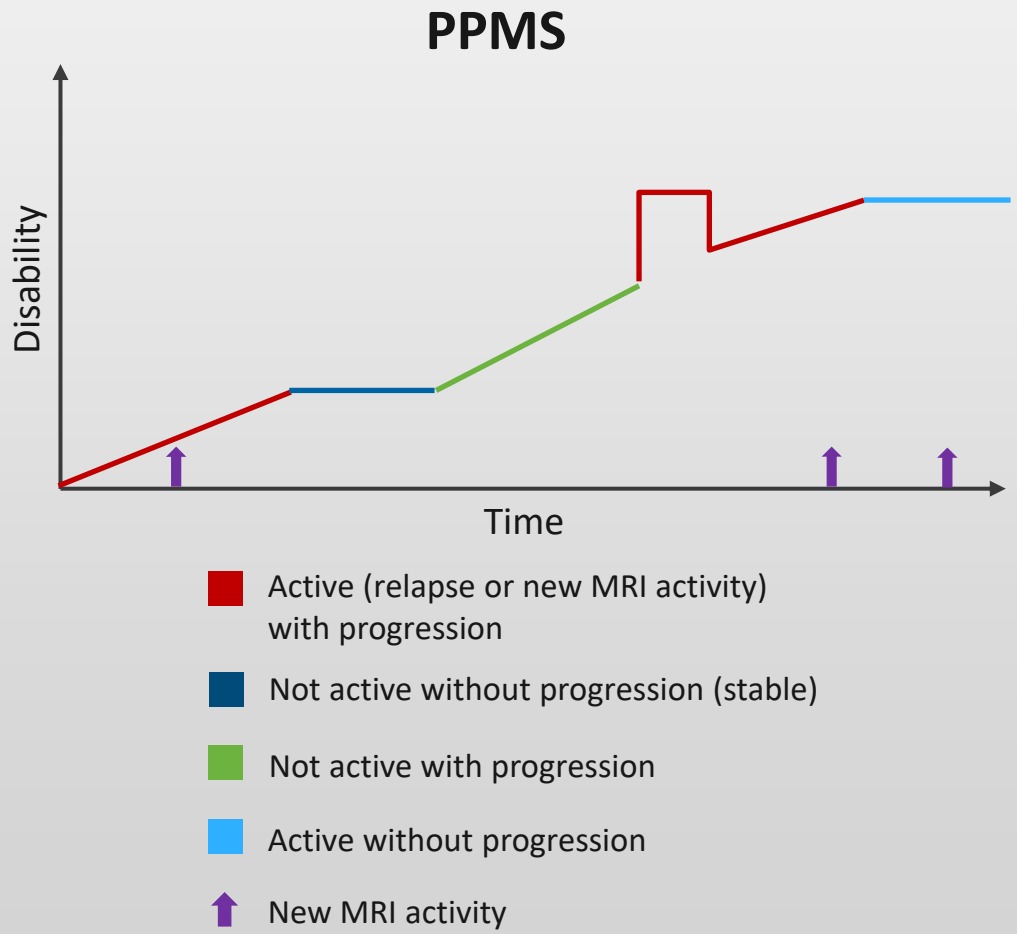



- SPMS follows an initial RRMS
- SPMS a progressive worsening of neurologic function (accumulation of disability) over time
- SPMS active – with relapses and/or evidence of new MRI activity
- SPMS not active, with progression (evidence of disability accumulation over time, with or without relapses or new MRI activity) or without progression

https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS. Accessed May 14, 2021.

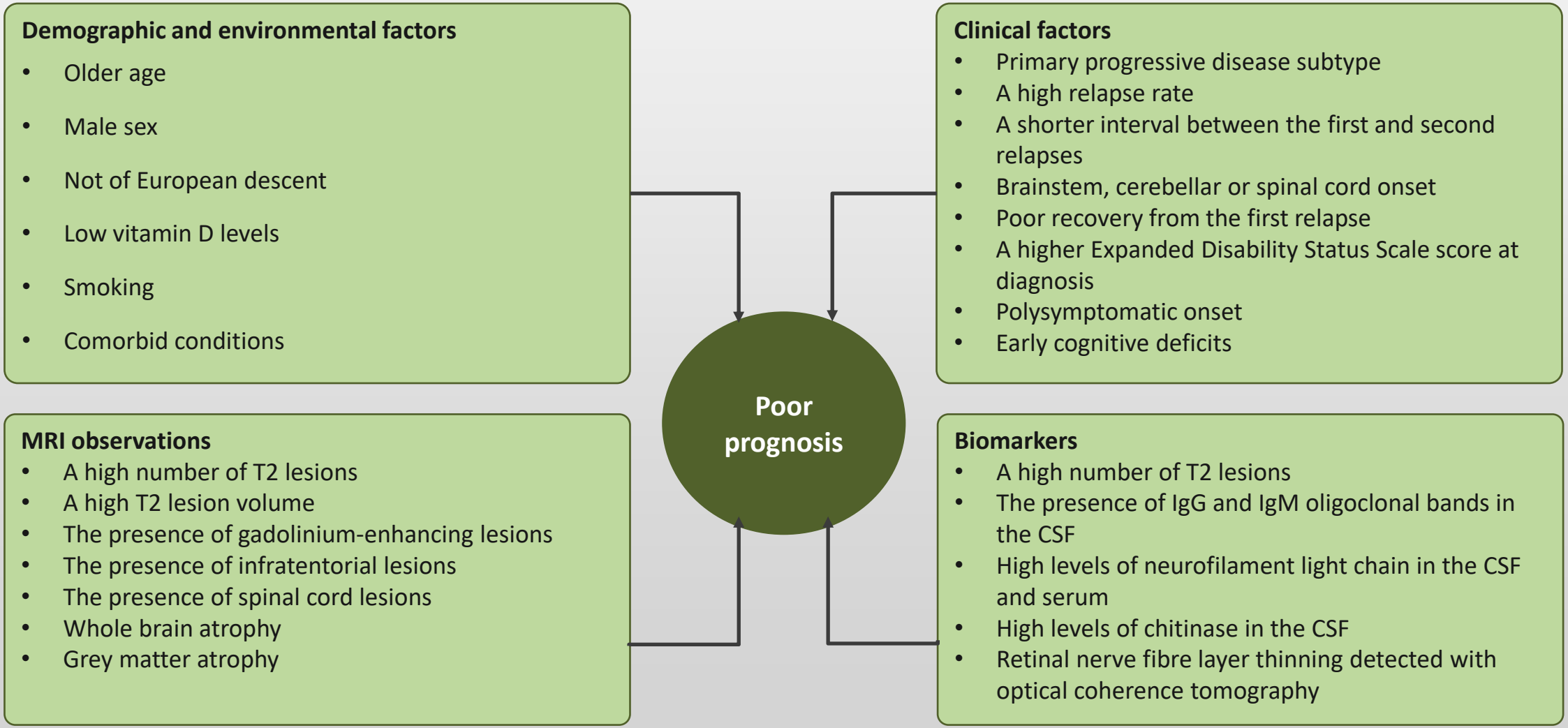
# Primary Progressive MS

- PPMS – worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions
- PPMS active (with an occasional relapse and/or evidence of new MRI activity over a specified period of time)
- PPMS not active, with progression (evidence of disability accumulation over time, with or without relapse or new MRI activity) or without progression



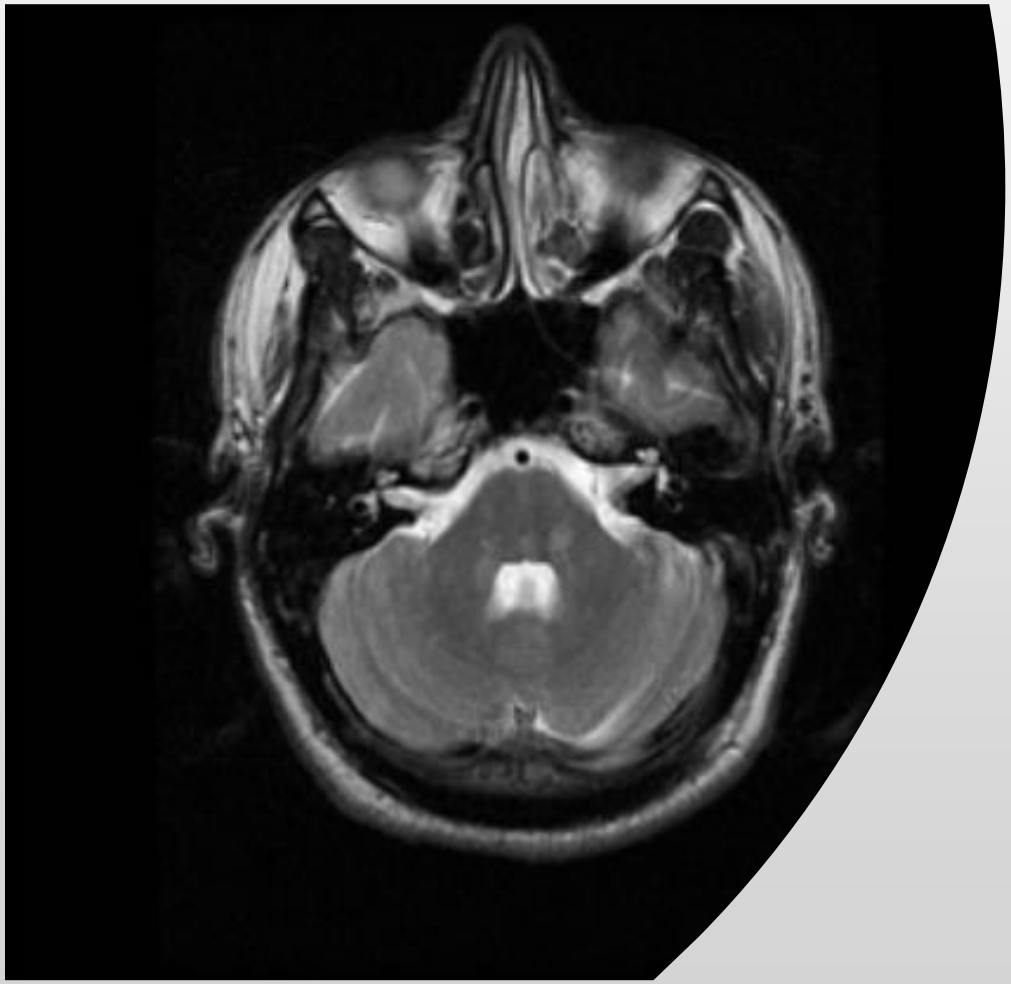

https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS. Accessed May 14, 2021.

# Multiple Sclerosis Prognosis




Rotstein D et al. *Nat Rev Neurol*. 2019;15:287-300.

# Clinical Case

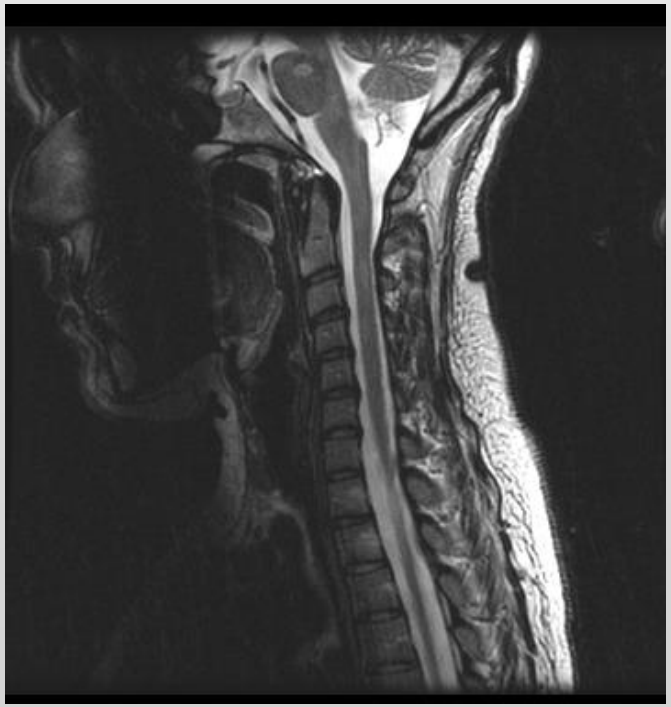


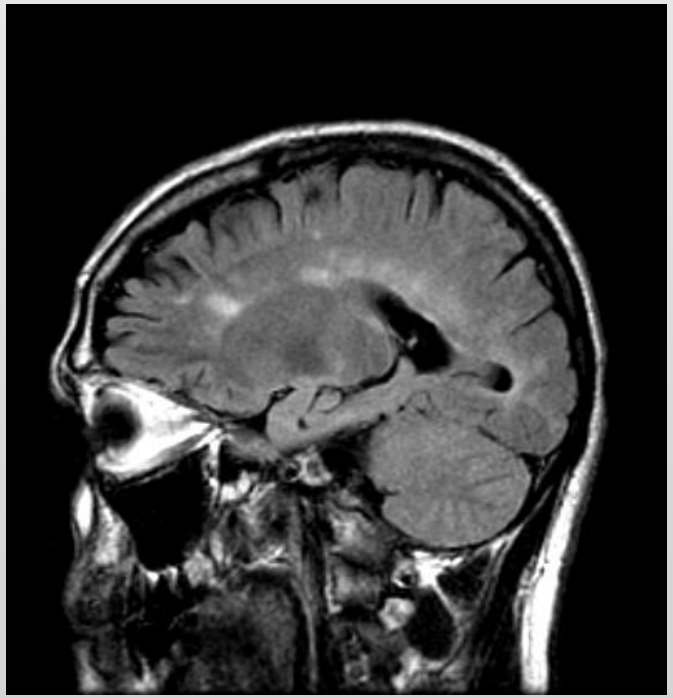
- 25-year-old Hispanic female
- New onset: weakness of left arm, Numbness
- Medical History: Optic neuritis 3 years ago, depression, smoker
- Current Medications: Vitamin D, partially adherent
- Cultural Considerations: her mother has never heard of the disease
- BRAIN MRI 3 years ago

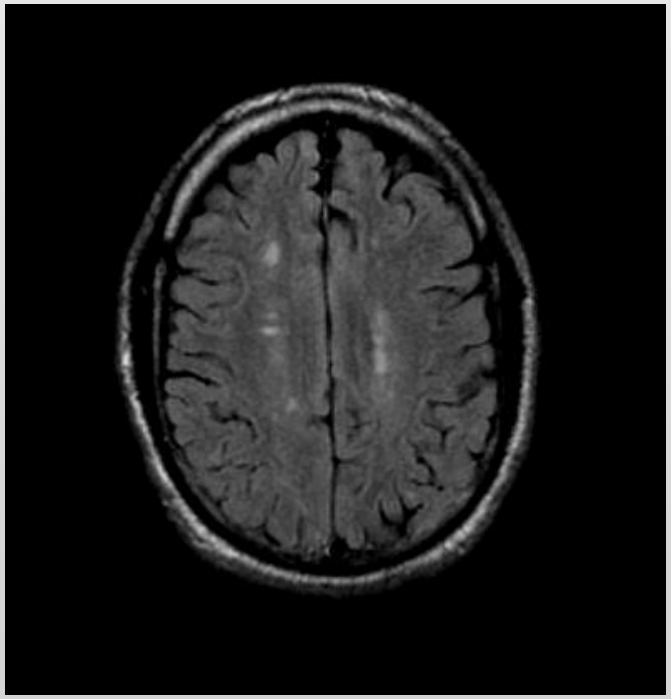
Courtesy of Aliza Ben-Zacharia, PhD, DNP, ANP-BC, FAAN.

# Meet Criteria?

| No. of Clinical attacks | No. of MRI lesions with objective clinical evidence | Additional data needed for diagnosis of multiple sclerosis |
|---|---|---|
| **Relapsing-remitting multiple sclerosis** | | |
| ≥2 | ≥2 | None |







Courtesy of Aliza Ben-Zacharia, PhD, DNP, ANP-BC, FAAN.

# Conclusion

- MS is a complex disease with multiple endophenotypes
- High-risk RIS and prodrome may become a part of the MS spectrum in the next version of the McDonald criteria
- Many patients previously labelled as CIS now receive the diagnosis of MS, making the prognosis of both CIS and RRMS milder
- Important to diagnose early and treat early
- Once diagnosed, important to assess the presence of poor prognostic indicators, symptoms, treating exacerbations, starting DMT and managing comorbidities

# Thank you!

THE 12TH ANNUAL LINDA MORGANTE MS Nurse Leadership Program