Multiple sclerosis disease education 101

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EMD SERONO

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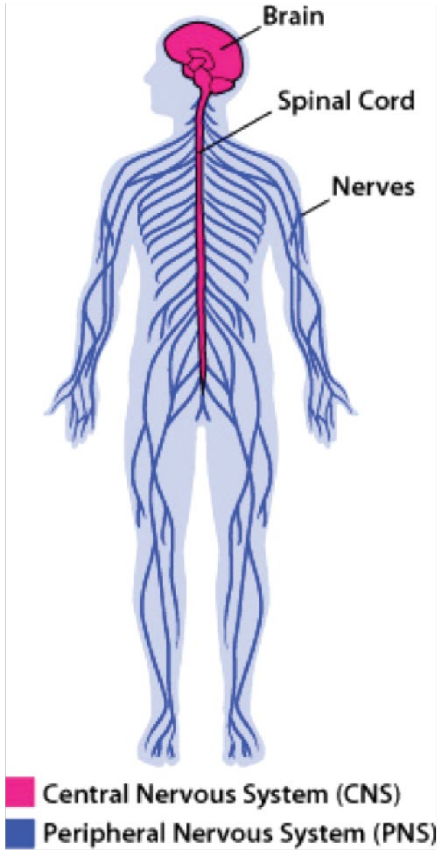
Etiology, prevalence of MS and risk factors

MS is a chronic autoimmune degenerative disease



- MS, a neuroinflammatory disease of the CNS, including the brain and spinal cord, that causes demyelination and neuronal injury, is one of the most common causes of nontraumatic disability among young adults (aged 18–40 years)[1]
- The chronic accumulation of physical and cognitive disability among people with multiple sclerosis has substantial effects on social, economic, and individual well-being[1]

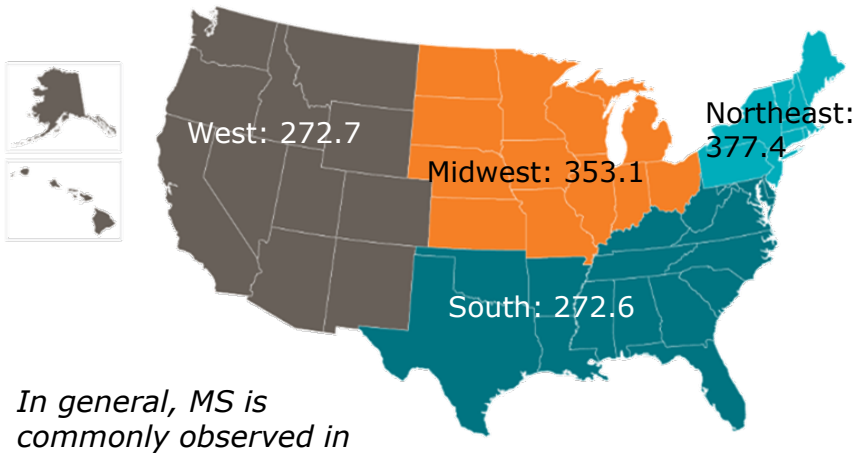
Figure from Sahyouni R, et al. Book chapter: Introduction to the Brain and Nervous System. Alzheimer's Disease Decoded, January 2, 2022, pp. 3-36.

CNS, central nervous system; MS, multiple sclerosis

1. Jakimovski D, et al. The Lancet. 2024;403:183-202.

MS in the US: Prevalence, demographics, regional distribution, and global trends

- Approximately 1 million people in the US live with MS; most people are diagnosed between **20** and **40 years of age**[1,2]
- Affects up to **3** times as many **women** as men[3]
- in primary-progressive MS, **both sexes** are similarly affected[4]
- MS prevalence is the highest among the white population,[5] with increasing rates observed among African Americans[6]
- Patients typically receive a confirmed diagnosis of MS within 1 year once they are under a neurologist's care[a,7]



In general, MS is commonly observed in areas farthest from the equator[8]

(Per 100,000 US Residents; 2010 US Census)[9]

- Based on the latest Multiple Sclerosis Atlas, a joint project between the Multiple Sclerosis International Federation and WHO, 2.8 million people in 2020 had multiple sclerosis worldwide[10,11]
- A global increase of half a million new cases of MS since 2013 is attributed to greater life expectancy and global population growth[10]

[a]Retrospective study based on claims data for patients diagnosed with MS between October 1, 2010 and May 31, 2014

MS, multiple sclerosis; US, The United States; WHO, World Health Organization

1.National Multiple Sclerosis Society. How Many People Live With MS? https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS/How-Many-People. Accessed June 11, 2024; 2. National Multiple Sclerosis Society. Pediatric Multiple Sclerosis. https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS/Pediatric-MS. Accessed June 11, 2024; 3. National Multiple Sclerosis Society. Women Living With Multiple Sclerosis. https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS/Women-with-MS Accessed June 11, 2024; 4. Multiple Sclerosis Association of America. Who Gets Multiple Sclerosis. https://mymsaa.org/ms-information/overview/who-gets-ms/. Accessed June 11, 2024; 5. Hittle M, et al. JAMA Neurol. 2023;80:693-701; 6. Amezcua L, McCauley JL. Mult Scler. 2020;26:561-567; 7. Visaria J, et al. Clin Ther. 2018;40:926-939; 8. National Multiple Sclerosis Society. Who Gets Multiple Sclerosis? Epidemiology of MS. https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS. Accessed June 11, 2024; 9. Wallin MT, et al. Neurology. 2019;92:e1029-e104; 10. Jakimovski D, et al. The Lancet. 2024;403:183-202; 11. Walton C, et al. Mult Scler. 2020;26:1816-1821.

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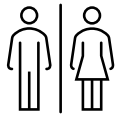
Demographics in MS: Trends in prevalence

Research has identified differences in the prevalence of MS by race, ethnic group, and sex. More research is warranted to confirm and further understand these trends[1-4]

Race and Ethnicity

- Data from a Kaiser Permanente retrospective study (2008 to 2010) reported the risk of MS across different racial and ethnic groups. Specifically, **African Americans** had a **47% increased** risk of MS, while **Hispanic Americans** had a **50% lower** risk; moreover, **Asian Americans** had an **80% lower** risk compared with White Americans[1,2]
- Another study involving the US military Veteran population, reported similar findings indicating higher rates of MS in African Americans[3]
- **Hispanics present with MS at a younger age** than Whites and African Americans[1]



Sex

- The prevalence of MS in females is higher compared with males, and this trend **may vary** across different demographic groups, based on race, ethnicity, and geography[4]

Age

- The prevalence of MS is the highest in the **45-64** years age group regardless of racial and ethnic classification[4]

1. Amezcua L, McCauley JL. Mult Scler. 2020;26:561-567; 2. Langer-Gould A, et al. Neurology. 2013;80(19):1734-1739; 3. Wallin MT, et al. Brain .2012;135:1778-1785; 4. Hittle M et al. JAMA Neurol. 2023;80:693-701.

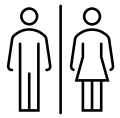
MS, multiple sclerosis; US, The United States

Demographics in MS: Trends in disability and prognosis

Research has identified differences in disability and prognosis by race, ethnic group, and sex. More research is warranted to confirm and further understand these trends[1-4]

Race and Ethnicity

- Using the P-MSSS, **significantly higher disability** scores have been reported for both **Hispanics** (3.9 ± 2.6) and **African Americans** (4.5 ± 3.0) than for White Americans (3.4 ± 2.6; $p < 0.0001$; adjusted for age)[1]



Sex

- The **rate of disability accumulation** is faster among **males** compared with **females in relapse-onset MS (RRMS, SPMS),** while it is **similar with PPMS**[2]
- **Cognition** has been shown to be **most severely affected in males**[3]
- Inflammatory cytokine responses to multiple MS-relevant myelin antigens are different between sexes[4]

Age

- Approximately 2/3 of people aged ≥ 65 years from a longitudinal study had a progressive form of MS[5]

1. Amezcua L, McCauley JL. Mult Scler. 2020;26:561-567; 2. Ribbons KA, et al. PLoS One. 2015;10:e0122686; 3. Golden LC, Voskuhl R. J Neurosci Res. 2017;95:633-643; 4. Moldovan IR, et al. J Neuroimmunol. 2008;193:161-169; 5. Minden SL, et al. NeuroRehabilitation. 2004;19:55-67.

MS, multiple sclerosis; P-MSSS, Patient-Derived Multiple Sclerosis Severity Score; PPMS, primary progressive MS; RRMS, Relapsing-remitting MS; SPMS, secondary progressive multiple sclerosis

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MS is multifactorial with infectious, environmental, and genetic components[1]

Infections[2]

Several viruses have been proposed as potential triggering agents in the development of MS

- Epstein-Barr
- Measles[7]
- Canine distemper[8]
- Human herpes virus-6
- Varicella-zoster

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Environmental factors[1,3-5]

Certain environmental factors can contribute to the risk of developing MS

- Geography (higher latitude increases the risk)
- Vitamin D (higher levels lower the risk)
- Diet (may change the risk level)
- Obesity (healthy body weight lowers the risk)
- Exposure to toxins (may be a trigger event)
- Smoking

Genetic risks[6]

People with a family history of MS may have a higher risk of developing MS

- **1%-2%** risk for second-degree relatives (e.g., grandparent, aunt)
- **2%-5%** risk for first-degree relatives (e.g., child, sibling)
- **25%** risk for monozygotic twins of individuals with MS

1. National Multiple Sclerosis Society. What causes MS? What Causes MS? https://www.nationalmssociety.org/understanding-ms/what-is-ms/what-causes-ms Accessed June 11, 2024; 2. Virtanen JO, Jacobson S. CNS Neurol Disord Drug Targets. 2012;11:528-544; 3. National Multiple Sclerosis Society. Diet and Nutrition. https://www.nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Diet-Nutrition. Accessed June 11, 2024; 4. Hachim MY, et al. Toxins (Basel). 2019;11:147; 5. Nishanth K, et al. Cureus. 2020;12(8):e9564; 6. Goodin DS. BMC Neurol. 2010;10:101; 7. Tucker WG, Paskauskas RA Med Hypotheses. 2008;71:682-689; 8. Rohowsky-Kochan C et al. Brain Behav. 2021;11(1):e01920.

MS, multiple sclerosis

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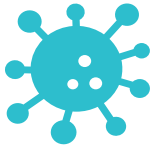

Several viruses have been proposed as potential triggering agents in the development of MS

- Epstein-Barr
- Measles[7]
- Canine distemper[8]
- Human herpes virus-6
- Varicella-zoster

EBV[9,10,11]

Over the past 20 years, studies have suggested a link between EBV infection and MS development

EBV infection is thought to be a necessary but not sufficient requirement for MS development

In a study on active duty in the US military involving >10 million young adults, the risk of MS increased 32-fold after infection with EBV but showed no increase after infection with other viruses

Symptomatic EBV infection (infectious mononucleosis) is more prevalent among people with MS

1. National Multiple Sclerosis Society. What causes MS? What Causes MS? | National MS Society. Accessed June 11, 2024; 2. Virtanen JO, Jacobson S. CNS Neurol Disord Drug Targets. 2012;11:528-544; 3. National Multiple Sclerosis Society. Diet and Nutrition. https://www.nationalmssociety.org/Living-Well-With-MS/Diet-Exercise-Healthy-Behaviors/Diet-Nutrition. Accessed June 11, 2024; 4. Hachim MY, et al. Toxins (Basel). 2019;11:147; 5. Nishanth K, et al. Cureus. 2020;12(8):e9564.; 6. Goodin DS. BMC Neurol. 2010;10:101; 7. Tucker WG, Paskauskas RA Med Hypotheses. 2008;71:682-689; 8. Rohowsky-Kochan C et al. Brain Behav. 2021;11(1):e01920. 9. Soldan, SS, Lieberman, PM., Nat Rev Microbiol 2023;21,51-64; 10. Jacobs BM, et al. Mult Scler. 2020;26:1281-1297; 11. Bjornevik K, et al. Science. 2022;375:296-301.

EBV, Epstein-Barr virus; MS, multiple sclerosis; US, The United States of America

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MS symptoms may present with one dominant symptom or a cluster of symptoms[1]

The clinical presentation of MS can be affected by the extent and location of lesions within the CNS, severity of damage, and rate of lesion accumulation[2]

General[1]

- **Fatigue**
- **Pain**
- **Altered sensation** (e.g., numbness or tingling)

Muscle and movement[1]

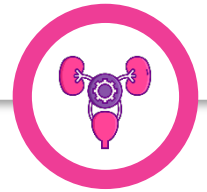
- **Weakness/involuntary muscle spasms**
- **Incoordination of movement**

Neurologic[3-5]

- **Cognitive changes, emotional changes, or mood disorders[3]**
- **Sleep issues[4]**
- **Visual disorders[5]**

Urinary and genital[6]

- **Sexual dysfunction**
- **Bladder/bowel problems**



Symptoms of MS may appear and disappear randomly, and the symptom intensity may change throughout the course of MS[5]

1. National Multiple Sclerosis Society. MS Signs & Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed June 11, 2024; 2.Hunter SF. Am J Manag Care. 2016;22:S141-S150; 3. National Multiple Sclerosis Society. emotional-well-being https://www.nationalmssociety.org/managing-ms/living-with-ms/emotional-well-being/mood-changes. Accessed August 20, 2024. 4.National Multiple Sclerosis Society. diet-exercise-and-healthy-behaviors. https://www.nationalmssociety.org/managing-ms/living-with-ms/diet-exercise-and-healthy-behaviors/sleep. Accessed August 20, 2024; 5. National Multiple Sclerosis Society. Vision Disorders and Multiple Sclerosis https://www.nationalmssociety.org/understanding-ms/what-is-ms/ms-symptoms/vision-problems Accessed August 20, 2024; 6. National Multiple Sclerosis Society. Sexual Dysfunction https://www.nationalmssociety.org/for-professionals/for-healthcare-professionals/managing-and-treating-ms/symptom-management/sexual-dysfunction. Accessed August 20, 2024.

CNS; central nervous system, MS, multiple sclerosis

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CNS-specific signs and symptoms can vary based on MS heterogeneity[1]

Symptom/Sign	Key points
MS hug (Dysesthesia)[2]	A squeezing sensation around the torso that feels like tightening of a blood pressure cuff
Numbness or tingling[2]	Numbness of the face, body, or extremities (arms and legs)
Vision problems[2,3]	Can include optic neuritis, diplopia (double vision), nystagmus (uncontrolled movement of the eyes that impairs vision)
Walking (Gait) difficulties[2,4]	Related to several factors, including weakness, spasticity, loss of balance, sensory deficit, and fatigue
Spasticity[2]	Characterized by muscle stiffness and involuntary contractions
Lhermitte[5]	Mostly described as an electric shock-like condition. This sensation occurs when the neck is moved in an incorrect manner or rather flexed. It can also travel down to the spine, arms, legs, and sometimes the trunk
Paroxysmal phenomena[1]	Epileptic seizures, nonepileptic paroxysmal motor, or sensory phenomena

1. Hunter SF. Am J Manag Care. 2016;22:S141-S150; 2. National Multiple Sclerosis Society. MS Signs & Symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed June 11, 2024; 3. Gigengack NK, et al. Scientific Reports. 2022;12, 17545; 4. National Multiple Sclerosis Society. Treatment and medications. https://www.nationalmssociety.org/managing-ms/treating-ms/rehabilitation. Accessed August 20, 2024; 5. Khare S, Seth D. Ann Indian Acad Neurol. 2015;18(2):154-156.

CNS, central nervous system; MS, multiple sclerosis

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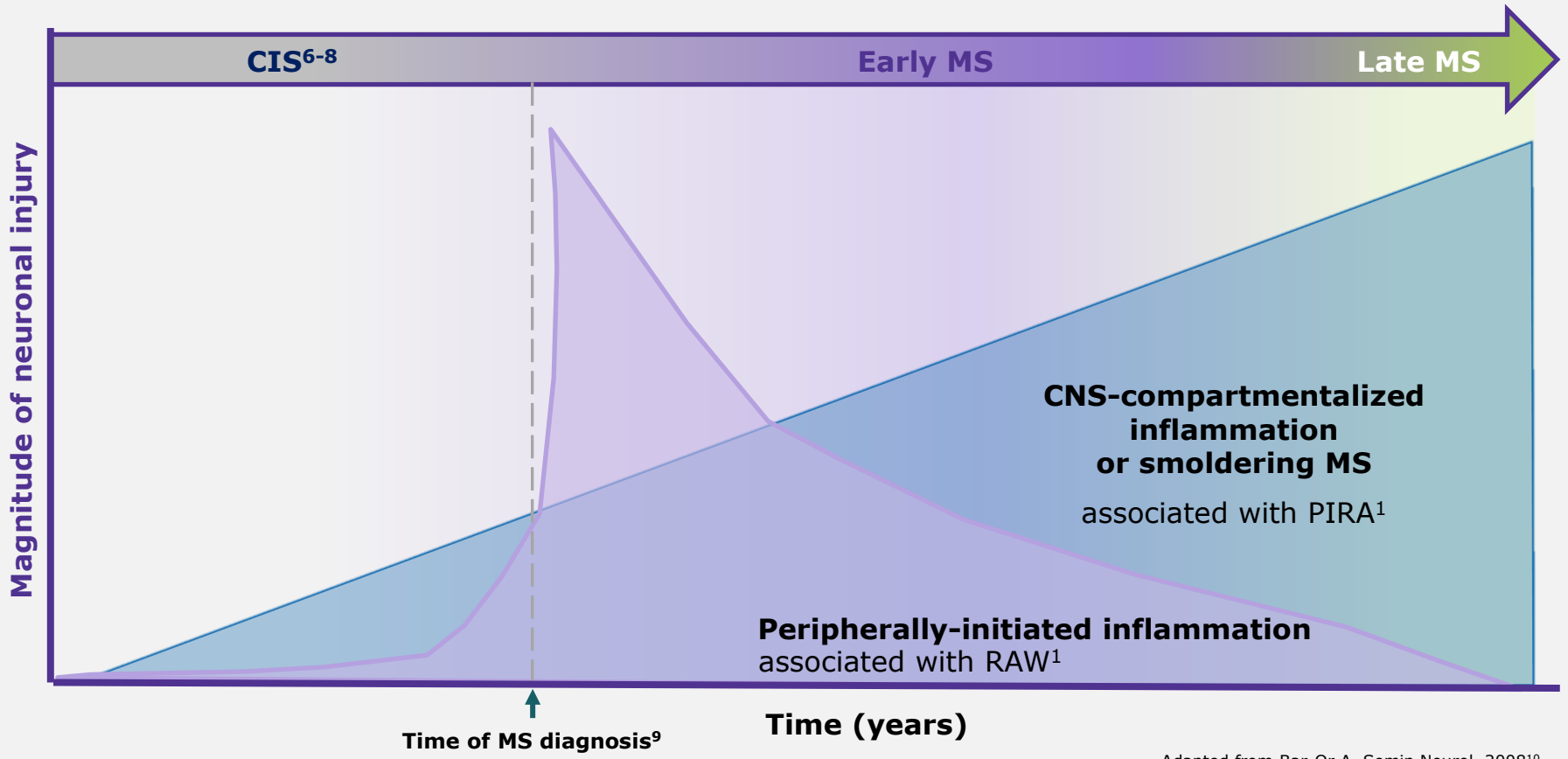
phenotypes and presentation

Current evidence suggests that MS is driven by two parallel processes[1-3]

- Instead of two separate stages, MS is driven by **two parallel processes**[1-3]
- Neurodegeneration occurs **early** and **may predicate** the accumulation of disability[2,3]
- The **phenotypic presentation** of MS can be thought of as a **continuum**[1-5]

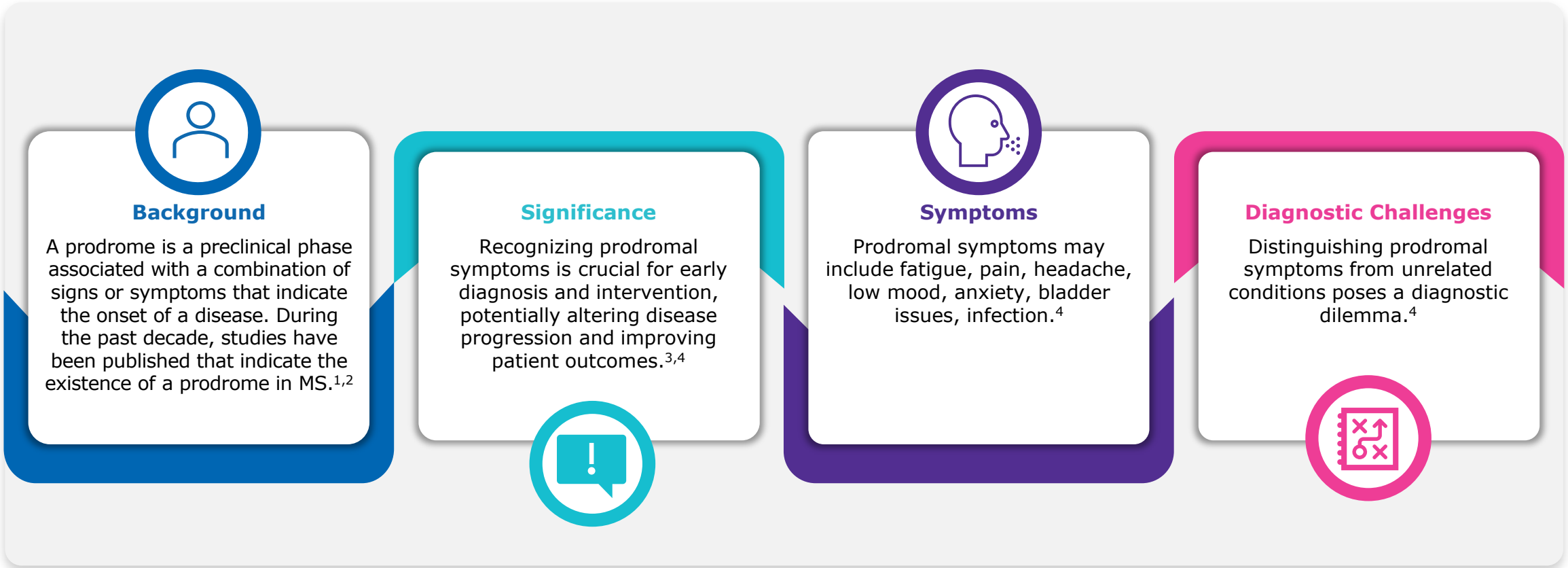


Adapted from Bar-Or A. Semin Neurol. 2008[10]

CIS, clinically isolated syndrome; CNS, central nervous system; MS, multiple sclerosis; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening

1. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:17562864211066751; 2. Kuhlmann T, et al. Lancet Neurol. 2023;22:78-88; 3. Kappos L, et al. JAMA Neurol. 2020;77:1132-1140; 4. Vollmer T, et al. Neurol Clin Pract. 2021;11:342–351; 5. Lublin F, et al. Brain. 2022;145:3147-3161; 6. Tremlett H, et al. Front Neurol. 2022;12:761408; 7. Tremlett H, Marrie RA. Mult Scler. 2021;27(1):6-12; 8. Giovannoni G. Lancet Neurol. 2017;16(6):413-414; 9. Filippi M, et al. Nat Rev Dis Primers. 2018;4:43; 10. Bar-Or A. Semin Neurol. 2008;28:29-45.

MS prodrome has clinical relevance



1. MS prodrome. The multiple sclerosis prodrome – why does it matter? https://www.msbrainhealth.org/evidence/the-multiple-sclerosis-prodrome-why-does-it-matter/ Accessed June 11, 2024; 2. Makhani N, et al. Nat Rev Neurol. 2021;17:515-521; 3. Tremlett H, et al. Front Neurol. 2022;12:761408; 4. Tremlett H, Marrie RA. Mult Scler. 2021;27:6-12.

MS, multiple sclerosis

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Radiologically isolated syndrome (RIS)

- RIS refers to an entity in which **white matter lesions** fulfilling the criteria for MS occur in individuals **without a history of a clinical demyelinating attack** or alternative etiology[1]
- Patients with RIS fall between at-risk and clinical phases as they do not have typical MS symptoms but have CNS white matter lesions highly suggestive of inflammatory demyelination[2]
- The prevalence of RIS remains unknown, however, white matter lesions resembling demyelination occur in 0.1%–0.7% of the population[1]
- ~50% of patients may develop MS clinical symptoms within 10 years after being believed to have RIS. At this point, patients may present with a first acute inflammatory demyelinating event or the onset of a progressive neurological syndrome fulfilling the criteria for PPMS[2]
- In most cases of RIS:
  - The diagnosis resulted from an evaluation of headache, trauma, or nonspecific dizziness[1]
  - Patients do not have prior clinical episodes of neurologic deficits[1]

CNS, central nervous system; MS, multiple sclerosis; PPMS, Primary Progressive Multiple Sclerosis; RIS, radiologically isolated syndrome

1. Hosseiny M, Newsome SD, Yousem DM. AJNR Am J Neuroradiol. 2020;41:1542-1549; 2. Lebrun-Frénay C, et al. Brain. 2023;146(8):3431-3443.

Clinically isolated syndrome (CIS)

- CIS refers to the **first episode of neurologic symptoms** that last at least **24 hours**, and is caused by inflammation and demyelination in the CNS[1,2]
- Symptoms of the first episode may not be explained by fever or infections[2]
- The first episode is usually followed by a complete or partial recovery from symptoms[2]
- ~80% of CIS cases progress to MS within 20 years[2]

CIS Episodes

- **Monofocal Episode:**
  - Single region of the CNS affected: such as experiencing optic neuritis[2]
- **Multifocal Episode**
  - Multiple symptoms due to the presence of lesions in multiple areas of the CNS: such as optic neuritis with leg numbness/tingling[2]

CIS, clinically isolated syndrome; CNS, central nervous system; MS, multiple sclerosis

1. National Multiple Sclerosis Society. https://www.nationalmssociety.org/understanding-ms/what-is-ms/clinically-isolated-syndrome-cis. Accessed June 11, 2024; 2. Wexler M. Clinically Isolated Syndrome. Multiple Sclerosis News Today. https://multiplesclerosisnewstoday.com/clinically-isolated-syndrome-cis/. Accessed June 11, 2024.

Each form of MS has distinct characteristics

	RRMS	SPMS	PPMS
	• RRMS is the most common form of MS, which typically presents as distinct attacks, or relapses, followed by periods of partial or complete recovery[1]	• In SPMS, the disease gradually changes from the inflammatory process seen in RRMS to a more steadily progressive phase characterized by nerve damage or loss[2]	• PPMS is a less common form of MS, which involves much less inflammation of the type seen in RRMS. Patients with PPMS tend to have more lesions in the spinal cord than in the brain[3]
	• RRMS represents **~85%** of cases at initial diagnosis[4] • MS is approximately 3 times more common among women than men and is more prevalent in women of childbearing age than in any other age group[5]	• **~50%** of patients with RRMS will progress to SPMS within 10 years, and the transition may be rapid or gradual[2]	• PPMS constitutes of **~15%** of cases at initial diagnosis[1] • About equal distribution of men and women are diagnosed with PPMS[6]
	**Clinical Characteristics[4]:** • Clearly defined relapses of new or increasing symptoms • Relapses are followed by periods of partial or complete recovery • During remissions, all symptoms may disappear, or some symptoms may continue and become permanent	**Clinical Characteristics[2]:** • Neurologic function worsens over time and disability increases • Can be characterized as active (with relapses and/or evidence of new MRI activity during a specified period of time) or not active, as well as with progression (evidence of more disability over time, with or without relapses or new MRI activity) or without progression	**Clinical Characteristics[1]:** • Worsening of neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions • Disease experience may vary significantly from patient to patient

MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, Primary Progressive MS; RRMS, Relapsing-remitting MS, SPMS, Secondary Progressive MS

1. National Multiple Sclerosis Society. https://www.nationalmssociety.org/What-is-MS/Types-of-MS. Accessed June 11, 2024; 2. National Multiple Sclerosis Society. https://www.nationalmssociety.org/understanding-ms/what-is-ms/types-of-ms/secondary-progressive-ms. Accessed June 11, 2024; 3. National Multiple Sclerosis Society. https://www.nationalmssociety.org/understanding-ms/what-is-ms/types-of-ms/primary-progressive-ms. Accessed June 11, 2024; 4. National Multiple Sclerosis Society. https://www.nationalmssociety.org/understanding-ms/what-is-ms/types-of-ms/relapse-remitting-ms. Accessed June 11, 2024; 5. National Multiple Sclerosis Society. https://www.nationalmssociety.org/understanding-ms/what-is-ms/who-gets-ms. Accessed June 11, 2024; 6. Multiple Sclerosis Trust. https://mstrust.org.uk/a-z/primary-progressive-ms. Accessed June 11, 2024.

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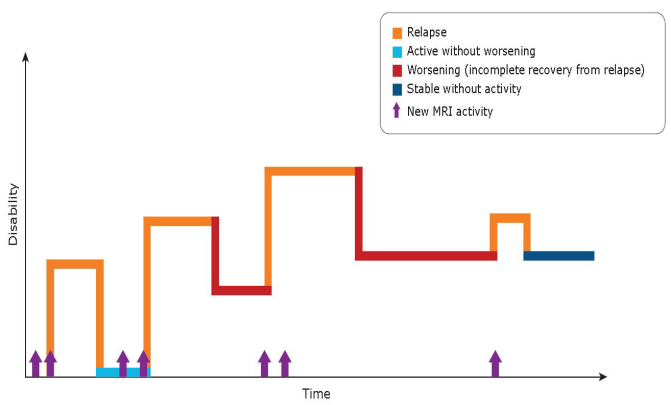
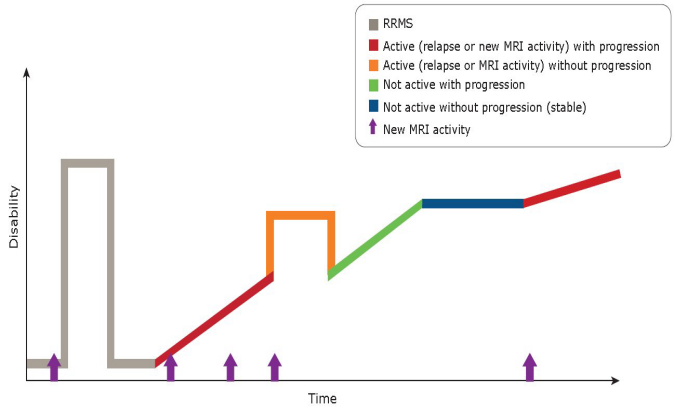
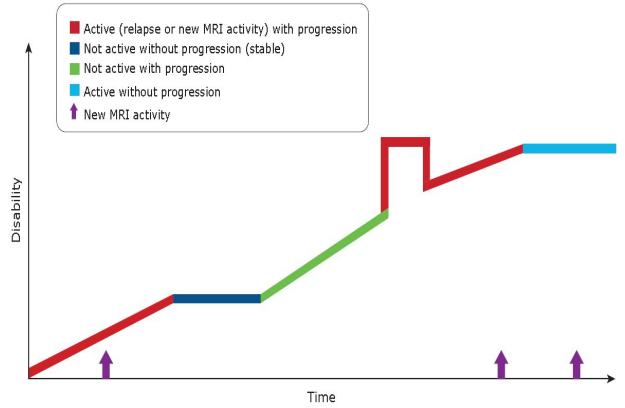
Patterns of disability over the course of MS subtypes

RRMS	SPMS	PPMS
Remyelination (the repair of myelin) is thought to occur when a symptom flare-up subsides and goes into remission.[1]	In progressive forms of MS, the cells that produce and maintain myelin are unable to repair damaged myelin, and therefore symptoms do not remit.[1]	In progressive forms of MS, the cells that produce and maintain myelin are unable to repair damaged myelin, and therefore symptoms do not remit.[1]







Adapted from National Multiple Sclerosis Society website[2]

1. Multiple Sclerosis Association of America. https://mymsaa.org/ms-information/overview/immune-system/. Accessed June 11, 2024; 2. National Multiple Sclerosis Society. https://www.nationalmssociety.org/What-is-MS/Types-of-MS. Accessed June 11, 2024.

MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, Primary Progressive MS; RRMS, Relapsing-remitting MS, SPMS, Secondary Progressive MS

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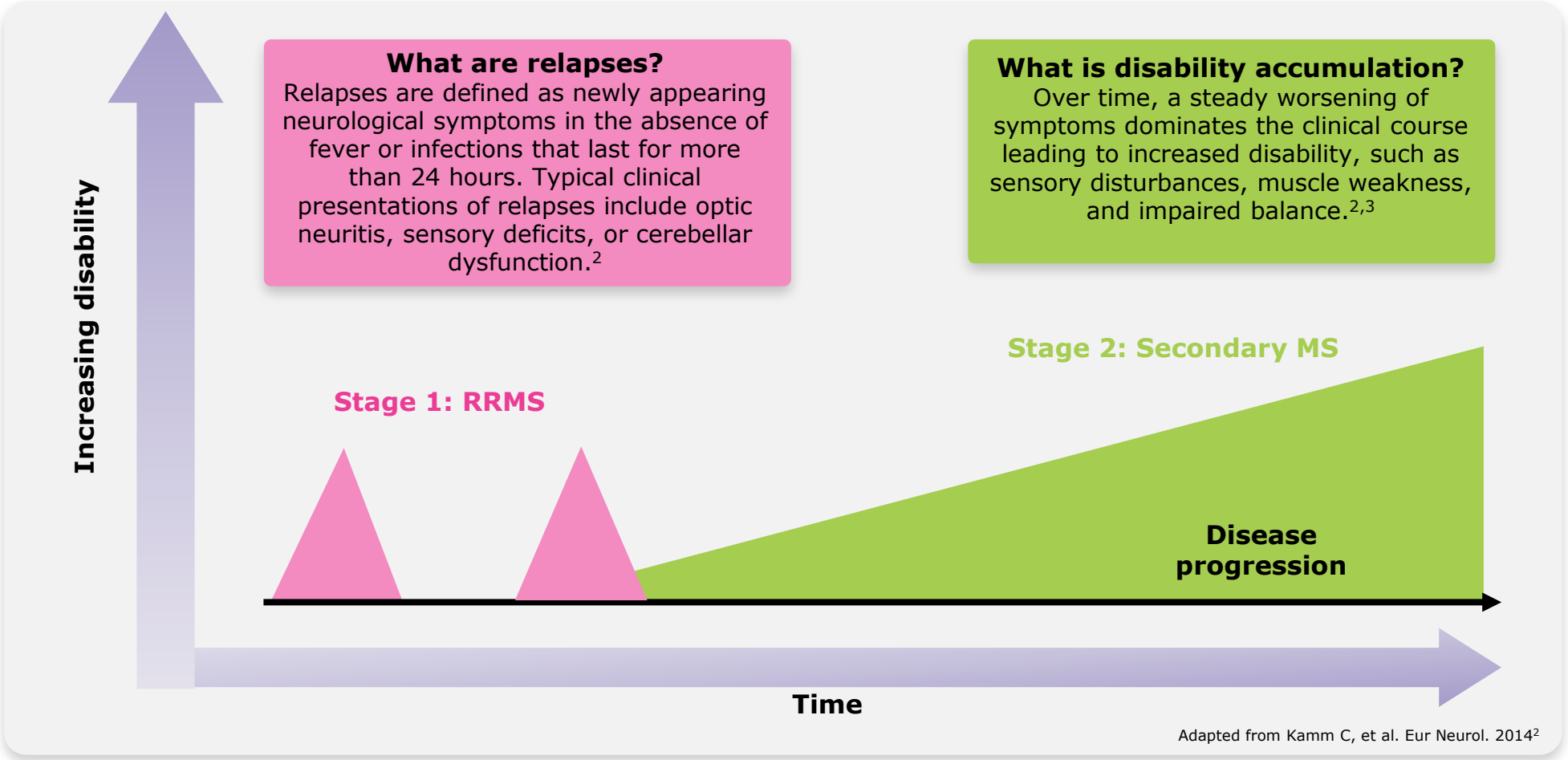
The old paradigm: MS as a two-stage disease[1]



Adapted from Kamm C, et al. Eur Neurol. 2014[2]

MS, multiple sclerosis; RRMS, Relapsing-remitting MS

1. Leray E, et al. Brain. 2010;133:1900-1913; 2. Kamm C, et al. Eur Neurol. 2014;72:132-141; 3. Huang WJ, et al. Exp Ther Med. 2017;13:3163-3166.

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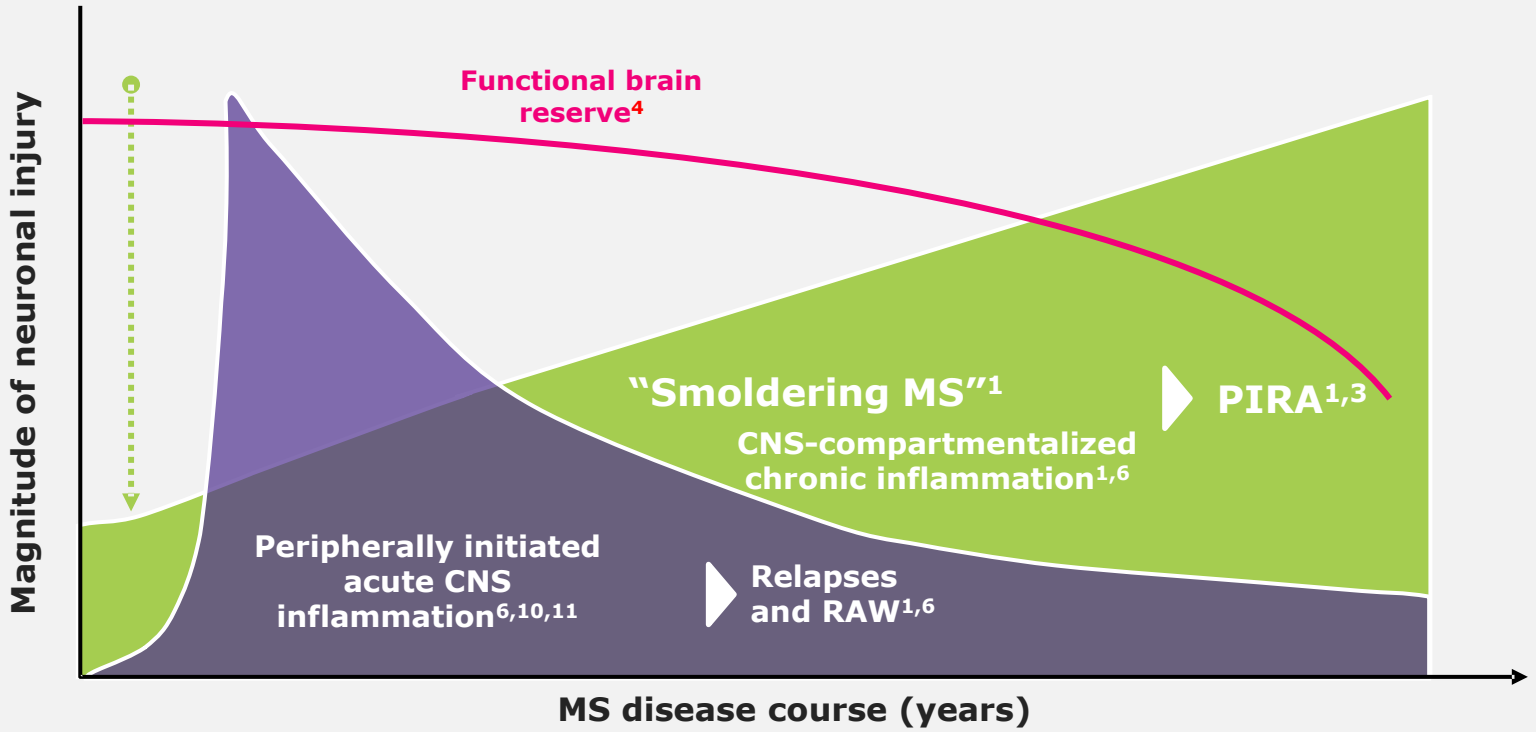
The emerging paradigm: PIRA and RAW drive total disability accumulation[1]

The phenotypic presentation of MS can be thought of as a continuum of peripherally initiated and CNS-compartmentalized inflammation.[1-5]

"Smoldering MS" refers to **CNS-compartmentalized** neuroinflammation that leads to accumulation of disability independent of relapse activity.[1,6]

PIRA is an increase in disability that occurs independently of relapse measured after re-baselining following relapse.[1,3,7]

RAW is a sustained increase in disability that begins with an incomplete relapse recovery.[1,3]



Adapted from Bar-Or A. Semin Neurol, 2008[6]

CNS, central nervous system; MS, multiple sclerosis; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening

1. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:17562864211066751; 2. Kuhlmann T, et al. Lancet Neurol 2023;22:78-88; 3. Kappos L, et al. JAMA Neurol. 2020;77:1132-1140; 4. Vollmer T, et al. Neurol Clin Pract. 2021;11:342–351; 5. Lublin F, et al. Brain. 2022;145:3147-3161; 6. Bar-Or A. Semin Neurol. 2008;28:29-45; 7. Tur C, et al. JAMA Neurol. 2023;80:151-160; 8. Portaccio E, et al. Brain. 2022;145:2796-2805; 9. Bayas A, et al. Mult Scler Relat Disord. 2022;68:104166; 10. Baker D, et al. EBioMedicine. 2017;16:41-50; 11. Papiri G, et al. Curr Issues Mol Biol. 2023;45(2):1443-1470.

PIRA and RAW are key contributors to total disability accumulation[1-3]

Acute focal inflammatory lesions (i.e., T1 Gd+)

↓

Relapses

↓

RAW[2]

A sustained increase in disability that begins with an incomplete relapse recovery

→ **Total Disability Accumulation** ←

Chronic active lesions (i.e., slowly expanding lesions, paramagnetic rim lesions)[1,4]

↓

Independent of relapses

↓

PIRA[2]

A sustained increase in disability that occurs independently of relapse activity

↑

Additional patient factors affecting disability accumulation[1-3,5-9]

Comorbidities | Biological age | Symptom management | Brain age | Socioeconomic factors

Gd+, gadolinium-enhancing; MS, multiple sclerosis; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening

1. Hauser SL, Cree BAC. Am J Med. 2020;133:1380-1390; 2. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:1-18; 3. Lublin F, et al. Brain. 2022;145:3147-3161; 4. Cagol A, et al. Neurology. 2023;102(1):e207768; 5. Scalfari A, et al. Neurology. 2011;77:1246-1252; 6. Marrie RA. Nat Rev Neurol. 2017;13:375-382; 7. Gustavsen S, et al. BMC Neurol. 2021;21(1):317; 8. Rubin SM. Dis Mon. 2013;59(7):253-260; 9. Brier MR, et al. Ann Clin Transl Neurol. 2023;10(6):990-1001.

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MS continuum: Proposed timeline

Time

At risk period → **Disease initiation** → **Prodromal phase** → **Classical MS symptom onset**

RISK FACTORS

Non-modifiable	Environmental
• Family history • Genetics • Female sex (after puberty) • Race	• EBV infection • Tobacco smoke exposure • Low sunlight • Inadequate Vitamin D nutrition • Obesity during childhood/ adolescence

Clinical/Behavioral
- Fatigue, pain, headache/migraine
- Depression, anxiety
- Higher rates of infections, visits to hospital, physician and pharmacy
- Fewer pregnancies

Putative Biomarkers
- Radiologically Isolated Syndrome (RIS)
- Increasing serum neurofilament light chain
- Other imaging or novel biomarkers

Potential for primary MS prevention
- Prevention of EBV infection (EBV vaccine)
- Increased (judicious) sun exposure
- Improve Vitamin D nutrition (sun exposure/supplements)
- Avoid cigarette smoking
- Reduce obesity levels in children and adolescents

Potential for secondary MS prevention
- Earlier recognition of MS and earlier DMT use or early use of novel neuroprotective agents
- Intervene on areas generally associated with better MS prognosis:
  - Optimize physical activity
  - Smoking cessation
  - Optimize weight
  - Improve Vitamin D nutrition

Adapted from Tremlett H, Munger KL, Makhani N. Front Neurol. 2022[1]

DMT, Disease modifying therapies; EBV, Epstein-Barr virus infection; MS, multiple sclerosis

1. Tremlett H, Munger KL, Makhani N. Front Neurol. 2022;12:761408.

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Differential Dx and Diagnostic Considerations

Prognosis of MS

Most patients with MS eventually experience progressive neurological disability[1]

9-11 years

Estimated time from onset of MS to onset of the progressive phase[2]

Older age

Onset of progression is more dependent on age than on the presence or duration of pre-progression disease course[3]

Studies have shown that early treatment with high-efficacy DMTs may delay irreversible central nervous system damage and MS-related disability progression[4]

Death as a direct consequence of MS is uncommon; however, MS is associated with an increased risk of mortality[5,6]

16%-30% Patients experience incomplete recovery following their first MS episode[2]

1. Cree BAC, Hauser SL. Harrison's Principles of Internal Medicine, 20th Edition; Part 13, Chapter 436. McGraw-Hill Education, 2018; 2. Confavreux C, Vukusic S. In: Goodin DS, ed. Handbook of Clinical Neurology. Vol. 122. Amsterdam: Elsevier, 2014; 3. Tutuncu M et al. Mult Scler.2013;19:188-198; 4. Filippi M, et al. J Neurol. 2022; 269: 5382-394; 5. Titcomb TJ, et al. Mult Scler J Exp Transl Clin. 2022;8(2):20552173221104009; 6. Scalfari A, et al. Neurology. 2013;81(2):184-192.

[a]Duration of the disease in newly-diagnosed patients with MS without severe disabilities.
DMT, disease-modifying therapies; MS, multiple sclerosis

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Patient and disease characteristics may inform MS prognosis

Better prognosis	Poor Prognosis
Demographic factors (At onset)[1-3]	
• White • Female • Age (<40 years) at disease onset	• African American • Afro–Latino • Male sex • Older age (>40 years) at disease onset
Relapse features and disability[3] (At different time points during the disease course)	

• Low relapse rate during the first 2–5 years
• High degree of remission after first relapse
• Long interval to second relapse
• Mild relapse
• No or low disability at 5 years
	• High relapse rate first 2–5 years
	• Short interattack latency
	• Short interval to second relapse
	• Severe relapse
	  ○ ≥1 moderate or severe attack
	  ○ Steroids/hospitalization required
	  ○ Severe effect on activities of daily living
	  ○ >1 functional system affected
	  ○ Severe motor/cerebellar brainstem involvement
	• Disability at 2 or 5 years

MRI features[2,3] (At different time points; onset and follow-up)	

• Low (≤386 ng/L) neurofilament light levels
• Absence of oligoclonal IgG bands
• Absence of IgM bands
• Low lesion load on MRI
	• Elevated (>386 ng/L) neurofilament light levels
	• Presence of oligoclonal IgG bands and ≥10 brain T2 lesions
	• Presence of IgM bands
	• Baseline brain atrophy
	• Abnormal MRI
	  ○ ≥2 Gd+/new or newly enlarging T2 hyperintense lesions
	  ○ ≥2 T1 hypointense lesions
	  ○ ≥2 spinal cord lesions

This is not an exhaustive list

Gd+, gadolinium-enhancing; Ig, immunoglobulin; MRI, magnetic resonance imaging; MS, multiple sclerosis

1.Ford C, Morrow SA, CMSC DMT Guideline Writing Group. Practical Guidelines for the Selection of disease-modifying therapies in multiple Sclerosis. Published online February 28, 2019. Accessed June 14, 2024; 2. Rush CA, et al. Nat Rev Neurol. 2015;11:379-389; 3. Pardo G, Jones DE. J Neurol. 2017;264(12):2351-2374.

Comprehensive evaluation for MS diagnosis

Medical and family history[1,2]

Evaluation of past and present symptoms and family medical history

MRI[1-3]

Evaluation of the brain and/or spinal cord for demyelinating lesions

Neurologic examination[1,2]

- Walking/balance
- Vision/eye movement
- Hearing
- Strength
- Speech or reflexes

Laboratory testing[1,2,4]

- **Blood tests** that help rule out other diseases
- **CSF analysis or spinal tap:** analyses of the spinal fluid for abnormal immune responses within the CNS such as oligoclonal bands
- **Evoked potential:** measurement of the CNS electrical activity

CSF, cerebrospinal fluid; CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis

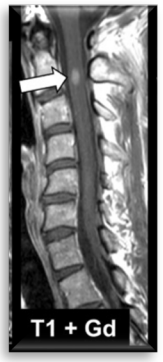
1. National Multiple Sclerosis Society. How MS is Diagnosed. https://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-MS. Accessed June 26, 2024; 2. MS Society. How is MS diagnosed. https://www.mssociety.org.uk/about-ms/diagnosis/the-tests-for-ms. Accessed June 29, 2024. 3. National Multiple Sclerosis Society. Magnetic Resonance Imaging (MRI) for diagnosing multiple sclerosis. https://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools/MRI. Accessed June 29, 2024; 4. Šoda J, et al. Sensors (Basel). 2023;23(1):497.

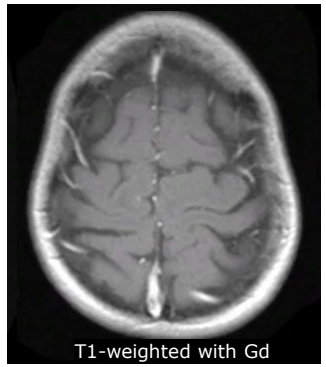
MRI is a key imaging method to diagnose and monitor MS

MRI types used to diagnose and/or monitor MS[1-5]

T-1 weighted (with Gd)

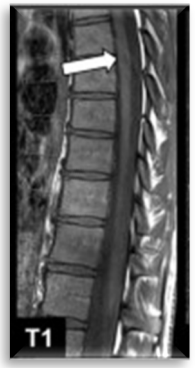
Identifies bright areas that indicate early active inflammation and disruption of BBB

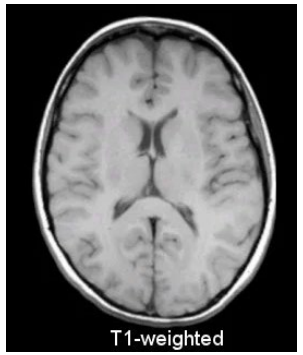


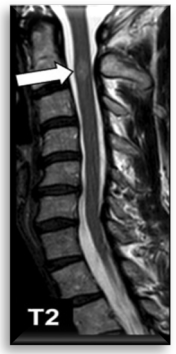


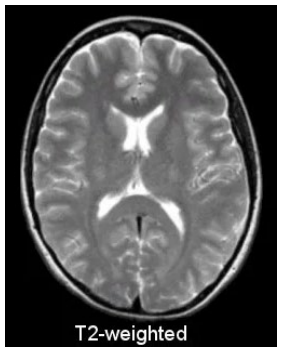
T-1 weighted (no Gd)

Identifies dark areas that indicate possible permanent nerve damage



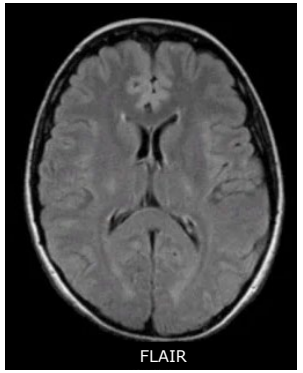






T-2 weighted

Captures overall disease burden or lesion load
(total number of lesions, both old and new)



FLAIR

Shows MS activity by reducing interference from the spinal fluid

1. National Multiple Sclerosis Society. Magnetic Resonance Imaging (MRI). https://www.nationalmssociety.org/Symptoms-Diagnosis/Diagnosing-Tools/MRI. Accessed August 20, 2024. 2. Saade C et al. Am J Neuroradiol. 2018;39:2168-2176; 3. Riederer I, et al. Eur Radiol. 2021;31:9316-9323; 4. Magnetic Resonance Imaging (MRI) of the Brain and Spine: Basics. https://case.edu/med/neurology/NR/MRI%20Basics.htm. Accessed June 11, 2024; 5. Filippi M, et al. J Neurol Neurosurg Psychiatry. 1996;61(6):632-635.

BBB, blood-brain barrier; FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis

Standardized brain MRI protocol for MS diagnosis[1,2]

The protocol was released in 2021 by CMSC-MAGNIMS-NAIMS for MS diagnosis, optimizing field strength, acquisition methods, and scan orientation to ensure accurate lesion assessment and disease monitoring

	Brain	Spinal cord	Optic nerve
Field strength	≥1.5 T (preferably 3 T)	≥1.5 T (3 T has no added value compared with 1.5 T)	≥1.5 T
Slice thickness	3D: 1 mm isotropic[a] 2D: ≤3 mm, no gap[b]	Sagittal ≤3 mm, no gap Axial ≤5 mm, no gap	≤2-3 mm, no gap
In-pane resolution	≤1 mm × 1 mm	≤1 mm × 1 mm	≤1 mm × 1 mm
Coverage	Whole brain (covering as much of cervical cord as possible)	Cervical and thoracolumbar spinal cord, to include conus	Optic nerve and optic chiasm
Axial scan orientation	Subcallosal plane to prescribe (ie, for 2D imaging) or reformat (ie, for 3D imaging) axial oblique slices	Perpendicular to the sagittal axis of the spinal cord	Align to optic nerve and optic chiasm orientation

Table adapted from Wattjes MP, et al. Lancet Neurol. 2021;20(8):653-670.
[a]1 mm isotropic is preferred but, if over-contiguous (through plane and in plane), not >1.5 mm with 0.75 mm overlap.
[b]except for diffusion-weighted imaging for which slice thickness should be ≤5 mm with a 10%-30% slice gap.

2D, two dimensional; 3D, three dimensional; CMSC, Consortium of Multiple Sclerosis Centers; MS, multiple sclerosis; MAGNIMS, Magnetic Resonance Imaging in Multiple Sclerosis; MRI, magnetic resonance imaging; NAIMS, North American Imaging in Multiple Sclerosis; T, Tesla

1. Wattjes MP, et al. Lancet Neurol. 2021;20:653-670;
2. The Consortium of Multiple Sclerosis Centers. 2021 MAGNIMS-CMSC-NAIMS Standardized MRI Protocol. https://mscare.sharefile.com/share/view/s16fa7f9d0c214c1cb5bd8f809ac07215. Accessed August 28, 2024.

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2021 CMSC-MAGNIMS-NAIMS standardized brain MRI protocol recommendations[1,2]

Brain	Diagnosis	Follow-up monitoring	Safety monitoring
Axial T_2		±[a]	±[a]
Sagittal and axial T2-weighted FLAIR (preferably 3D)			
Post-Gd axial (or 3D sagittal) T_1			
Diffusion-weighted imaging		DDx	
DIR or PSIR			
High-resolution isotropic 3D T_1 (brain volume assessment)			
Susceptibility-weighted imaging			

Optic nerve	Diagnosis	Follow-up monitoring	Safety monitoring
Axial & coronal fat-suppressed T_2 or STIR			
Post-Gd[b] axial & coronal fat-suppressed T_1			
Spinal cord	**Diagnosis**	**Follow-up monitoring**	**Safety monitoring**
Sagittal at least two of: T2 (TSE or FSE), PD (TSE or FSE), or STIR			
Sagittal 3D T_1 (PSIR, MPRAGE)[c] for cervical only			
Axial T_2 (TSE or FSE) or gradient-recalled echo T_2^*			
Pre-Gd sagittal T_1 (TSE or FSE)			
Post-Gd[b] sagittal T_1 (TSE or FSE)			
Post-Gd[b] axial T_1 (TSE or FSE)			

Color representations:

Recommended core	Optional	Not required

[a]±, Axial T_2 optional if sagittal 3D T2-weighted FLAIR and multiplanar reconstructions in sagittal/axial planes are available; [b]No additional Gd necessary if immediately following Post-Gd brain examination; [c]Could substitute for one of T_2, PD or STIR.

Gd, macrocyclic agent, 0.1 mmol/kg body weight, minimum delay 5-10 minutes; **High resolution 3D T_1**, e.g. MPRAGE/MP2RAGE magnetization-prepared rapid acquisition of gradient echoes, IR-SPGR, TFE; **T_1**, TSE/FSE; **T_2**, TSE/FSE.

3D, three dimension; CMSC, Consortium of Multiple Sclerosis Centers; DIR, double inversion recovery; DMT; disease modifying treatment; DDx, differential diagnosis; FLAIR, fluid-attenuated inversion recovery, with optional fat suppression; FSE, Fast-spin-echo; Gd, gadolinium; IR-SPGR, inversion recovery prepared spoiled gradient; MAGNIMS, Magnetic Resonance Imaging in Multiple Sclerosis; MPRAGE, magnetization-prepared rapid acquisition with gradient echo; MP2RAGE, Magnetization Prepared 2 Rapid Acquisition Gradient Echoes; MS, multiple sclerosis; NAIMS, North American Imaging in Multiple Sclerosis; PD, proton-density: PSIR, phase-sensitive inversion recovery; Sm, safety monitoring for DMT, e.g., screening for risk of progressive multifocal leukoencephalopathy; STIR, short tau inversion recovery; TFE, turbo field-echo; TSE, Turbo-spin-echo

1. Wattjes MP, et al. Lancet Neurol. 2021;20:653-670;
2. The Consortium of Multiple Sclerosis Centers. 2021 MAGNIMS-CMSC-NAIMS Standardized MRI Protocol. https://mscare.sharefile.com/share/view/s16fa7f9d0c214c1cb5bd8f809ac07215. Accessed August 28, 2024.

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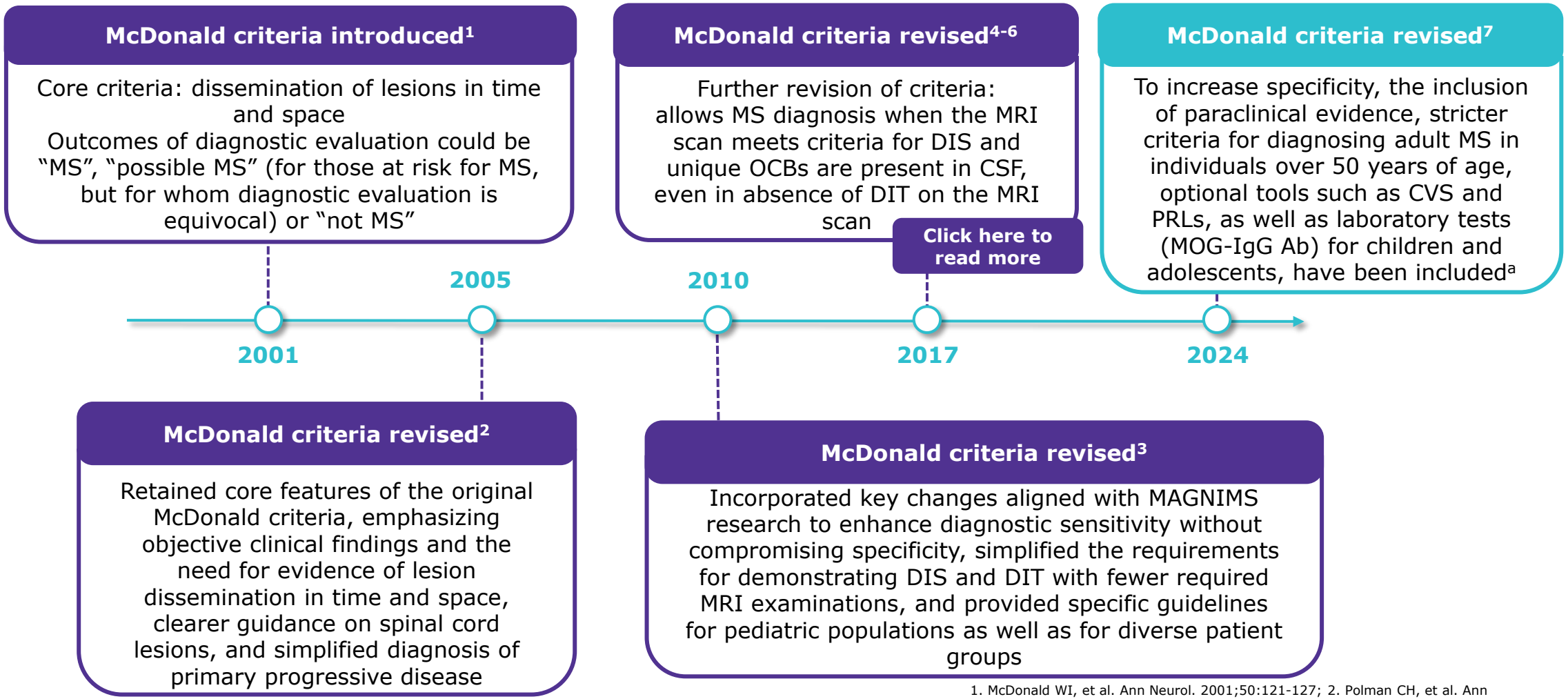
McDonald criteria are used worldwide to diagnose MS



[a]The description is based on an oral presentation at ECTRIMS 2024 and may still be undergoing revisions. Finalized criteria will be available upon manuscript publication. Please refer to the published work for the most accurate information. CSF, cerebrospinal fluid; CVS, central vein sign; DIS, dissemination in space; DIT, dissemination in time; MOG-IgG Ab, myelin oligodendrocyte glycoprotein immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis; PRL, paramagnetic rim lesion; OCBs, oligoclonal bands

1. McDonald WI, et al. Ann Neurol. 2001;50:121-127; 2. Polman CH, et al. Ann Neurol. 2005;58:840-846; 3. Polman CH, et al. Ann Neurol. 2011;69:292-302; 4. Thompson AJ, et al. Lancet Neurol. 2018;17:162-173; 5. van der Vuurst de Vries RM, et al. JAMA Neurol. 2018;75(11):1392-1398; 6. Schwenkenbecher P, et al. Front Neurol. 2019;10:188; 7. Montalban X, et al. ECTRIMS 2024

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The McDonald criteria 2017

The 2017 McDonald criteria for diagnosis of MS in patients with an attack at onset

Number of clinical attacks	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of MS
≥2 clinical attacks	≥2	None[a]
≥2 clinical attacks	1 *(As well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)*[b]	None[a]
≥2 clinical attacks	1	DIS demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥2	DIT demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands[c]
1 clinical attack	1	DIS demonstrated by an 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[c]

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If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. [a]No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. [b]Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. [c]The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

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

CSF, cerebrospinal fluid; DIT, dissemination in time; DIS, dissemination in space; MRI, magnetic resonance imaging; MS, multiple sclerosis

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2017 McDonald criteria for demonstration of DIS and DIT by MRI in a patient with a CIS

DIS[1]

DIS can be demonstrated by one or more T2-hyperintense lesions[a] that are characteristic of multiple sclerosis in two or more of four areas of the CNS:

- periventricular,[b]
- cortical or juxtacortical,
- infratentorial brain regions,
- and the spinal cord

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

[b]For some patients, individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.

DIT[1]

DIT can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions[a] at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

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

MS can be diagnosed more frequently at the time of the first clinical event using the 2017 McDonald criteria than using the 2010 McDonald criteria[2]

1. Thompson AJ, et al. Lancet Neurol. 2018;17(2):162-173;
2. Schwenkenbecher P, et al. Front Neurol. 2019;10:188.

CIS, clinically isolated syndrome; CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; MRI, magnetic resonance imaging; MS, multiple sclerosis

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The McDonald criteria were updated in 2024

2024 recommended changes	
RIS	In patients with RIS, meeting the following is sufficient for diagnosing MS: • DIS and DIT • DIS and OCB • DIS ≥6 CVS
Optic nerve as a 5th topography	Findings which may serve as evidence of optic nerve involvement: • MRI: ≥1 typical short segment intrinsic optic nerve lesions with no better explanation identified • VEP: Abnormal peak time using a full field pattern reversal • OCT: Abnormal
DIT is no longer needed	
Updated DIS criteria	• DIS is met when 2 out of 5 topographies (ON, JC/IC, PV, IT, spinal cord) show typical lesions, regardless of whether these lesions are symptomatic • In patients with progressive disease, 2 spinal cord lesions are sufficient to demonstrate DIS • Meeting the criteria of DIS and DIT (as per 2017 McDonald criteria) is sufficient to diagnose MS • Meeting the criteria of DIS plus OCB and/or KFLC (as per 2017 McDonald Criteria) is sufficient to diagnose MS • In patients with typical symptoms, the presence of typical lesions in ≥4 topographies is sufficient to diagnose MS • In patients with typical symptoms and typical lesions in 1 topography, the presence of 6 CVS or PRLs plus DIT or CSF positive is sufficient to diagnose MS

NOTE: The information provided is based on an oral presentation at ECTRIMS 2024 and may still be undergoing revisions. Finalized criteria will be available upon manuscript publication. Please refer to the published work for the most accurate information.

CSF, cerebrospinal fluid; CVS, central vein sign; DIS, dissemination in space; DIT, dissemination in time; IC, intracortical; IT, infratentorial; JC, juxtacortical; KFLC, kappa free light chain; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCB, oligoclonal band; OCT, optical coherence tomography; ON, optic nerve; PRL, paramagnetic rim lesions; PV, periventricular; RIS, radiologically isolated syndrome; VEP, visual evoked potential

Montalban X, et al. ECTRIMS 2024

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The McDonald criteria were updated in 2024 (cont.)

2024 recommended changes	
KFLCs as a tool for diagnosis of MS	• KFLC are interchangeable with OCB
Same criteria for PPMS and RMS diagnosis	• PPMS: ≥2 spinal cords lesions is evidence for DIS in the diagnosis of PPMS
Need of paraclinical evidence to diagnose MS	
Stricter features for confirming diagnosis in individuals over 50 years, or with headache disorders (including migraine), or with vascular disorders	• A spinal cord lesion, positive CSF or CVS can serve as an additional feature
Addition of CVS and PRLs as optional tools for diagnosis in certain situations	• In patients with typical symptoms and typical lesions in 1 topography: presence of 6 CVS or ≥1 PRL plus DIT or CSF positive
Pediatric MS	• Presence of CVS in ~50% of T2 lesions strongly suggests MS • MOG-IgG Ab cell-based assay testing strongly recommended in children with initial demyelinating incident <12 years of age • ≥12 years of age with demyelinating event: MOG-IgG Ab cell-based assay testing is recommended for atypical presentation of MS

NOTE: The information provided is based on an oral presentation at ECTRIMS 2024 and may still be undergoing revisions. Finalized criteria will be available upon manuscript publication. Please refer to the published work for the most accurate information.

Ab, antibody; CSF, cerebrospinal fluid; CVS, central vein sign; DIT, dissemination in time; Ig, immunoglobulin; KFLC, kappa free light chain; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; OCB, oligoclonal band; PPMS, primary progressive MS; PRL, paramagnetic rim lesions; RMS, relapsing MS

Montalban X, et al. ECTRIMS 2024

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It is important to distinguish MS from other conditions

Differential diagnosis: Diseases that mimic MS[1,2]	
Autoimmune disorders • Sjögren syndrome • SLE	Demyelinating disease • ADEM
Infectious diseases • HIV • Lyme disease • Syphilis	Neoplasms • CNS: glioma, lymphoma
CADASIL	Sarcoidosis
Migraine	Stroke
Hereditary spastic paraplegia and ataxia	Vasculitis
Behçet disease	

This is an illustrative but not an exhaustive list

ADEM, acute disseminated encephalomyelitis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; HIV, human immunodeficiency virus; MS, multiple sclerosis; SLE, systemic lupus erythematosus

1. Scolding N. J Neurol Neurosurg Psychiatry. 2001;71:ii9–ii15; 2. Deangelis TM, Miller A. Handb Clin Neurol. 2014;122:317-342.

MRI scans of long-standing MS and coexisting CNS disease

Periventricular and subcortical confluent
.

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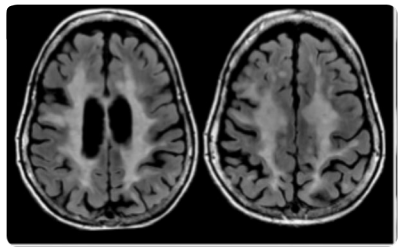

Central pontine lesions (solid arrows)

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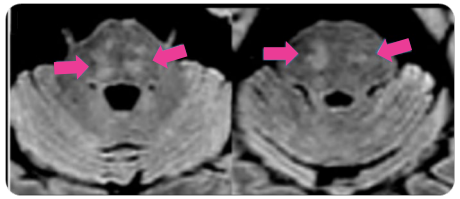

Enlarging meningioma

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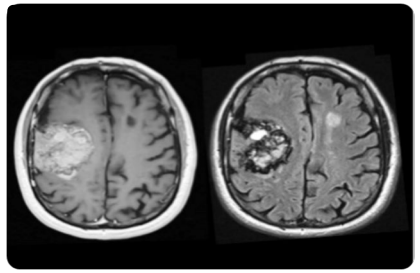

Compression on the spinal cord exerted by intervertebral disc protrusion at the C6-C7 level

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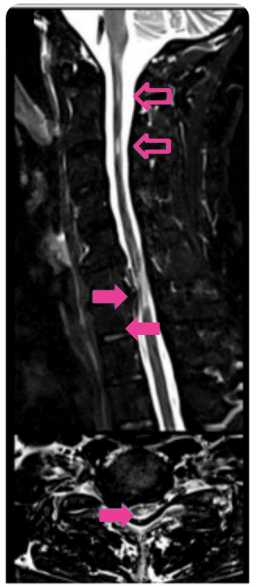

Formerly discrete lesions

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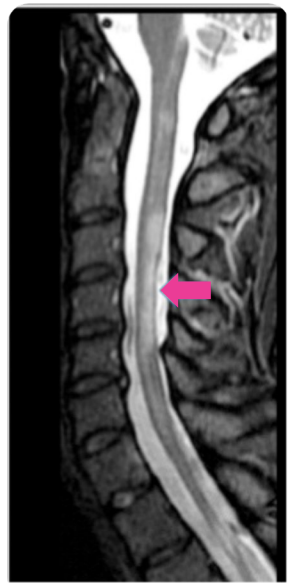

Solomon AJ, et al. Neurol Clin Pract. 2022;12:263-269.

CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis

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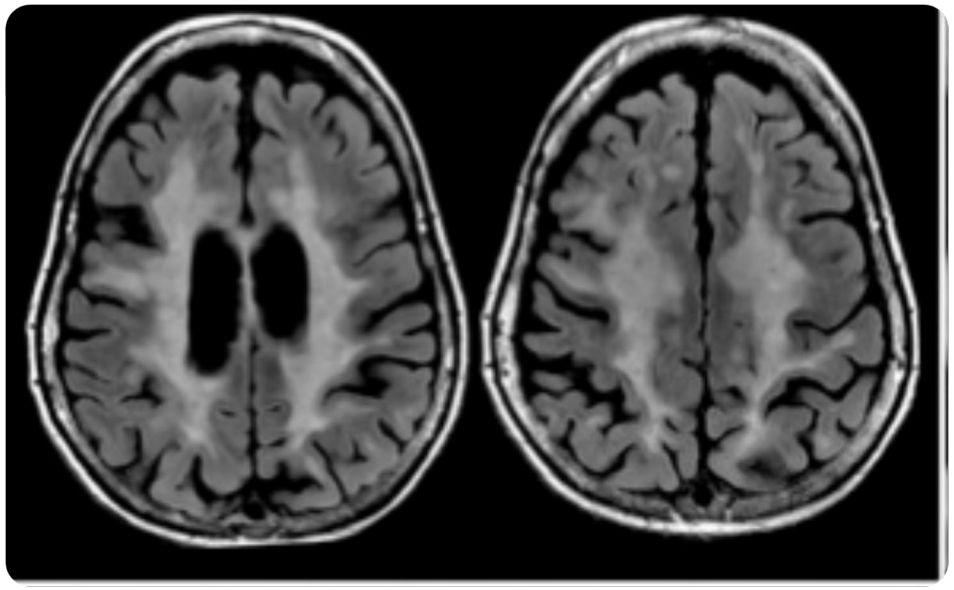
Periventricular and subcortical confluent MRI signal abnormalities mimicking chronic small vessel ischemic disease or leukodystrophy in a patient with long standing MS without a history of, or risk factors for, vascular disease.



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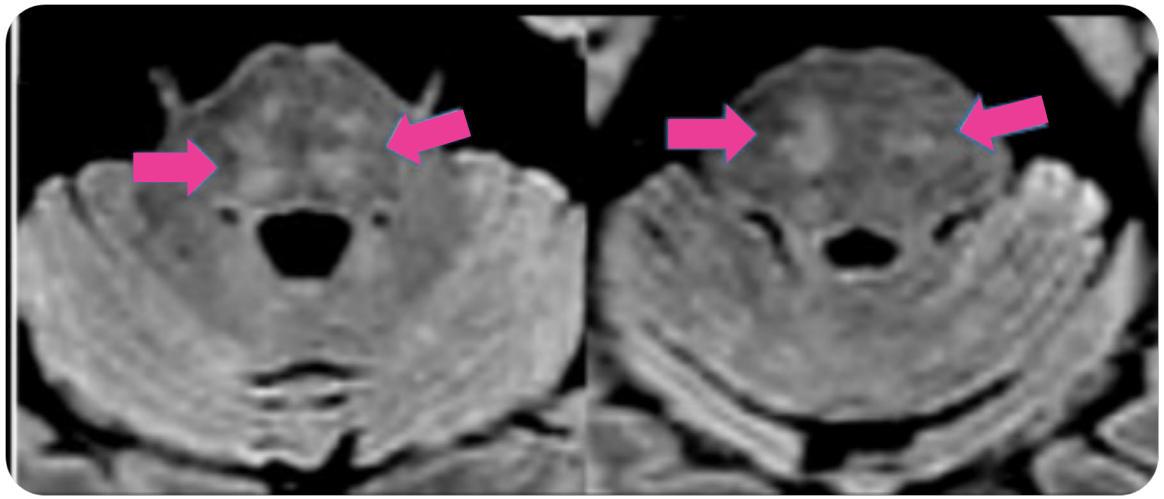
Central pontine lesions (solid arrows) suggestive of small vessel ischemic disease in a patient with both MS and vascular disease.



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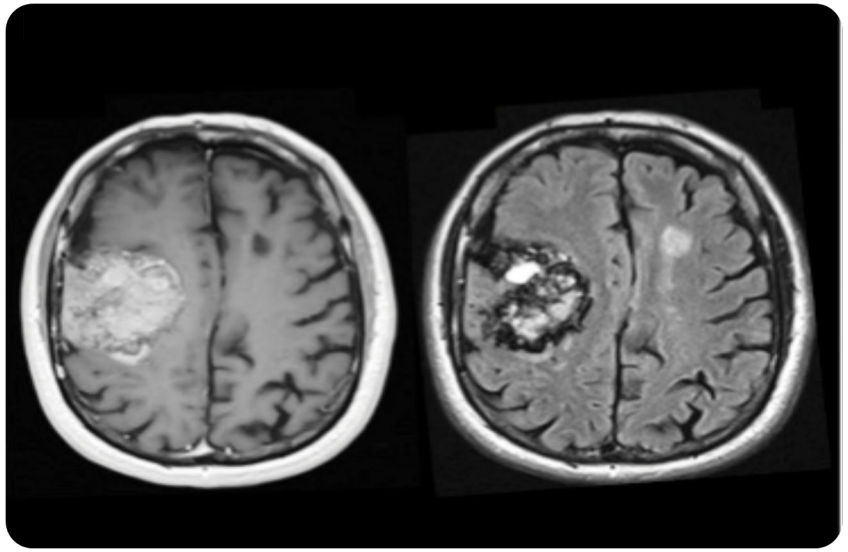
A patient with MS who presented with gradually progressive left arm and leg weakness due to an **enlarging meningioma**.



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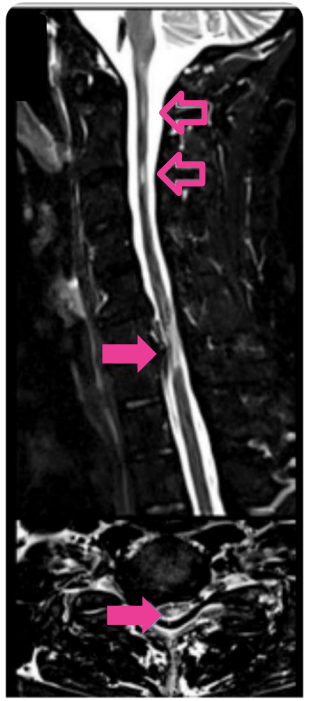
A patient with MS and progressive leg weakness due to compressive cervical myelopathy. Images show **compression on the spinal cord exerted by intervertebral disc protrusion at the C6-C7 level**, associated with central spinal cord signal changes (solid arrow), and lesions from MS seen superiorly (open arrows).



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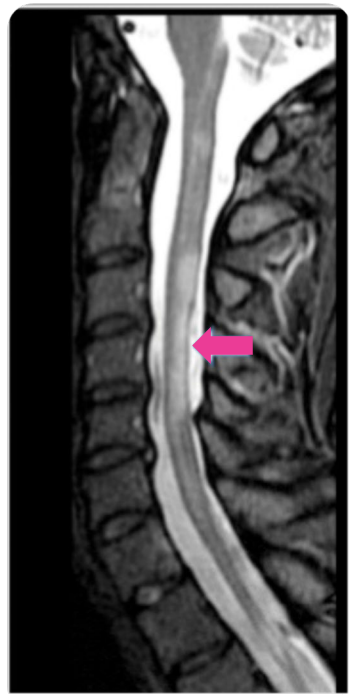
Formerly discrete lesions in a patient with MS, which over time have formed the appearance of longitudinally extensive myelitis (solid arrow).



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Comorbidities can be associated with delays in diagnosis, disability progression, and decreased quality of life[1]

Comorbidities are common in patients with MS and may include the following [1]:

- Depression
- Diabetes
- Cardiovascular diseases *(hypertension and hypercholesterolemia)*
- Chronic lung disease
- Anxiety
- Other autoimmune conditions *(thyroid and inflammatory bowel disease)*

Impact in MS

- Type 1 diabetes is possibly associated with an increase in brain atrophy in patients with MS[2]
- Both diagnostic delays and disability at diagnosis are influenced by comorbidities[3]
  - Diagnostic delay increased with the presentation of obesity, smoking, or physical or mental comorbidities[3]
- Comorbidities increase the complexity of patient management and have health, social, and economic consequences for patients with MS[1]

1. Magyari M, Sorensen SP et al. Front Neurol. 2020; 11: 851; 2. Lorefice L et al. J Neurol. 2018;265:1096-1110; 3. Marrie RA, et al. Neurology. 2009;72:117-124.

MS, multiple sclerosis

Immunology and pathophysiology of MS

B and T cell involvement

Cells of the adaptive immune system provide antigen-specific responses and have the capacity for memory.[1] In MS, B and T cell activity in the CNS is thought to play major role in disease activity[2]

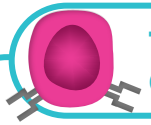
Adaptive immunity[1]

- Develops in response to a foreign substance or microorganism
- The primary functions of the adaptive immune response include recognition of specific "non-self" antigens in the presence of "self" antigens
- Includes development of immunologic memory that can rapidly eliminate a specific pathogen in case of subsequent infections

B Cells[1, 3]
Humoral immunity

B cells originate in the bone marrow, migrate to the lymph tissues to attain maturity and await activation via contact with an antigen

- B cells multiply and transform into plasma cells or memory B cells when exposed to foreign antigens
- Memory B cells are long-lasting and possess antigen-binding receptors for quick reactivity upon re-exposure
- Plasma cells are short-lived cells that undergo apoptosis when the inciting agent that induced the immune response is eliminated



T Cells[1, 3]
Cell-mediated immunity

T cells originate in the bone marrow and migrate to the thymus to mature. In the thymus, T cells acquire the ability to distinguish "self" antigens from "non-self" antigens, an essential function of determining whether the particles the T cells encounter are invaders

- These cells express a unique antigen-binding receptor on their membrane, known as the TCR
- T cells require the action of APCs (usually dendritic cells, but also macrophages, B cells, fibroblasts, and epithelial cells) to recognize a specific antigen

1. Warrington R et al. Allergy Asthma Clin Immunol. 2011;7 Suppl 1:S1; 2. Langelaar JV et al. Front Immunol. 2020; 11: 760; 3. Beltina.org. Lymphocytes? https://www.beltina.org/health-dictionary/lymphocyte-definition-what-are-b-t-high.html. Accessed September 26, 2024.

APC, antigen-presenting cells; CNS, central nervous system; MS, multiple sclerosis; TCR, T cell receptor

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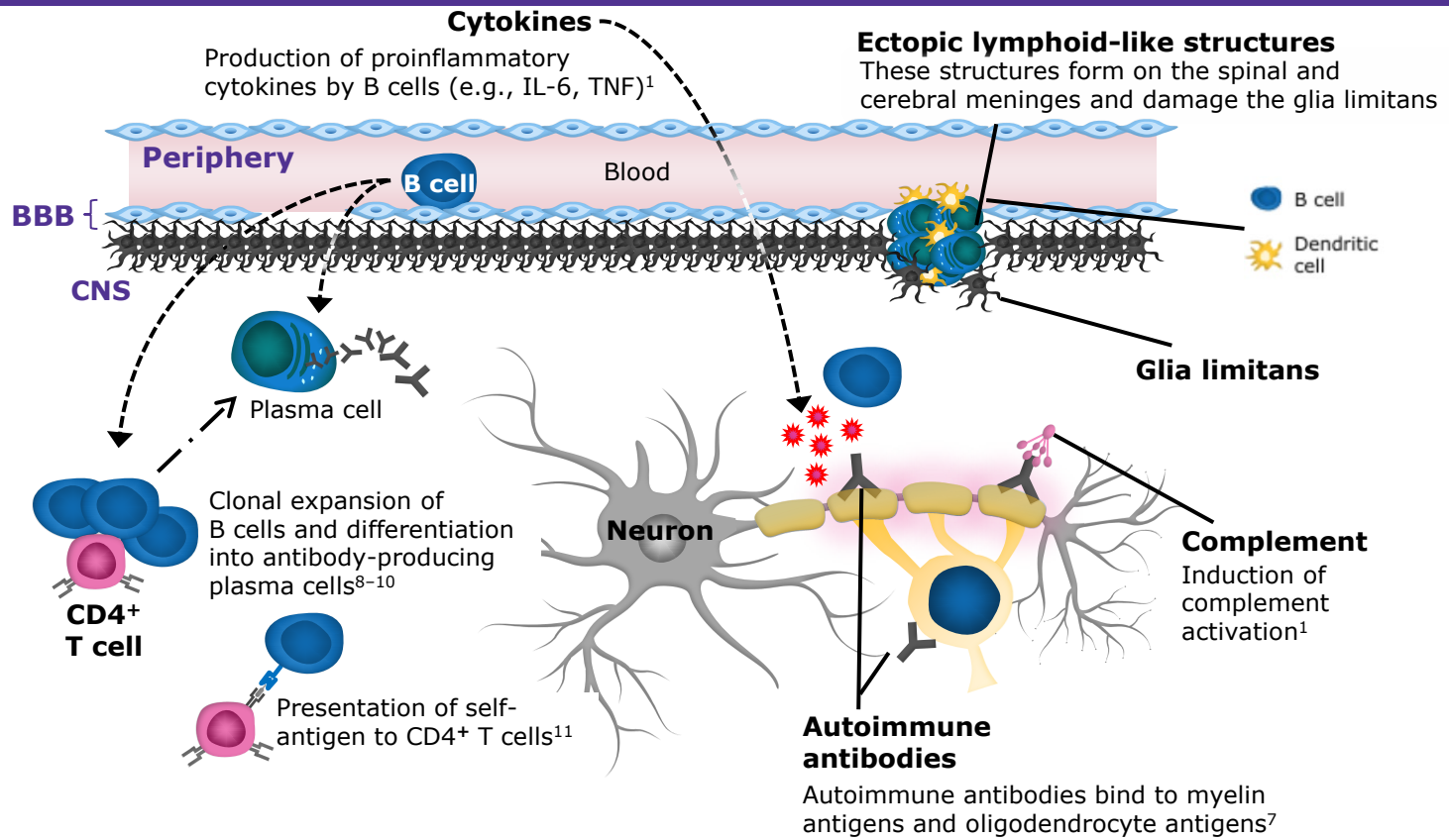
B cells in MS

B cells may contribute to MS disease activity through multiple mechanisms: antigen presentation, inflammatory cytokine secretion, and antibody production[1–3]



- In patients with MS, B cells may be found within the CNS, including the CSF[4]
- Although the T cell composition of infiltrates does not differ as the disease develops, the relative proportion of B cells and plasma cells increase[5]
- B-cell exchange may occur in both the peripheral nervous system and the CNS[6]
- Inflammatory B-cell aggregates (ectopic lymphoid-like structures) are often observed at later stages of MS and are associated with cortical demyelination and tissue injury[5]

Figure developed based on information from Noseworthy JH, et al. N Engl J Med. 2000;343:938-952

BBB, blood-brain barrier; CD, cluster of differentiation; CNS, central nervous system; CSF, cerebrospinal fluid; IL, interleukin; MS, multiple sclerosis; TNF, tumor necrosis factor

1. Hoffmann F, Meinl E. Eur J Immunol. 2014;44:1247-1250; 2. Baker D, et al. EBioMedicine. 2017;16:41-50; 3. Blauth K, et al. Front Immunol. 2015;6:565; 4. Obermeier B, et al. J Neuroimmunol. 2011;233:245-248; 5. Dendrou CA, et al. Nat Rev Immunol. 2015;15:545-558; 6. von Büdingen HC, et al. J Clin Invest. 2012;122:4533-4543; 7. von Büdingen HC, et al. Curr Opin Immunol. 2011;23:713-720; 8. Warrington R, et al. Allergy Asthma Clin Immunol. 2011;7:S1; 9. Noseworthy JH, et al. N Engl J Med 2000;343:938-952; 10. Michel L, et al. Front Immunol. 2015;6:636; 11. Abbas AK, et al. In: Cellular and Molecular Immunology. 8th edn. Philadelphia, PA: Elsevier Saunders, 2015:239-263.

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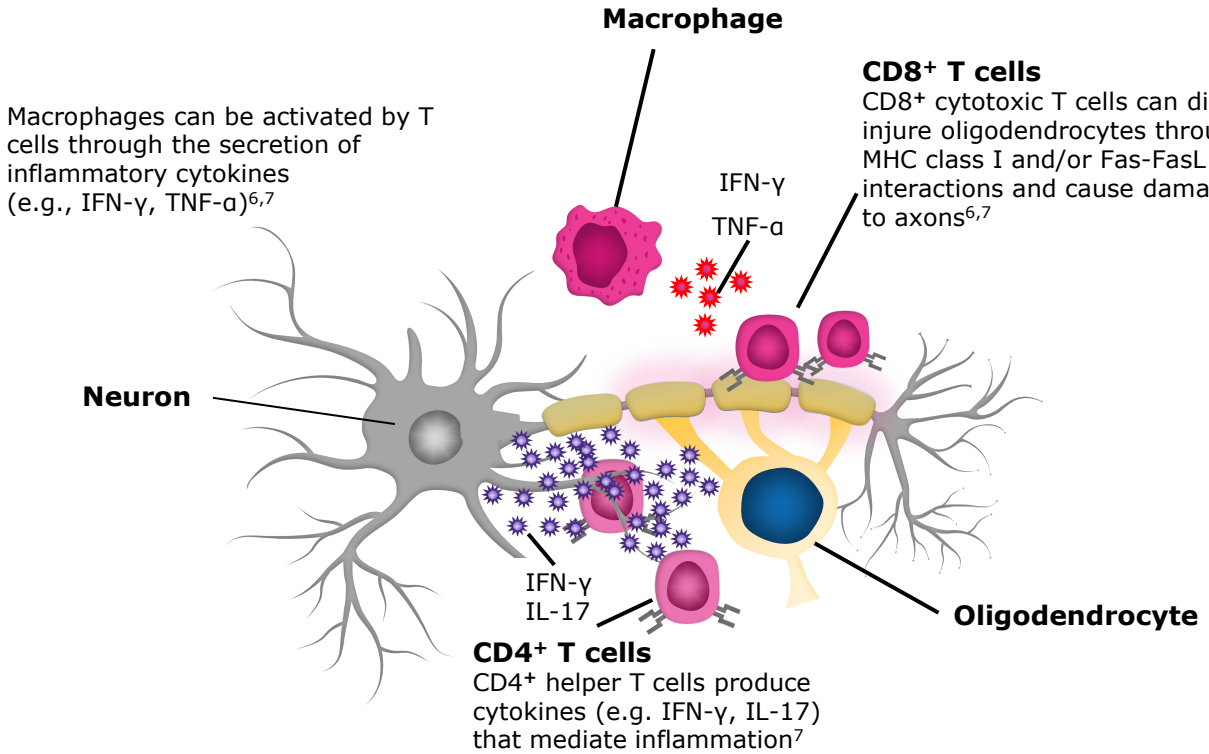
T cells in MS

MS is believed to be driven, in part, by myelin basic protein-specific autoreactive T cells that infiltrate the CNS and mediate an inflammatory response, resulting in demyelination and axon degradation[1,2]



- It remains unclear how T cells become activated against self-antigen in MS; possible causes include infectious agents resembling part of a self-antigen, leading to T cell activation via molecular mimicry, novel auto-antigen presentation, release of sequestered CNS antigen, and bystander activation[3]
- Reactivated CD8+ and CD4+ T cells can directly damage oligodendrocytes and neurons;[4] they can also release cytokines that regulate inflammation and result in CNS damage[5,6]

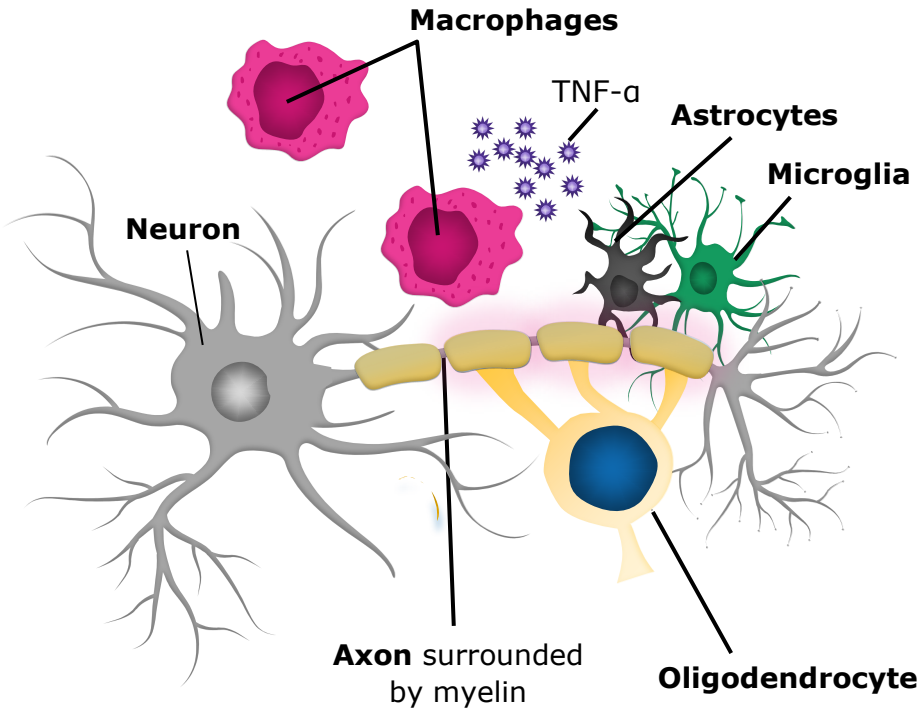
Figure developed based on information from Noseworthy JH, et al. N Engl J Med. 2000;343:938-952

APC, antigen-presenting cell; CD, cluster of differentiation; CNS, central nervous system; FasL, Fas ligand; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; MS, multiple sclerosis; TNF, tumor necrosis factor

1. Chastain E, et al. Biochim Biophys Acta. 2011;1812:265-274; 2. Frohman EM, et al. N Engl J Med. 2006;354:942-955; 3. Dendrou CA, et al. Nat Rev Immunol. 2015;15:545-558; 4. Hemmer B, et al. Curr Neurovasc Res. 2004;1:141-150; 5. Schreiner B, Becher B. Swiss Med Wkly. 2015;145:w14199; 6. Friese MA, Fugger L. Brain. 2005;128:1747-1763; 7. Noseworthy JH, et al. N Engl J Med. 2000;343:938-952.

Other cells in MS pathology

Macrophages, microglia, and astrocytes can present antigens to lymphocytes in the CNS and produce cytokines that support the inflammatory environment in MS[1–4]



- Monocyte-derived **macrophages** infiltrate the CNS and may initiate demyelination at disease onset[1]
- **Microglia** are CNS-resident macrophages that have pro- and anti-inflammatory roles; they can also present antigens, but this process is less efficient compared with that of other cells[1,2]
- In response to inflammatory stimuli, macrophages and microglia[2,3]:
  - Produce proinflammatory cytokines (e.g., TNF-α) that stimulate the proliferation of $CD4^+$ T cells
- The relative role of microglia vs monocyte-derived macrophages in MS has not been fully elucidated[1]
- Similar to microglia, **astrocytes can produce** inflammatory mediators (such as cytokines, chemokines, and ROS) that promote and sustain neuroaxonal damage and thus leading to neurodegeneration[1]

Figure developed based on information from Noseworthy JH et al. N Engl J Med. 2000;343:938–52.

CD, cluster of differentiation; CNS, central nervous system; IFN, interferon; ROS, reactive oxygen species; MS, multiple sclerosis; TNF, tumor necrosis factor

1. Dendrou CA, et al. Nat Rev Immunol. 2015;15:545-558; 2. Chastain E, et al. Biochim Biophys Acta. 2011;1812:265-274; 3. Noseworthy JH, et al. N Engl J Med. 2000;343:938-952; 4. Rawji KS, Yong VW. Clin Dev Immunol. 2013;2013:948976.

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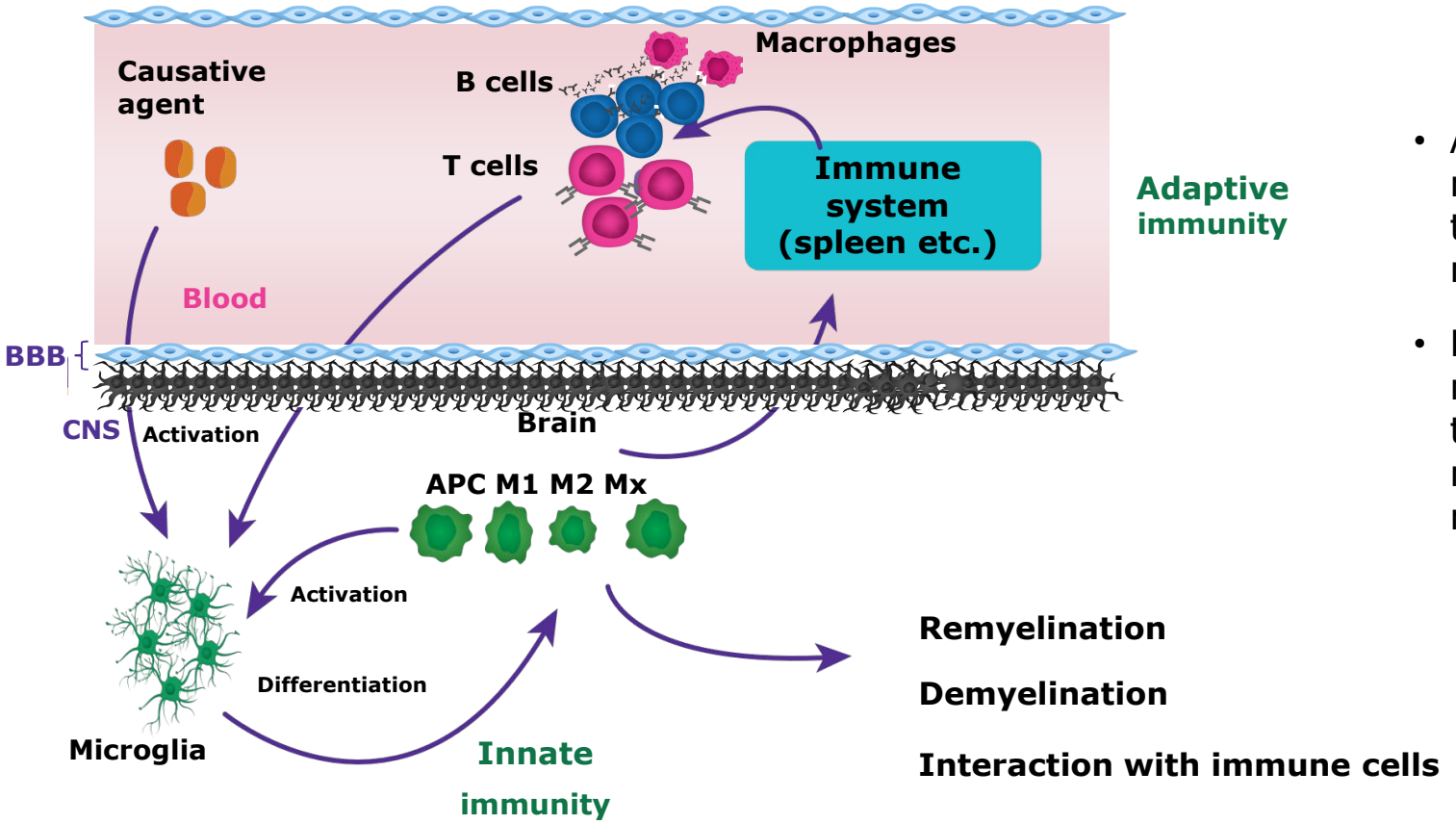
Role of microglia in the pathogenesis of MS

Microglia are CNS-resident macrophages that have pro- and anti-inflammatory roles

Proposed model for the role of microglia in MS



- Activated microglia produce ROS and NO radicals in MS lesions, which suggests their role in the demyelination and neurodegenerative process of MS
- Recent evidence also suggests the role of microglia in promoting remyelination through the expression of anti-inflammatory molecules, phagocytosis of debris, and repair of tissues

APC, antigen-presenting cell; BBB, blood-brain barrier; CNS, central nervous system; MS, multiple sclerosis; M1, M2, Mx, microglia subgroups; NO, nitric oxide; ROS, reactive oxygen species

Luo C, et al. Neuropsychiatr Dis Treat. 2017;13:1661-1667.

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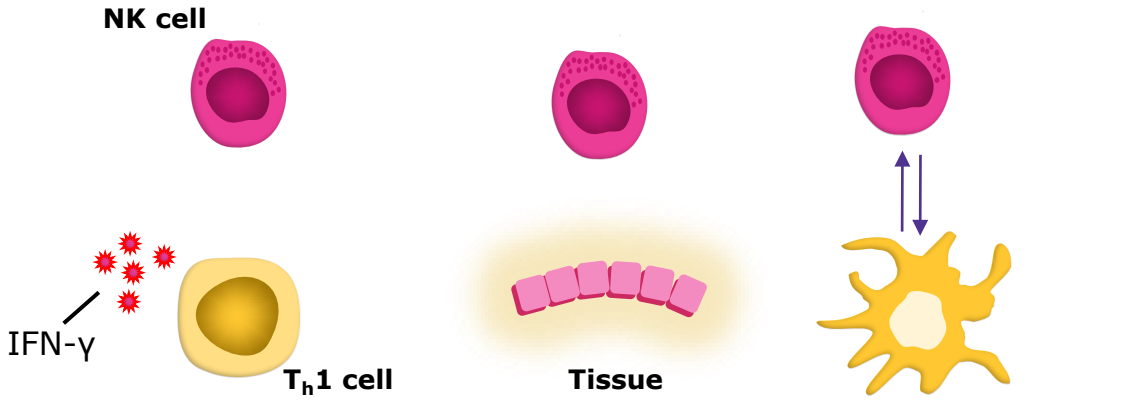
NK cells in MS

In MS, NK cells can have both pathogenic and protective roles

Pathogenic mechanisms



Protective mechanisms

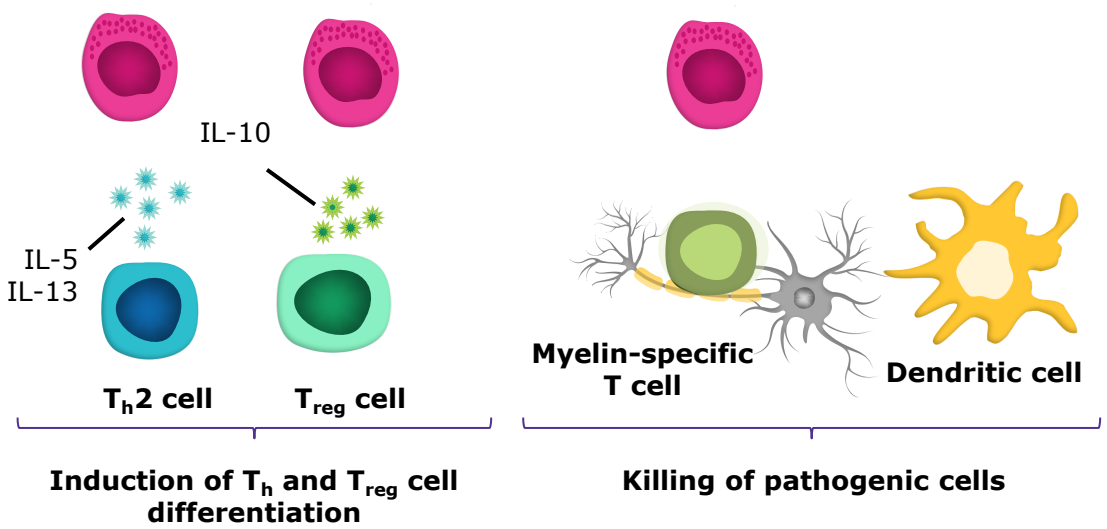


Figure developed based on information from Morandi B, et al. Pharmacol Res. 2008;57:1-5

CNS, central nervous system; IFN, interferon; IL, interleukin; MS, multiple sclerosis; NK, natural killer; T_h, helper T; T_{reg}, regulatory T

Morandi B, et al. Pharmacol Res. 2008;57:1–5.

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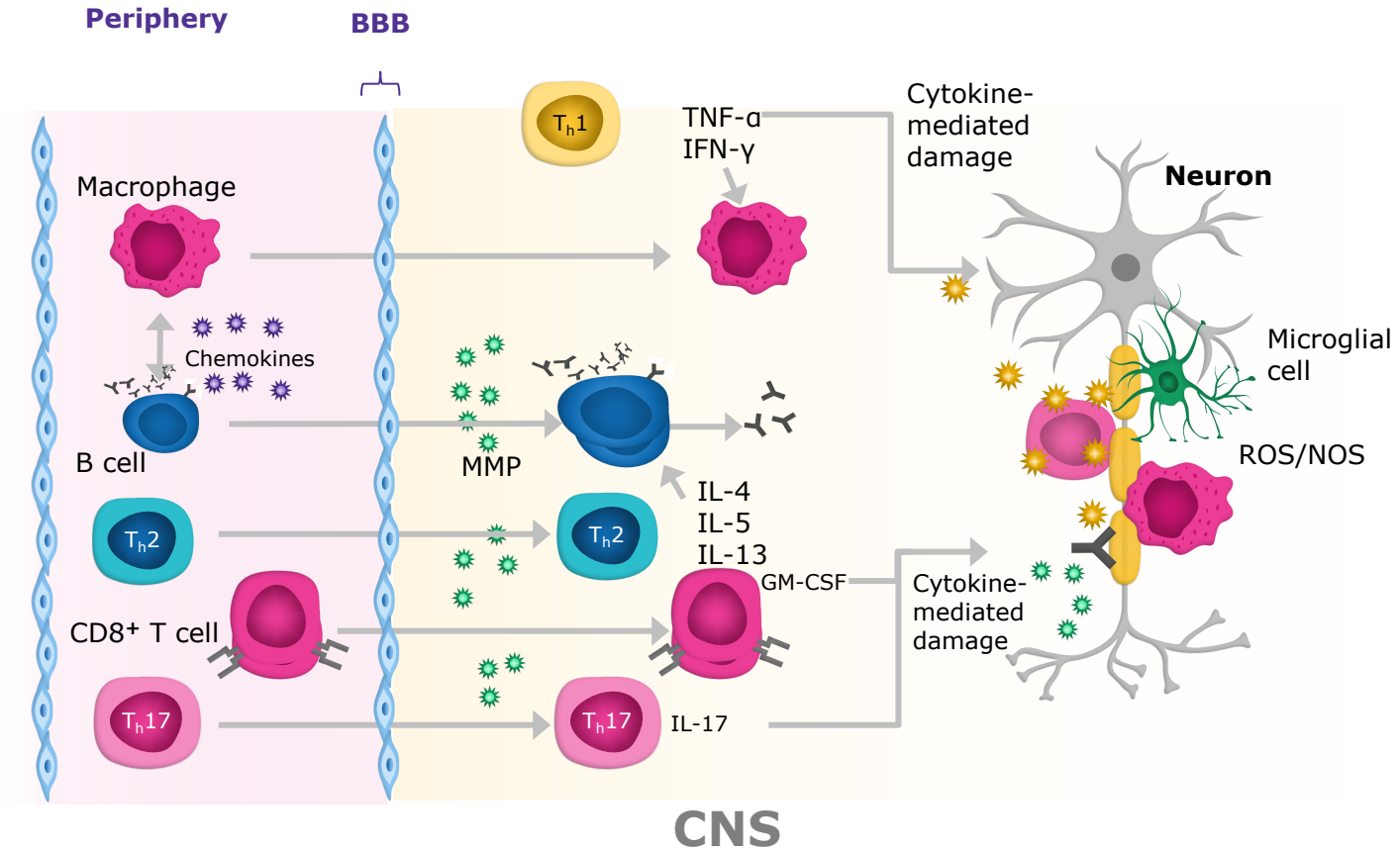
Cytokines and CNS damage in MS

Immune cells secrete cytokines, which mediate the injury of oligodendrocytes and myelin, and thus drive MS pathology[1,2]



- Activated T cells produce pro-inflammatory cytokines that stimulate multiple immune cells[1,3,4]
- CNS-resident cells, mainly microglia and astrocytes, as well as infiltrating macrophages, can produce neurotoxic inflammatory mediators that promote neuroaxonal damage and, consequently, neurodegeneration[3–6]
- Several cytokine-directed therapies are in clinical development for MS, such as monoclonal antibodies directed against pro-inflammatory cytokines (IL-2 and IL-17)[1]

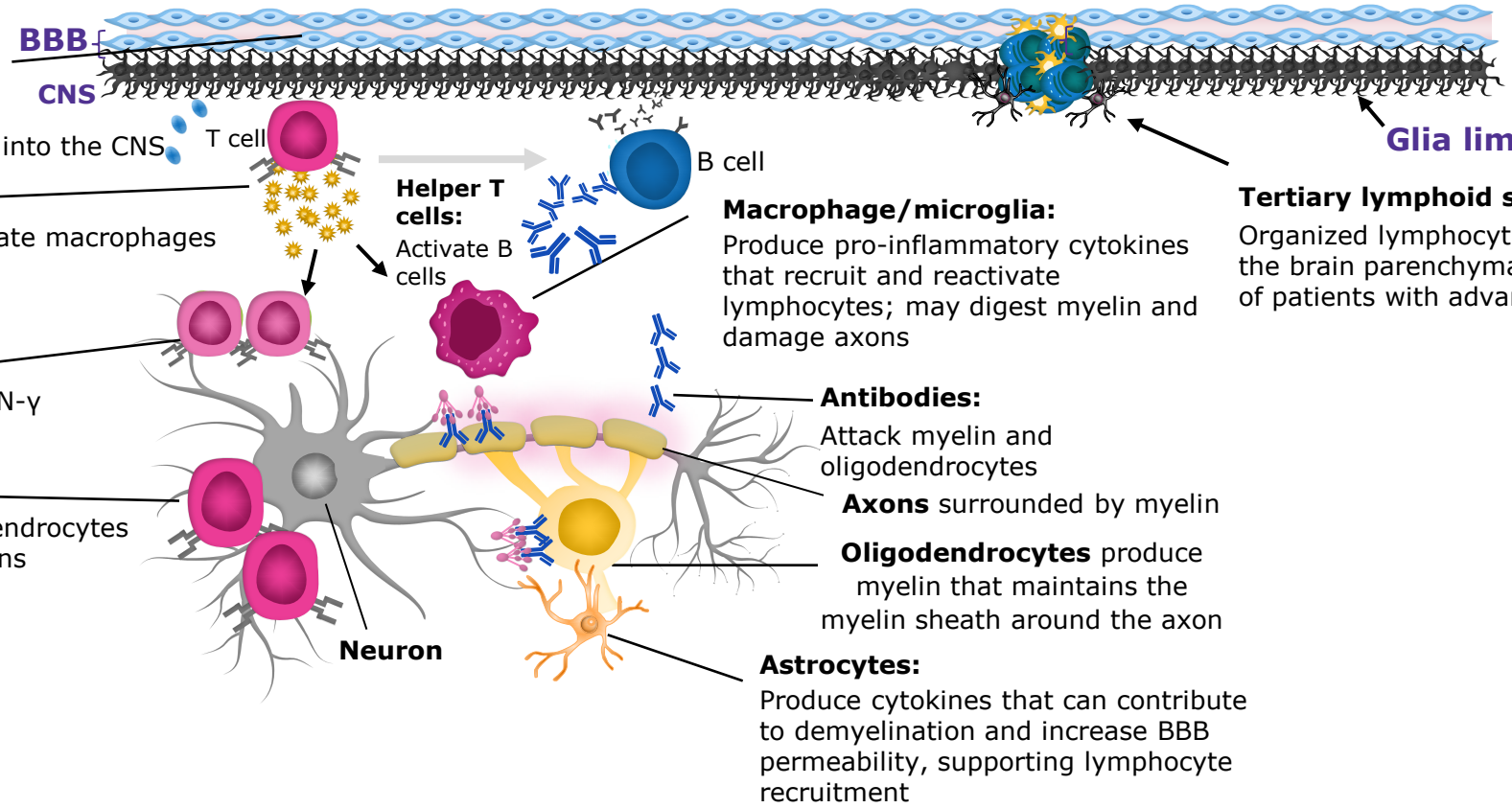
Figure developed based on information from Noseworthy JH, et al. N Engl J Med, 2000;343:938-952 and Dendrou CA, et al. Nat Rev Immunol. 2015;15:545-558

BBB, blood–brain barrier; CD, cluster of differentiation; CNS, central nervous system; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MMP, Matrix metalloproteinases; MS, multiple sclerosis; NOS, nitric oxide synthase; ROS, reactive oxygen species; T_h, helper T; TNF, tumor necrosis factor

1. Schreiner B, Becher B. Swiss Med Wkly. 2015;145:w14199; 2. Friese MA, Fugger L. Brain. 2005;128:1747-1763; 3. Warrington R, et al. Allergy Asthma Clin Immunol. 2011;7:S1; 4. Chaplin DD. Allergy Clin Immunol. 2010;125:S3-S23; 5. Noseworthy JH, et al. N Engl J Med. 2000;343:938-952; 6. Dendrou CA, et al. Nat Rev Immunol. 2015;15:545-558

Current model of MS pathogenesis

The deregulated actions of many adaptive and innate immune cell types result in demyelination, the hallmark of MS pathogenesis[1-7]



Inflammation:
Breaks down BBB

Chemokines:
Recruit inflammatory cells into the CNS

Cytokines:
IFN-γ and TNF-α can activate macrophages

CD4⁺ helper T cells:
Produce cytokines (e.g. IFN-γ and IL-17)

CD8⁺ T cells:
Can directly injure oligodendrocytes and cause damage to axons

Macrophage/microglia:
Produce pro-inflammatory cytokines that recruit and reactivate lymphocytes; may digest myelin and damage axons

Antibodies:
Attack myelin and oligodendrocytes

Axons surrounded by myelin

Oligodendrocytes produce myelin that maintains the myelin sheath around the axon

Astrocytes:
Produce cytokines that can contribute to demyelination and increase BBB permeability, supporting lymphocyte recruitment

Glia limitans[a]

Tertiary lymphoid structures:
Organized lymphocytic aggregates identified in the brain parenchyma, CSF and meningeal tissue of patients with advanced MS

[a]Astrocytes line neuronal tissue to form the glia limitans, which creates a barrier to the CNS

BBB, blood–brain barrier; CD, cluster of differentiation; CNS, central nervous system; CSF, cerebrospinal fluid; IFN, interferon; IL, interleukin; MS, multiple sclerosis; TNF, tumor necrosis factor

1. van Langelaar J, et al. Front Immunol. 2020;11:760; 2. Noseworthy JH, et al. N Engl J Med. 2000;343:938–952; 3. Chastain E, et al. Biochim Biophys Acta. 2011;1812:265–274; 4. von Büdingen HC, et al. Eur Neurol. 2015;73:238–246; 5. Dendrou CA, et al. Nat Rev Immunol. 2015;15:545–558; 6. Hemmer B, et al. Nat Rev Neurosci. 2002;3:291–301; 7. Wang J, Lu QR. Neurobiol Dis. 2020;144:105040.

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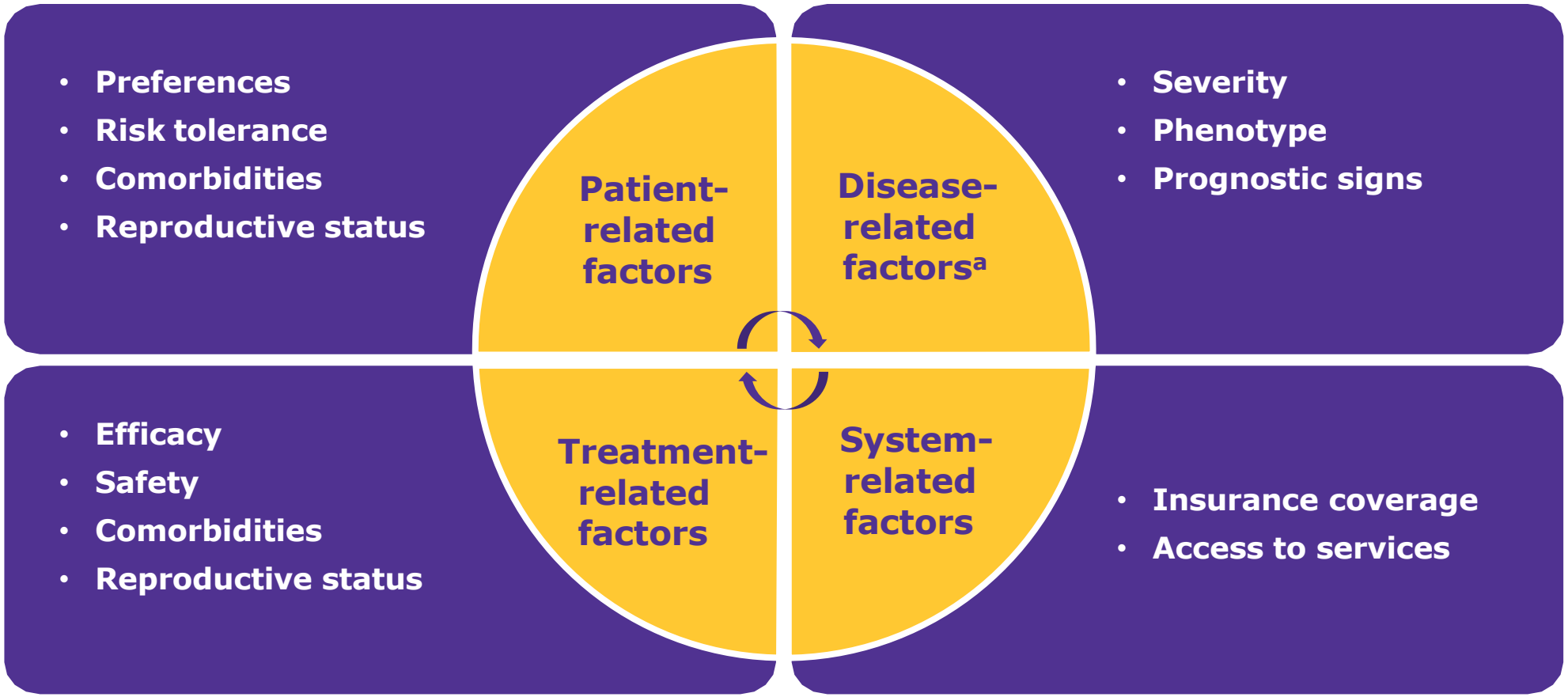
Goals of disease-Modifying therapy

Therapy selection considerations



Fred D Lublin. CMSC Best practices in multiple sclerosis therapies. https://www.mscare.org/page/practice_guidelines. Accessed June 14, 2024.

[a]The risk of not treating or undertreating the disease itself is also considered.

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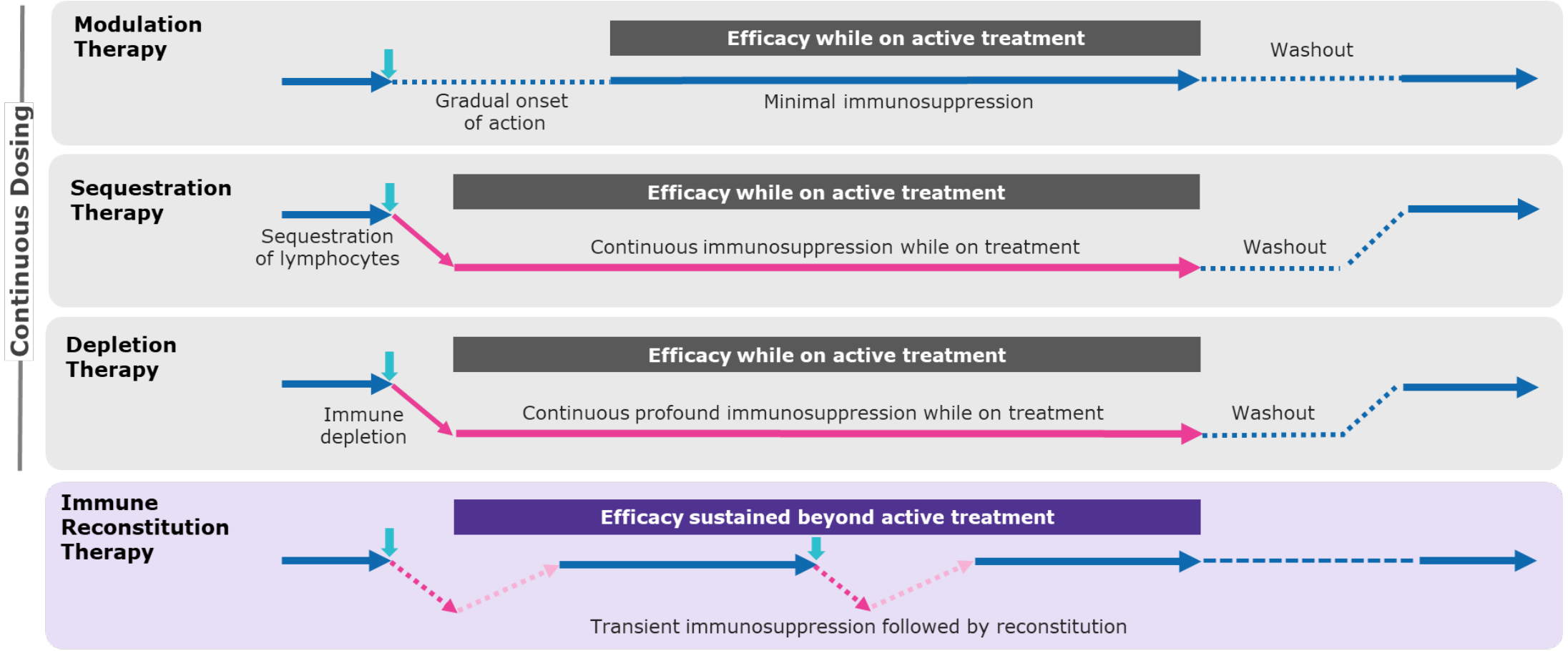
Different MS treatment approaches contribute to differences in degree and duration of immunosuppression[1-6]



DMT, disease-modifying therapy; MS, multiple sclerosis

1. Giovannoni G. Curr Opin Neurol. 2018;31(3):233-243; 2. Sorensen PS, Sellebjerg F. Ther Adv Neurol Disord. 2019;12:1756286419836913; 3. Hauser SL et al. N Engl J Med. 2017;376(3):221-234; 4. Baker D et al. Neurol Neuroimmunol Neuroinflamm. 2017;4(4):e360; 5. Pardo G, Jones DE. J Neurol. 2017;264(12):2375–2377; 6. Hamidi V et al. J Clin Med Res. 2018;10(2):88–105.

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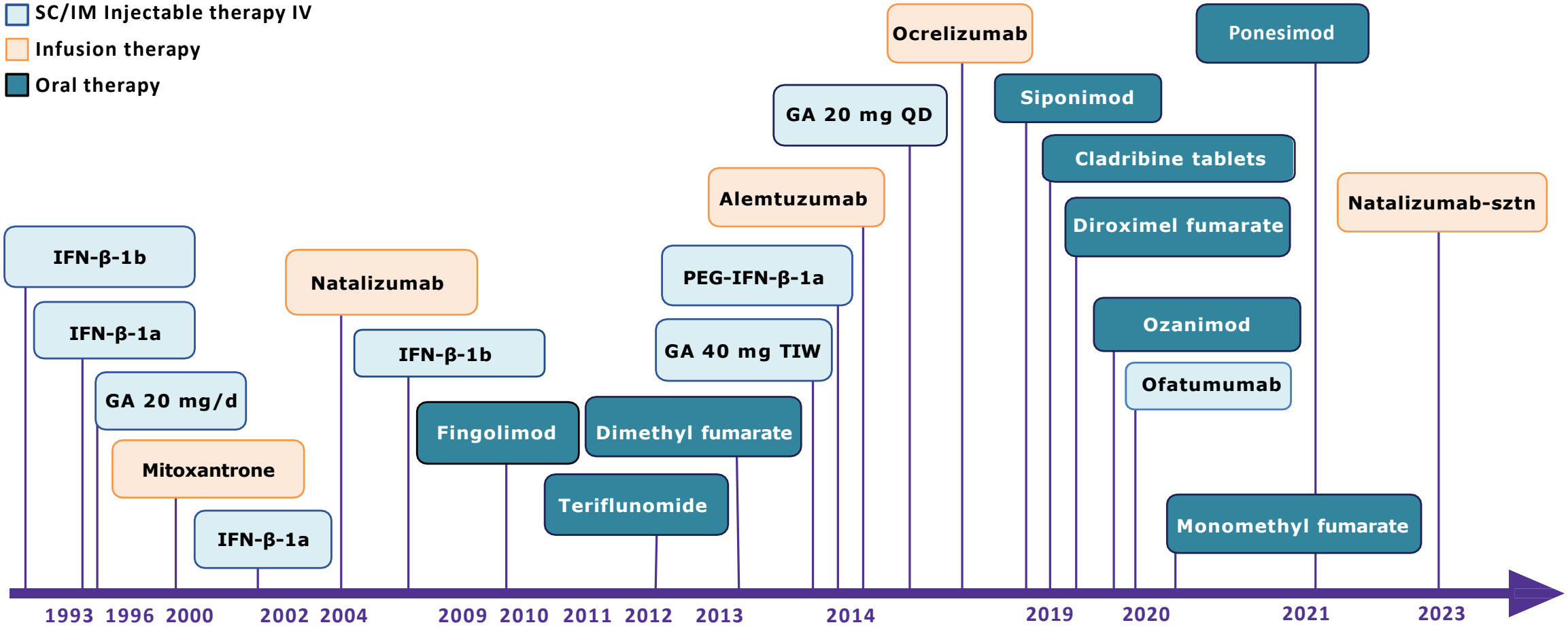
Currently approved MS therapeutic options[1,2]



d, day; GA, glatiramer acetate; SC, subcutaneous; IV, intravenous; IFN, interferon; MS, multiple sclerosis; PEG, peginterferon

1.Lublin FD. CMSC Best practices in multiple sclerosis therapies https://www.mscare.org/page/practice_guidelines. Accessed June 14, 2024;
2. US Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-first-biosimilar-treat-multiple-sclerosis. Published August 24, 2023. Accessed July 13, 2024.

Goals of therapy and indicators of suboptimal response

Therapeutic Goals	Indicators of Poor Response to Treatment
Prevent acute exacerbations	• No decrease in relapse rate while on therapy • Patients experience ≥1 relapses per year • Patients experience ≥1 relapse every 3 years • Incomplete recovery from relapses
Slow worsening on the neurologic exam/delay time to secondary progressive course	• Sustained, objective worsening on EDSS, 25-foot walk test, or cognitive testing, especially those affecting ADLs, employment or quality of life
Prevent or minimize new lesions on MRI (T2, T1, enhancing), and other indicators of neurologic damage (nonconventional measures to detect microscopic injury such as atrophy)	• ≥2 Gd-enhancing lesions in the first year of treatment • 2 or 3 new T2 lesions in the first year of treatment (on scans ≥3 months apart)

When a patient experiences suboptimal response to therapy, DMT switching may be considered

ADLs, activities of daily living; EDSS, Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging

Lublin FD. CMSC Best practices in multiple sclerosis therapies. https://www.mscare.org/page/practice_guidelines. Accessed June 14, 2024.

Several treatment- or patient-related factors determine the treatment switch

Indicators of suboptimal response to therapy	Patient related reasons for switching DMT
• One significant relapse with or without full recovery • Relapse within a year of starting therapy • Evidence of new activity on consecutive MRIs – MRI activity characterized by large or multiple T2 or enhancing lesions – Two or more T2 or enhancing lesions in 1 year – New T2 or enhancing lesions during first year of therapy – Lesion size and location should be considered • Unexpected change in progression of disability • Confirmed worsening on neurologic exam, including cognition	• Adherence issues for patient • Patient desire to change or try an agent with different modes of dose administration • Perceived lack of efficacy • Lifestyle or job-related issues • Insurance issues • Newer DMT is a better fit for a patient • Symptoms, quality of life issues, pregnancy • Prescriber- or Payer-related Reasons – Patient has new prescriber who switches therapy – Changes in practice of existing prescriber – Change in payer or payer formulary choices forces switch due to lack of coverage

DMT, disease-modifying therapy; MRI, magnetic resonance imaging

Lublin FD. CMSC Best practices in multiple sclerosis therapies. https://www.mscare.org/page/practice_guidelines. Accessed June 14, 2024.

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considerations for disease Monitoring of MS

Patient and disease characteristics may inform MS prognosis

Better prognosis	Poor Prognosis
Demographic factors (At onset)[1-3]	
• White • Female • Age (<40 years) at disease onset	• African American • Afro–Latino • Male sex • Older age (>40 years) at disease onset
Relapse features and Disability[3] (At different time points during the disease course)	

• Low relapse rate first 2–5 years
• High degree of remission after first relapse
• Long interval to second relapse
• Mild relapse
• No or low disability at 5 years
	• High relapse rate first 2–5 years
	• Short interattack latency
	• Short interval to second relapse
	• Severe relapse
	  ○ ≥1 moderate or severe attack
	  ○ Steroids/hospitalization required
	  ○ Severe effect on activities of daily living
	  ○ >1 functional system affected
	  ○ Severe motor/cerebellar brainstem involvement
	• Disability at 2 or 5 years

MRI features[2,3] (At different time points; onset and follow up)	

• Low (≤386 ng/L) neurofilament light levels
• Absence of oligoclonal IgG bands
• Absence of IgM bands
• Low lesion load on MRI
	• Elevated (>386 ng/L) neurofilament light levels
	• Presence of oligoclonal IgG bands and ≥10 brain T2 lesions
	• Presence of IgM bands
	• Baseline brain atrophy
	• Abnormal MRI
	  ○ ≥2 Gd+/new or newly enlarging T2 hyperintense lesions
	  ○ or ≥2 T1 hypointense lesions
	  ○ ≥2 spinal cord lesions

This is not an exhaustive list

Gd+, gadolinium-enhancing; Ig, immunoglobulin; MRI, magnetic resonance imaging; MS, multiple sclerosis

1.Ford C, Morrow SA, CMSC DMT Guideline Writing Group. Practical Guidelines for the Selection of disease-modifying therapies in multiple Sclerosis. Published online February 28, 2019. Accessed June 14, 2024; 2. Rush CA, et al. Nat Rev Neurol. 2015;11:379-389; 3. Pardo G, Jones DE. J Neurol. 2017;264(12):2351-2374.

MS disease monitoring: To assess disability stability or progression

Follow-up clinical neurological examination

- **Functional instruments:**
  - EDSS (neurological impairment)
  - MSFC (extent of functional impairment)
- **Gait:**
  - T25FW (walking disability)
  - 6MWT (motor fatigue function)
- **Balance:**
  - TUG
- **Dexterity:**
  - 9HPT (to assess impairment of the upper extremity)

- **Cognition:**
  - **SDMT** (information processing speed)
  - **PASAT** (sustained attention and information processing speed alterations)
- **Vision:**
  - **LCLA**
- **Anatomical instruments:**
  - **MRI** (objective measure of disease activity in the CNS)
  - **OCT measuring RNFL** (neurodegenerative changes in the retina)
- **Biological instruments:**
  - OCB and CHI3L1
  - sNfL

PRO tools

SF-36 (Patient-reported quality of life)

MSQoL-54 (Patient-reported quality of life)

MFIS (Fatigue)

6MWT, Six-minute walk test; 9-HPT 9-Hole Peg Test; CHI3L1, chitinase-3-like protein 1; EDSS, Expanded Disability Status Scale; LCLA, low-contrast letter acuity; MFIS, Modified Fatigue Impact Scale; MSFC, multiple sclerosis functional composite; MRI, magnetic resonance imaging; MSQoL, Multiple Sclerosis Quality of Life; OCB, oligoclonal bands; OCT, optical coherence tomography; PASAT, Paced Auditory Serial Addition Test; RNFL, retinal nerve fiber layer; sNFL, serum neurofilament light chain; SDMT Symbol Digit Modalities Test; SF-36, 36-item short form health survey; TUG Timed Up and Go

Pardo G, et al. J Neurol. 2022;269:1282-1297.

The EDSS is a familiar and widely used, albeit imperfect, standard that will likely remain an important part of clinical assessment of MS for the foreseeable future[1]

How does it work?

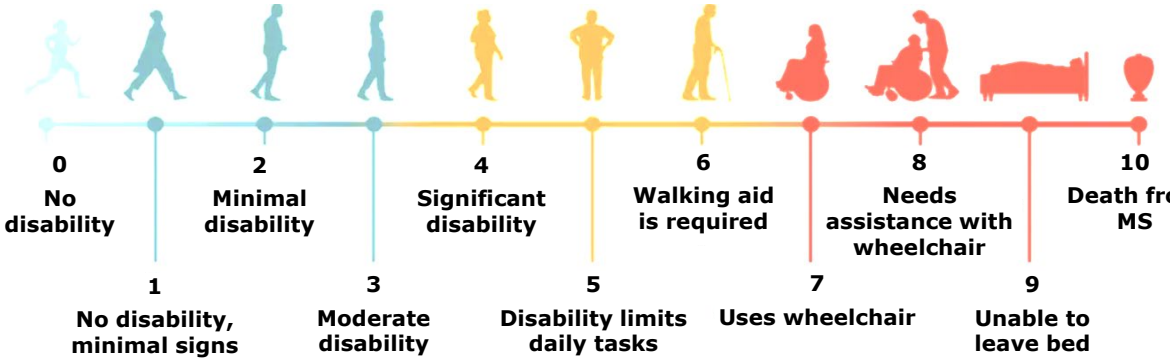
Standardized neurologic examination of a patient's **functional system** scores used in **conjunction** with observations and information regarding **gait** and **use of assistive devices**[1]

Functional systems measured[2]

- Pyramidal
- Cerebellar
- Cerebral or Mental
- Bowel and Bladder
- Sensory
- Visual
- Brainstem
- Other

Limitations of EDSS: EDSS scores can vary due to the complex scoring rules and the subjective nature of the neurological examination[2]

The Expanded Disability Status Scale[2,3]



1. National Multiple Sclerosis Society. Functional Systems Scores (FSS) and Expanded Disability Status Scale (EDSS). https://www.nationalmssociety.org/for-professionals/for-researchers/researcher-resources/research-tools/clinical-study-measures/fss-edss. Accessed June 8, 2024; 2. MS Trust. Expanded Disability Status Scale (EDSS). https://mstrust.org.uk/a-z/expanded-disability-status-scale-edss. Accessed June 8, 2024; 3. Behring S. What to Know About Multiple Sclerosis Progression in Chart Form. Healthline. https://www.healthline.com/health/progressing-ms/ms-progression-chart. Accessed June 8, 2024.

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis

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Standardized brain MRI protocol for MS diagnosis[1,2]

The protocol was released in 2021 by CMSC-MAGNIMS-NAIMS for MS diagnosis, optimizing field strength, acquisition methods, and scan orientation to ensure accurate lesion assessment and disease monitoring

	Brain	Spinal cord	Optic nerve
Field strength	≥1.5 T (preferably 3 T)	≥1.5 T (3 T has no added value compared with 1.5 T)	≥1.5 T
Slice thickness	3D: 1 mm isotropic[a] 2D: ≤3 mm, no gap[b]	Sagittal ≤3 mm, no gap Axial ≤5 mm, no gap	≤2-3 mm, no gap
In-pane resolution	≤1 mm × 1 mm	≤1 mm × 1 mm	≤1 mm × 1 mm
Coverage	Whole brain (covering as much of cervical cord as possible)	Cervical and thoracolumbar spinal cord, to include conus	Optic nerve and optic chiasm
Axial scan orientation	Subcallosal plane to prescribe (ie, for 2D imaging) or reformat (ie, for 3D imaging) axial oblique slices	Perpendicular to the sagittal axis of the spinal cord	Align to optic nerve and optic chiasm orientation

Table adapted from Wattjes MP, et al. Lancet Neurol. 2021;20(8):653-670.
[a]1 mm isotropic is preferred but, if over-contiguous (through plane and in plane), not >1.5 mm with 0.75 mm overlap.
[b]except for diffusion-weighted imaging for which slice thickness should be ≤5 mm with a 10%-30% slice gap.

2D, two dimensional; 3D, three dimensional; CMSC, Consortium of Multiple Sclerosis Centers; MS, multiple sclerosis; MAGNIMS, Magnetic Resonance Imaging in Multiple Sclerosis; MRI, magnetic resonance imaging; NAIMS, North American Imaging in Multiple Sclerosis; T, Tesla

1. Wattjes MP, et al. Lancet Neurol. 2021;20:653-670;
2. The Consortium of Multiple Sclerosis Centers. 2021 MAGNIMS-CMSC-NAIMS Standardized MRI Protocol. https://mscare.sharefile.com/share/view/s16fa7f9d0c214c1cb5bd8f809ac07215. Accessed August 28, 2024.

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2021 CMSC-MAGNIMS-NAIMS standardized brain MRI protocol recommendations[1,2]

Brain	Diagnosis	Follow-up monitoring	Safety monitoring
Axial T_2		±[a]	±[a]
Sagittal and axial T2-weighted FLAIR (preferably 3D)			
Post-Gd axial (or 3D sagittal) T_1			
Diffusion-weighted imaging		DDx	
DIR or PSIR			
High-resolution isotropic 3D T_1 (brain volume assessment)			
Susceptibility-weighted imaging			

Optic nerve	Diagnosis	Follow-up monitoring	Safety monitoring
Axial & coronal fat-suppressed T_2 or STIR			
Post-Gd[b] axial & coronal fat-suppressed T_1			
Spinal cord	**Diagnosis**	**Follow-up monitoring**	**Safety monitoring**
Sagittal at least two of: T2 (TSE or FSE), PD (TSE or FSE), or STIR			
Sagittal 3D T_1 (PSIR, MPRAGE)[c] for cervical only			
Axial T_2 (TSE or FSE) or gradient-recalled echo T_2^*			
Pre-Gd sagittal T_1 (TSE or FSE)			
Post-Gd[b] sagittal T_1 (TSE or FSE)			
Post-Gd[b] axial T_1 (TSE or FSE)			

Color representations:

Recommended core	Optional	Not required

[a]±, Axial T_2 optional if sagittal 3D T2-weighted FLAIR and multiplanar reconstructions in sagittal/axial planes are available; [b]No additional Gd necessary if immediately following Post-Gd brain examination; [c]Could substitute for one of T_2, PD or STIR.

Gd, macrocyclic agent, 0.1 mmol/kg body weight, minimum delay 5-10 minutes; **High resolution 3D T_1**, e.g. MPRAGE/MP2RAGE magnetization-prepared rapid acquisition of gradient echoes, IR-SPGR, TFE; **T_1**, TSE/FSE; **T_2**, TSE/FSE.

3D, three dimension; CMSC, Consortium of Multiple Sclerosis Centers; DIR, double inversion recovery; DMT; disease modifying treatment; DDx, differential diagnosis; FLAIR, fluid-attenuated inversion recovery, with optional fat suppression; FSE, Fast-spin-echo; Gd, gadolinium; IR-SPGR, inversion recovery prepared spoiled gradient; MAGNIMS, Magnetic Resonance Imaging in Multiple Sclerosis; MPRAGE, magnetization-prepared rapid acquisition with gradient echo; MP2RAGE, Magnetization Prepared 2 Rapid Acquisition Gradient Echoes; MS, multiple sclerosis; NAIMS, North American Imaging in Multiple Sclerosis; PD, proton-density: PSIR, phase-sensitive inversion recovery; Sm, safety monitoring for DMT, e.g., screening for risk of progressive multifocal leukoencephalopathy; STIR, short tau inversion recovery; TFE, turbo field-echo; TSE, Turbo-spin-echo

1. Wattjes MP, et al. Lancet Neurol. 2021;20:653-670;
2. The Consortium of Multiple Sclerosis Centers. 2021 MAGNIMS-CMSC-NAIMS Standardized MRI Protocol. https://mscare.sharefile.com/share/view/s16fa7f9d0c214c1cb5bd8f809ac07215. Accessed August 28, 2024.

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Neuropsychological test batteries used in MS

Two specific groups (or "batteries"), of neuropsychological tests, the BRB-N and MACFIMS, have been proposed by experts because these groups combine tests evaluating the cognitive domains usually affected in MS

	Batteries		
	BICAMS	**MACFIMS**	**BRB-N**
Functions			
– Attention	SDMT	SDMT	SDMT
– Working memory		PASAT	PASAT
– Executive function		D-KEFS sorting test	
– Verbal episodic memory	CVLT-II	CVLT-II	SRT
– Visuospatial episodic memory	BVMT-R	BVMT-R	SPART (10/36)
– Language		COWA	WLG
– Spatial processing		JOL	

BICAMS, Brief International Cognitive Assessment for MS; BRB-N, Brief Repeatable Battery of Neuropsychological Tests; BVMT-R, Brief Visuospatial Memory Test-Revised Version; COWA, Controlled Oral Word Association; CVLT-II, California Verbal Learning Test–Second Edition; D-KEFS, Delis-Kaplan Executive Function System; JOL, Judgement of Line Orientation; MACFIMS, Minimal Assessment of Cognitive Function in MS;
MS, multiple sclerosis; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; SPART, Spatial Recall Test; SRT, Selective Reminding Test; WLG, Word List Generation

MSIF. MS and cognition. https://www.msif.org/wp-content/uploads/2014/09/MS-in-focus-22-Cognition-English1.pdf. Accessed June 22, 2024.

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QoL and burden of disease

MS may compromise the QoL of patients by interfering with the ability to work, engaging in hobbies or leisure activities, and complete daily tasks[1]

Impact of MS on QoL[1-4]

A broad spectrum of physical and social challenges for patients, may include the following:

- Fatigue
- Depression
- Chronic pain
- Difficulty in employment
- Difficulty in relationships
- Difficulty completing daily activities

Additional considerations[4,5]

As MS may be perceived as a "female disease," **men with MS** may **experience challenges** in accepting their diagnosis and asking for support with their disease

Studies are ongoing to further understand why **Black patients may have more aggressive disease progression**, greater disability, more frequent relapses, and earlier disability onset

Click here to read more

1. Hosseini ZS, et al. BMC Neurol. 2022;22:article 174; 2. National Multiple Sclerosis Society. Pain & Itching. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Pain. Accessed July 25, 2024; 3. National Multiple Sclerosis Society. Depression and MS. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Depression. Accessed July 25, 2024; 4. Safi NV, Krieger S. Pract Neurol. 2021. 37-40. https://practicalneurology.com/articles/2021-feb/men-with-multiple-sclerosis. Accessed July 25, 2024; 5. National Multiple Sclerosis Society. MS in the Black Community. https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS/MS-in-the-Black-Community. Accessed July 25, 2024.

MS, multiple sclerosis; QoL, quality of life

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Example of a patient QoL Questionnaire[6]

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

- Cut down the amount of time you spent on work or other activities (Y/N)
- Accomplished less than you would like (Y/N)
- Were limited in the kind of work or other activities (Y/N)
- Had difficulty performing the work or other activities (for example, it took extra effort) (Y/N)

1. Hosseini ZS, et al. BMC Neurol. 2022;22:article 174; 2. National Multiple Sclerosis Society. Pain & Itching. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Pain. Accessed July 25, 2024. 3. National Multiple Sclerosis Society. MS Symptoms & Signs of MS: Depression. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms/Depression. Accessed July 25, 2024. 4. Safi NV, Krieger S. Pract Neurol. 2021. 37-40. https://practicalneurology.com/articles/2021-feb/men-with-multiple-sclerosis. Accessed July 25, 2024; 5. National Multiple Sclerosis Society. MS in the Black Community. https://www.nationalmssociety.org/What-is-MS/Who-Gets-MS/MS-in-the-Black-Community. Accessed July 25, 2024. 6. Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36). https://www.brandeis.edu/roybal/docs/SF-36_website_PDF.pdf. Accessed August 25, 2024.

MS, multiple sclerosis; QoL, quality of life

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Patient-reported outcomes measures provide key data

What is a PRO?

A report on the **health status of a patient** that is obtained **directly from the patient**, without any influence[1]

How are PROs used?

PROs are used as **endpoints in clinical research** as well as in **clinical practice**[2]

How are PROs collected?

PROs are collected through tools or instruments that measure a patient's health status such as health-related quality of life. These tools are often self-completed questionnaires. PRO measures may quantify functional status, health-related quality of life, symptom and symptom burden, personal experience of care, and health-related behaviors such as anxiety and depression[3]

What can PROs help achieve?

PRO measure data support longitudinal reporting, clinical decision-making, and system review at the point of care. The data also facilitate patient education, interventions, and patient triage for additional services, emphasizing the significance of the reported information for patient care[2]

1. FDA. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims https://www.fda.gov/media/77832/download. Accessed June 12, 2024;
2. NIH Collaboratory Coordinating Center. Patient-reported outcomes. https://rethinkingclinicaltrials.org/resources/patient-reported-outcomes-3/#fda-2009. Accessed June 12, 2024; 3. Weldring T, Smith SM. Health Serv Insights. 2013;6:61-68.

PRO, patient-reported outcome

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Generic and MS-specific PRO measures are used to capture different aspects of patient experience in MS

Generic PRO measure[a]

Domain/PRO	Measure
Disability/overall health	UNDS/GNDS
Affect/mood	BDI CES-D HADS
HRQoL	EQ-5D
Treatment-related	TSQM
Socioeconomic	WPAI

MS-specific PRO measure[a]

Domain/PRO	Measure	
Disability/overall health	MSIS-29 PDDS	
HRQoL	FAMS HAQUAMS MSQLI	MSQoL-54 MusiQoL PRIMUS
Mobility	EMIQ MSWS-12	
Cognition and neuropsychology	MSNQ	
Fatigue	CFQ 11 FSMC FSS	MFIS WEIMuS
Socioeconomic	MS-HRS	

[a]This is not an exhaustive list of available PRO measure

BDI, Beck's Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CFQ 11, Chalder Fatigue Scale; EMIQ, Early Mobility Impairment Questionnaire; EQ-5D, EuroQol 5 Dimensions; FAMS, Functional Assessment of Multiple Sclerosis; FSMC, Fatigue Scale for Motor and Cognitive Functions; FSS, Fatigue Severity Scale; GNDS, Guy's Neurological Disability Scale; HADS, Hospital Anxiety and Depression Scale; HAQUAMS, Hamburg Quality of Life Questionnaire in Multiple Sclerosis; HRQoL, health-related quality of life; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; MS-HRS, Multiple Sclerosis Health Resource Utilization Survey; MSIS-29, Multiple Sclerosis Impact Scale; MSNQ, Multiple Sclerosis Neuropsychological Questionnaire; MSQLI, Multiple Sclerosis Quality of Life Inventory; MSQOL-54, Multiple Sclerosis Quality of Life-54 Instrument; MSWS-12, 12-Item Multiple Sclerosis Walking Scale; MusiQoL, Multiple Sclerosis International Quality of Life questionnaire; PDDS, Patient-Determined Disease Steps; PRIMUS, Patient-Reported Outcome Indices for Multiple Sclerosis; PRO, patient-reported outcome; TSQM, Treatment Satisfaction Questionnaire for Medication; UNDS, UK Neurological Disability Scale; WEIMuS, Würzburger Fatigue Inventory for MS; WPAI, Work Productivity and Activity Impairment

D'Amico E, et al. Mult Scler Relat Disord. 2019;33:61-66.

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Lifecycle considerations and shared decision Making

Importance of fertility and family planning in MS treatment decisions[1]

Impact of family planning and MS

Many women with MS may question their **ability** to **have children**[2]

Pregnancies in women with MS should generally **not** be considered **high risk**, and MS does **not typically influence** the **mode of delivery** or anesthesia unless it is associated with a significant disability[3]

Claims-data reported **no significant difference in live birth rate** following infertility treatments (oral or injectable) in **women with** and **without MS**[4]

DMTs can be **classified** based on their **potential** for **pregnancy-associated risk** and impact on **fetal outcome**[3]

- Some treatment options carry contraindications for pregnancy

Click here to read more

1. Bonavita B, et al. Front Neurol. 2021;12:620772; 2. Coyle PK, et al. Mult Scler Relat Disord. 2019;32:54-63; 3. Canibaño B, et al. J Drug Assess. 2020;9:20-36; 4. Houtchens MK, et al. Mult Scler Relat Disord. 2020;46:102541; 5.Hellwig K, Jorge C. Clin Immunol. 2013;149:219-224; 6. Brzosko B, et al. Neurology. 2018;90:Supplement 15; 7. Beroukhim G. et al, Curr Opin Obstet Gynecol. 2022;34:138-146.

DMT, Disease modifying therapies; MS, multiple sclerosis

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ART

- Studies have demonstrated that hormonal stimulation during ART increases the relapse risk after unsuccessful stimulation[5]
- A cohort study suggested that continued DMT use may decrease relapse risk after ART stimulation; however, this is an area of ongoing research[6]

Racial disparities

- Significant gaps in **access** to and **utilization** of **fertility care** have been consistently reported among racial and ethnic minorities, particularly **Black** and **Hispanic women**[7]
- Compared with White women, Black and Hispanic women tend to wait **20 months longer** before receiving care/treatment for infertility[8]

1. Bonavita B, et al. Front Neurol. 2021;12: 620772; 2. Coyle PK, et al. Mult Scler Relat Disord. 2019;32:54-63; 3. Canibaño B, et al. J Drug Assess. 2020;9:20-36; 4. Houtchens MK, et al. Mult Scler Relat Disord. 2020;46:102541; 5.Hellwig K, Jorge C. Clin Immunol. 2013;149:219-224; 6. Brzosko B, et al. Neurology. 2018;90:Supplement 15; 7. Beroukhim G. et al. Curr Opin Obstet Gynecol. 2022;34:138-146. 8. Weiss MS, Marsh EE. Obstet Gynecol. 2023;142:940-947.

ART, Assisted reproductive treatment, DMT, Disease-modifying therapies; MS, multiple sclerosis

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Management of the aging MS patient

The prevalence of MS in people aged >55 years is increasing, with increasing comorbitities adding challenges to overall MS disease management[1]

Impact of aging on patients with MS[1-3]

- Age may impact the body's ability to recover from a relapse
- Older individuals may be more sensitive to drug side effects
- Symptoms of MS can mimic and may be exacerbated by the physical effects of aging
- It may be difficult to determine whether presenting symptoms are due to MS or normal aging
- MS phenotype shift from predominantly inflammatory to neurodegenerative

Click here to read more

1. Balusha AAK, Morrow SA. Pract. Neurol. 2021:41-43. https://practicalneurology.com/articles/2021-feb/multiple-sclerosis-in-people-over-age-55. Accessed June 15, 2024; 2. DiLorenzo T. National Multiple Sclerosis Society. https://secure.nationalmssociety.org/docs/HOM/clinicalbulletin_aging.pdf. Accessed July 17, 2024; 3. Vaughn CB, et al. Nat Rev Neurol. 2019;15:329-342.

DMT, Disease modifying treatment; MS, multiple sclerosis

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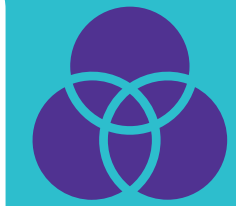

Overlapping symptoms of aging and MS[3-5]

- Diminished muscle strength
- Alteration in bowel/bladder function
- Balance problems
- Weakness
- Fatigue
- Reduced sensation
- Vision changes
- Cognitive impairment
- Osteoporosis
- Sleep disturbances

1. Balusha AAK, Morrow SA. Pract. Neurol. 2021:41-43. https://practicalneurology.com/articles/2021-feb/multiple-sclerosis-in-people-over-age-55. Accessed June 15, 2024; 2. DiLorenzo T. National Multiple Sclerosis Society. https://secure.nationalmssociety.org/docs/HOM/clinicalbulletin_aging.pdf. Accessed July 17, 2024; 3. Vaughn CB, et al. Nat Rev Neurol. 2019;15:329-342; 4. Stern M, et al. Phys Med Rehabil Clin N Am. 2005;16:219-234. 5. Stern M, et al. Phys Med Rehabil Clin N Am. 2010;21:403-417.

MS, multiple sclerosis

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Management of the aging MS patient

The immune system and other parts of the body change with aging, which may impact a patient's disease manifestation and treatment plan recommendations[1,2]

Impact of aging on the immune system[1]

- Progressive loss of innate and adaptive immune system activity and ability to elicit an adequate immune response (**immunosenescence**)
- Immune system repair capacity is believed to decrease, and axonal degeneration, iron deposition, and oxidative stress may occur, leading to decreased natural brain reserve
- Low-grade inflammatory processes are thought to occur from previous viral infections throughout life, which may result in the formation of senescent immune cells that no longer play a role in tissue repair (**inflamm-aging**)
- Immune system aging plays a key role in MS progression, and DMT efficacy may be reduced by immune system changes and aging

1. Balusha AAK, Morrow SA. Multiple Sclerosis in People Over Age 55. Pract Neurol. 2021:41-43. https://practicalneurology.com/articles/2021-feb/multiple-sclerosis-in-people-over-age-55. Accessed June 12, 2024; 2. Macaron G, et al. Front Neurol. 2023;14:1197212.

DMT, disease-modifying therapies; MS, multiple sclerosis

Clinical studies continue to examine MS treatment in aging populations

Clinical evidence[1-5]

- **Infections:** Studies have shown increased risks of HSV1 and VZV reactivation with aging and DMT use, likely due to immunosenescence[1]
- **Progressive multifocal leukoencephalopathy:** PML is a severe adverse effect of DMTs. Old age may be associated with a higher risk of PML development and severe outcomes[2,3]
- **Vaccinations:** Current evidence suggests that some DMTs (B-cell depleting therapies) significantly diminish the humoral immune response to several vaccines, including influenza, tetanus toxoid, and pneumococcal vaccines[1,4,5]

DMT, disease-modifying therapies; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; MS, multiple sclerosis; VZV, varicella zoster virus

1. Thakolwiboon S, et al. Front Aging. 2023;4:1234572; 2. Warnke C, et al, Trends Pharmacol. Sci. 2015;36:799-801; 3. Schweitzer F, et al, Curr. Opin. Neurology. 2019;32:305-312; 4. Amit BO, et al, Neurology. 2020;95:e1999-e2008; 5. Ciotti JR, et al, Mult Scler Relat Disord.2020;45:102439; 6. Corboy JR, Morrow SA. Lancet Neurol. 2023;22:568-577.

A recent study examining MS treatment in an aging population

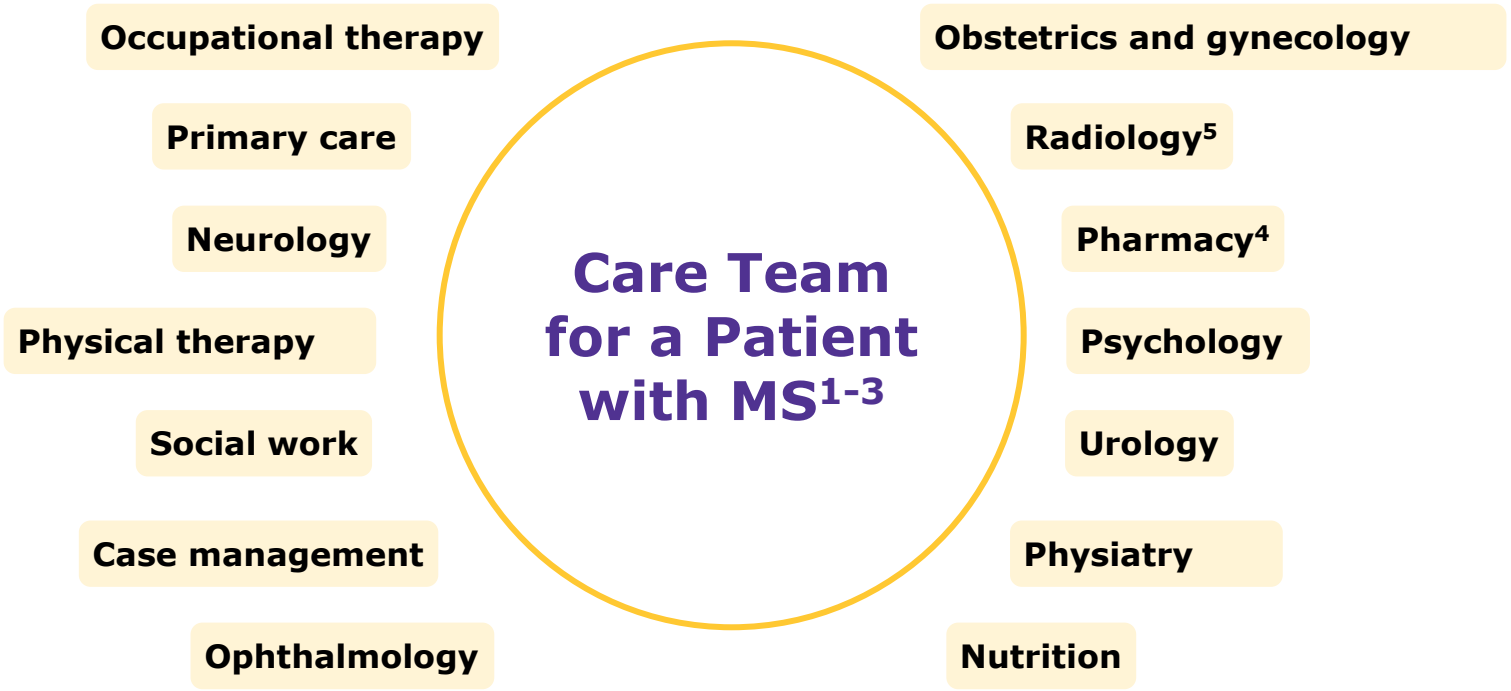
DISCOMS trial[1]

- A study including 259 patients of aged ≥55 years evaluated the risk of recurrence of disease activity in patients who continued or discontinued DMT treatment
- Clinically, there was modest disease activity overall, and the study did not find a significant difference in relapses or disability progression between the two groups
- An increased risk of relapse or new MRI activity was observed among the patients who discontinued compared with patients who continued DMT treatment (12.2% vs. 4.7%) respectively
- There is an ongoing extension of the DISCOMS study, which will provide further information about the safety of DMT discontinuation

DMT, disease-modifying therapies; MRI magnetic resonance imaging; MS, multiple sclerosis

1. Corboy JR, Morrow SA. Lancet Neurol. 2023;22:568-577.

A multidisciplinary MS care approach can benefit providers and their patients



1. National Multiple Sclerosis Society. Comprehensive Care. https://www.nationalmssociety.org/Treating-MS/Comprehensive-Care. Accessed June 9, 2024; 2. National Multiple Sclerosis Society. Developing a Healthcare Team. https://www.nationalmssociety.org/Treating-MS/Comprehensive-Care/Developing-a-health-care-team. Accessed June 9, 2024; 3. American Association of Neuroscience Nurses and Association of Rehabilitation Nurses Clinical Practice Guideline Series for Nursing Management of the Patient with Multiple Sclerosis V.1.2011. https://iomsn.org/wp content/uploads/2016/07/AANN-ARN-IOMSN-MS-Guideline_FINAL.pdf Accessed June 9, 2024; 4. May A, et al. Int J MS Care. 2021;23:16-20; 5. McNamara C, et al. Am J Neuroradiol. 2017;39:1664-1671.

MS, multiple sclerosis

Shared Decision-Making

Shared Decision-Making can potentially improve decision-making for patients with MS and it involves discussing the available options, considering the risks and benefits, and considering the patient's preferences and values with HCPs[1,2]

Importance of SDM in MS[1]

SDM has shown to consistently improve patient knowledge, risk perceptions, and decisional conflict

Key components of SDM in MS[3]

- ✓ Describe treatment options
- ✓ Consider patient preferences
- ✓ Make the decision

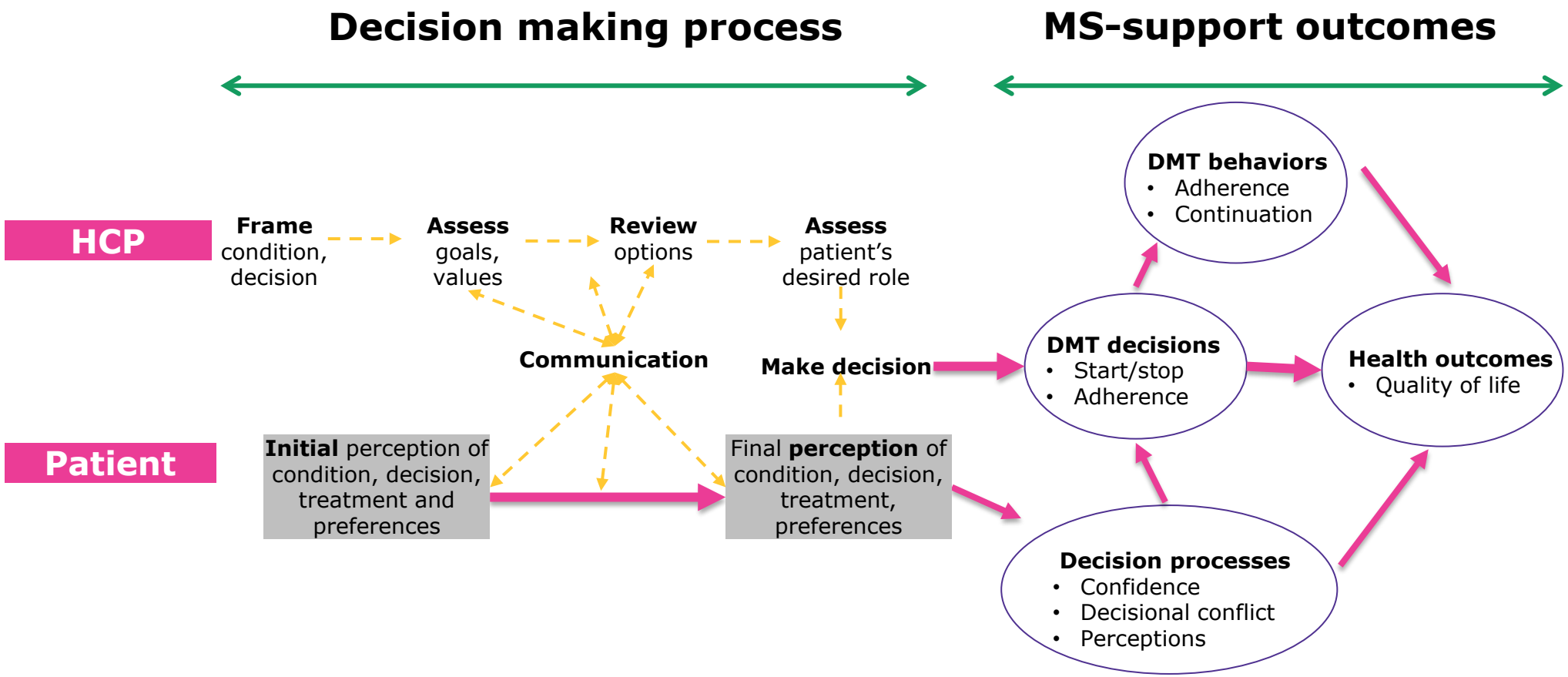
Benefits of SDM in MS[4]

- ✓ Support patient experience
- ✓ Adhere to treatment
- ✓ Improve patient outcomes

HCP, healthcare professional; MS, multiple sclerosis; SDM, Shared decision-making

1. Col NF, et al. Mult Scler Relat Disord. 2023;80:105092; 2. Colligan E, et al. Mult Scler. 2017;23(2):185-190. 3. Bomhof-Roordink H, et al. BMJ Open. 2019;9:e031763; 4. Stoll S. et al. Neurol Ther. 2024;13:21-37.

SDM has a potential impact on DMT decisions, behaviors, and quality of life



DMT, disease-modifying therapy; HCP, healthcare professional; MS, multiple sclerosis; SDM, Shared decision-making

Col NF, et al. Mult Scler Relat Disord. 2023;80:105092.

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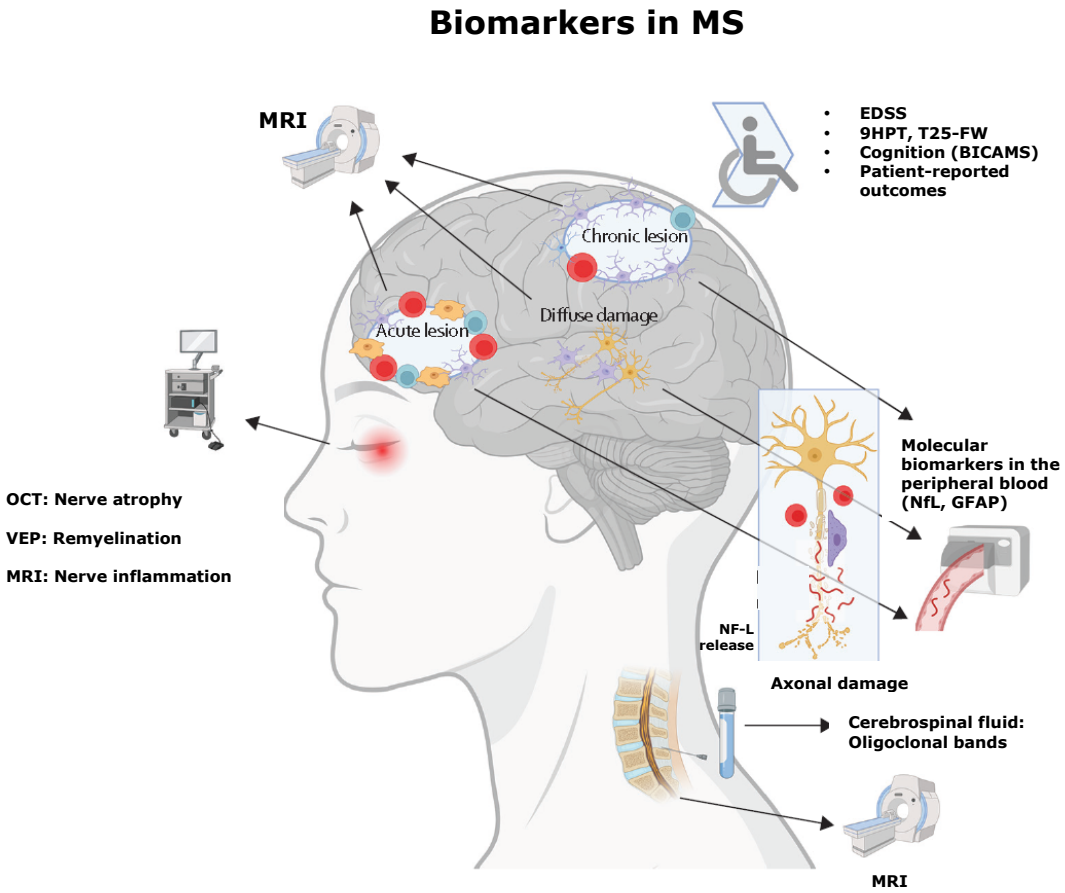
research and emerging biomarkers

Novel diagnostic and prognostic biomarkers in MS



Pathological processes in MS can be assessed and quantified using different tests, including brain and spinal cord MRI, OCT, analysis of cerebrospinal fluid, and peripheral blood tests (via single molecule array).

Figure adapted from Jakimovski D, et al. The Lancet. 2024;403:183-202.

BICAMS, brief international cognitive assessment for multiple sclerosis; EDSS, expanded disability status scale; GFAP, Glial fibrillary acidic protein; OCT, optical coherence tomography; MRI, magnetic resonance imaging; MS, multiple sclerosis; NFL, Neurofilament light chain T25-FW, timed 25-foot walk; VEP, visual evoked potentials; 9HPT, nine-hole peg test

Jakimovski D, et al. The Lancet. 2024;403:183-202.

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Novel diagnostic and prognostic biomarkers in MS

CAL

Chronic Active Lesions[1]

- Chronic active lesions are characterized by progressive tissue matrix damage and axonal loss due to ongoing low-grade inflammation in the absence of contrast enhancement
- Chronic active lesions may be indicators of clinical worsening and disease progression

PRL

Paramagnetic Rim Lesions[2]

- On MRI, the paramagnetic properties of iron-enriched macrophages and microglia at the edge of lesions enable some chronic active lesions to be identified on SWI
- PRLs are commonly observed in patients with MS,[1] one study found that presence of four PRLs may be associated with increased motor and cognitive disability

SEL

Slowly Expanding Lesions[2,3]

- SELs are observed in all MS phenotypes; however, they appear more numerous with progressive (primary and secondary) MS than with relapsing-remitting MS and have been associated with neurological and cognitive disability
- SELs represent a high fraction of the total lesion burden
- Detection of SELs requires advanced imaging techniques, and their identification may involve analyzing changes in existing T2-lesions over time using methods such as calculated deformation fields to assess gradual and concentric expansion[3]

MRI, magnetic resonance imaging; MS, multiple sclerosis; PRL, paramagnetic rim lesions; SEL, slowly expanding lesions; SWI, susceptibility-weighted imaging

1. Eisele P, et al. Eur J Neurol. 2021;28:2392-2395; 2. Calvi A, et al. Mult Scler. 2023;29:352-362; 3. Arnold DL, et al. Mult Scler. 2021; 27: 1681-1683.

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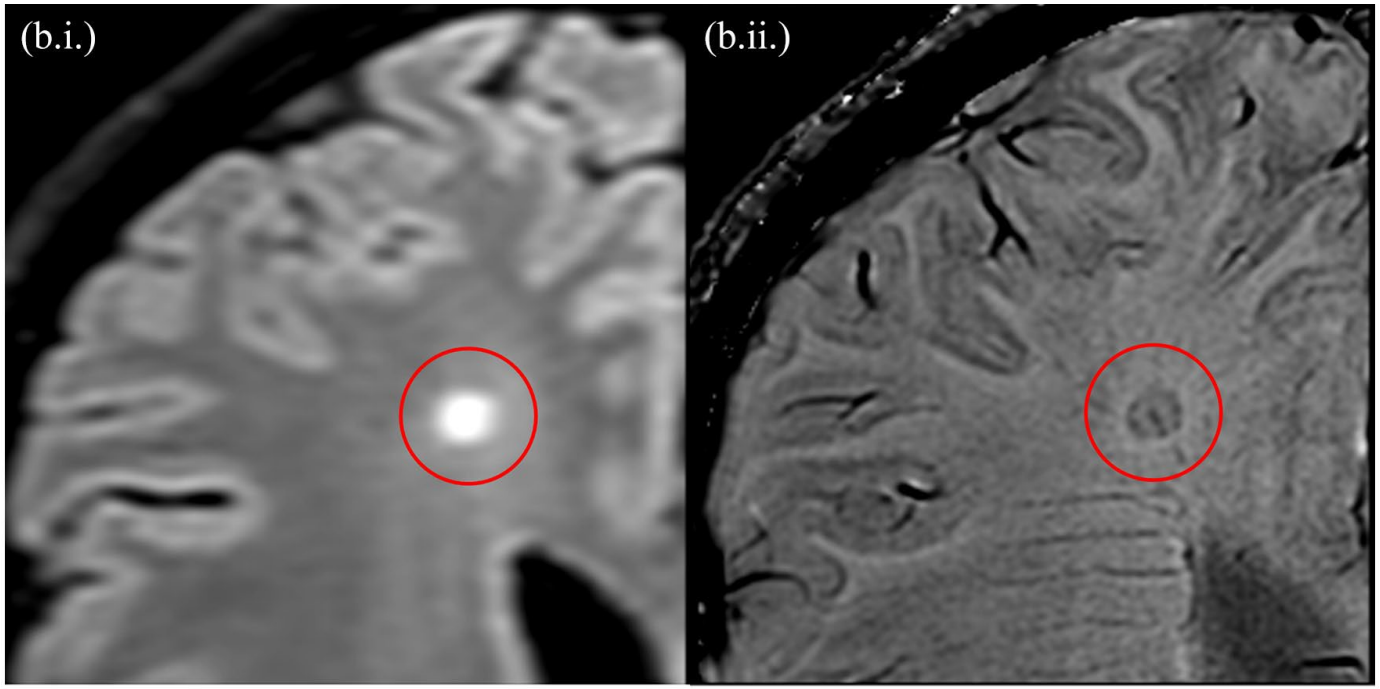
PRLs

PRLs are a biomarker for ongoing neurodegeneration linked to long-term disability accumulation

PRLs[1]: On average, PRLs constitute ~10% of the overall lesion count[2]



PRLs detected using the fluid-attenuated inversion recovery (b.i.) and phase-sensitive imaging (b.ii.) at 3 T. Figure from Meaton I, et al.

PRLs appear as hypointense, ring-like structures that surround WMLs on phase-sensitive MRI sequences (SWI or QSM)[1,2]

PRLs are associated with a rim of iron laden macrophages and microglia and are estimated to occur in 40% of patients with MS[1,2]

PRLs are observed as early as CIS and may be associated with more aggressive disease[1,2]

Paramagnetic rims are a potential imaging biomarker, containing potential diagnostic and prognostic value[1,2]

MRI, magnetic resonance imaging; MS, multiple sclerosis; PRLs, paramagnetic rim lesions; QSM, quantitative susceptibility mapping; RIS, Radiologically isolated syndrome; SWI, susceptibility-weighted imaging; WML, white matter lesion

1. Meaton I, et al. Mult Scler. 2022;28:2212-2220; 2. Calvi A, et al. Mult Scler. 2023;29:352-362.

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SELs

SELs are a biomarker for ongoing neurodegeneration linked to long-term total disability accumulation[1-3]

SELs demonstrate a **progressive decrease** in **T1 intensity over time,** reflecting accumulation of axonal damage within the SEL core[3]

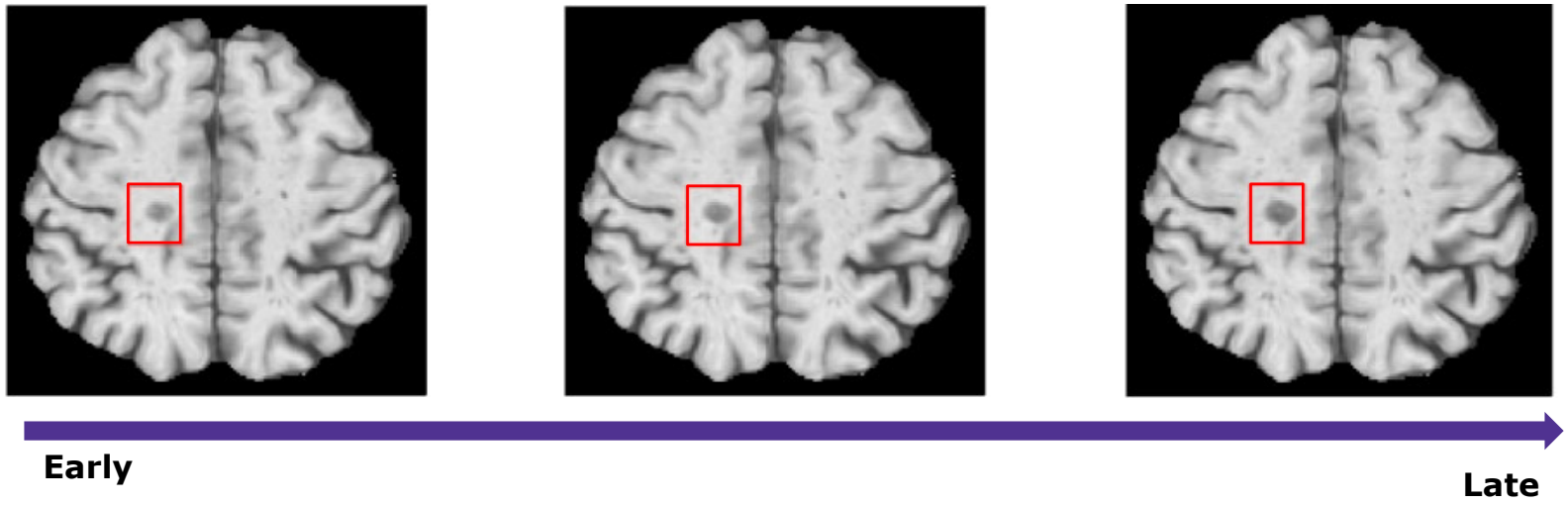

Figure: Example of SELs on a T1-weighted MRI scan
(SELs indicated by red squares; image courtesy of Dr Colm Elliott)

SELs (defined on MRI) can be identified as areas within pre-existing T2 lesions that show gradual, radial expansion over time. These SELs help identify areas of ongoing tissue damage within chronic lesions and a subset of chronic active lesions that show expansion over time[2,3]

The quantification of SELs may identify patients with RRMS at higher risk of long-term disability progression and SPMS conversion conversion, based on a median follow-up of 9.1 years[4]

MRI, magnetic resonance imaging; RRMS, relapsing-remitting MS; SEL, slowly expanding lesion; SPMS, secondary progressive MS

1. Arnold D, et al. ECTRIMS 2021 [115]; 2. Elliott C, et al. Brain. 2019;142: 2787-2799; 3. Elliott C, et al. Mult Scler. 2019;25:1915-1925;
4. Preziosa P, et al. Neurol Neuroimmunol Neuroinflamm. 2022;9:e1139.

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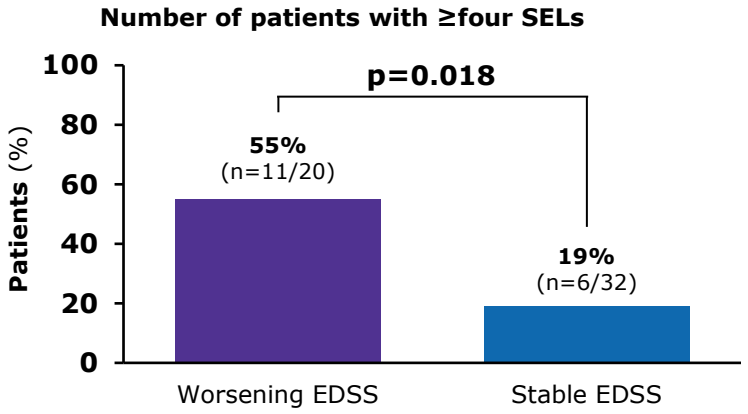
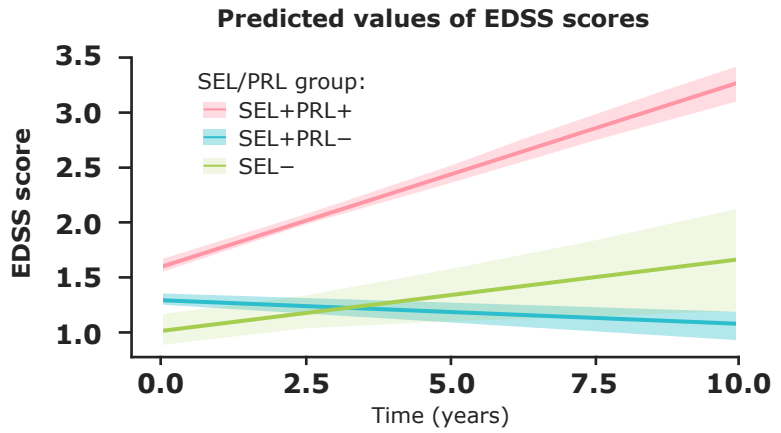
SELs and PRLs may serve as prognostic markers of EDSS progression

SELs can be seen from the early stages of MS and are associated with an aggressive disease course, indicated by:

- **Long-term disease progression**[1,2]
- **Disability worsening**[1–3]
- **Brain atrophy**[4]



EDSS worsening after 9.1 years was **significantly associated** with the **presence of ≥ four SELs**[1]



EDSS progression was predicted by **SEL counts** and PRL+ status[5]

There is potential to **use SELs as a proxy measure to assess smoldering MS**[6-8]

CNS, central nervous system; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PRL, paramagnetic rim lesions; SEL, slowly expanding lesions

1. Preziosa P, et al. Neurol Neuroimmunol Neuroinflamm. 2022;9:e1139; 2. Arnold DL, et al. Mult Scler. 2021;27:1681-1683; 3. Calvi A, et al. Neuroimage Clin. 2022;35:103048; 4. Klistorner S, et al. Mult Scler. 2021;27:1533-1542; 5. Calvi A. ECTRIMS 2022 [O-159]; 6. Elliott C, et al. Mult Scler. 2019;25:1915-1925; 7. Bittner S and Zipp F. Curr Opin Neurol. 2022;35:293-298; 8. Giovannoni G, et al. Ther Adv Neurol Disord. 2022;15:1-18.