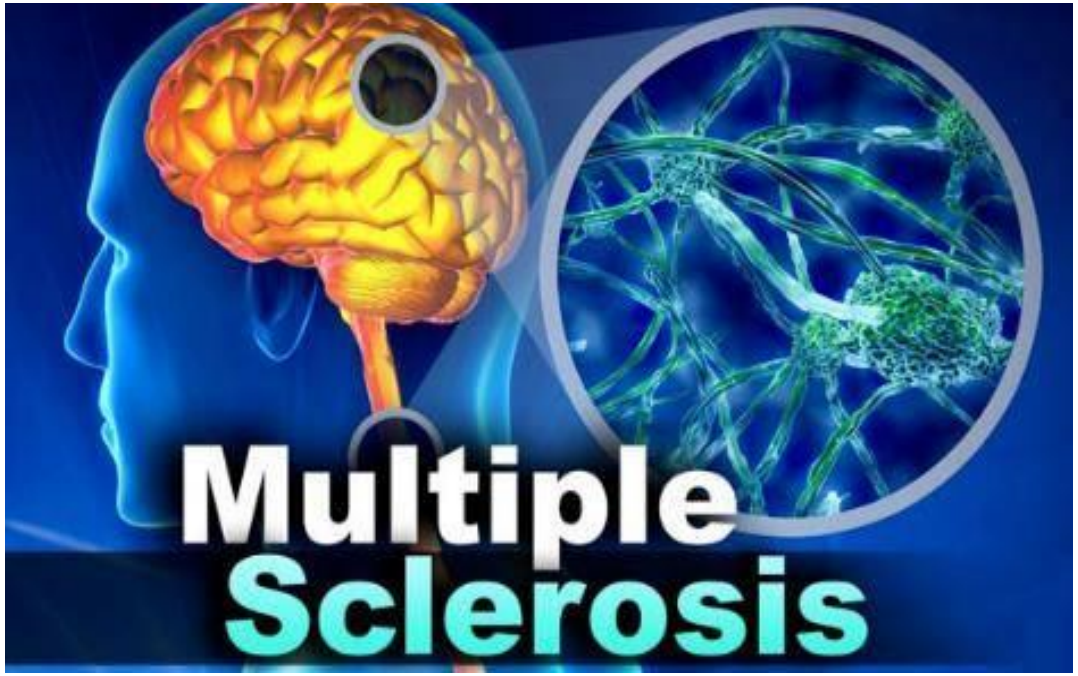
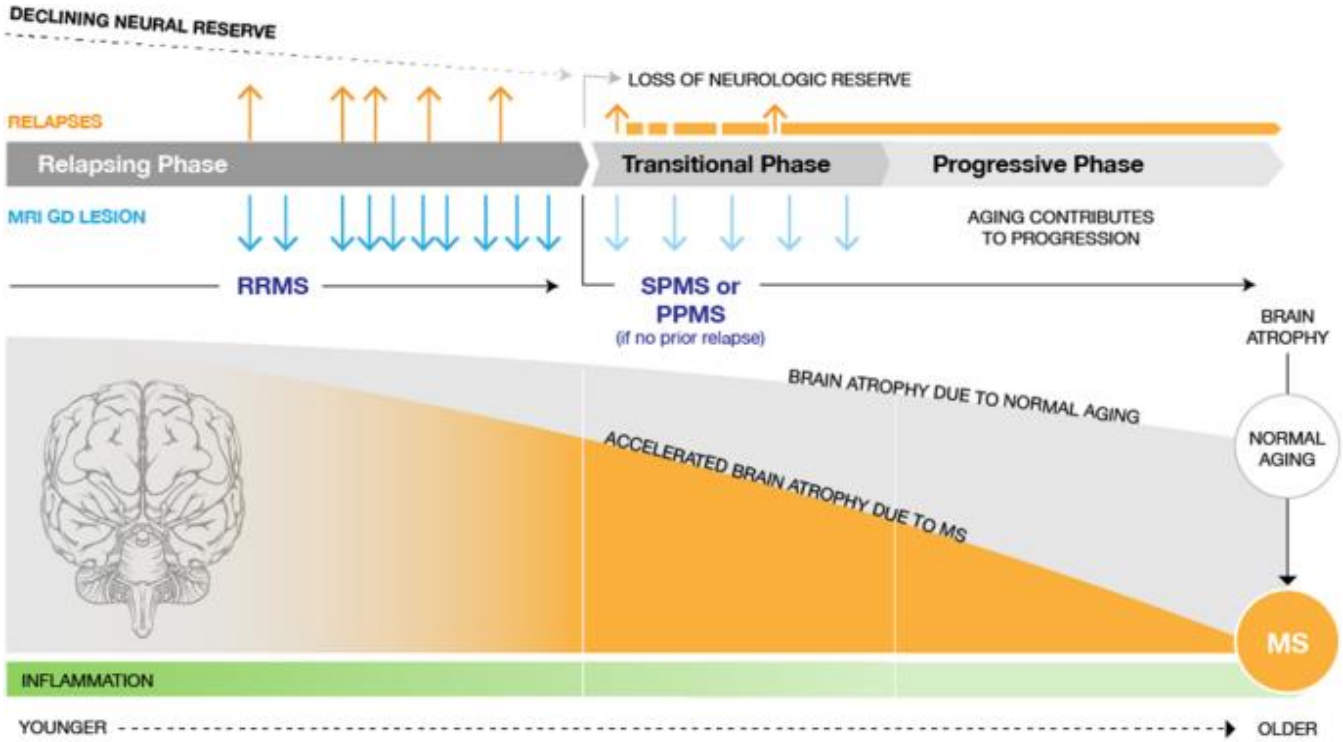
Updates on the Treatment of Multiple Sclerosis

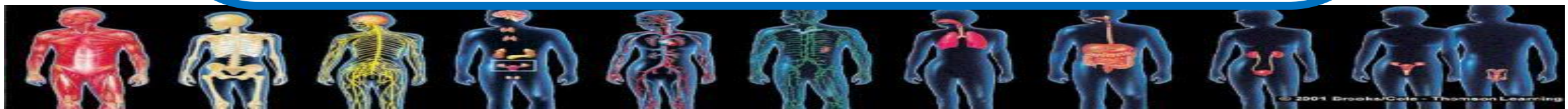




神經內科 張振書 Chen-Shu Chang, M.D. Ph.D.

OUTLINE

1. MS Introduction
2. MS Pathogenesis
3. MS Drugs – DMT choice
4. MS Progression – Smoldering process
5. MS New advanced DMT and Management
6. 健保使用規範



Fast Facts About Multiple Sclerosis

Vitamin D deficiency increases the risk and progression of MS

Considered an "invisible illness"

1 in 5 patients are misdiagnosed

There is no known cause

Populations located further from the equator experience higher rates

Pregnancy may improve symptoms

Women are 4 times more likely to develop MS

0.1%

Worldwide incidence

400, 000 people in US have MS

MULTIPLE SCLEROSIS AFFECT:

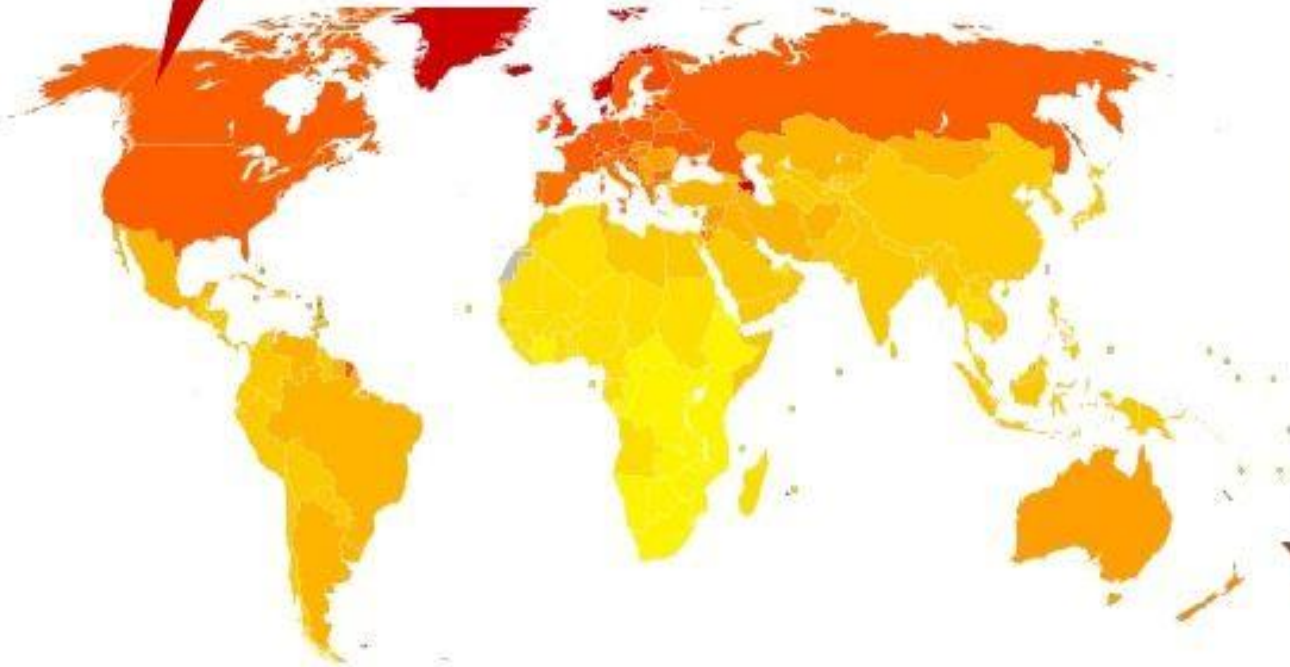
The ratio is increasing now

worse prognosis

Predominant age: **20-40**

1–3% risk of MS among 1st-degree relatives

Highly variable and unpredictable

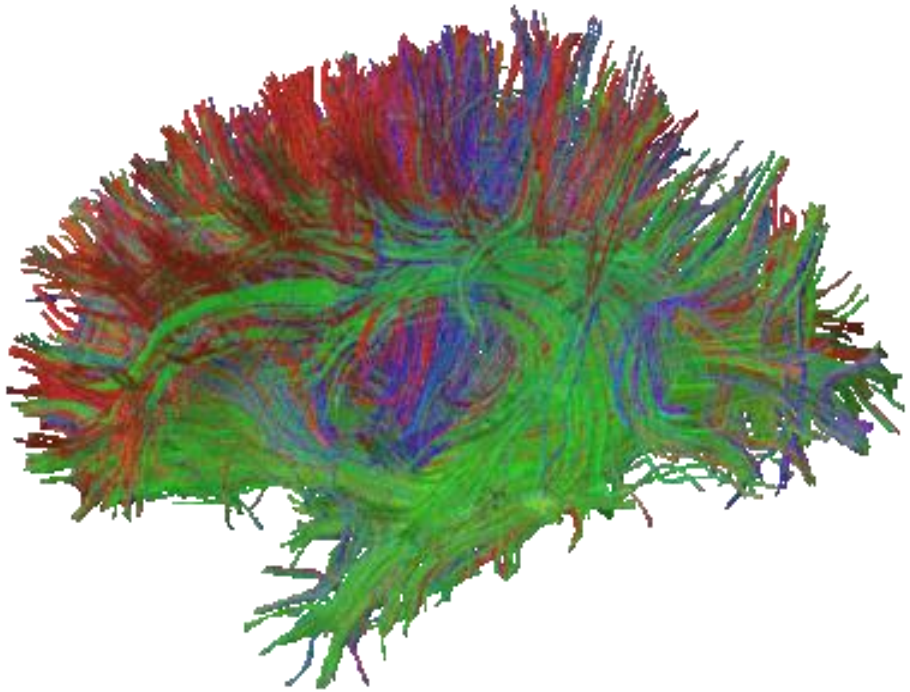


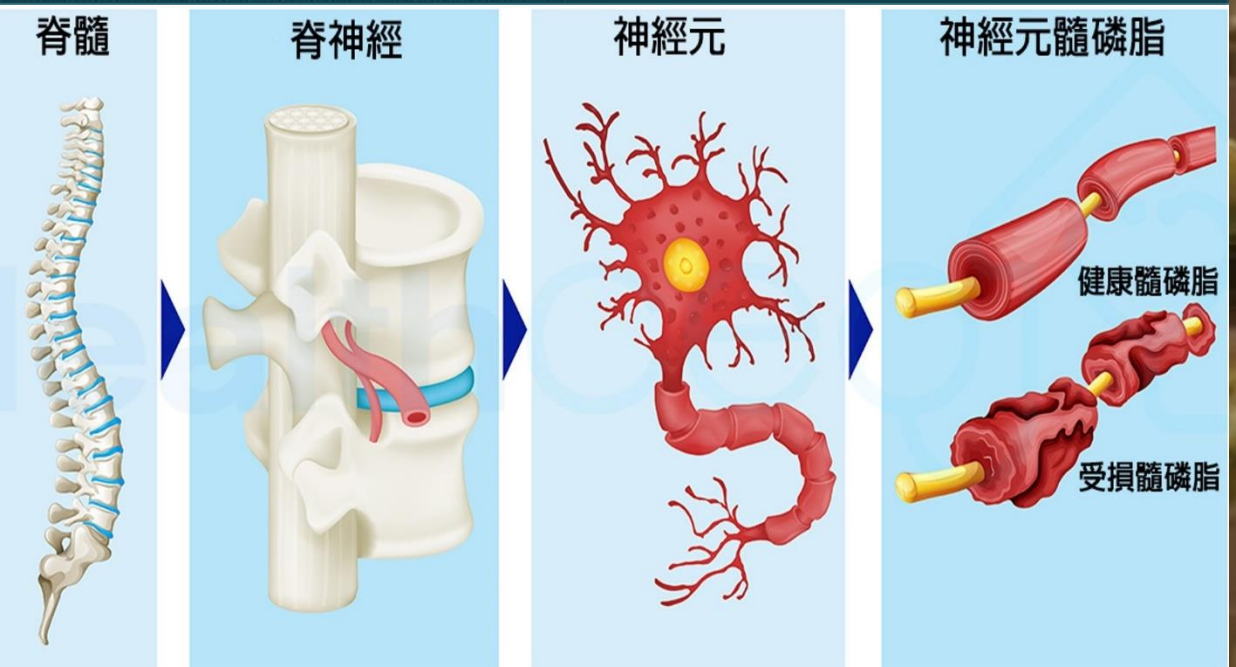
Higher incidence in **Northern European** descent and in temperate climate, but the latitude gradient is **decreasing**

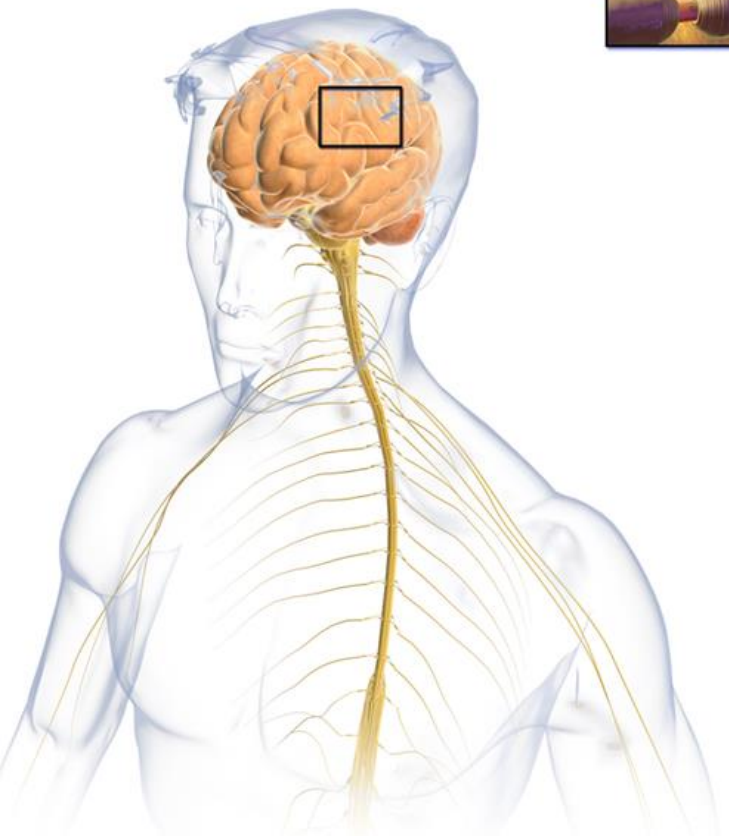
MULTIPLE SCLEROSIS

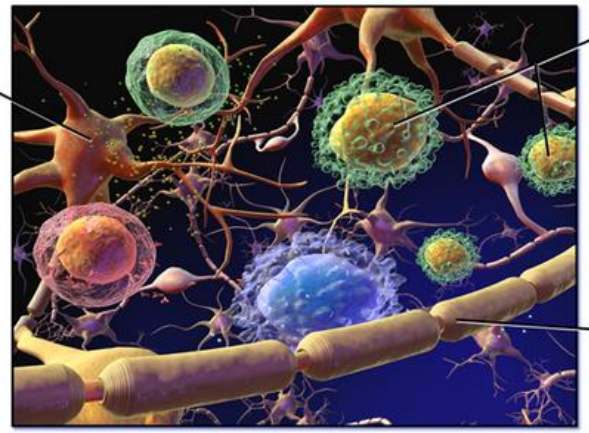
Classically multiple sclerosis (MS) has been regarded as an auto-immune disease of the white matter in the central nervous system leading to severe disability over the course of several decades. Over the years, substantial evidence emerged that gray matter (GM) is also heavily affected and that neurodegenerative phenomena such as neuronal/axonal damage and GM and White Matter (WM) atrophy play an important role in MS.

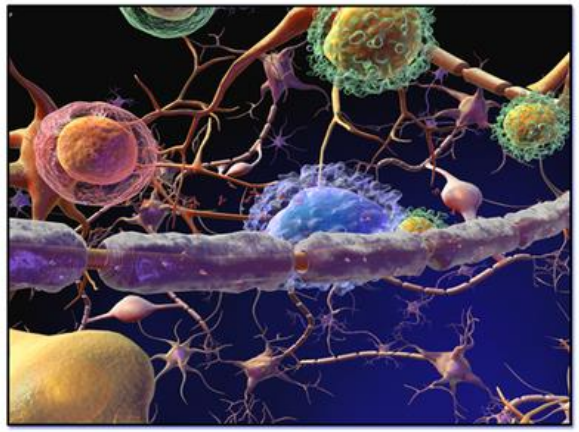
Barkhof et al. 2009, Lopez-Diego et al. 2009, Popescu et al. 2013





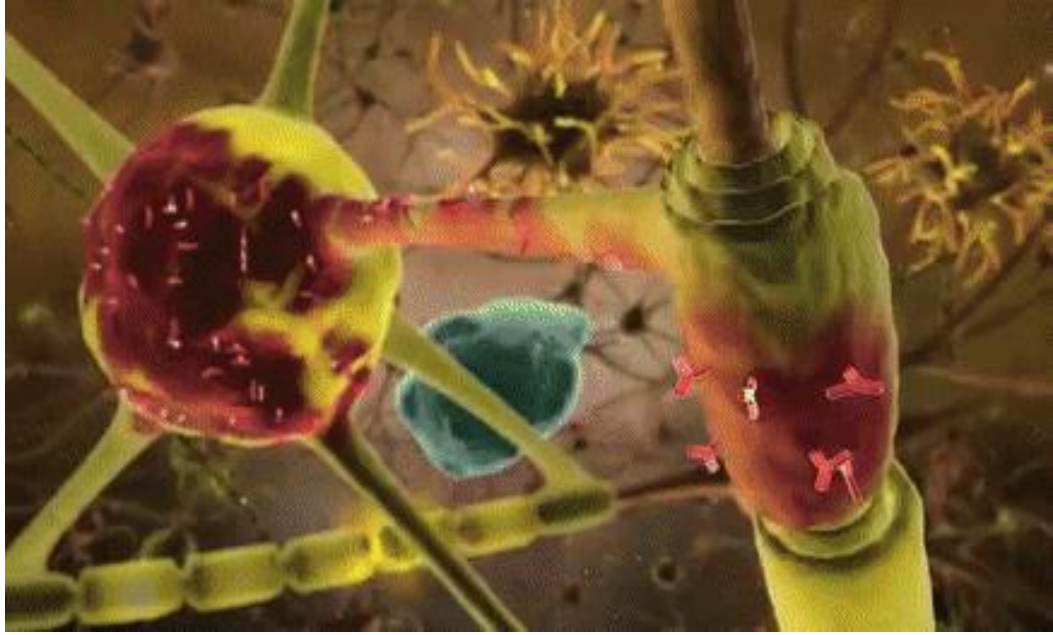


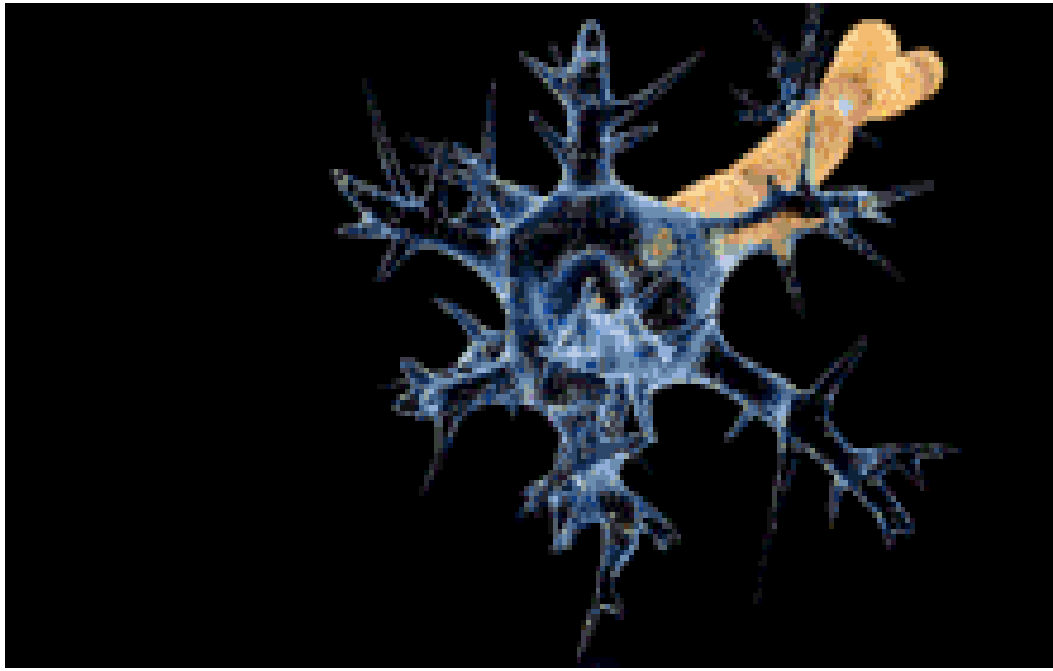




Myelin destroyed by body's own immune cells

Multiple Sclerosis





Risk Factors for Multiple Sclerosis

GENDER

Women are two times more likely to be affected.

VITAMIN D & B12 DEFICIENCY

These deficiencies may increase risk of developing MS.

SMOKING

People who smoke are **two times more likely** to develop MS.

GENETICS

People with a **first-degree relative** with MS are at increased risk.

LOCATION

MS is more common in **temperate regions** as you move away from the equator.

AUTOIMMUNE DISEASE

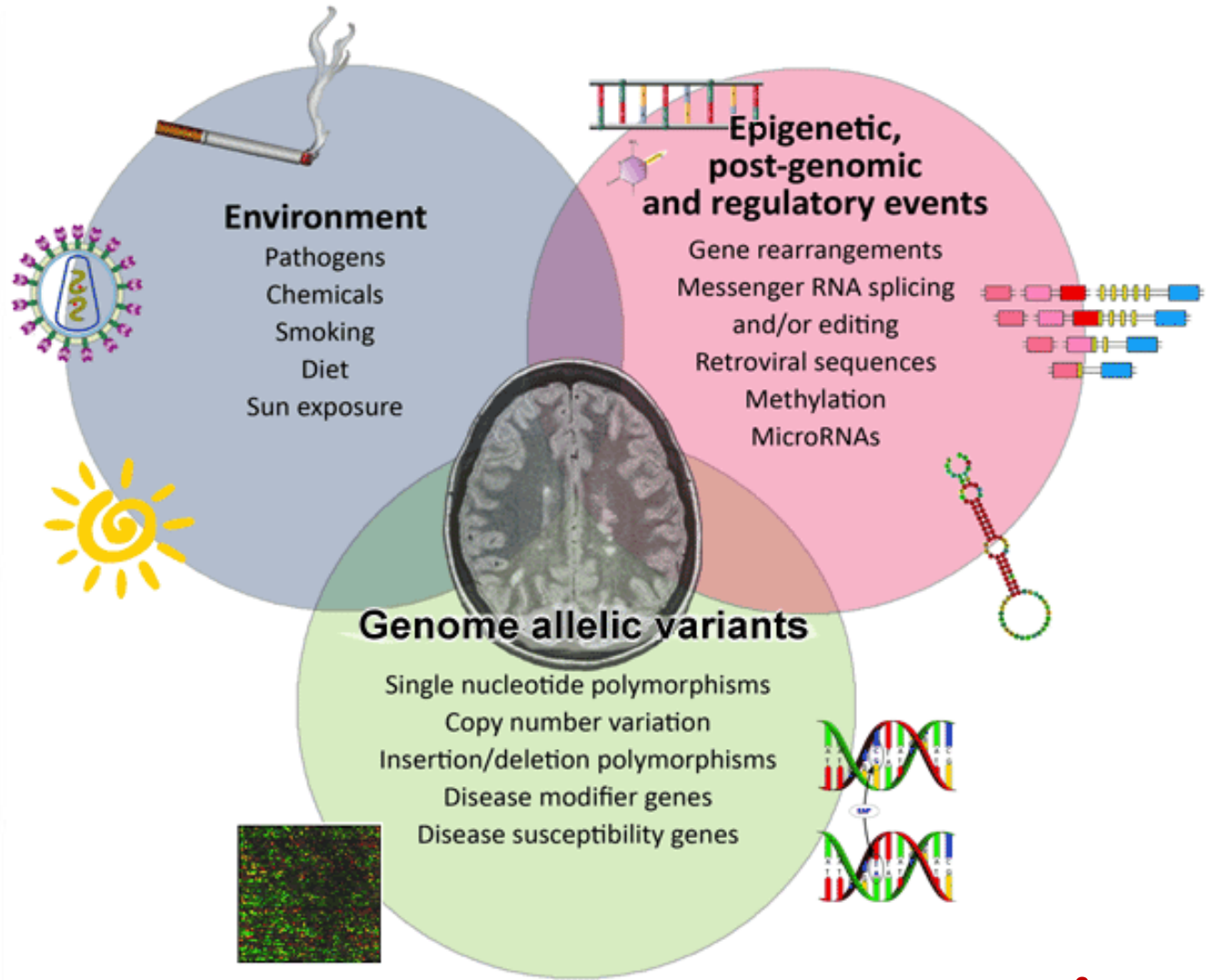
Diseases such as inflammatory bowel disease, thyroid disease, or type 1 diabetes can increase risk.

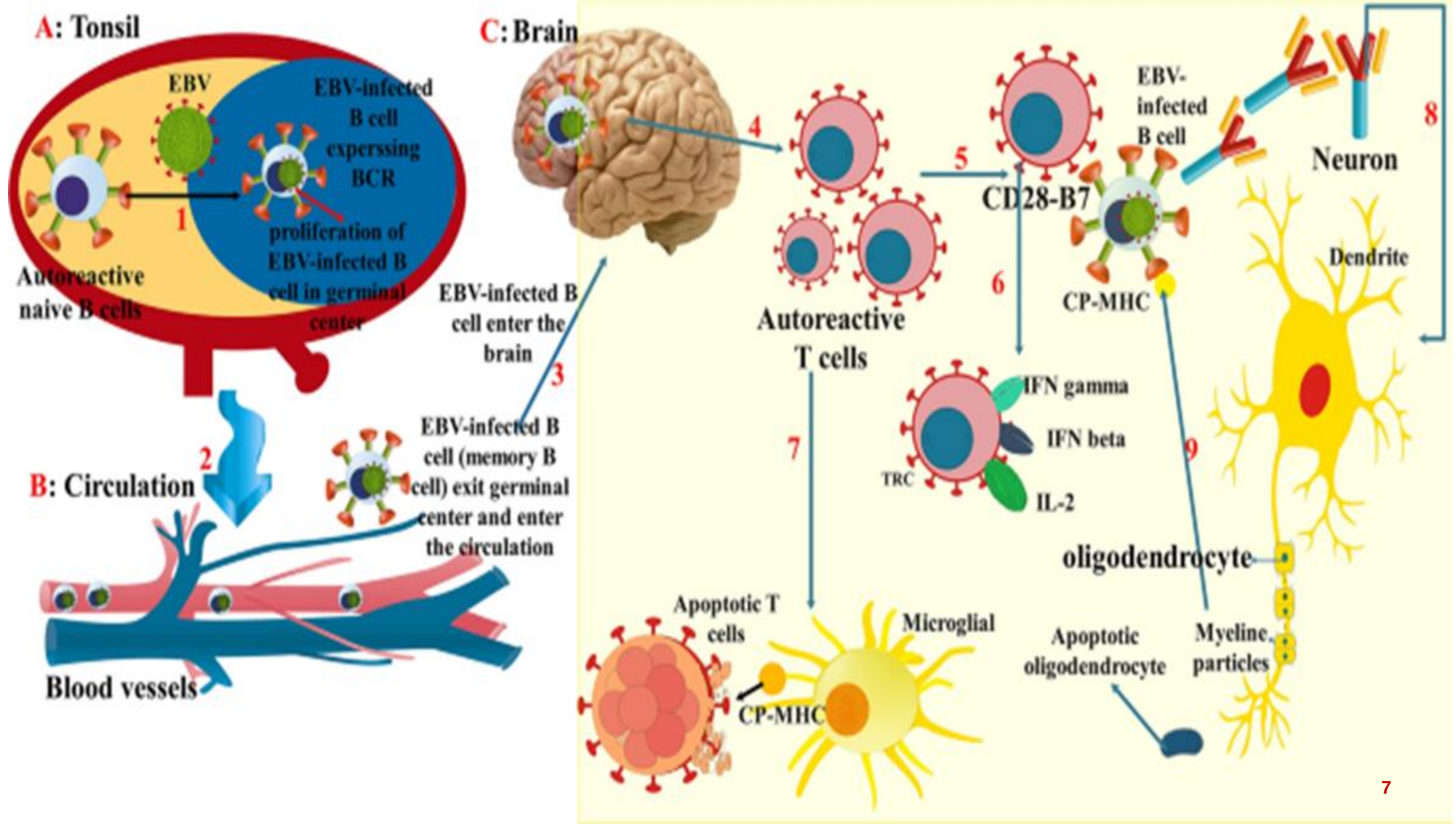
RACE/ETHNICITY

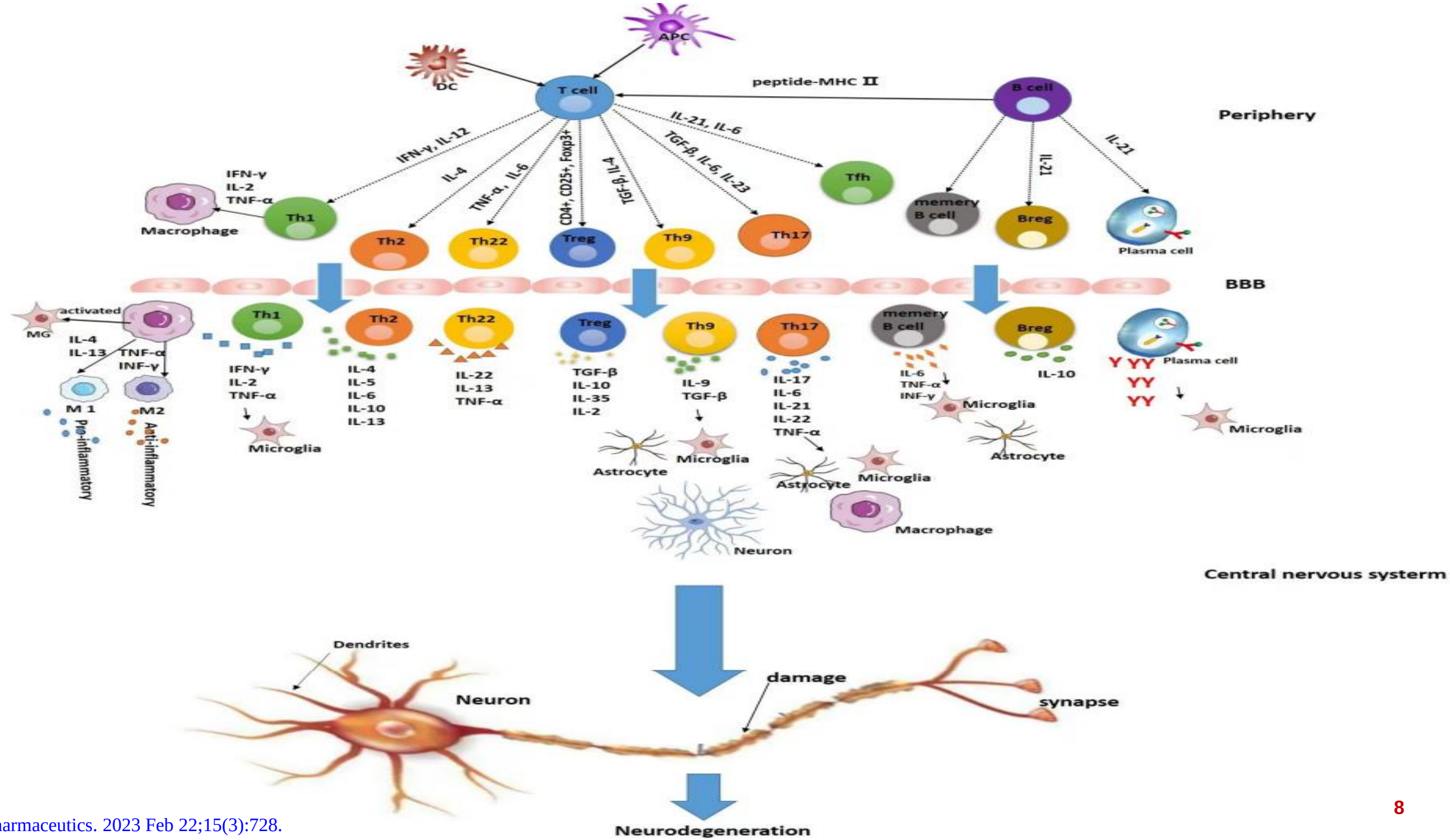
Caucasians are at higher risk (especially those of Northern European ancestry).

AGE

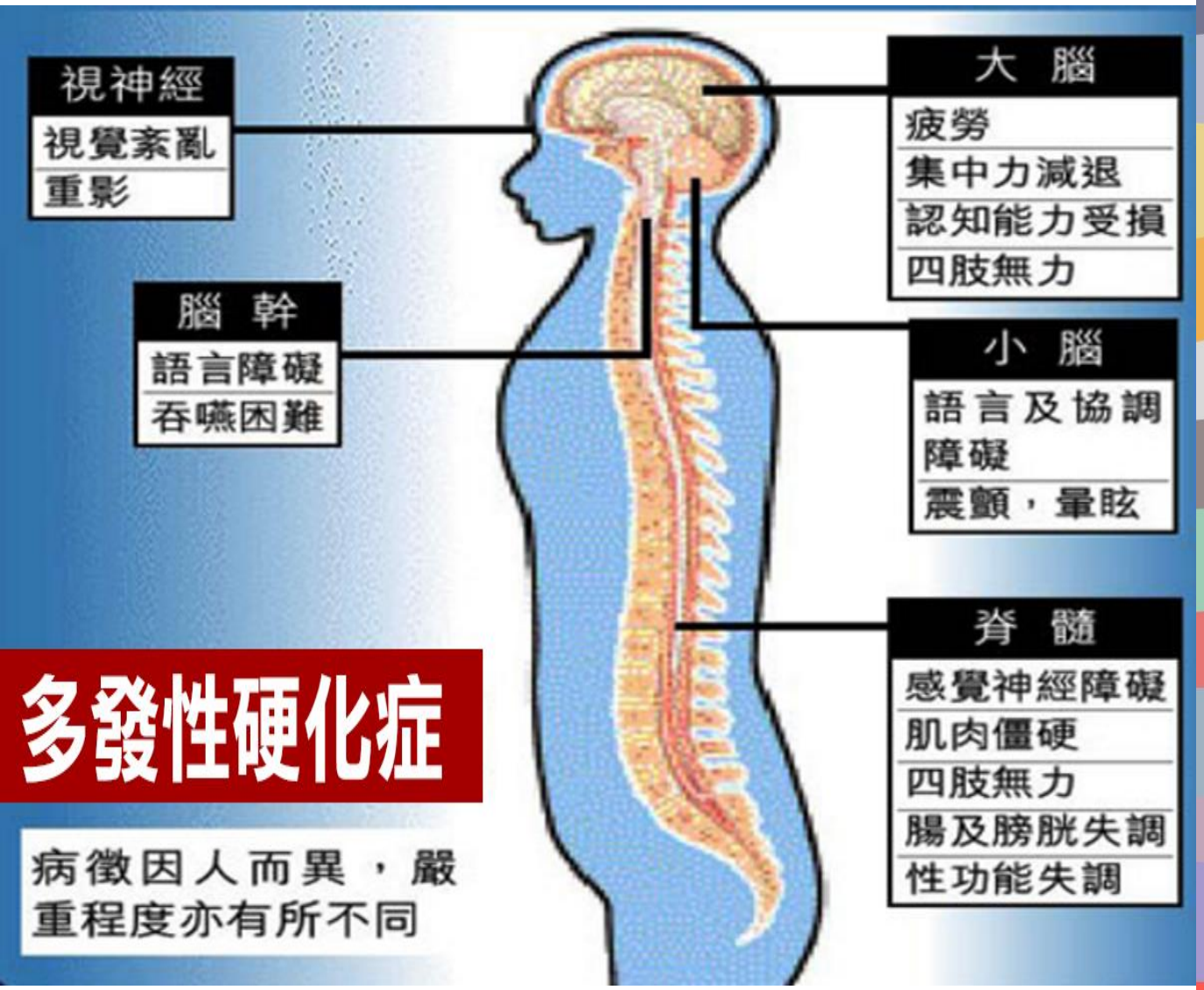
Most commonly diagnosed between the age of **20 and 40.**




A: Tonsil
EBV
EBV-infected B cell expressing BCR
1
proliferation of EBV-infected B cell in germinal center
Autoreactive naive B cells
2
B: Circulation
EBV-infected B cell (memory B cell) exit germinal center and enter the circulation
Blood vessels
3
EBV-infected B cell enter the brain
C: Brain
4
Autoreactive T cells
5
CD28-B7
EBV-infected B cell
6
CP-MHC
IFN gamma
IFN beta
IL-2
TRC
7
Apoptotic T cells
CP-MHC
Microglial
8
Neuron
Dendrite
oligodendrocyte
9
Apoptotic oligodendrocyte
Myeline particles



Pharmaceutics. 2023 Feb 22;15(3):728.



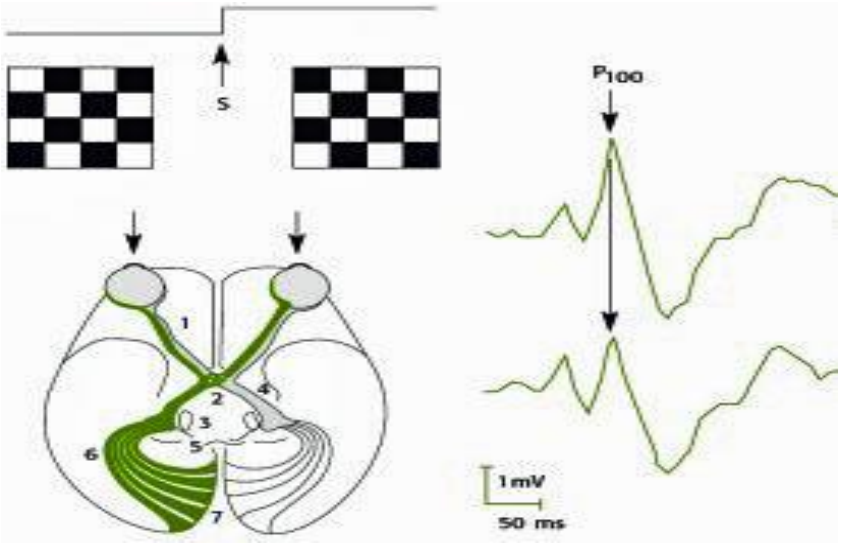
Initial Symptoms

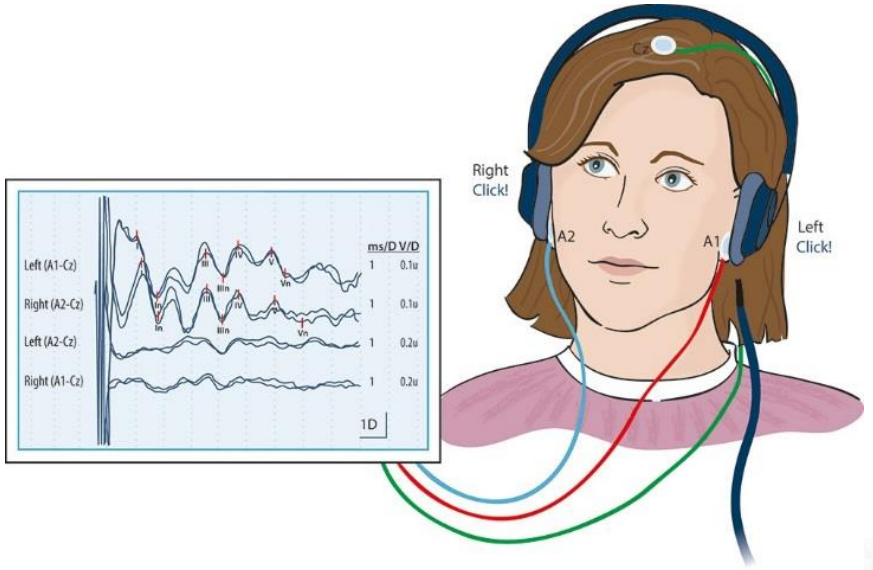
NUMBNESS, TINGLING, OR OTHER ALTERED SENSATIONS (EG, TASTE)	60%
WALKING/BALANCE/COORDINATION PROBLEMS	43%
FATIGUE	38%
VISION PROBLEMS/OPTIC NEURITIS	32%
MUSCLE WEAKNESS	28%
DIZZINESS/VERTIGO	27%
HEADACHES/MIGRAINES	22%
MUSCLE SPASMS/SPASTICITY	21%
HEAT SENSITIVITY/HEAT INTOLERANCE	21%
PAIN	20%

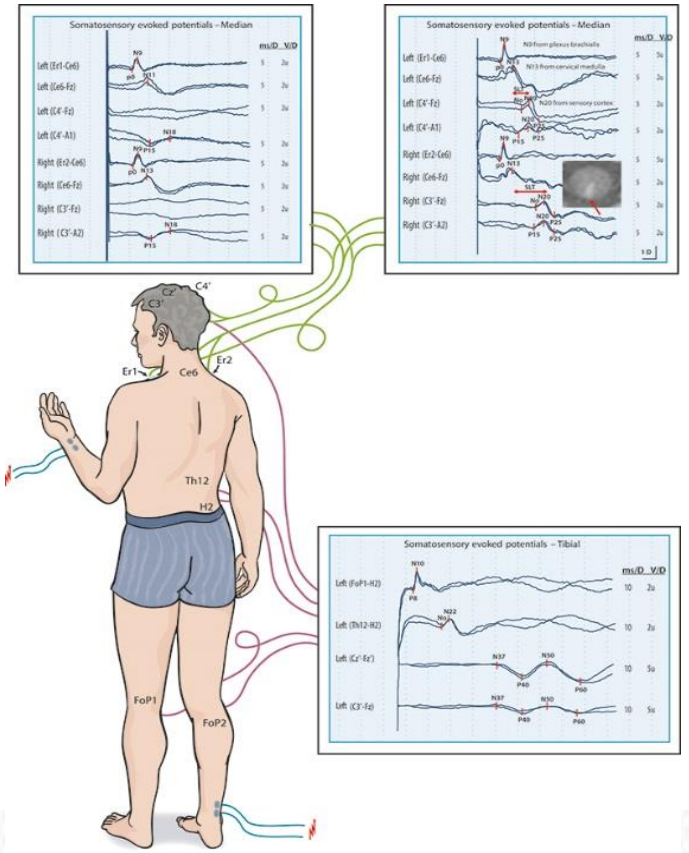
MS

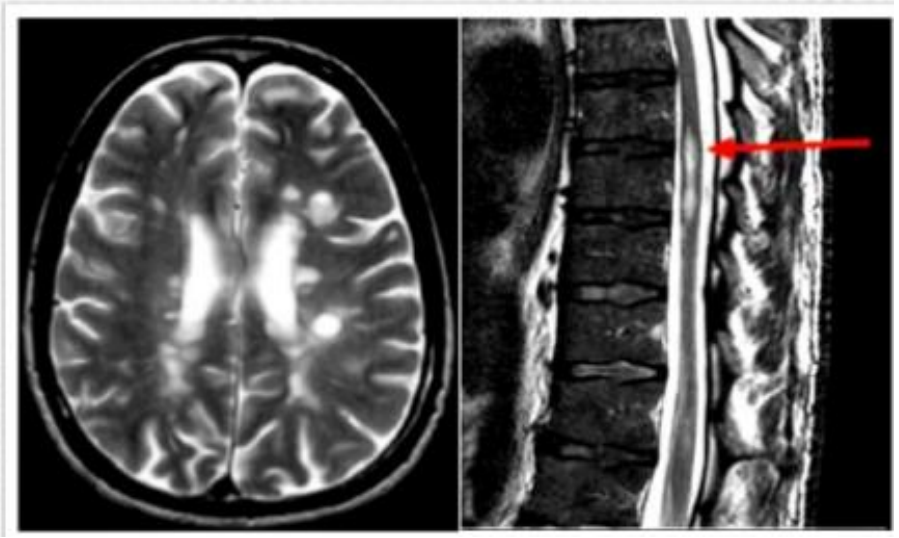
MS In America 2016: Being Diagnosed with Multiple Sclerosis

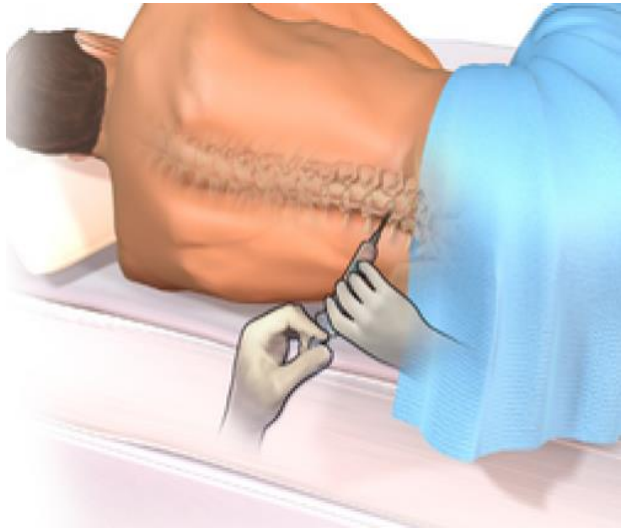
如何診斷多發性硬化症？











CSF examination:

- Abnormal in 85% to 90% of patients with MS.
- Elevated total IgG, an elevated IgG ratio, an increased IgG synthesis rate,
- Presence of two or more oligoclonal bands in the CSF that are not present in a simultaneously drawn serum sample

Classic Findings of Multiple Sclerosis (MS) on Brain MRI

Authors:
Evan Allarie
Davis Maclean
Viesha Ciura*
Reviewers:
Yan Yu*
** MD at time of publication*

Note: variation in findings exist. The findings shown here are not exhaustive but are some of the most common areas implicated on brain MRI in MS. Most common sites that lesions are observed are: juxtacortical regions, periventricular, infratentorial, spinal cord, and the optic nerve. However lesions can occur anywhere there is myelin in the CNS.

Inflammation within the central nervous system (CNS)

For further pathogenesis, see the Calgary Guide slide: *Multiple Sclerosis (MS): Pathogenesis and Clinical Findings*

T-cell, B-cell, and macrophages infiltrate CNS

Infiltration occurs through veins → local inflammation

Perivenular infiltrates around the medullary veins (perpendicular to ventricles)

infiltrates in the infratentorial region

Inflammation and blood-brain barrier destruction ↑ extravascular inflammatory fluid around lesions, which appears hyperintense/bright

Loss of neuronal/axonal density in affected region, replaced by gliosis over time

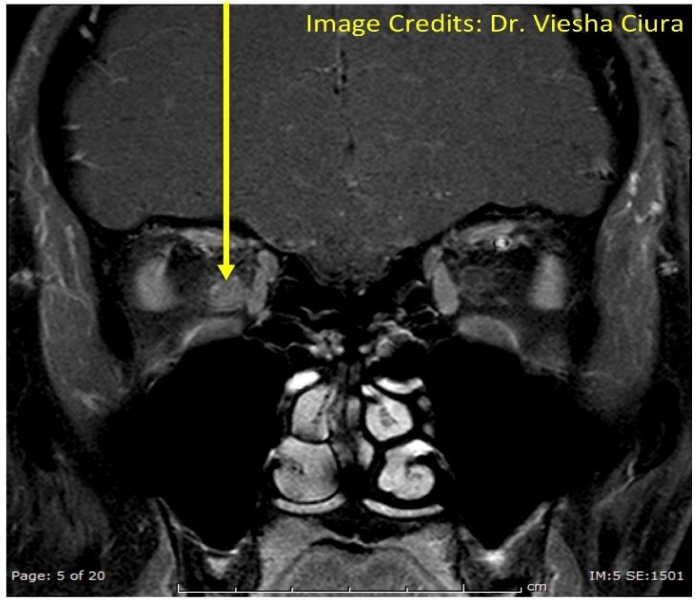
Active inflammation and destruction allows for gadolinium contrast to cross the blood-brain barrier, which can be visualized as a marker of active inflammation in MS

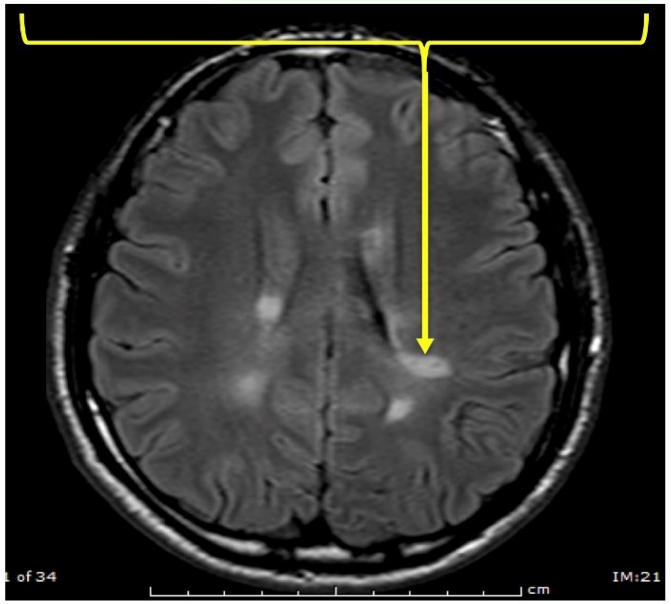
Classic optic nerve (CN II) lesion seen in optic neuritis. Gadolinium enhancement (↑ signal intensity of lesion after gadolinium injection) in this T1 image demonstrates active inflammation

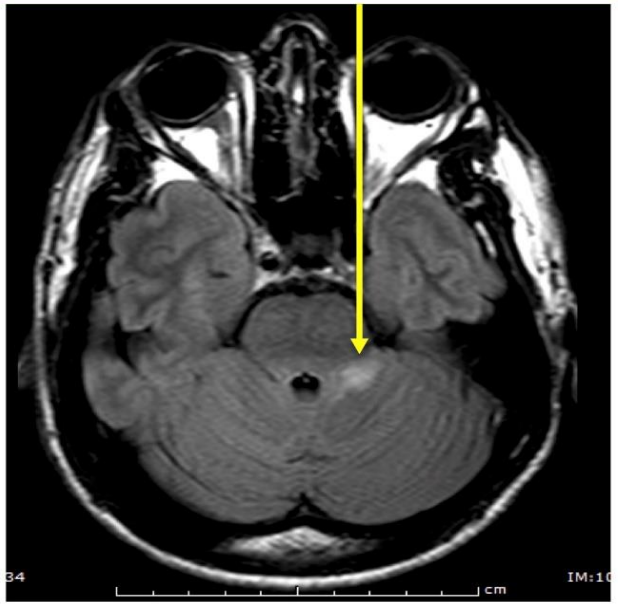
Lesions extend out around veins, creating characteristic **ovoid lesions**

Classic hyperintense T2/FLAIR perpendicular periventricular plaques following the medullary veins – '**Dawson's Fingers**'

Middle cerebellar peduncle T2/FLAIR **hyperintense lesion** in classic location for MS







Published **October 25, 2020** on www.thecalgaryguide.com

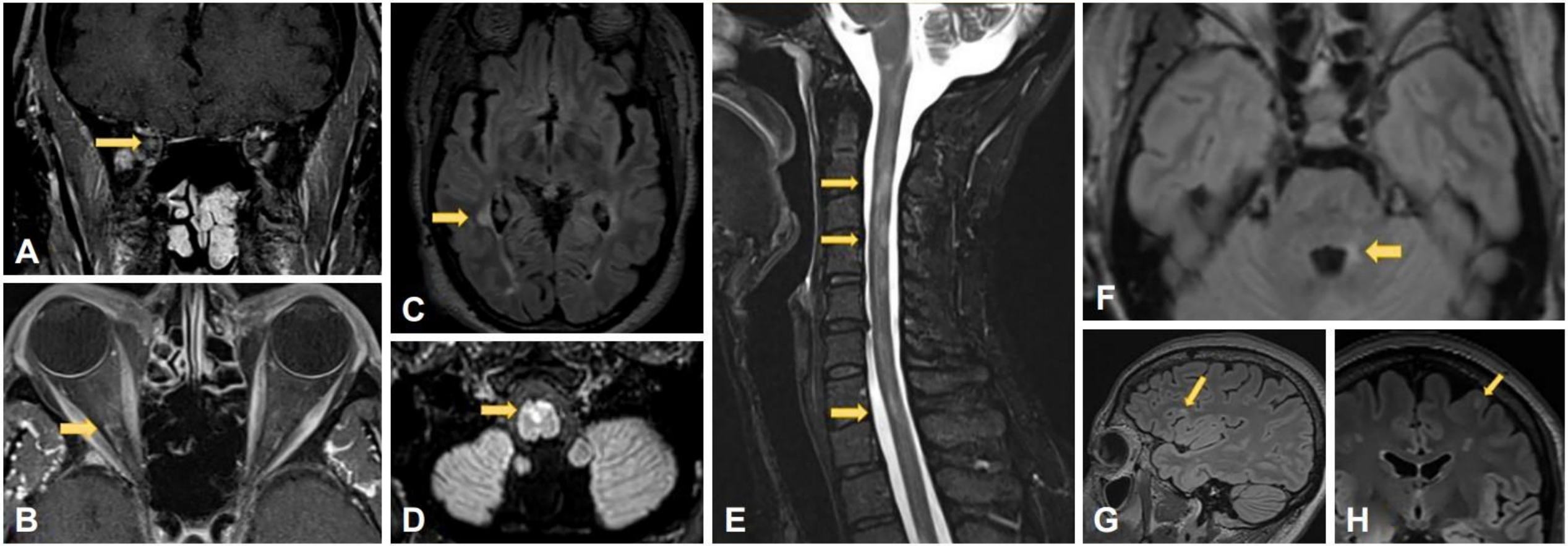


Fig. 1. Juxtacortical/cortical, periventricular, spinal cord, and brainstem lesions in multiple sclerosis. A (coronal) and B (axial): MRI T1-post contrast images show enhancement in the intraorbital segment of the optic nerve consistent with right optic neuritis (arrows). C: Right posterior periventricular lesion on axial T2-FLAIR (arrow). D: Ventral medullary demyelinating lesion on T2-FLAIR (arrow). E: MR cervical cord sagittal STIR demonstrating C2-3, C4, and C7 demyelinating lesions (arrows). F: Axial T2-FLAIR with demyelinating lesion in left brachium pontis (arrow). G (sagittal) and H (axial): T2-FLAIR images demonstrate left frontal juxtacortical demyelinating lesion (arrows). J Clin Neurol 2023;19(3):217-229

衛生福利部國民健康署「罕見疾病個案通報審查基準機制」(送審資料表) -多發性硬化症/[MS]

表2.泛視神經脊髓炎 [Neuromyelitis Optica Spectrum Disorders, NMOSD]

- 應檢附文件(必要)
- 病歷資料 (包括臨床表徵、發病年齡、家族史、發病次數、病程發展過程、神經學身體診察等)
- 相關科會診病歷紀錄(必要)：☐ 眼科會診　　☐ 免疫科會診　　☐ 血液腫瘤科會診

- ☐相關科會診病歷紀錄(必要)：
- ☐ 眼科會診　　☐ 免疫科會診　　☐ 血液腫瘤科會診
- ☐ 排除Sarcoidosis
- ☐ 排除中樞神經系統Lymphoma
- ☐ 排除Paraneoplastic Syndrome
- ☐ 排除系統性身體免疫等疾病侵入中樞神經系統之疾病

2017 revised McDonald criteria

Clinical presentation		Additional data needed?
Attacks (= DIT)	Clinical signs (=DIS)	
≥ 2	≥ 2	None
≥ 2	1	DIS: await clinical evolution, or on MRI
1	≥ 2	DIT: await clinical evolution, or on MRI *(or oligoclonal bands)*
1	1	DIS and DIT Clinical or MRI *(or oligoclonal bands ←→ DIT)*

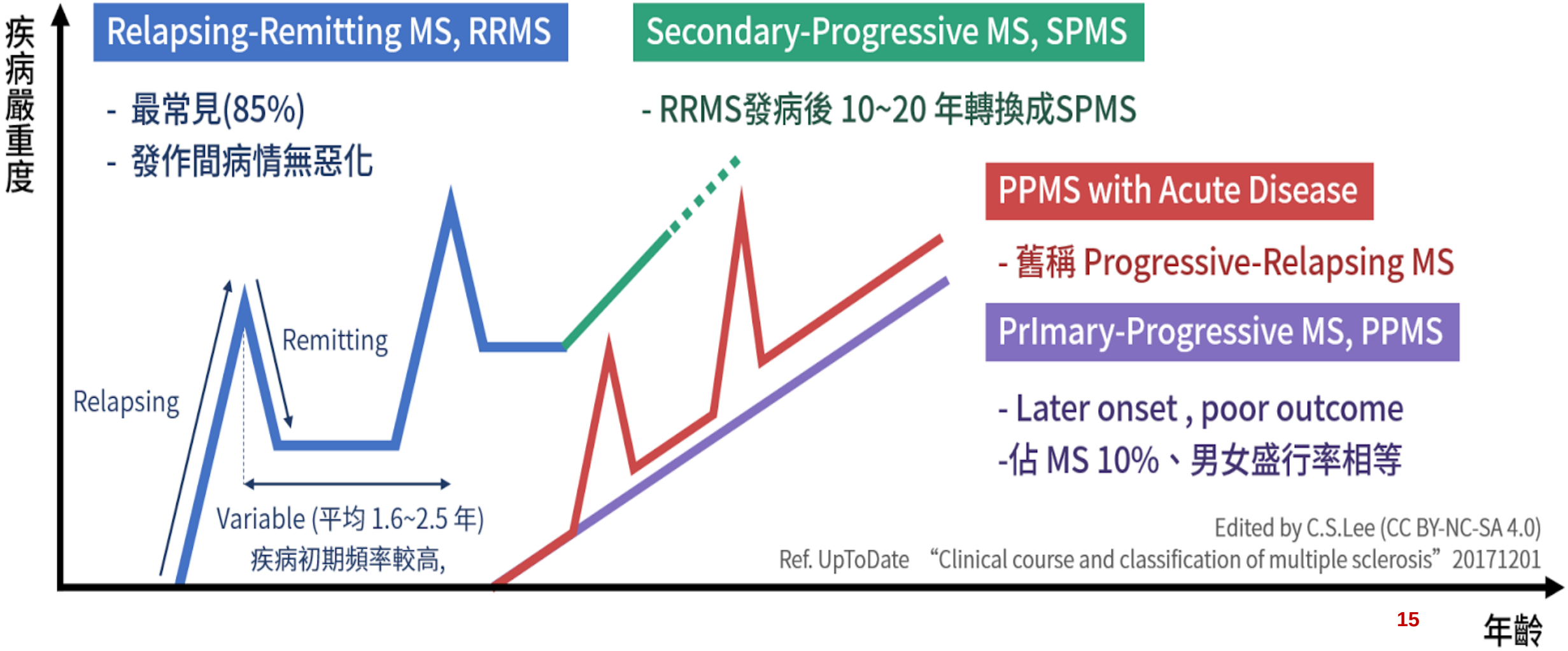
MS: diagnosis

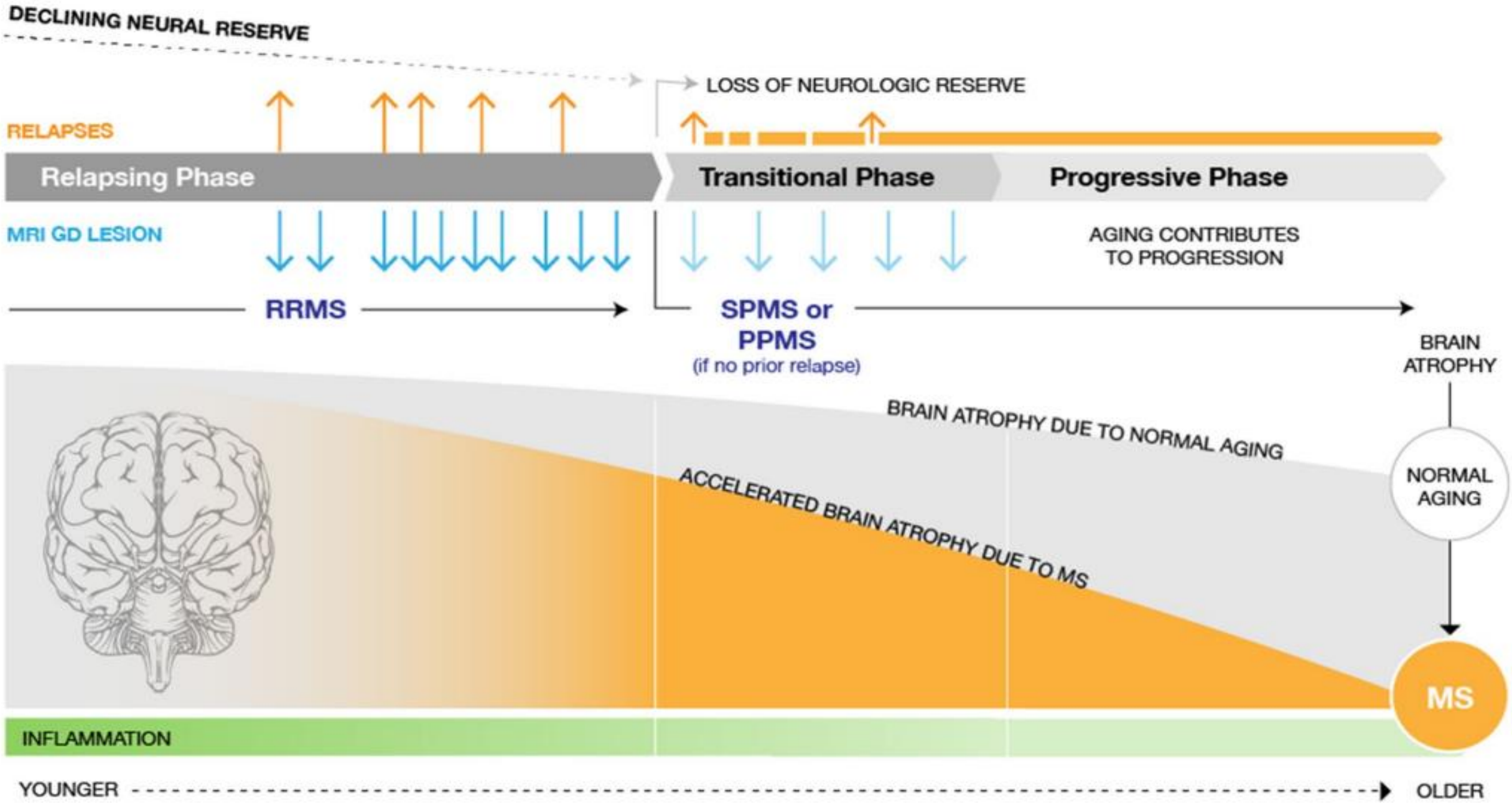
MS diagnosis is based on demonstrating dissemination of demyelinating lesions

Dissemination in space (DIS):
To different regions of the brain
Dissemination in time (DIT):
At multiple moments in time

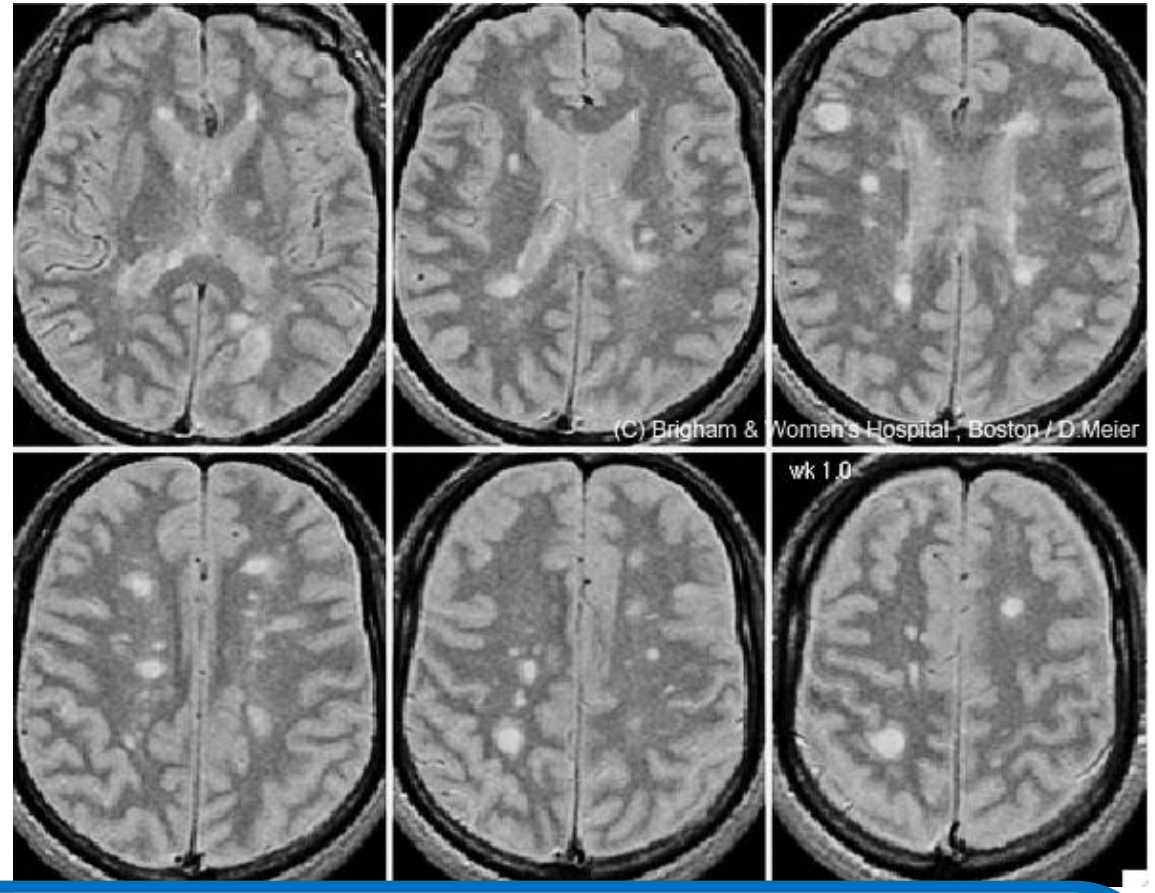
How do you define DIT and DIS on MRI?

大多數的MS病人，
在復發-緩解的病程之後，會進入持續惡化的階段

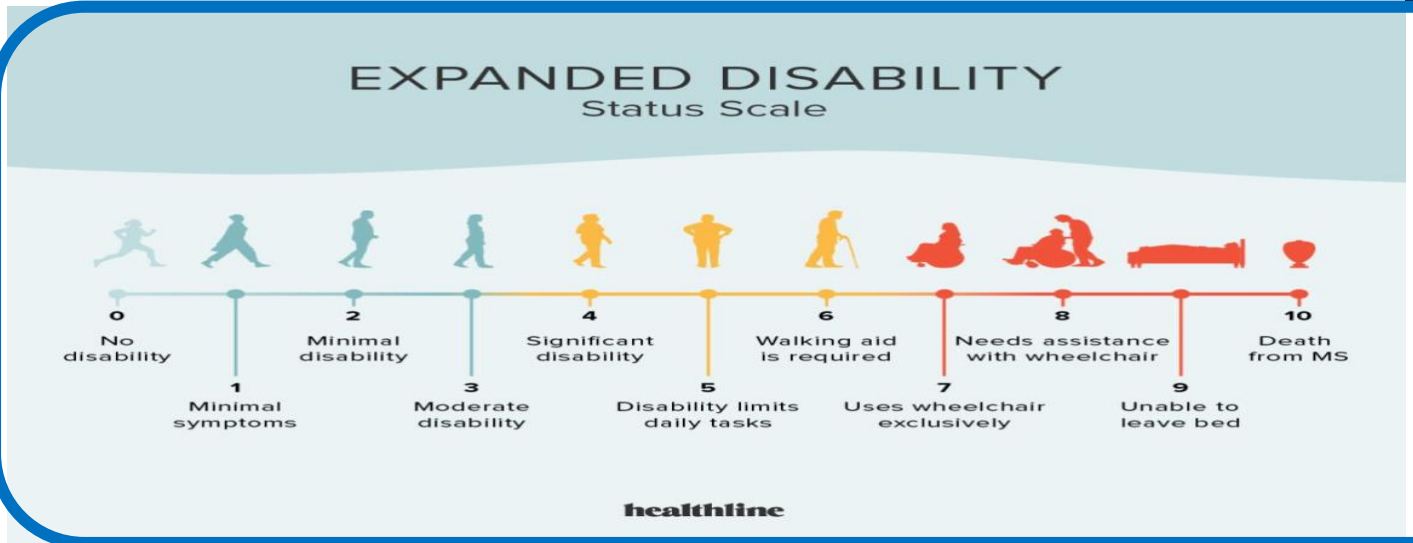


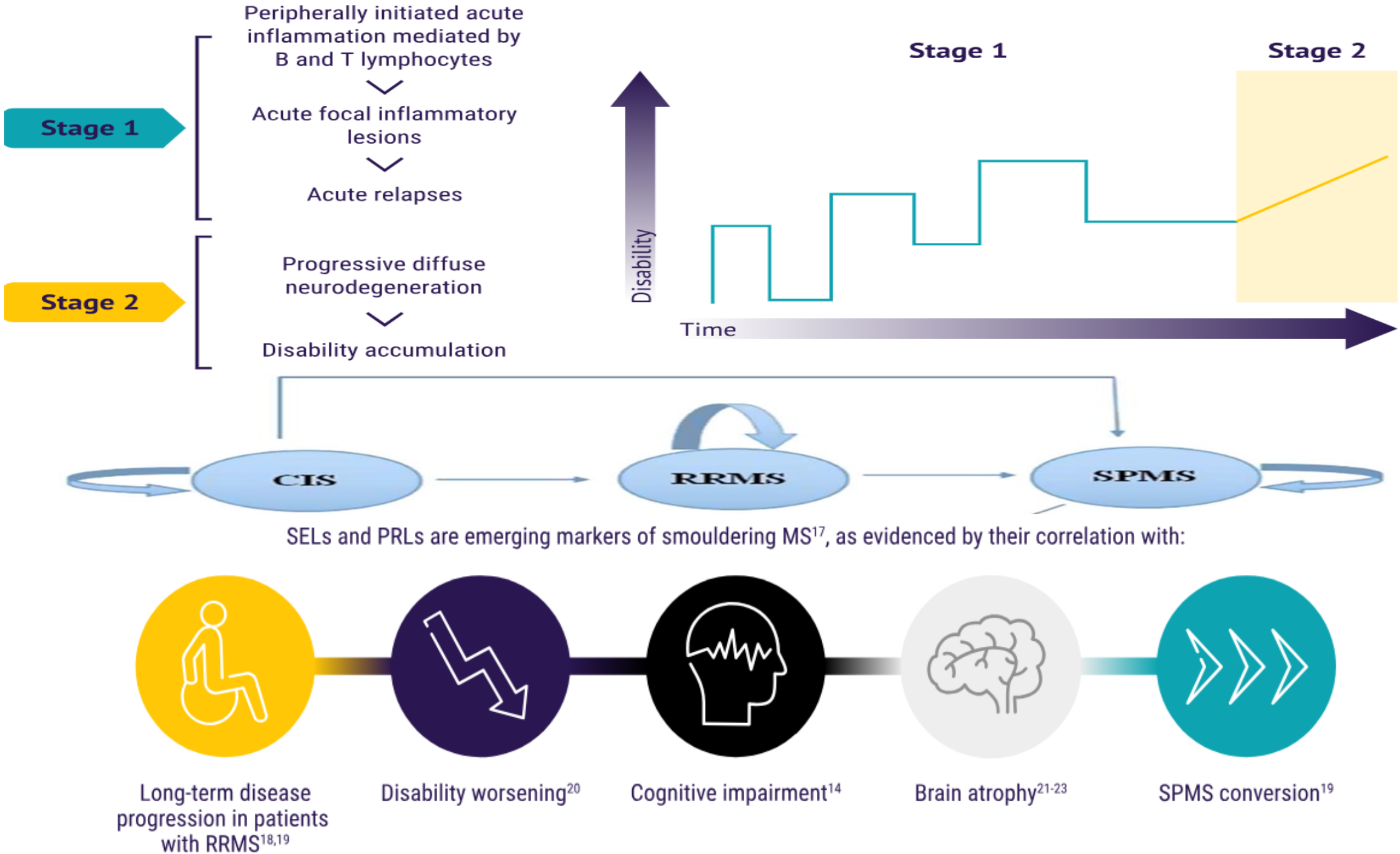


CNS Drugs (2022) 36:1285–1299



M33/DxJan2016/RRMS/UsedGilenya/NowOcrevus/Australia




Stage 1
Peripherally initiated acute inflammation mediated by B and T lymphocytes
Acute focal inflammatory lesions
Acute relapses
Stage 2
Progressive diffuse neurodegeneration
Disability accumulation
Stage 1
Stage 2
Disability
Time
CIS
RRMS
SPMS
SELs and PRLs are emerging markers of smouldering MS[17], as evidenced by their correlation with:
Long-term disease progression in patients with RRMS[18,19]
Disability worsening[20]
Cognitive impairment[14]
Brain atrophy[21-23]
SPMS conversion[19]

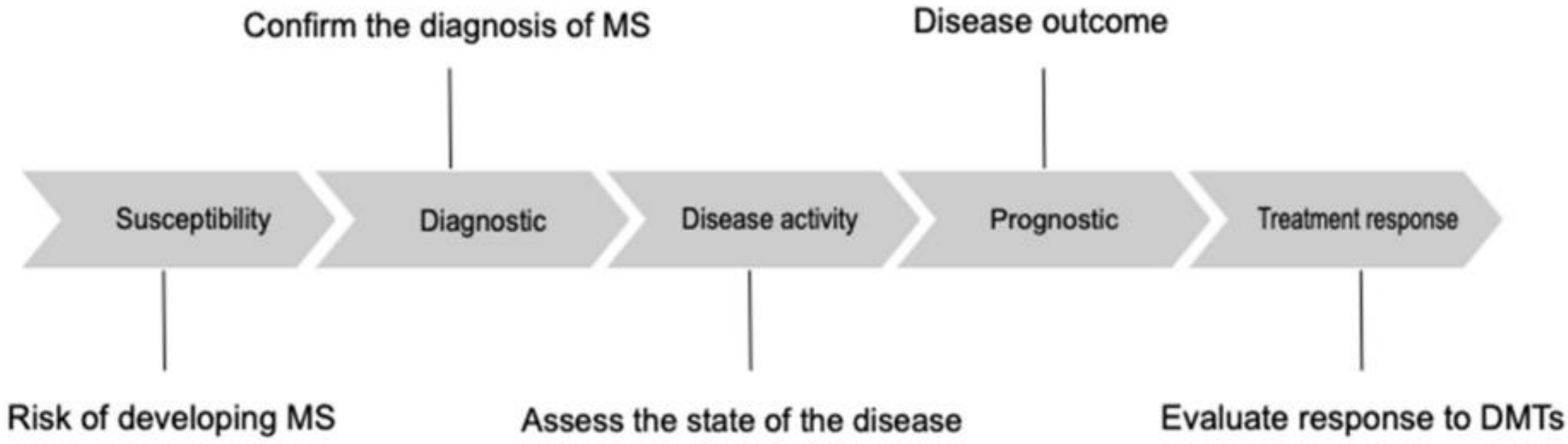
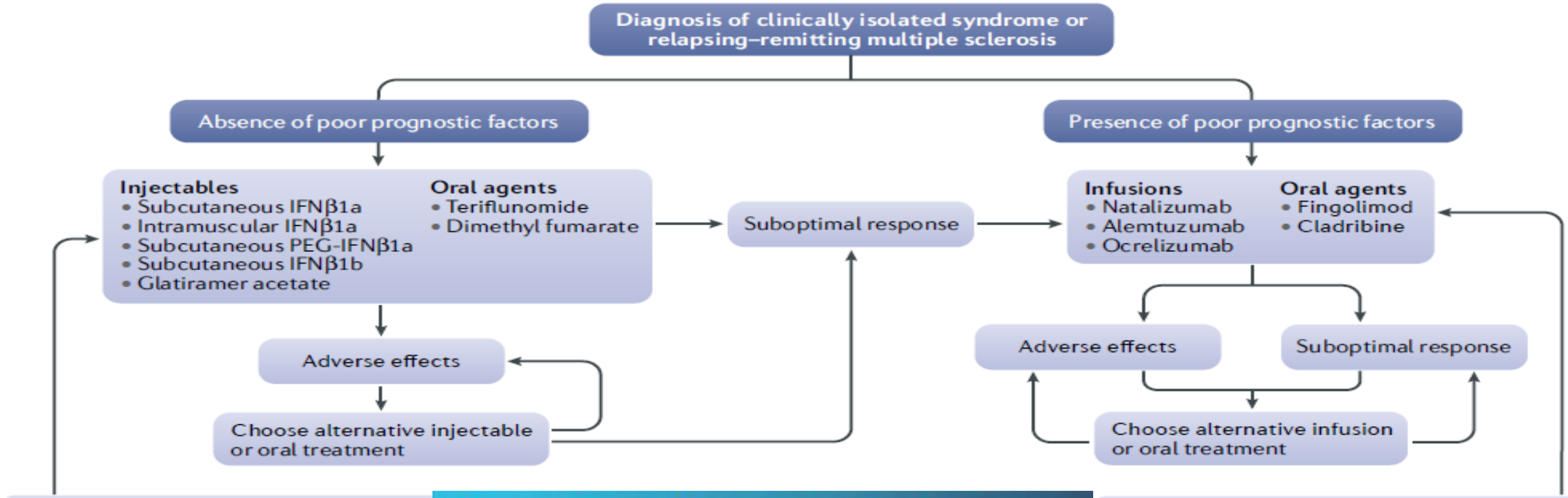


Figure 1. Different types of biomarkers in multiple sclerosis. DMTs, disease-modifying therapies.

Pharmaceutics. 2023 Feb 22;15(3):728.



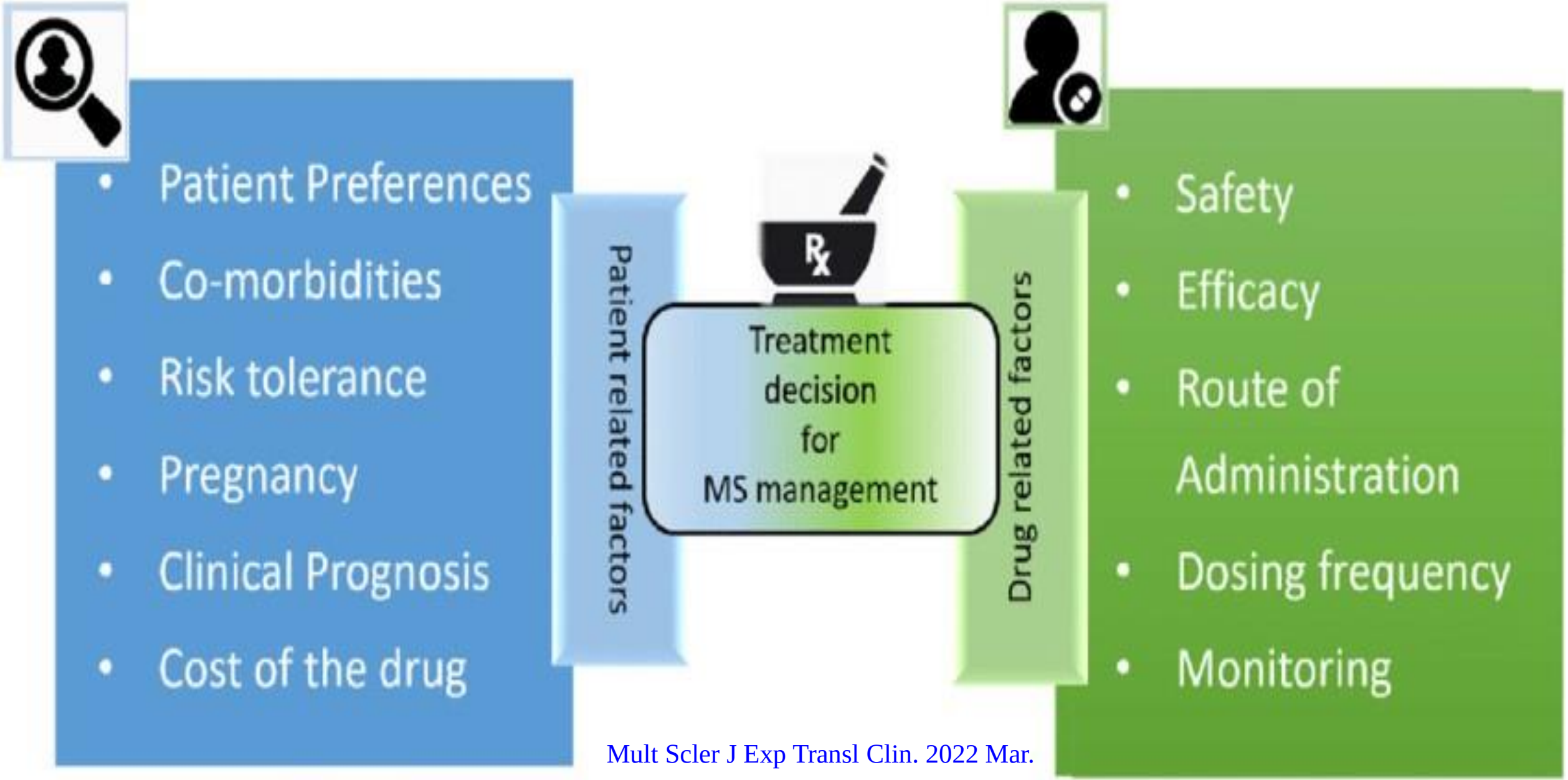
Factors that influence drug selection

Factors	Favoured drug(s)
Needle phobia	• Teriflunomide • Dimethyl fumarate
Monitoring	Glatiramer acetate
Pregnancy	• Glatiramer acetate • IFNβ
Safety	Glatiramer acetate

Factors that influence drug selection

Factors	Favoured drug(s)
JCV positivity	All but natalizumab[a]
History of poor adherence	• Natalizumab • Ocrelizumab
Monitoring	• Cladribine • Ocrelizumab
Efficacy	• Alemtuzumab • Natalizumab • Ocrelizumab
Pregnancy (with planning)	• Alemtuzumab • Cladribine • Natalizumab
Oral route of administration preferred	• Cladribine • Fingolimod
Induction preference	• Alemtuzumab • Cladribine

Nat Rev Neurol . 2019 May.

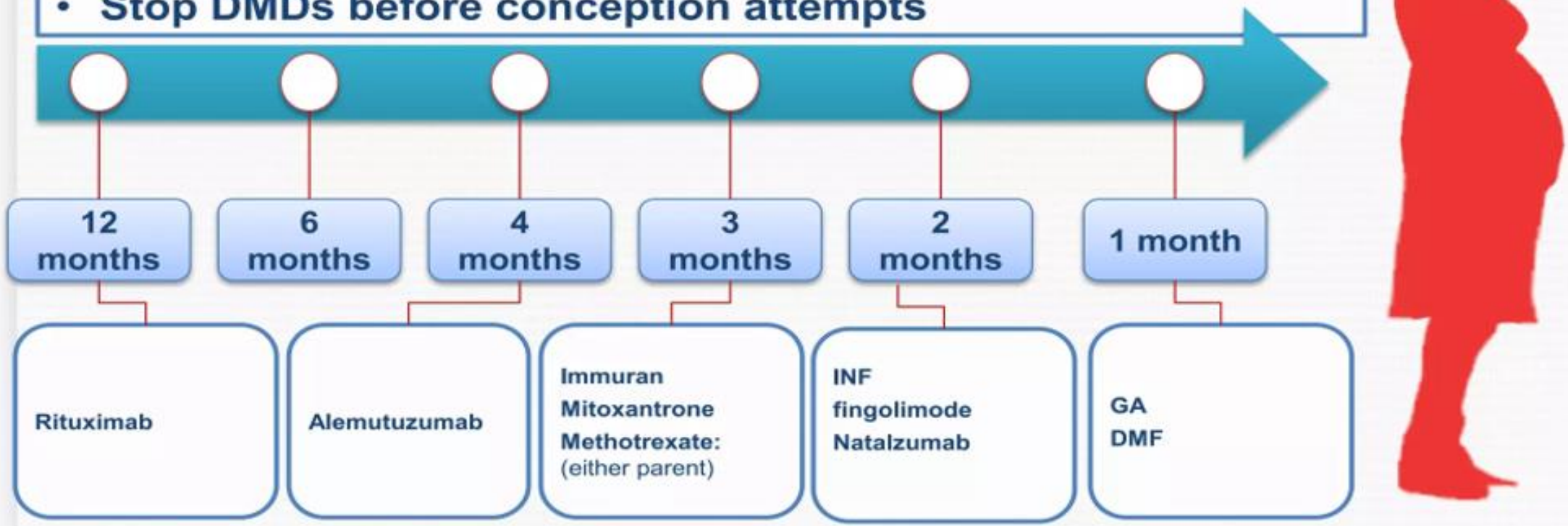


Mult Scler J Exp Transl Clin. 2022 Mar.

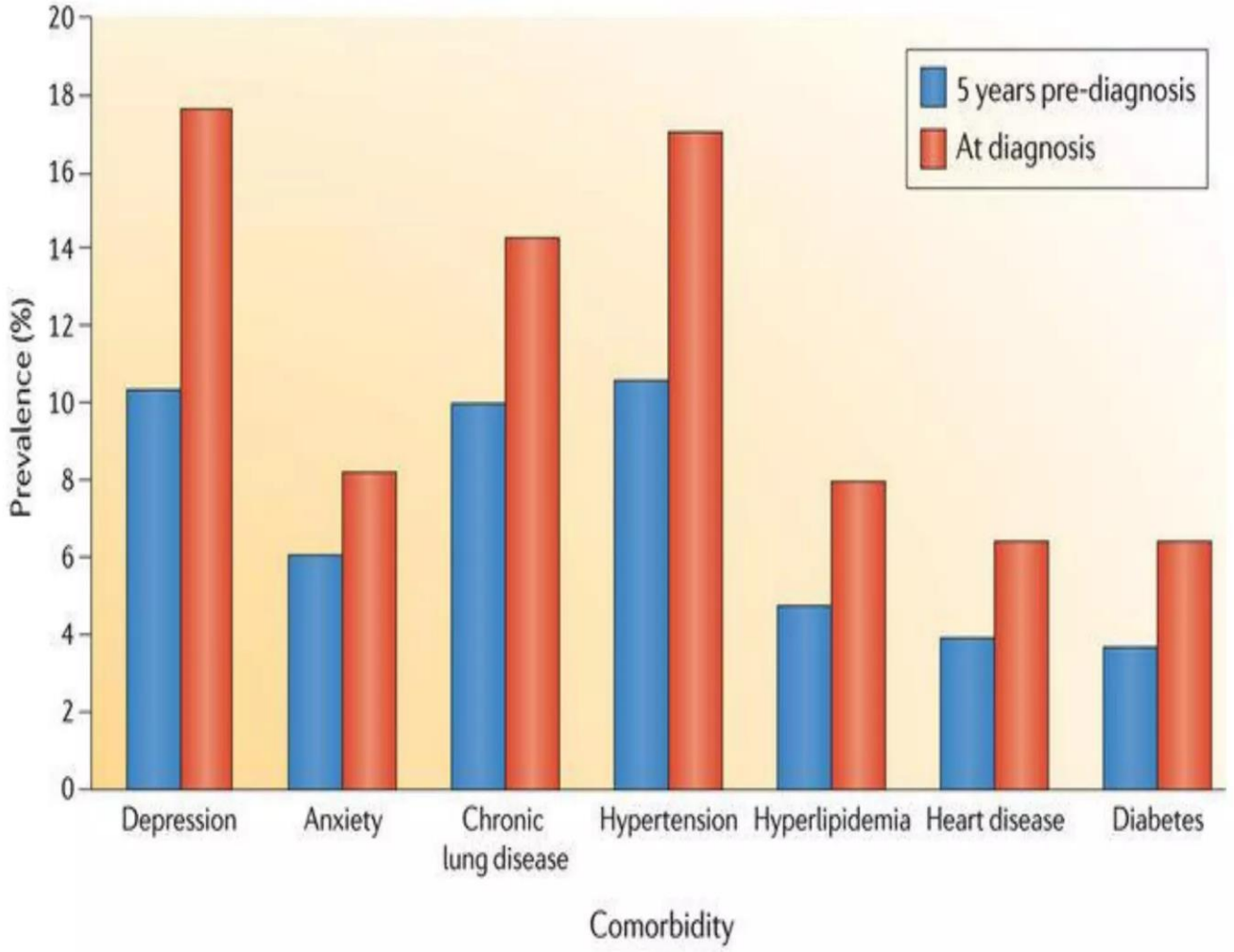
Pregnancy plans

Precautions before pregnancy.

- Try to stabilize patient 6 months -1 year prior to trials of pregnancy (attack free + stable MRI).
- Stop DMDs before conception attempts



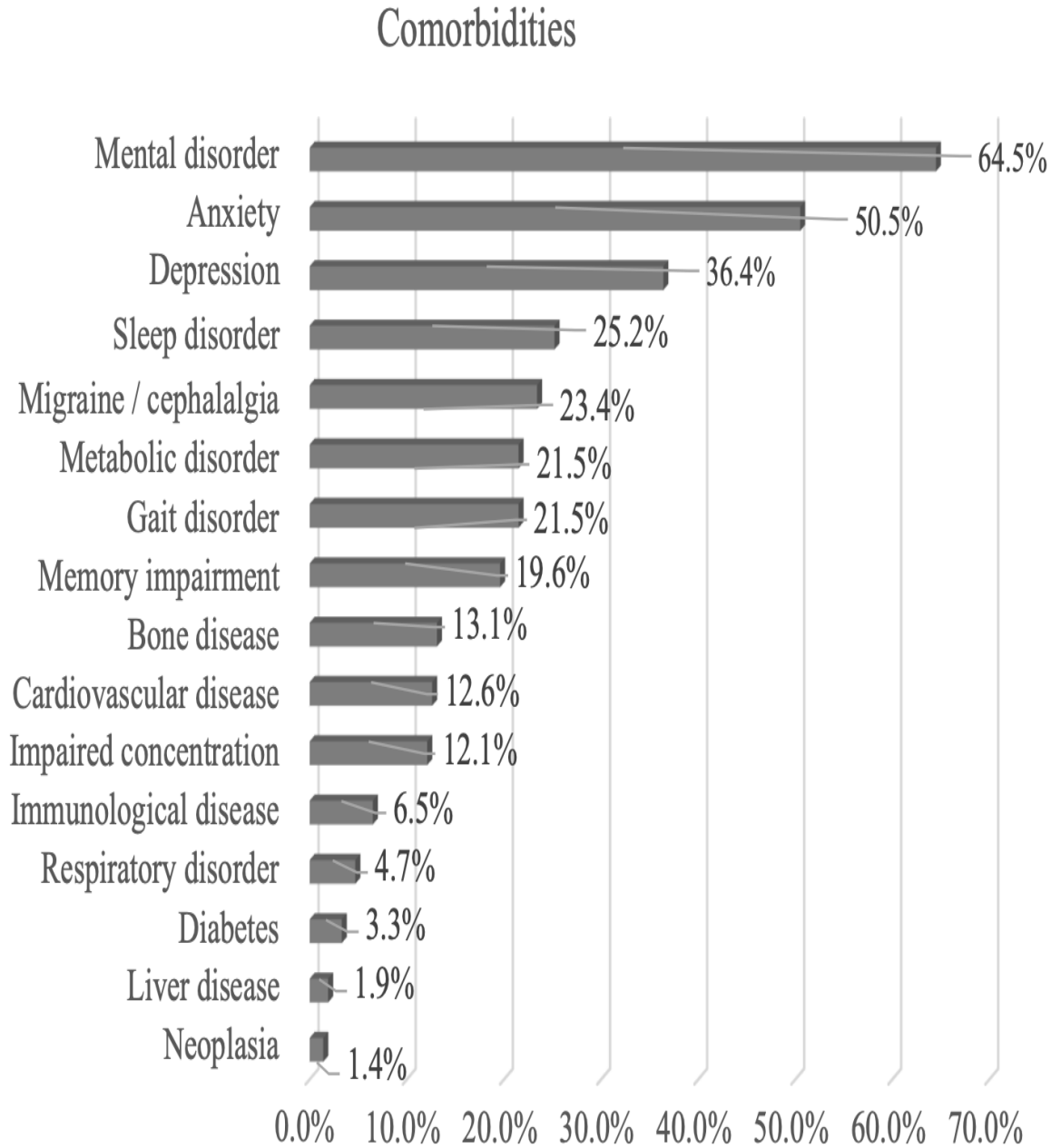
MS Comorbidities



Ruth Ann Marrie, *Nature Reviews Neurology* , **13**,375–382 (2017)

Nature Reviews | Neurology

Figure 1. Percentage of comorbidity types observed in patients with Multiple Sclerosis.



Common TEAE (treatment-emergent adverse event)

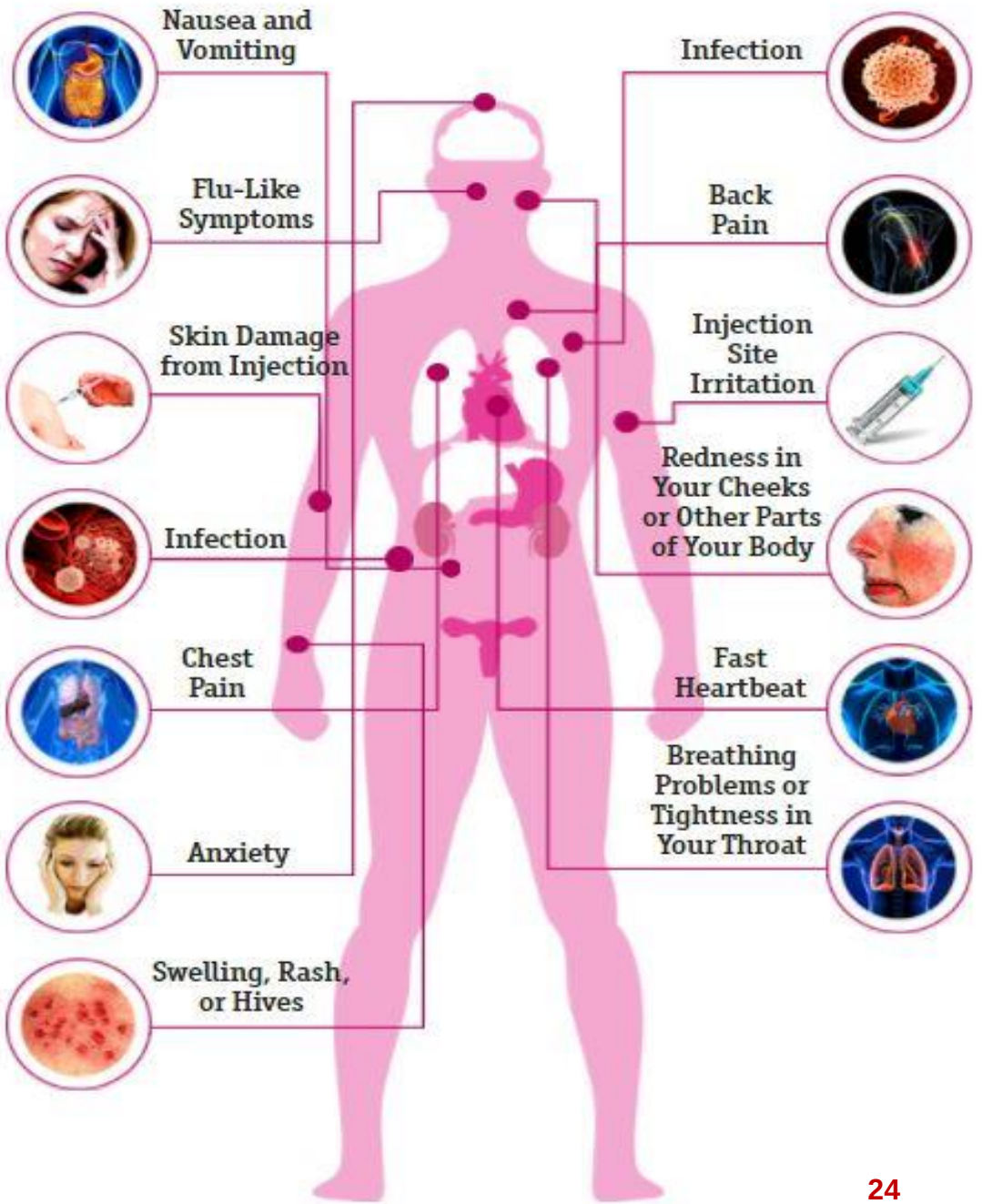
Medical

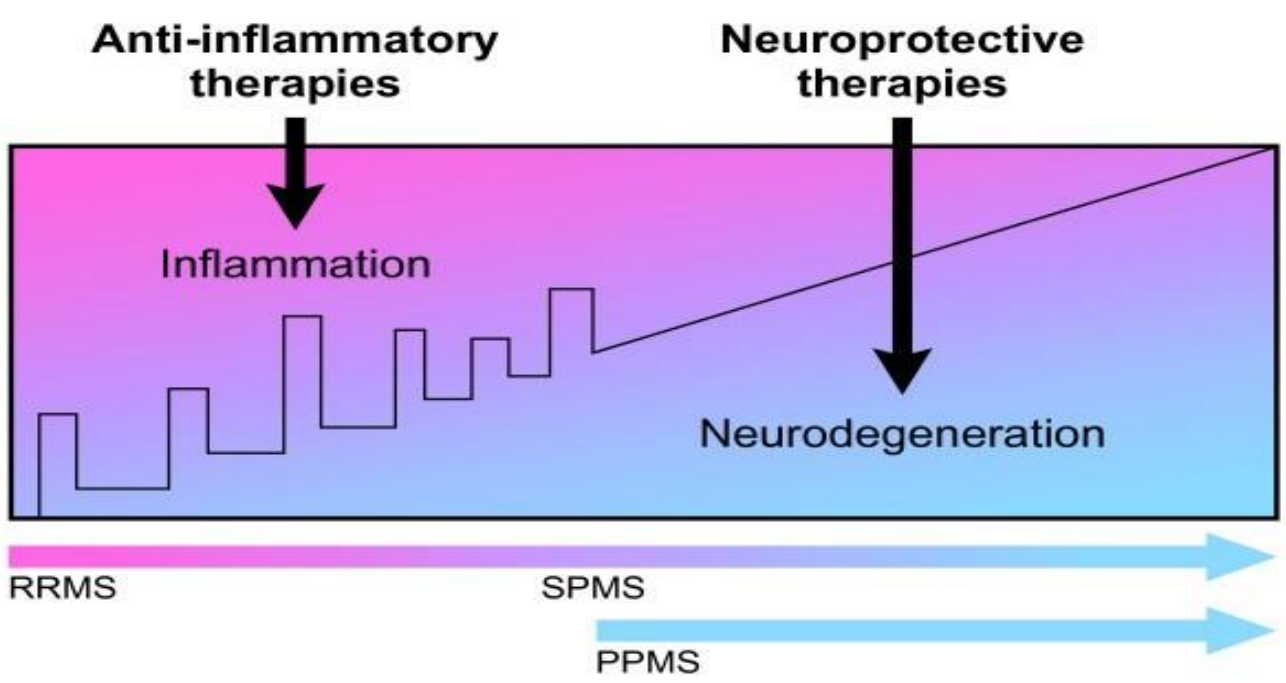
TEAE

means

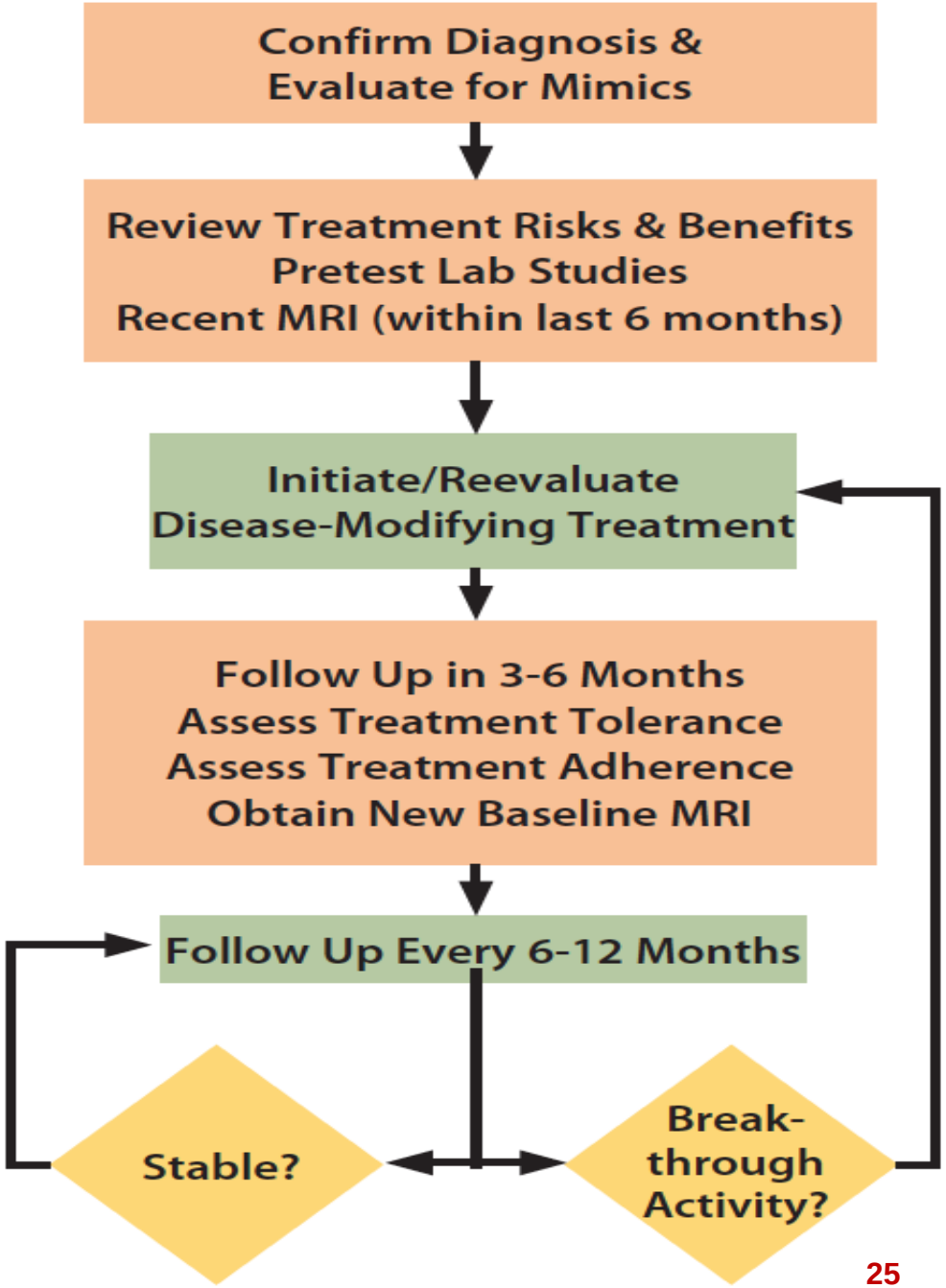
Treatment-Emergent Adverse Event

by acronymsandslang.com



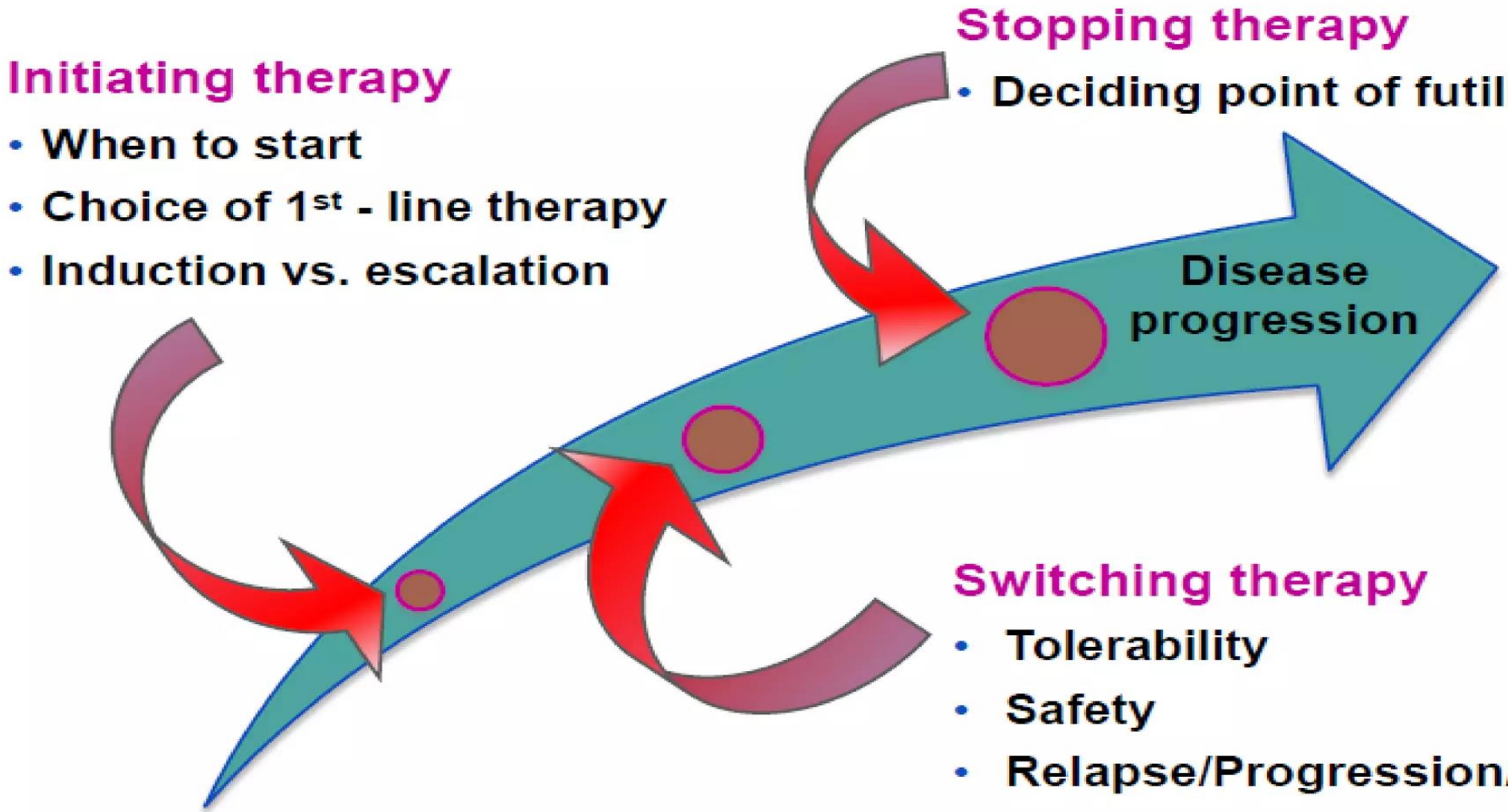


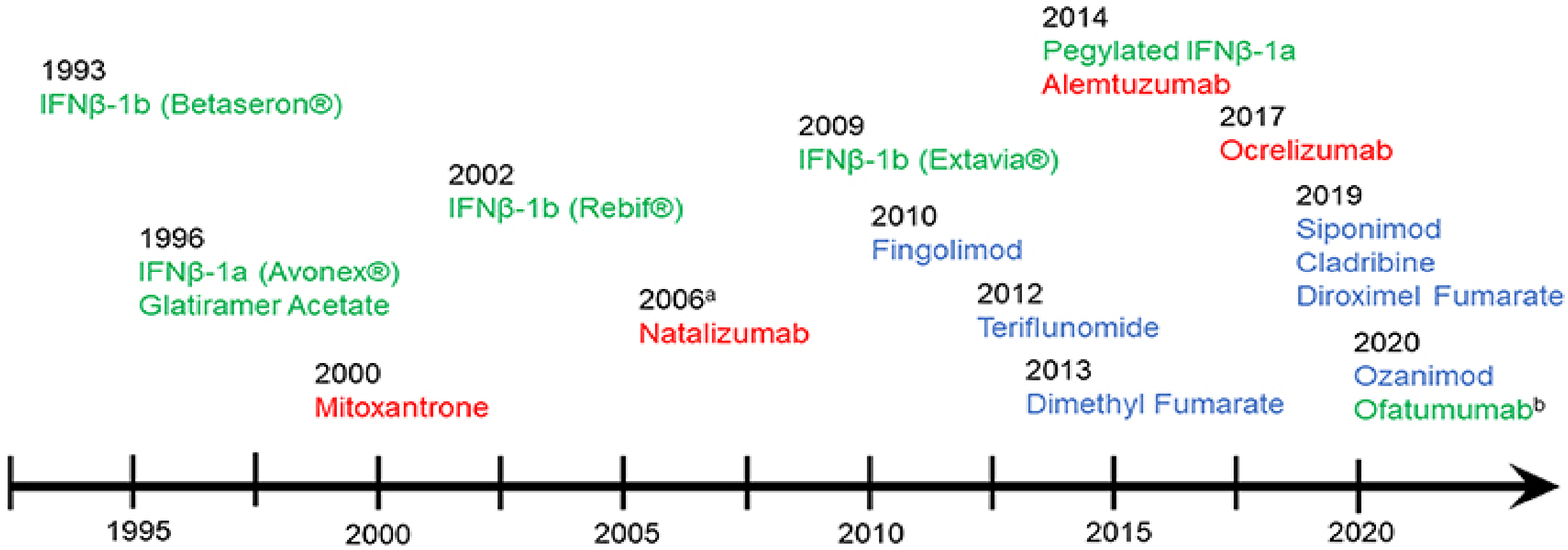
- slow disease progression
- reduce disease relapses
- limit new disease activity



BMC Medicine 2009, 7:74

Key decision making points in Treatment of MS





2002	2007	2009	2012	2014	2015	2018	2020	2021	2022
Interferon beta 1a (Avonex, Rebif) Interferon beta 1b (Betaferon) Glatiramer acetate (Copaxone)	Natalizumab intravenous (Tysabri)	Interferon beta 1b (Extavia)	Fingolimod (Gilenya)	Teriflunomide (Aubagio) Dimethyl fumarate (Tecfidera) Alemtuzumab (Lemtrada)	Peginterferon beta 1a (Plegridy SC) Glatiramer acetate (Copaxone) three times a week	Ocrelizumab (Ocrevus) Glatiramer acetate (Brabio)	Siponimod (Mayzent)	Peginterferon beta 1a (Plegridy IM) Ofatumumab (Kesimpta) Natalizumab subcutaneous (Tysabri)	Ponesimod (Ponvory)

Research Article

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Efficacy classification of modern therapies in multiple sclerosis

Imtiaz A Samjoo[1], Evelyn Worthington[1], Christopher Drudge[1], Melody Zhao[1], Chris Cameron*[,2], Dieter A Häring[3], Dee Stoneman[3], Luisa Klotz[4] & Nicholas Adlard[3]

Journal of Comparative Effectiveness Research

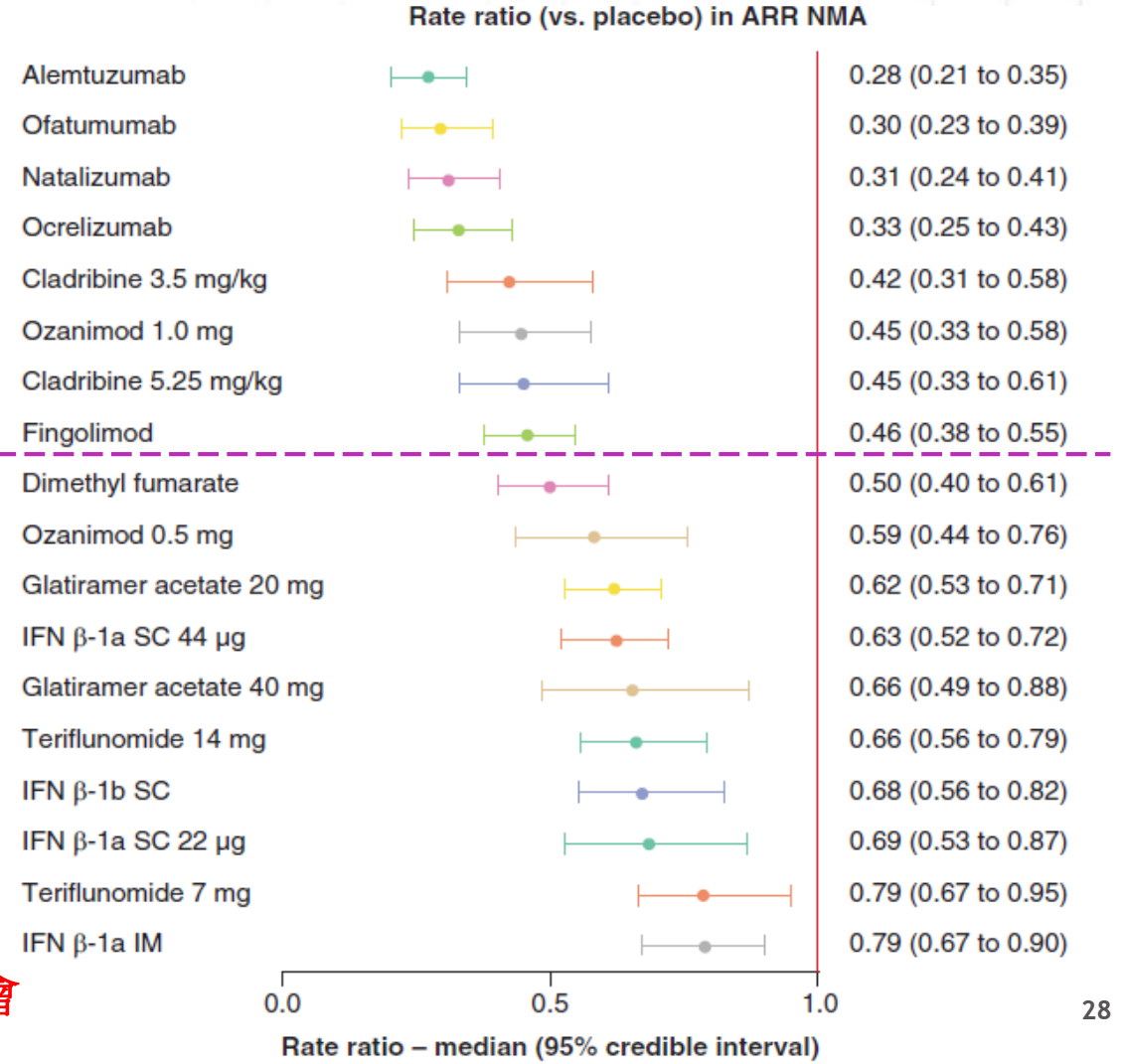
"According to the 2015 ABN guidelines, DMTs can be divided into two broad classes:

1. drugs of **high** efficacy, defined as average relapse reduction substantially more than 50%
2. drugs of **moderate** efficacy, defined as average relapse reduction between 30 and 50%"

Higher efficacy

50% reduction of ARR

Lower efficacy



ABN: Association of British Neurologists 英國神經病學家協會

J. Comp. Eff. Res. (2021) 10(6), 495-507

Journal of the American Pharmacists Association 63 (2023) 8–22

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journal homepage: www.japha.org

REVIEW

Comparative efficacy and safety of disease-modifying therapies in patients with relapsing multiple sclerosis: A systematic review and network meta-analysis

Chaoyang Chen, Enyao Zhang, Chunsu Zhu, Ran Wei, Lingyun Ma, Ruoming Li, Feng Sun, Ying Zhou, Yimin Cui*, Zhenming Liu*

Network meta-analysis results for ARR

ALEM																						
0.98[a] (0.74,1.30)	NAT																					
0.98[b] (0.70,1.39)	1.00[a] (0.74,1.36)	OMB																				
0.87[a] (0.67,1.13)	0.89[a] (0.66,1.20)	0.89[a] (0.63,1.27)	OCR																			
0.73[a] (0.52,1.03)	0.75[b] (0.54,1.02)	0.74[a] (0.51,1.08)	0.84[a] (0.58,1.19)	SIP																		
0.72[b] (0.50,1.03)	0.74[a] (0.53,1.02)	0.73[a] (0.50,1.07)	0.82[a] (0.57,1.19)	0.99[a] (0.67,1.45)	CLAD																	
0.67[b] (0.50,0.89)	**0.69[a] (0.53,0.89)**	**0.68[b] (0.50,0.95)**	0.77[a] (0.57,1.03)	0.92[a] (0.66,1.29)	0.93[a] (0.66,1.31)	OZA1																
0.67[b] (0.52,0.86)	**0.68[a] (0.55,0.84)**	**0.68[a] (0.51,0.90)**	**0.76[a] (0.59,0.99)**	0.91[a] (0.68,1.23)	0.93[a] (0.69,1.25)	0.99[a] (0.79,1.25)	FIN															
0.60[a] (0.45,0.80)	**0.62[a] (0.48,0.78)**	**0.61[a] (0.45,0.83)**	**0.69[a] (0.51,0.93)**	0.83[a] (0.60,1.13)	0.84[a] (0.60,1.16)	0.90[a] (0.69,1.17)	0.90[a] (0.73,1.11)	DMF														
0.53[b] (0.38,0.72)	**0.54[a] (0.41,0.70)**	**0.54[a] (0.40,0.71)**	**0.60[a] (0.44,0.83)**	0.72[a] (0.52,1.01)	0.73[a] (0.52,1.02)	0.78[a] (0.59,1.03)	**0.79[a] (0.63,0.99)**	0.87[a] (0.67,1.13)	PON													
0.51[a] (0.39,0.67)	**0.52[a] (0.41,0.67)**	**0.52[a] (0.38,0.71)**	**0.59[a] (0.44,0.78)**	**0.70[a] (0.51,0.97)**	**0.71[a] (0.51,0.99)**	**0.76[a] (0.63,0.92)**	**0.77[a] (0.62,0.95)**	0.85[a] (0.66,1.09)	0.97[a] (0.74,1.27)	OZA0.5												
0.48[a] (0.36,0.64)	**0.49[a] (0.38,0.63)**	**0.49[b] (0.35,0.67)**	**0.55[a] (0.40,0.75)**	**0.66[a] (0.47,0.91)**	**0.67[a] (0.47,0.93)**	**0.71[a] (0.54,0.94)**	**0.72[a] (0.57,0.90)**	0.79[a] (0.61,1.03)	0.91[a] (0.69,1.20)	0.94[a] (0.72,1.23)	PEG											
0.47[a] (0.38,0.60)	**0.48[a] (0.39,0.60)**	**0.48[a] (0.36,0.64)**	**0.54[b] (0.42,0.70)**	**0.65[a] (0.48,0.87)**	**0.66[a] (0.49,0.89)**	**0.71[a] (0.56,0.89)**	**0.71[a] (0.60,0.85)**	**0.79[a] (0.64,0.97)**	0.90[a] (0.71,1.15)	0.93[a] (0.74,1.16)	0.99[a] (0.79,1.25)	GA40										
0.47[a] (0.40,0.55)	**0.48[a] (0.38,0.60)**	**0.48[a] (0.36,0.64)**	**0.54[a] (0.44,0.65)**	**0.64[a] (0.48,0.87)**	**0.65[a] (0.48,0.89)**	**0.70[a] (0.56,0.87)**	**0.70[a] (0.59,0.84)**	**0.78[a] (0.62,0.97)**	0.89[a] (0.69,1.15)	0.92[a] (0.74,1.13)	0.98[a] (0.77,1.24)	0.99[a] (0.85,1.16)	SC44									
0.44[a] (0.35,0.56)	**0.45[a] (0.37,0.55)**	**0.45[a] (0.34,0.59)**	**0.51[a] (0.39,0.65)**	**0.60[a] (0.46,0.80)**	**0.61[a] (0.46,0.82)**	**0.66[a] (0.53,0.82)**	**0.66[a] (0.57,0.76)**	**0.73[a] (0.61,0.88)**	0.84[a] (0.68,1.04)	0.86[a] (0.70,1.06)	0.92[a] (0.74,1.15)	0.93[a] (0.79,1.09)	0.94[a] (0.80,1.11)	GA20								
0.44[a] (0.35,0.56)	**0.45[a] (0.37,0.54)**	**0.45[a] (0.34,0.59)**	**0.50[a] (0.39,0.65)**	**0.60[a] (0.46,0.80)**	**0.61[a] (0.46,0.82)**	**0.66[a] (0.53,0.81)**	**0.66[a] (0.57,0.76)**	**0.73[a] (0.61,0.88)**	0.84[a] (0.68,1.04)	0.86[a] (0.71,1.05)	0.92[a] (0.75,1.13)	0.93[a] (0.80,1.08)	0.94[a] (0.80,1.10)	1.00[a] (0.90,1.11)	SC250							
0.44[a] (0.34,0.57)	**0.45[a] (0.36,0.55)**	**0.45[a] (0.36,0.56)**	**0.50[a] (0.38,0.66)**	**0.60[a] (0.45,0.81)**	**0.61[a] (0.45,0.82)**	**0.65[a] (0.52,0.82)**	**0.66[a] (0.55,0.78)**	**0.73[a] (0.59,0.90)**	**0.83[a] (0.70,1.00)**	0.86[a] (0.69,1.07)	0.92[a] (0.73,1.15)	0.93[a] (0.77,1.11)	0.94[a] (0.77,1.13)	0.99[a] (0.85,1.16)	1.00[a] (0.86,1.15)	TERI14						
0.39[a] (0.30,0.51)	**0.40[a] (0.32,0.50)**	**0.40[a] (0.31,0.52)**	**0.45[a] (0.34,0.59)**	**0.54[a] (0.40,0.72)**	**0.54[a] (0.40,0.74)**	**0.58[a] (0.46,0.74)**	**0.59[a] (0.49,0.70)**	**0.65[a] (0.53,0.81)**	**0.75[a] (0.61,0.92)**	**0.77[a] (0.62,0.96)**	0.82[a] (0.65,1.03)	**0.83[a] (0.69,1.00)**	0.84[a] (0.69,1.02)	0.89[a] (0.76,1.04)	0.89[a] (0.77,1.04)	0.89[a] (0.78,1.02)	TERI7					
0.37[a] (0.30,0.46)	**0.38[a] (0.31,0.46)**	**0.38[a] (0.29,0.50)**	**0.43[a] (0.34,0.54)**	**0.51[a] (0.38,0.68)**	**0.52[a] (0.39,0.69)**	**0.55[a] (0.46,0.66)**	**0.56[a] (0.49,0.64)**	**0.62[a] (0.51,0.75)**	**0.71[a] (0.57,0.88)**	**0.73[a] (0.62,0.86)**	**0.78[c] (0.63,0.96)**	**0.79[a] (0.68,0.91)**	**0.79[a] (0.70,0.91)**	**0.84[a] (0.75,0.96)**	**0.85[a] (0.75,0.95)**	**0.85[a] (0.73,0.98)**	0.95[a] (0.81,1.10)	IM30				
0.34[c] (0.22,0.51)	**0.34[c] (0.23,0.51)**	**0.34[c] (0.22,0.53)**	**0.38[a] (0.25,0.59)**	**0.46[a] (0.30,0.72)**	**0.47[a] (0.30,0.73)**	**0.50[a] (0.33,0.75)**	**0.50[a] (0.35,0.73)**	**0.56[a] (0.38,0.83)**	**0.64[a] (0.43,0.96)**	**0.66[a] (0.44,0.98)**	0.70[c] (0.47,1.05)	0.71[c] (0.49,1.03)	0.72[c] (0.49,1.05)	0.76[c] (0.53,1.10)	0.76[c] (0.53,1.10)	0.76[a] (0.53,1.11)	0.86[a] (0.59,1.25)	0.90[a] (0.63,1.30)	SC22		
0.31[a] (0.25,0.39)	**0.31[a] (0.27,0.37)**	**0.31[a] (0.24,0.40)**	**0.35[a] (0.28,0.45)**	**0.42[a] (0.32,0.55)**	**0.43[a] (0.32,0.56)**	**0.46[a] (0.37,0.56)**	**0.46[a] (0.41,0.52)**	**0.51[a] (0.43,0.61)**	**0.59[a] (0.48,0.71)**	**0.60[a] (0.50,0.73)**	**0.64[a] (0.53,0.78)**	**0.65[a] (0.57,0.74)**	**0.66[a] (0.57,0.76)**	**0.70[a] (0.63,0.77)**	**0.70[a] (0.64,0.76)**	**0.70[a] (0.62,0.79)**	**0.78[a] (0.69,0.89)**	**0.83[a] (0.75,0.91)**	0.92[a] (0.64,1.31)	PLA

Key Points

Background:

- Nineteen disease-modifying therapies (DMTs) have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with relapsing forms of multiple sclerosis.
- Clinical selection of treatment requires comparisons of efficacy and safety across different DMTs.

Findings:

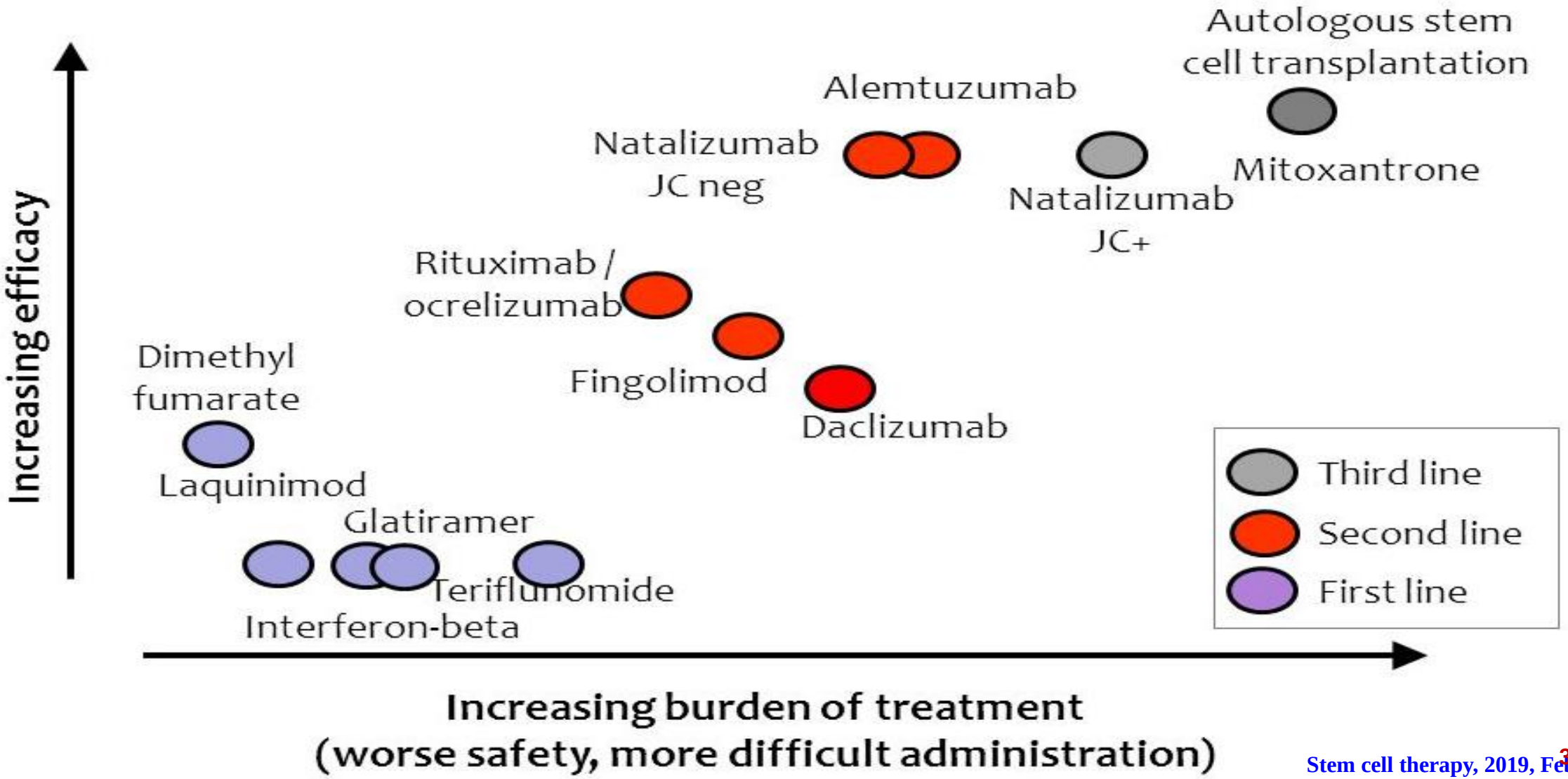
- Alemtuzumab and ofatumumab presented the highest efficacy among DMTs.

Table 2. Low-, moderate-, and high-efficacy treatments for multiple sclerosis[56]

Low-efficacy treatments	Moderate-efficacy treatments	High-efficacy treatments
• Interferons	• Cladribine*	• Ocrelizumab
• Glatiramer acetate	• s1p inhibitors*	• Ofatumumab
• Teriflunomide	• Fumarates	• Natalizumab
		• Alemtuzumab

*May be considered to have moderate-to-high efficacy.

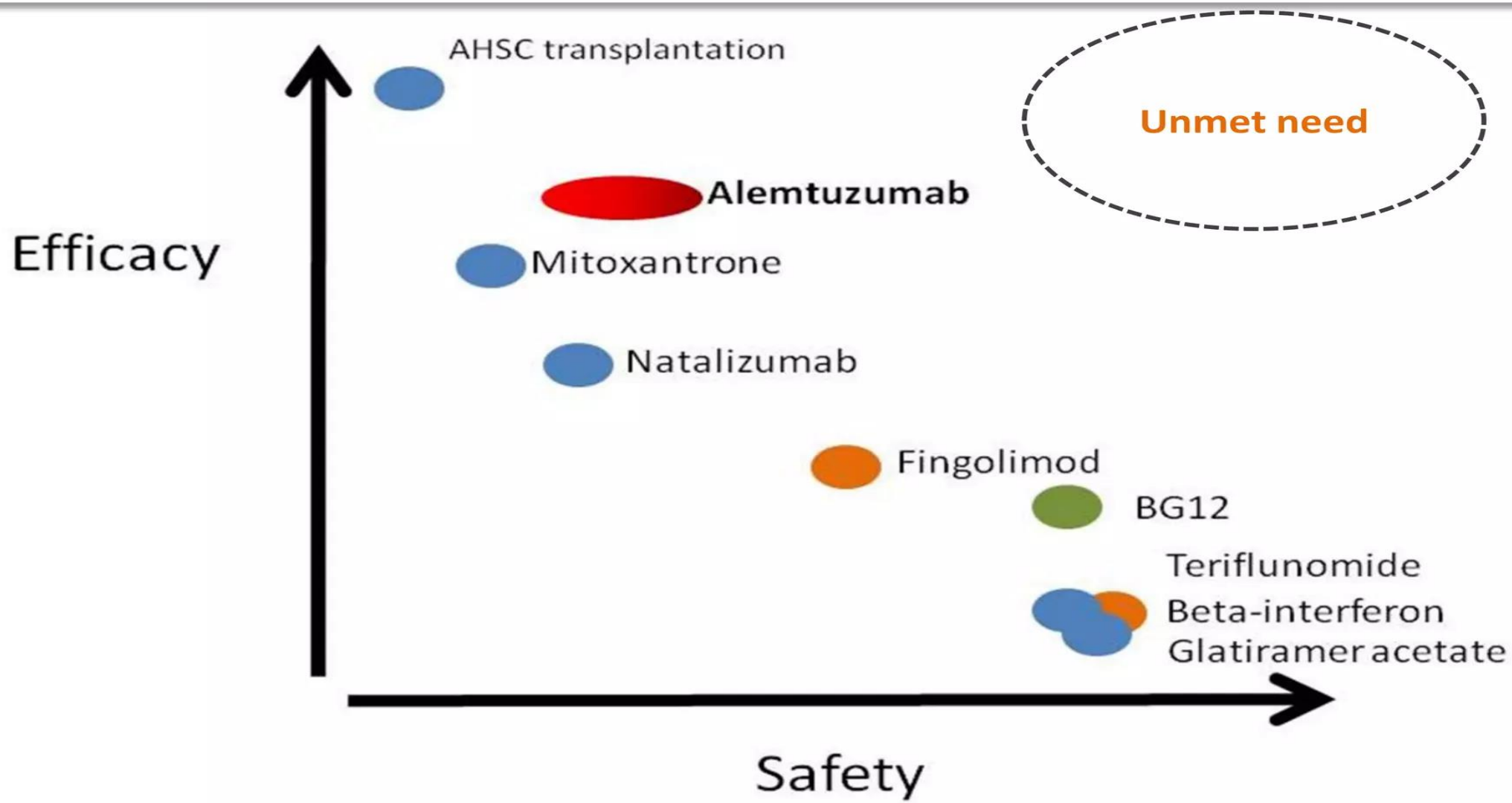
First, second and third line therapies



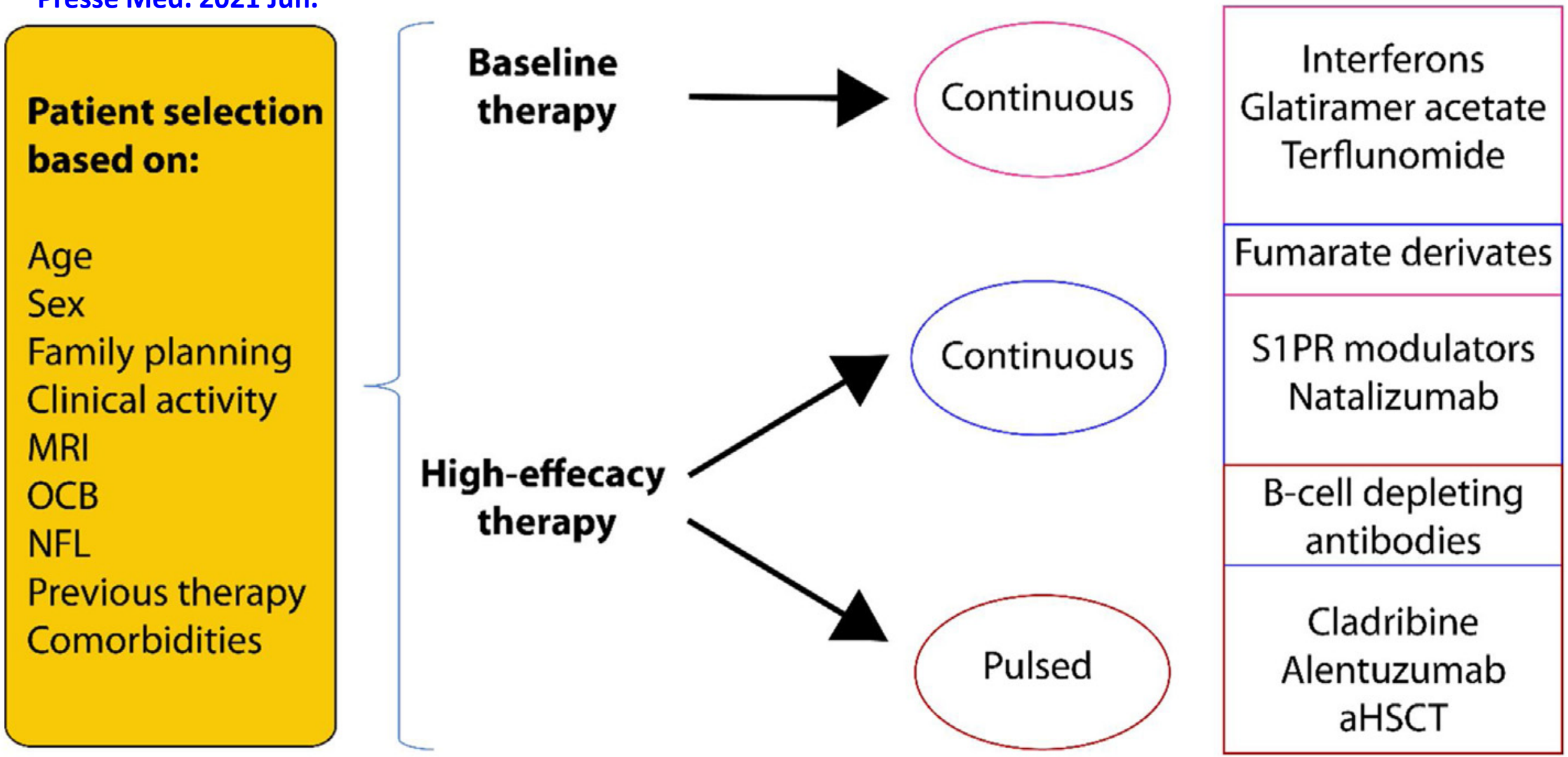
Comparison of first-line and second-line therapies for RRMS

Criteria	First-line therapies	Second-line therapies
Efficacy	Moderate to high	High
Compliance	Low to moderate	Moderate to high
Relapse rate	Moderate	Low
Adverse effects	Mild to moderate	High
Discontinuation rate	Moderate	High
Cost	Moderate to high	High

Efficacy Vs Safety



Presse Med. 2021 Jun.



- **S1PR 1, 5（sphingosine 1-phosphatase, S1P1 & S1P5）**
- **鞘氨醇1-磷酸酶受體 1（sphingosine 1-phosphatase, S1P1）和受體 5（S1P5）激動劑**

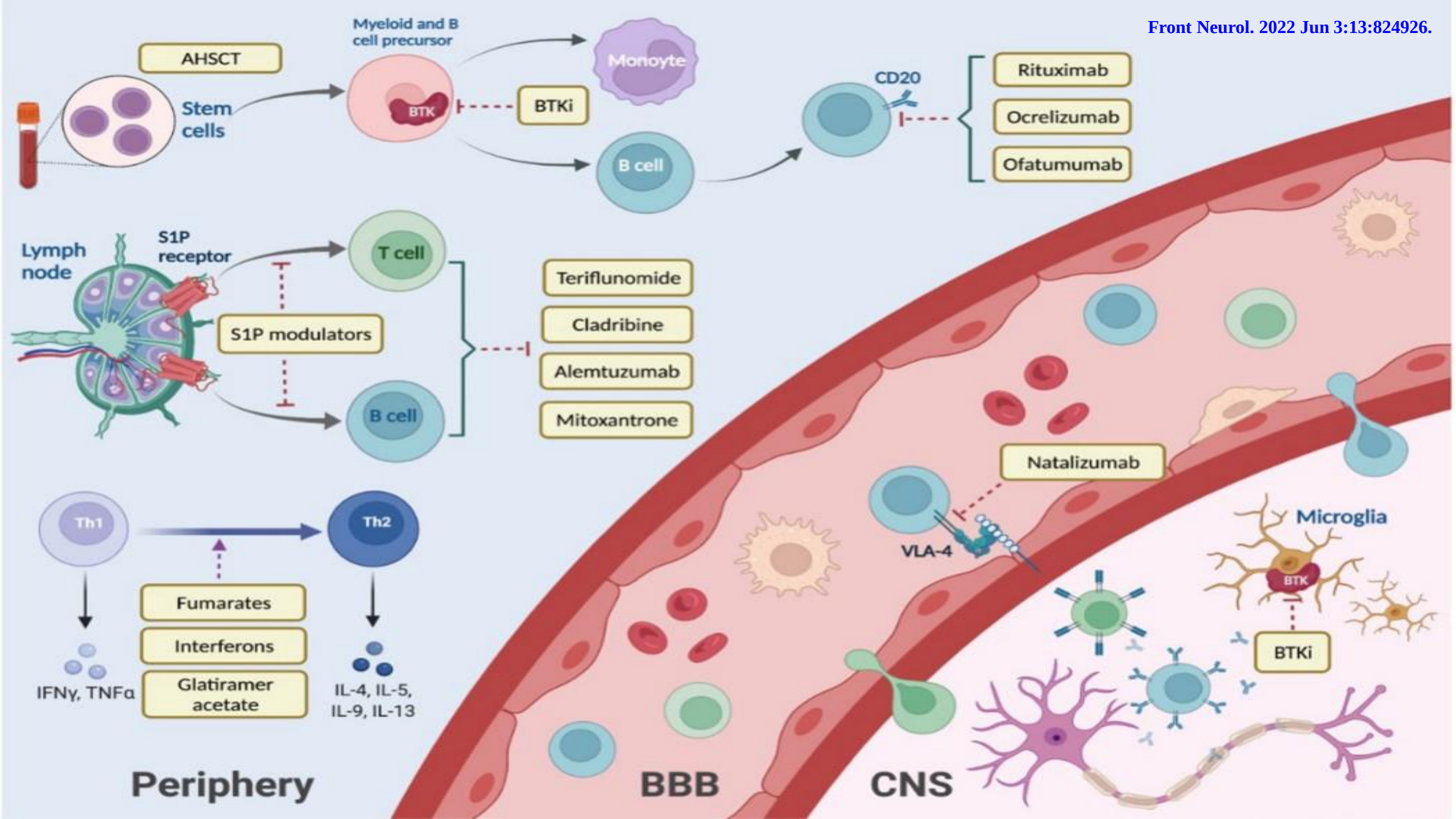
Comparative Efficacy of DMTs

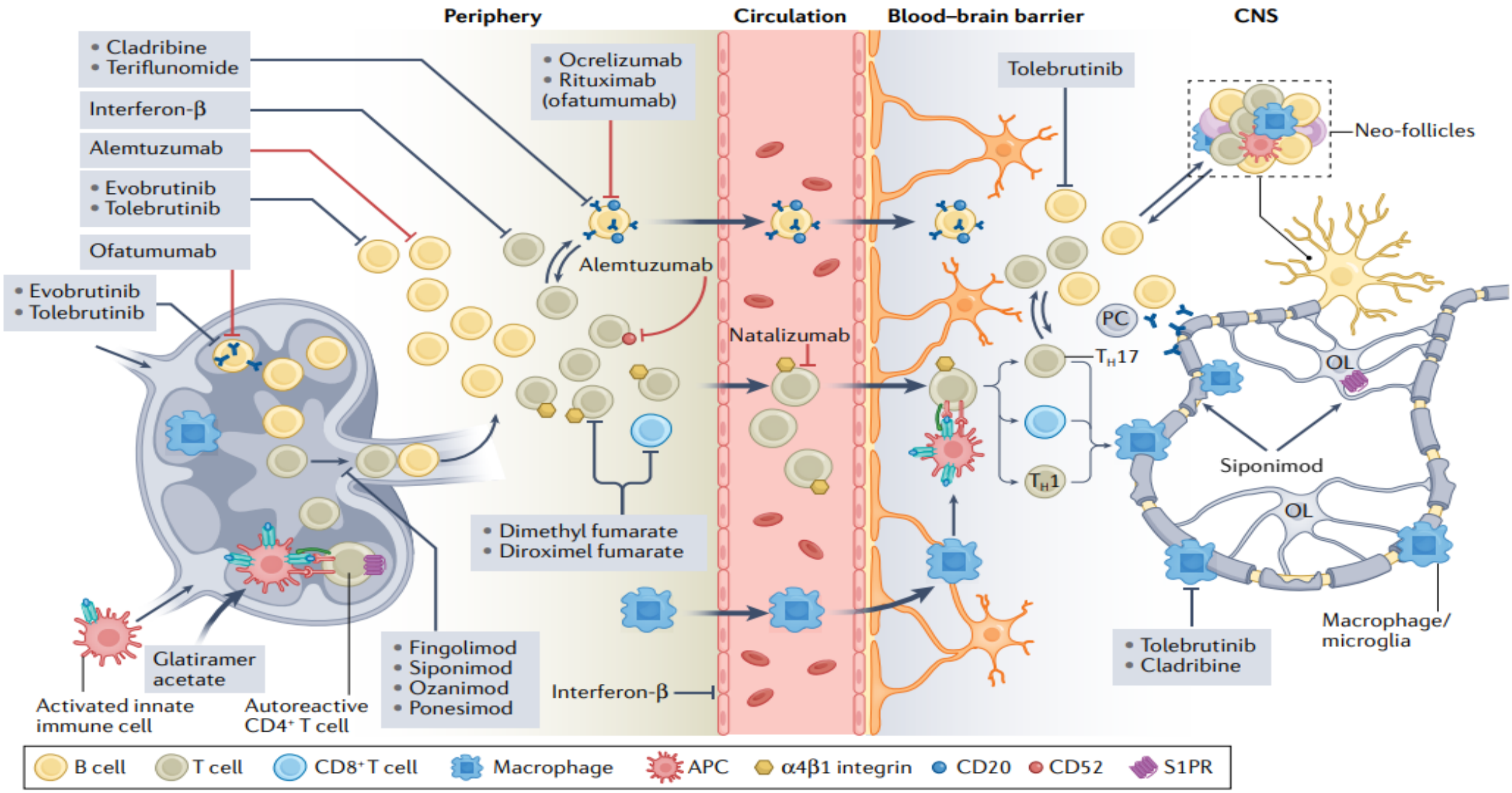
Moderately effective DMTs for RRMS		
DMT	**Pivotal studies**	**Relative risk reduction in relapse rates**
Dimethyl fumarate	DEFINE CONFIRM	53% vs placebo ($P<0.001$) 44% vs. placebo ($P<0.001$)
Fingolimod	FREEDOMS FREEDOMS II	55% vs. placebo ($P<0.001$) 48% vs. placebo ($P<0.0001$)
Glatiramer	Co-Polymer 1 MS Study	29% vs. placebo ($P=0.007$)
Interferon beta Formulations	IFNB MS Study PRISMS	34% vs. placebo ($P=0.0001$) 32% vs. placebo ($P<0.005$)
Teriflunomide	TOWER TESMO	36% vs. placebo ($P=0.0001$) 31.5% vs. placebo ($P<0.001$)
Ponesimod	OPTIMUM	30.5% vs. teriflunomide ($P=0.0003$)

Highly effective disease-modifying therapies (DMTs) for RRMS		
DMT	**Pivotal studies**	**Relative risk reduction in relapse rates**
Alemtuzumab	Care-MS I Care-MS II	54.9% versus interferon beta ($P<0.0001$) 49.4% vs. interferon beta ($P=0.008$)
Cladribine	CLARITY	57.6% vs. placebo ($P<0.001$)
Natalizumab	AFFIRM	68% vs. placebo ($P<0.001$)
Ocrelizumab	Opera I Opera II	46% vs. interferon beta ($P<0.001$) 47% vs. interferon beta ($P<0.001$)
Ofatumumab	ASCLEPIOS I ASCLEPIOS II	50.5% vs. teriflunomide ($P<0.001$) 58.5% vs. teriflunomide ($P<0.001$)

DMTs for progressive MS		
DMT	**Pivotal studies**	**Reduction in risk of progression in disability**
Ocrelizuamb for PPMS	ORATORIO	24% vs. placebo (overall reduction after six months)
Siponimod for SPMS	EXPAND	37% vs. placebo (after 6 months)

Front Neurol. 2022 Jun 3:13:824926.





Pharmaceutics. 2023 Feb 22;15(3):728.

Cell Types	Drugs	Mechanism of Action	Refs
Microglia	Fingolimod	Downregulates activated microglial production of pro-inflammatory cytokines as TNF-α, IL-1β, and IL-6; Upregulates microglial production of brain-derived neurotrophic factor and glial cell-derived neurotrophic factor	[24]
	Dimethyl fumarate	Reduce the synthesis of TNF-α, IL-1β, IL-6 and nitric oxide, thereby inhibiting MG-associated inflammatory mediator release	[25]
Macrophages	IFN-β	Promotes IL-27 secretion by Microglia and macrophages, inhibit Th17 cell differentiation and inflammatory response	[26,27]
	Fingolimod	Regulate microglia and macrophage mediated immune inflammation, promote tissue repair and myelin regeneration	[24,28]
Dendritic cells	Fingolimod	Down-regulate the expression of CC chemokine receptor 6, reduces the migration of DCs	[29]
	Dimethyl fumarate	Inhibits the expression of costimulatory molecules and proinflammatory cytokines in DCs	[30]
	Glatiramer acetate	Reduces the expression of costimulatory molecules in DCs	[31]

DMTs Mechanism of action

- The pathophysiology of MS is not currently well understood; however, the adaptive immune system (which includes T and B lymphocytes) is thought to play an important role and therefore is the main target of DMTs, that act by:

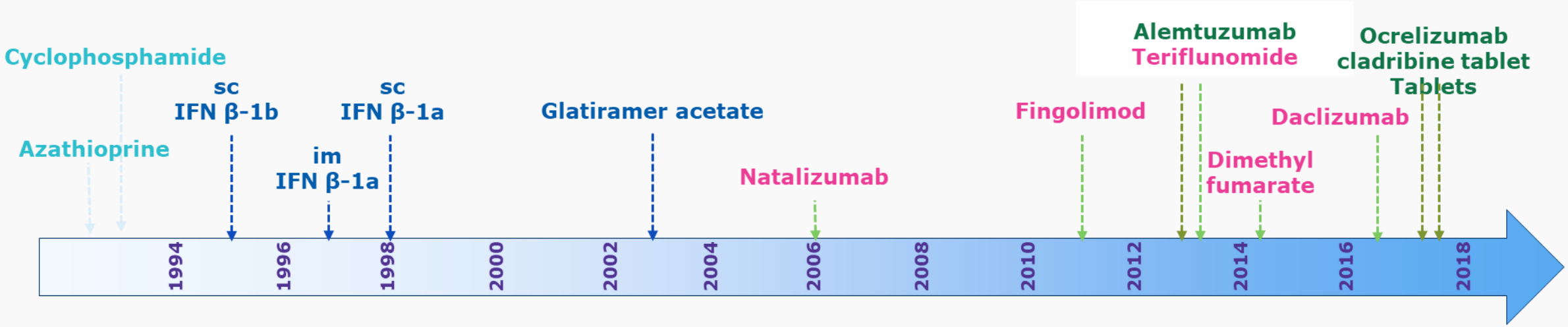
1. **Altering lymphocyte trafficking** — natalizumab binds to α4B1 integrin receptor on T cells preventing lymphocytes from crossing the blood brain barrier; fingolimod, siponimod and ponesimod are sphingosine-1-phosphate (S1P) receptor agonists, they bind to S1P receptors on T and B cells, preventing their egress into the blood stream, resulting in retention in the lymph tissue
2. **Lymphocyte depletion via cell lysis** — alemtuzumab targets CD52 receptors on T and B cells; ocrelizumab and ofatumumab target CD20 receptors on B cells; cladribine is a nucleoside analogue of deoxyadenosine, it is a prodrug targeting T and B cells
3. **Disruption of lymphocyte replication** — teriflunomide binds to and inhibits the enzyme dihydroorotate dehydrogenase, resulting in reduced proliferation of activated T and B cells

- The mechanism of action of interferon beta, glatiramer acetate and dimethyl fumarate are not fully understood; they are considered as immunomodulatory (as opposed to immunosuppressant). They act by promoting the regulatory aspects of the immune system, which results in suppression of pro-inflammatory processes

Currently Available Therapies for RRMS

Immunomodulators	Anti-Trafficking Agents	Immune Cell-Depleting Agents
Interferon beta-1a (injectable)	Natalizumab (infusion	Mitoxantrone (infusion)
Interferon beta-1b (injectable)	Fingolimod (oral)	Cladribine (oral)
Glatiramer acetate (injectable)	Siponimod (oral)	Alemtuzumab (infusion)
Teriflunomide (oral)		Ocrelizumab (infusion)
Dimethyl Fumarate (oral)		

Disease modifying drugs (DMDs) in multiple sclerosis



廣效免疫抑制
Broad-spectrum immunosuppression

1990年前，MS治療選擇只有廣效免疫抑製劑

免疫調節
Immunomodulation/

慢性長期藥物治療，在不抑制免疫功能的情況下達到免疫調節

只有在有效治療時才有臨床療效

選擇性、持續性免疫抑制
Selective, continuous immunosuppression

慢性長期藥物治療，持續抑制免疫功能

只有在有效治療時才有臨床療效

有疾病緩解潛力的治療？
Therapies with potential for remission?

短期療程

在非有效治療時期仍有臨床療效

25 January 2018 Mavenclad (cladribine tablets) for the Treatment of Relapsing-Remitting Multiple Sclerosis

MULTIPLE SCLEROSIS

New Classification of DMT therapy for RRMS

維持/增量療法
Maintenance/escalation therapy (MET)

隨時間維持或增量的長期治療，
只有在有效治療時才會造成免疫功能變化

免疫調節
Immunomodulation

持續性免疫調節的MET

Interferon B

Glatiramer acetate

長期免疫抑制
Chronic immunosuppression

持續性免疫抑制的MET

e.g.
Fingolimod
Siponimod
Dimethyl fumarate
Teriflunomide
Natalizumab
Ocrelizumab

免疫重建療法
Immune reconstitution therapy (IRT)

短期治療重建免疫系統，
造成長期的免疫系統質量改變

非選擇性免疫重建療法
Non-selective IRT (NIRT)

影響先天性及適應性免疫系統的IRT
e.g. alemtuzumab
(Lemtrada, IV一年一次，一次五天)

Haematopoietic stem cell transplant

選擇性免疫重建療法
Selective IRT (SIRT)

只影響適應性免疫系統的

e.g. cladribine tablet

MULTIPLE SCLEROSIS

CNS Drugs (2022) 36:1285–1299
https://doi.org/10.1007/s40263-022-00965-7

REVIEW ARTICLE

High-Efficacy Therapies for Treatment-Naïve Individuals with Relapsing–Remitting Multiple Sclerosis

Léorah Freeman[1] · Erin E. Longbrake[2] · Patricia K. Coyle[3] · Barry Hendin[4] · Timothy Vollmer[5]

Key Points

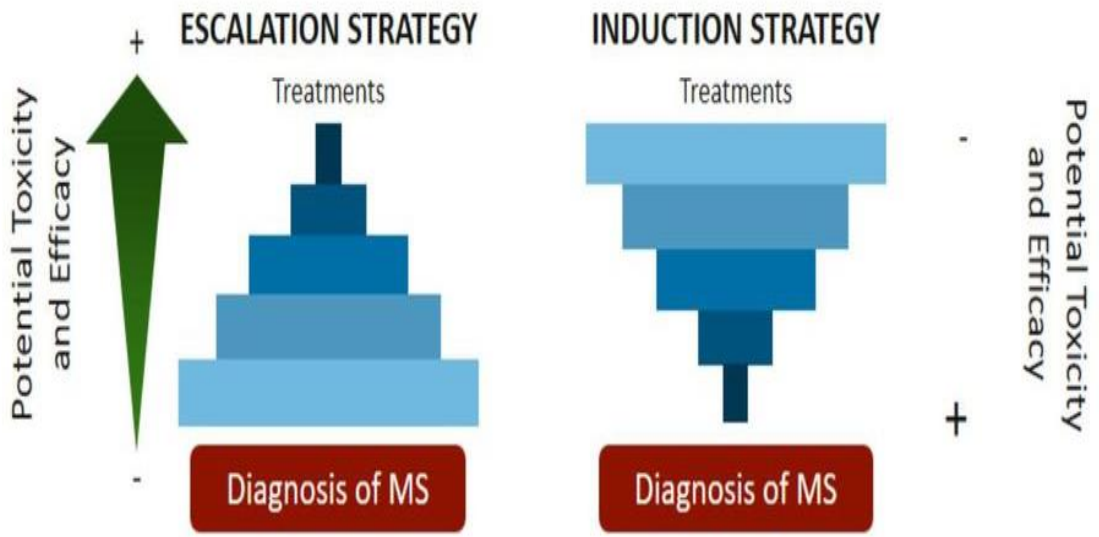
- Earlier use of higher-efficacy DMTs may forestall PIRA and slow the accumulation of disability.

Neurological damage begins in the early stages of multiple sclerosis, and may even precede clinically evident symptoms.

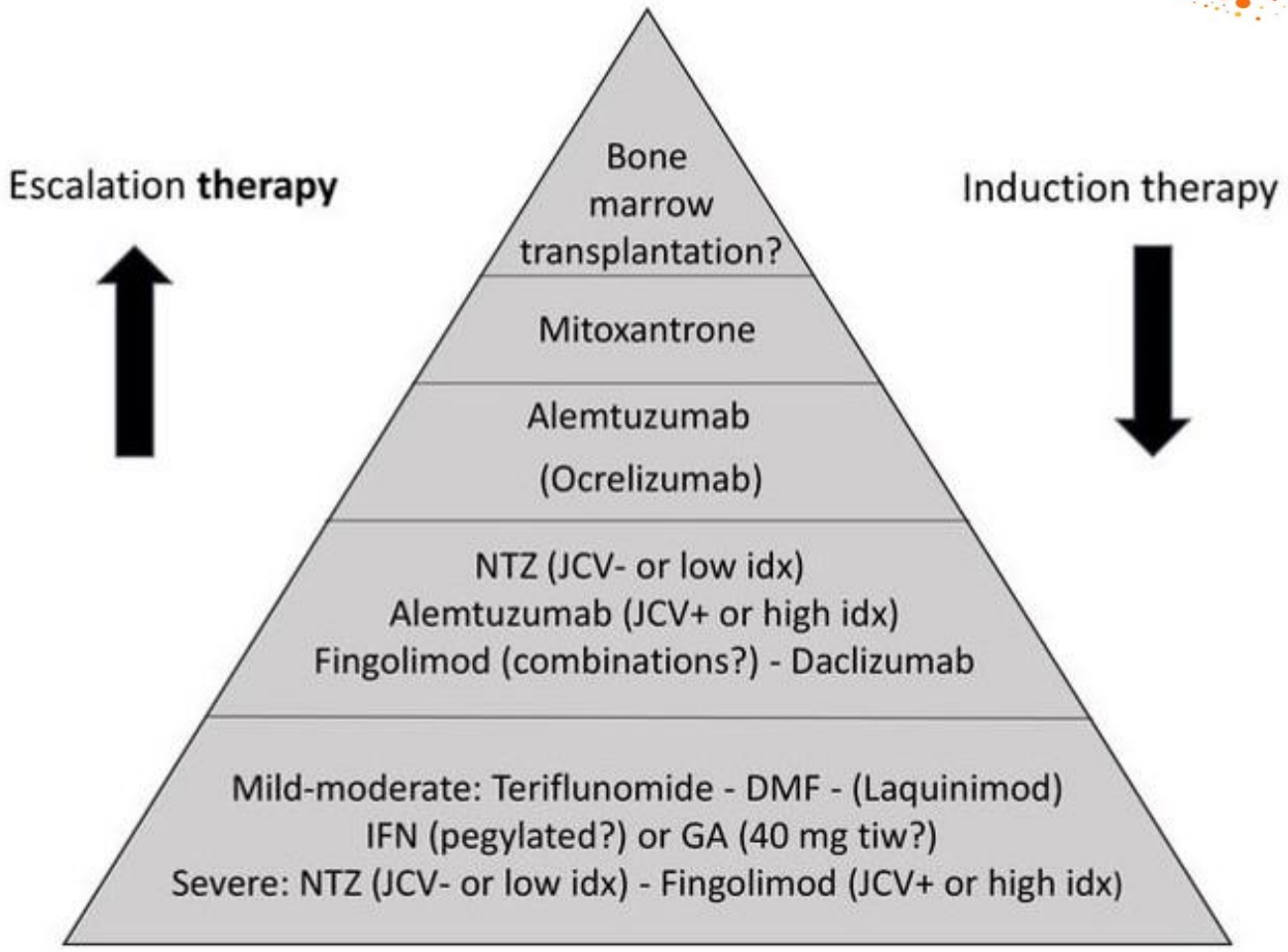
Early treatment with high-efficacy therapies may enhance long-term clinical outcomes by minimizing the accumulation of neurological damage that occurs in the early stages of disease.

Treatment Strategies

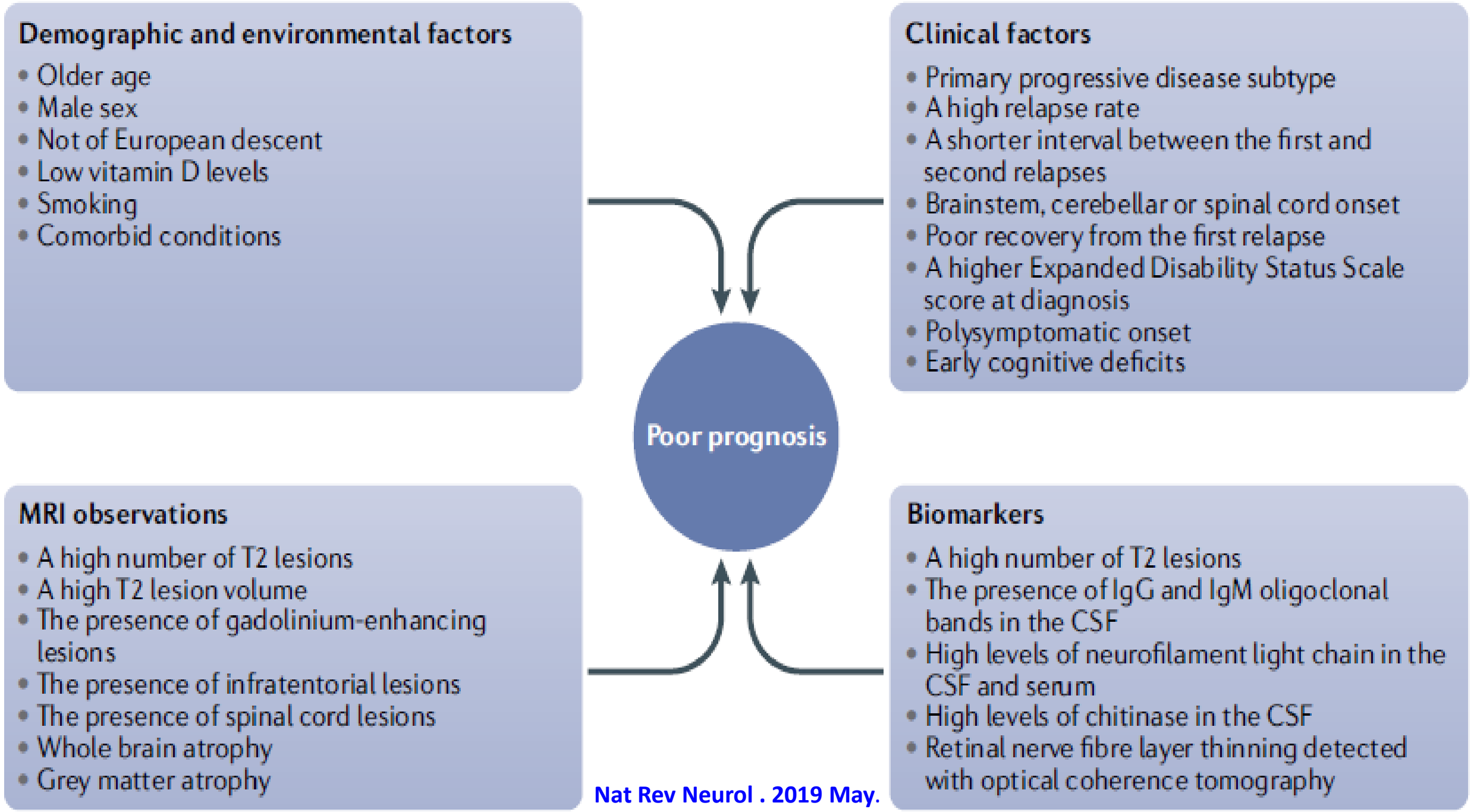
Escalation vs Induction



Prognostic factors evaluated on the basis of the clinical presentation and disease activity on MRI should guide clinicians in selecting treatments



Ruggieri S, et al. *Mult Scler Demyelinating Disord*. 2018;3:5.



Nat Rev Neurol . 2019 May.

Multiple sclerosis progression: time for a new mechanism-driven framework

Lancet Neurol 2023; 22: 78–88

Tanja Kuhlmann, Marcello Moccia, Timothy Coetzee*, Jeffrey A Cohen*, Jorge Correale*, Jennifer Graves, Ruth Ann Marrie*, Xavier Montalban*, V Wee Yong, Alan J Thompson,* Daniel S Reich,* on behalf of the International Advisory Committee on Clinical Trials in Multiple Sclerosis†

Traditionally, multiple sclerosis has been categorised by distinct clinical descriptors—relapsing-remitting, secondary progressive, and primary progressive—for patient care, research, and regulatory approval of medications. Accumulating evidence suggests that the clinical course of multiple sclerosis is better considered as a **continuum, with contributions from concurrent pathophysiological processes that vary across individuals and over time.** The apparent evolution to a progressive course reflects a partial **shift from predominantly localised acute injury to widespread inflammation and neurodegeneration, coupled with falure of compensatory mechanisms,** such as neuroplasticity and remyelination. Ageing increases neural susceptibility to injury and decreases resilience. These observations encourage a new consideration of the course of multiple sclerosis as a spectrum defined by the relative contributions of **overlapping pathological and reparative or compensatory processes.** New understanding of key mechanisms underlying progression and measures to quantify progressive pathology will potentially have important and beneficial implications for clinical care, treatment targets, and regulatory decision-making

ONCE SPARKED,

SMOLDERING NEUROINFLAMMATION

IN MULTIPLE SCLEROSIS IS DESTRUCTIVE[1,2]

VISIT US AT THE 2023 AAN ANNUAL MEETING

SmolderingMS.com

A New Way of Thinking about Multiple Sclerosis

References: 1. Cree BAC, Hollenbach JA, Bove R, et al; University of California, San Francisco MS-Epic Team. Silent progression in disease activity-free relapsing multiple sclerosis. *Ann Neurol*. 2019;85(5):653-666.
2. Ziemssen T, Derfuss T, de Stefano N, et al. Optimizing treatment success in multiple sclerosis. *J Neurol*. 2016;263(6):1053-1065.

Smoldering inflammation

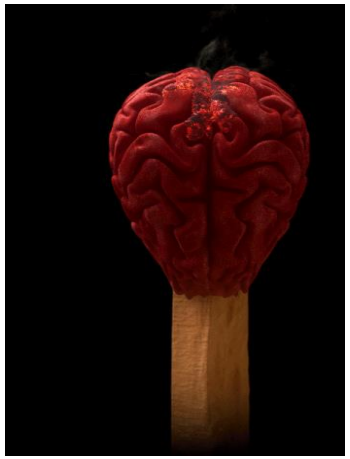
- biological aspects that underlie compartmentalized CNS inflammation and chronic neuronal damage
- chronically inflamed CNS provides a unique tissue microenvironment characterized by alterations in nutrient availability, pH value, lactate levels, and cytokine profiles
- tissue-resident memory T cells, microglia, and astrocytes are key immune cells in smoldering inflammation

➢ can adapt their metabolic profiles in response to the inflamed microenvironment

- environmental and lifestyle factors are increasingly recognized as modulators of immune cell metabolism
- modulation of immune cell metabolism and the inflammatory microenvironment might foster novel treatment approaches in smoldering inflammation

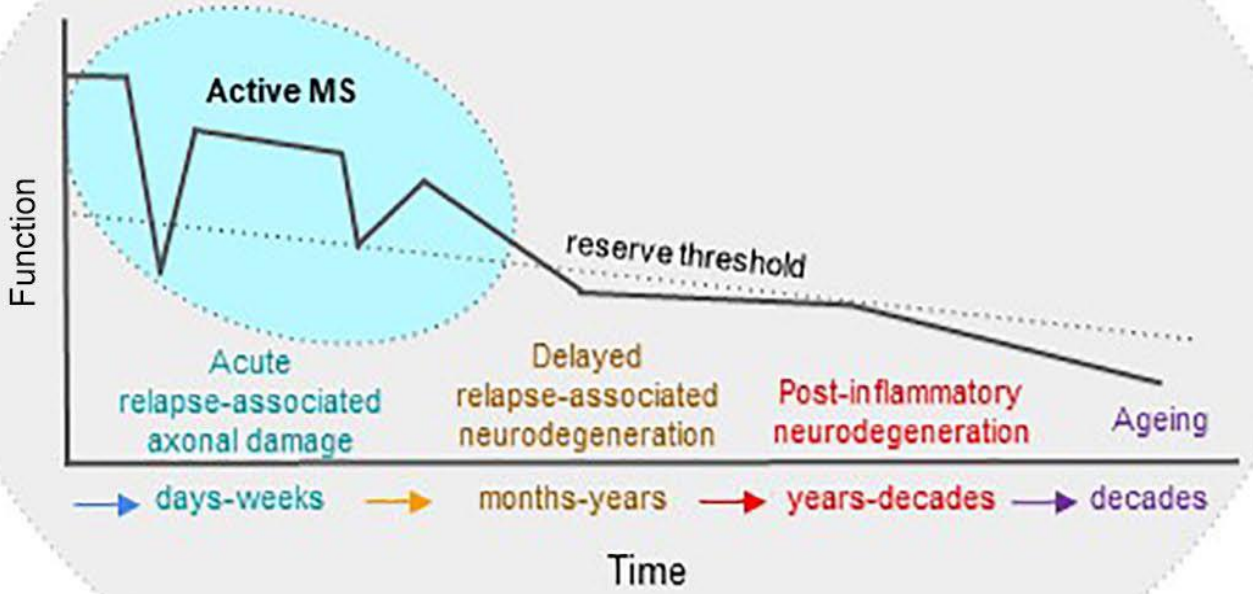
Lifestyle factors and comorbidities
Lack of exercise, smoking, poor diet, etc.

Innate immune activation
Microglial activation, astrocytosis



CNS and systemic Infections
EBV, HERVs, UTIs, Chest infections, periodontal disease, sinusitis, etc.

Smouldering MS



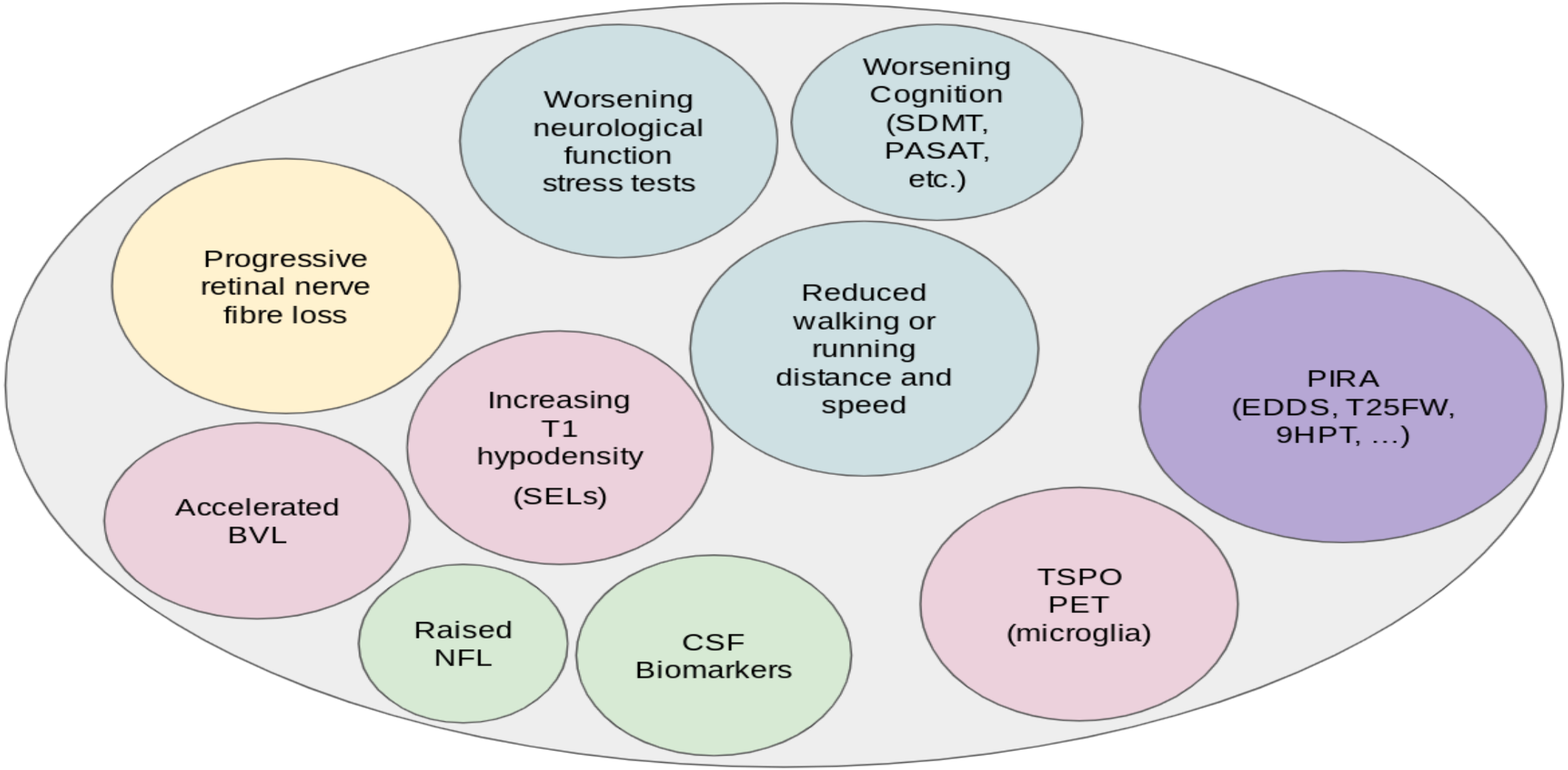
Demyelination and energy deficits
Demyelination, axonal plasticity, mitochondria dysfunction

Ageing mechanisms
Age-related iron accumulation, telomere shortening, remyelination failure, etc.

Adaptive immunity: intrathecal B-cell, plasma cells and T-cells
Oligoclonal IgG bands, complement activation, FcR-activation. Persistent helper and cytotoxic T-cell activation.

Giovannoni *et al.* 2022.

Smouldering MS



PIRA (progression independent of relapse activity)

- an increasing NfL level predicted relapse-associated disability worsening at one year, and non-relapse-associated worsening (i.e. PIRA) at two years.

PERSPECTIVES

OPINION

Can we measure long-term treatment effects in multiple sclerosis?

NEUROLOGICAL DISEASE UPDATES

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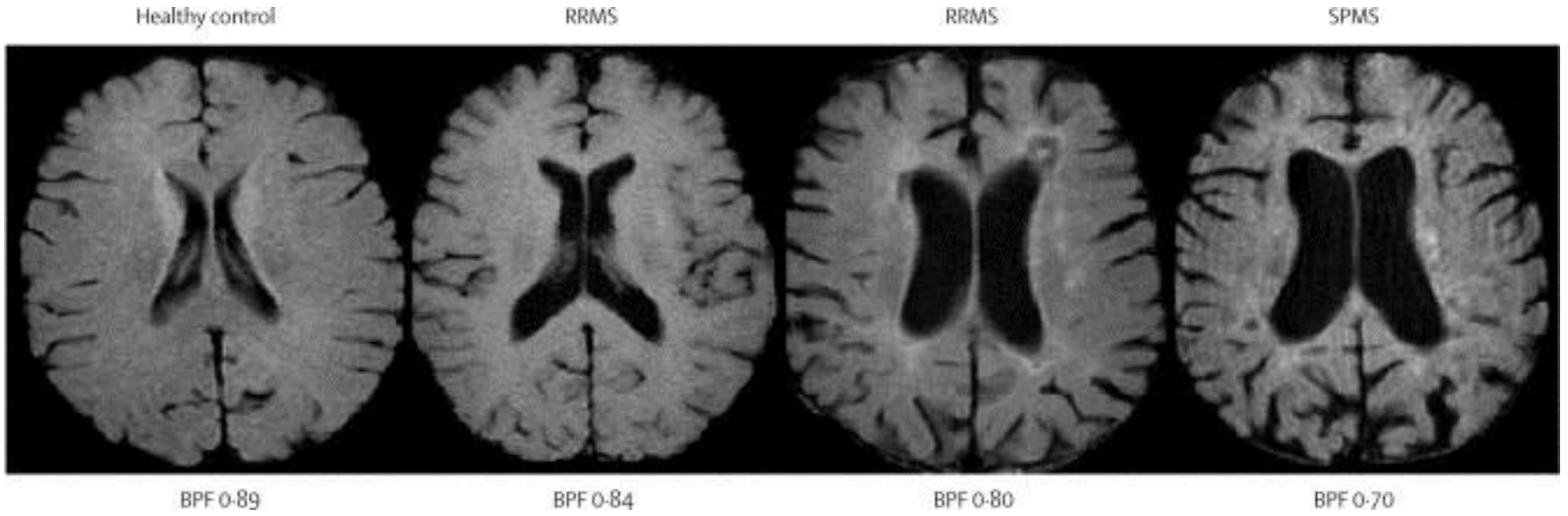
VOL. 5 | NO. 6 | NOVEMBER 2022

The Multiple Sclerosis Issue

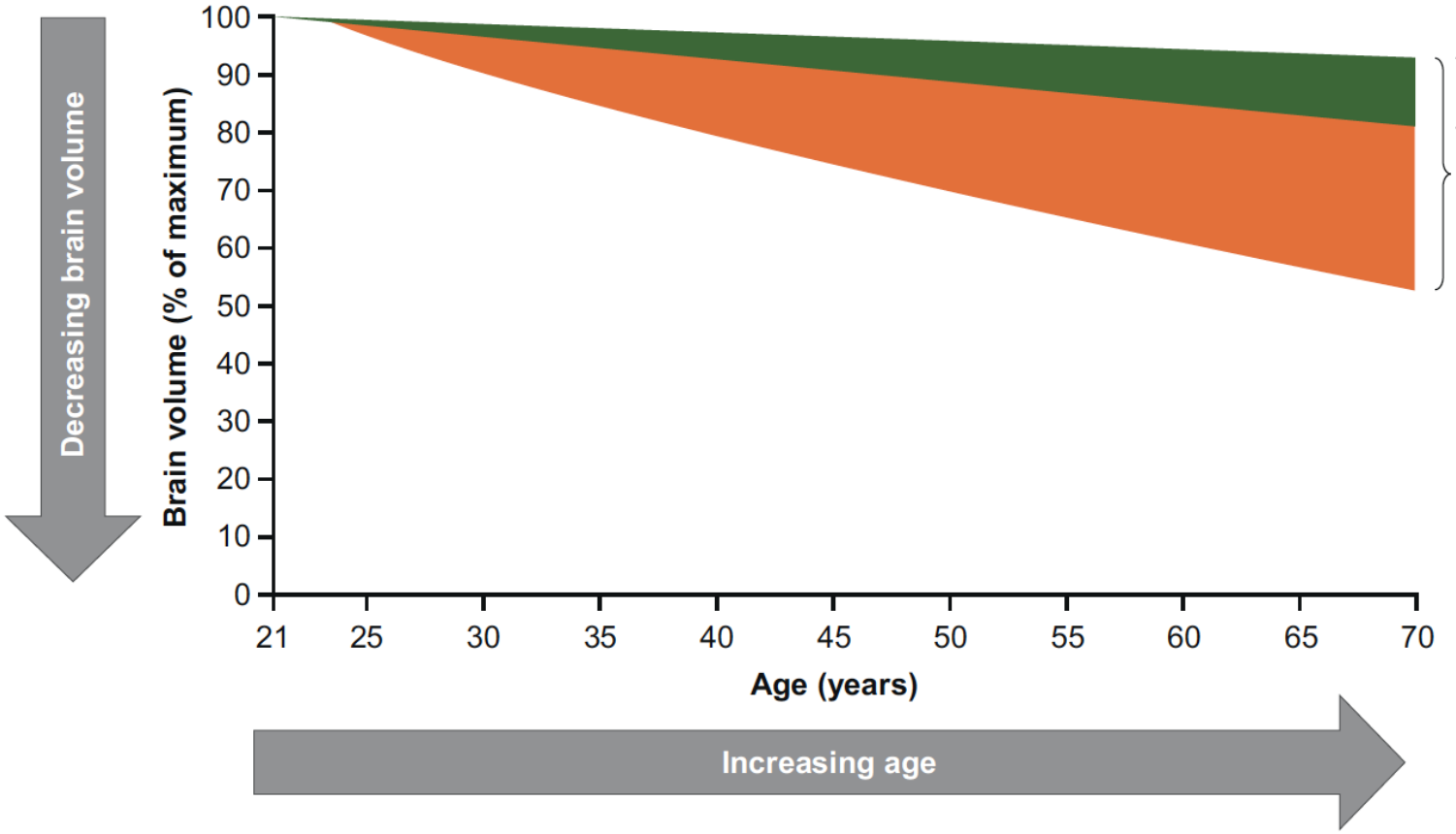
Cognition Issues in Multiple Sclerosis Are Vital to Address

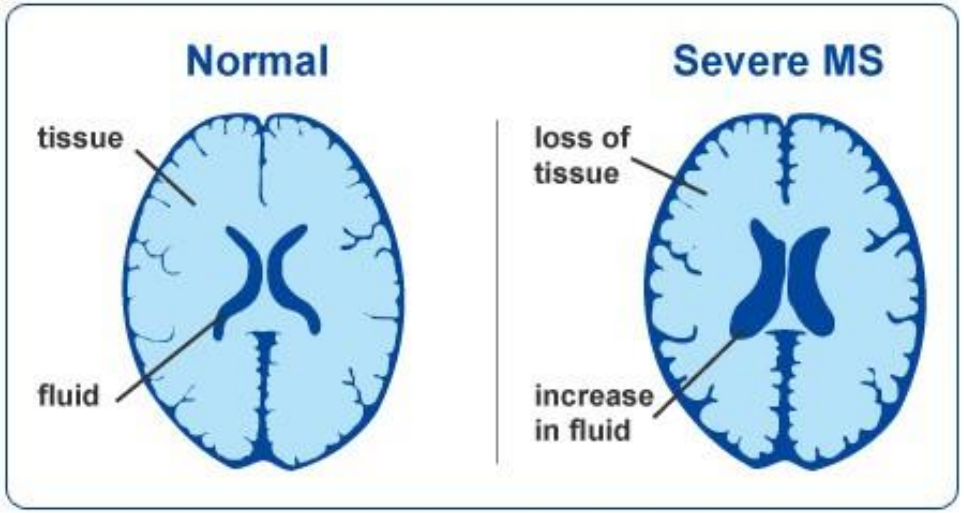
Gray matter atrophy



- with 0.40 % per year performing best for detecting physical disability progression
- a well-established imaging marker of neurodegeneration in MS
- occurs in all phenotypes of MS
- associated with disability accumulation

Brain Atrophy Occurs Early in MS

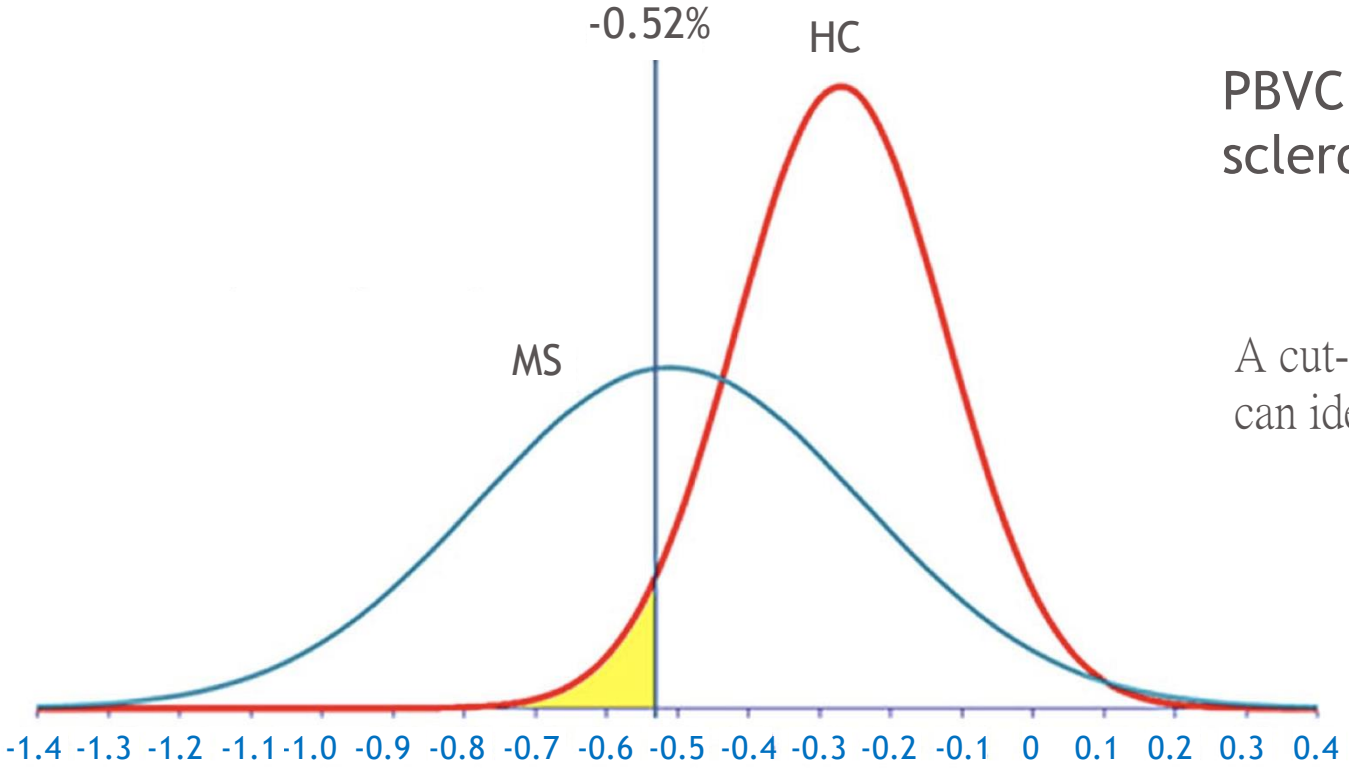




Brain atrophy in many people with MS is faster than usual and proceeds throughout the disease course.[1]

1. Giovannoni G, et al. 2016 Mult Scler Relat Disord. This example uses atrophy rates from studies in people with untreated MS (De Stefano N, et al. 2010 Neurology and De Stefano N, et al. 2014a CNS Drugs) and healthy individuals (De Stefano N, et al. 2016 J Neurol Neurosurg Psychiatry) to illustrate how brain atrophy may be accelerated in a person with MS disease onset at 25 years of age.

The Rate of Yearly Brain Volume Loss Can Identify PwMS



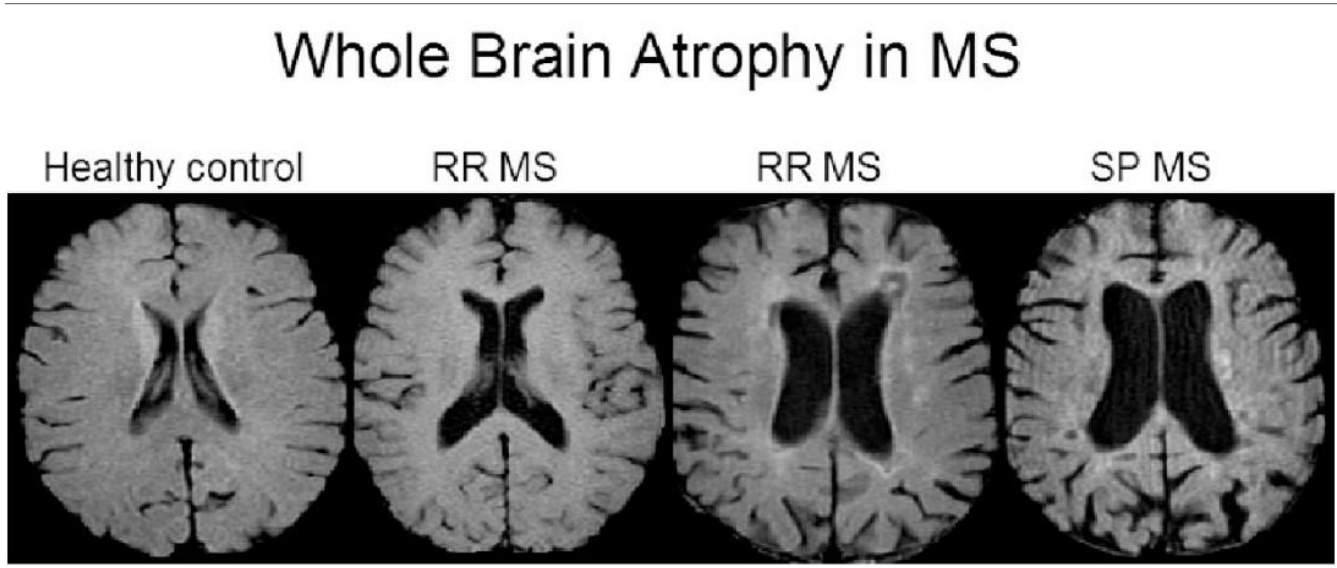
PBVC/y in distinguishing patients with multiple sclerosis (MS) and healthy controls (HC)

A cut-off higher than −0.52% (i.e., defining as "pathological") can identify a PwMS with a 5% rate of false-positive results*

PBVC/y can be used to distinguishing patients with MS from healthy controls

HC, healthy controls; PBVC, percentage brain volume change; PwMS, patients with multiple sclerosis.
Adapted from De Stefano N, et al. 2015 J Neurol Neurosurg Psychiatry. Region of values of "pathological" brain volume loss (with an error rate of 5%, specificity-95%).
* A 5% of HC will be defined erroneously as PwMS using this cut-off.

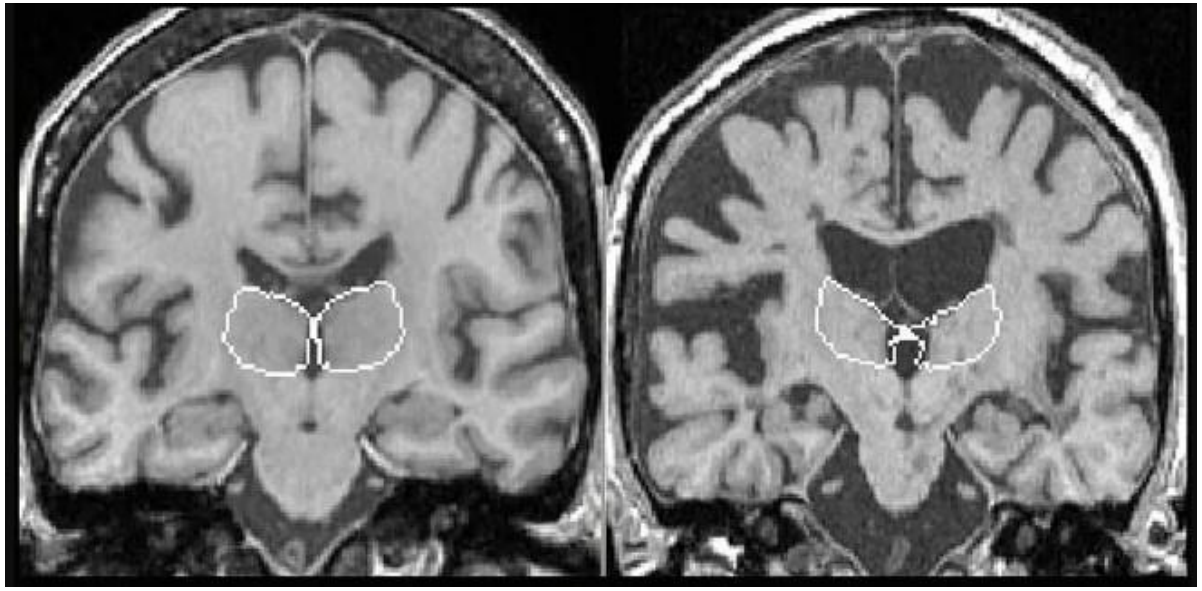
MRI - Brain Atrophy



☐ Cortical atrophy

- accelerate in progressive MS compared to RRMS (−0.87 vs. −0.48%, respectively)
- some brain areas display earlier atrophy compared to others, namely, cingulate cortex, insular and temporal cortical gray matter, and the deep gray matter (putamen, caudate nucleus)
- stronger association with clinical (especially cognitive) dysfunction than global cortical atrophy

MRI - Brain Atrophy



☐ Thalamic atrophy

- another MRI volumetric measure of neurodegeneration in MS
- associated with higher risk for 5-year EDSS increase as well as for not reaching criteria of no evidence of disease activity (NEDA-3) after 2 years

✓ atrophy of **anterior thalamic nucleus**

- associated with decreased cognitive processing speed

TABLE 1. COGNITIVE IMPAIRMENT BY MULTIPLE SCLEROSIS SUBTYPE

Multiple sclerosis subtype	Mean age	Median EDSS (IQR)	CI prevalence
Clinically isolated syndrome (n=167)	33.9 (9.8)	1.5 (1.0; 2.0)	34.5%
Relapsing-remitting (n=759)	39.9 (10.2)	2.0 (1.5; 3.5)	44.5%
Secondary progressive (n=74)	51.6 (9.5)	6.0 (4.5; 6.5)	79.4%
Primary progressive (n= 40)	49.3 (10.9)	5.25 (5.0; 6.0)	91.3%
Overall (n=1,040)	40.1 (11.0)	0.2 (2.5; 3.5)	46.3%

Abbreviations: CI, cognitive impairment, IQR, interquartile range, EDSS, Expanded DisabilityStatus Scale.

Cognitive impairment at diagnosis of PWMS

1) predicts time to reach EDSS score of 4
2) significantly associated with loss of employment and deterioration in employment status 3.5 years[6] and 7 years later, respectively
3) associated with significantly higher odds of progressing from RRMS to SPMS (odds ratio, 2.29)
4) conversion to SPMS 10 years later
5) a significantly higher hazard of death (HR, 3.07)

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The impact of disease modifying therapies on cognitive functions typically impaired in multiple sclerosis patients: a clinician's review

Karolina Kania[1]*, Wojciech Ambrosius[1], Wojciech Kozubski[1] and Alicja Kalinowska-Łyszczarz[2]

TABLE 1 Summary of the most important studies on cognitive functions and DMTs.

Authors	Year of publication	DMT	No of subjects	Test	DMT efficacy	Follow-up
Fischer et al.	2000	INFβ-1a im/placebo	83/83	Brief Np. Battery	Yes	2 y
Patti et al.	2013	INFβ-1a sc, COGIMUS Study	201	BRB, Stroop Test	Yes	5 y
Mori et al.	2012	INFβ-1a sc	80	PASAT	Yes	2 y
Benesova et al.	2017	INFβ-1a sc, SKORE Study	300	PASAT	Yes	2 y
Penner et al.	2012	INFβ-1b, BENEFIT Study	468	PASAT	Yes	5 y
Kappos et al.	2016	INFβ-1b, BENEFIT Study	278	PASAT	Yes	11 y
Barak et al.	2002	INFβ-1b/placebo	18 /23	BRB tests	Yes	1 y
Lacy et al.	2013	INFβ-1b	16	Wechsler Memory Scale, Stroop tasks	Yes	16 y
Weinstein et al.	2002	GA/placebo	125 /126	BRB	No	2 y
Ziemsen et al	2014	GA, COPTIMIZE Study	672	PASAT	Yes	2 y
Ziemsen et al.	2016	GA, QualiCOP	754	PASAT, MUSIC	Yes	2 y
Cinar et al.	2017	INFβ-1a sc/INFβ-1b/GA	53/52/56	BICAMS	Yes	1 y
Gartner et al.	2017	INFβ-1b, BETAPAEDIC Study	68	Wechsler Scale, Raven Matrices	Yes	2 y
Coyle et al.	2018	Teriflunomide,TERI-PRO	100	SDMT	Yes	48 weeks
Wuerfel et al.	2022	Teriflunomide/placebo, TEMSO	358/363	PASAT	Yes	2 y
Giovannoni et al.	2016	DMF/placebo DEFINE, CONFIRM	769 / 771	PASAT	Yes	96 weeks
Amato et al.	2020	DMF	217	BRB, Stroop tes	Yes	2 y
Kappos et al.; Cohen et al.	2016	Fingolimod/placebo freedoms, transforms studies	783/773	PASAT	Yes	2 y
Ozakbas et al.	2016	Fingolimod	96	SDMT, BVMTR, CVLT2	Yes	6 months
Barak et al.	2019	Fingolimod	29	Mindstream Computerized Global Assessment Battery	Yes	1 y
Cree et al.	2018	Fingolimod/injectable, PREFERMS Study	433/428	SDMT	No	48 weeks
Comi et al.	2017	Fingolimod/INFβ-1b, GOLDEN Study	106/51	Rao, BRB	Yes	18 months
Schulze et al.	2021	Fingolimod, PANGAEA Study	2,428	SDMT	Yes	2 y
Weinstock-Guttman	2012	Natalizumab/Placebo,AFFIRM Study	627/315	PASAT	Yes	2 y
Perumal et al.	2019	Natalizumab, STRIVE Study	222	SDMT	Yes	2 y
Wilken et al.	2013	Natalizuamb, ENER-G Study	89	ANAM	Yes	48 weeks
Giovannoni et al.	2017	Alemtuzumab/ INFβ-1a, CARE-MS Study	426/202	PASAT	Yes	2 y
Cohan et al.	2020	Ocrelizumab/INFβ-1a, OPERA I, II Studies	827/829	SDMT	Yes	96 weeks
Giovannoni	2021	Siponimod/placebo, EXTEND Core Study	903/427	SDMT	Yes	5 y
Benedict	2022	ofatumumab/teriflunomide ASCLEPIOS I/II	492/468	SDMT	Yes	2 y

BRB, Brief Repeatable Battery; MUSIC, Multiple Sclerosis Inventory Cognition Scale.

Cognitive impairment of PWMS

- more than 50% of MS clinics do not assess for cognitive problems at all
- whereas 19% rely on self-reporting
- less than one-third of all clinics doing any type of formal screening or testing

多發性硬化症病人的認知處理速度 (Cognitive processing speed, CPS) 是逐漸受到重視的治療目標，通常會以符號數字轉換測驗 (Symbol Digit Modalities Test, SDMT) 評估。以下呈現此次 ECTRIMS 會議中，使用 Ozanimod 治療後，RMS 病人的 SDMT 分數變化與其腦容量、疾病活性程度的關聯性。

SDMT is a highly sensitive measure for cognitive performance outcome in MS

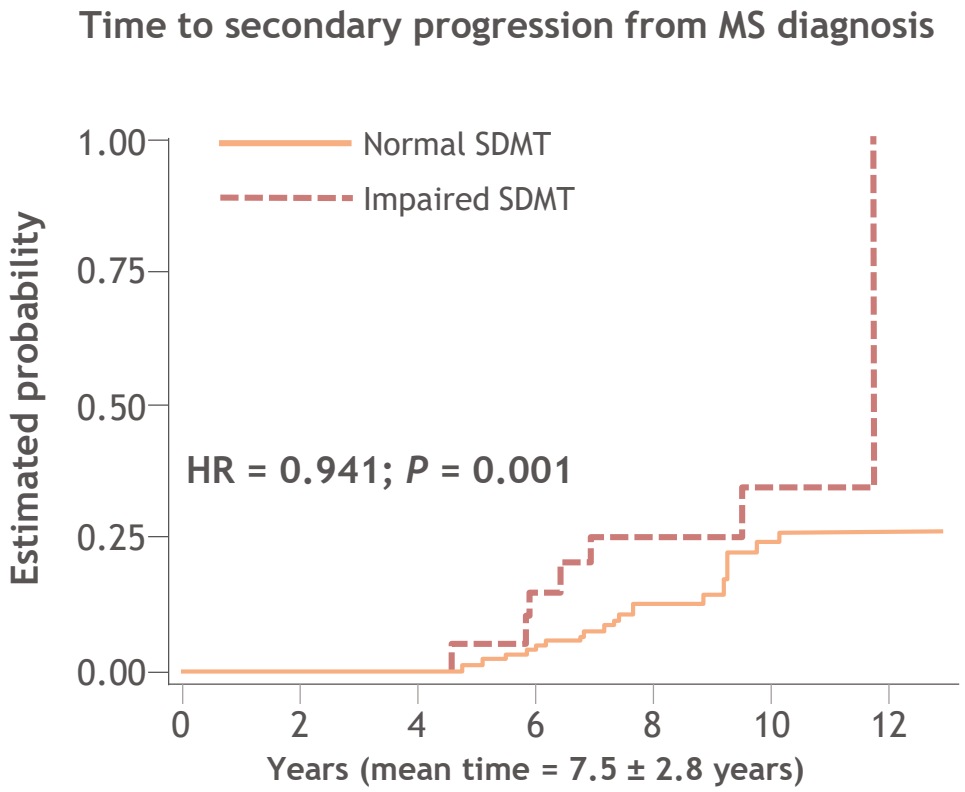
- SDMT measures has shown:
  - Robust correlations with and disease progression[1,2]
  - To be predictive of future cognitive decline[3]
  - To be a valid clinical trial endpoint for measuring clinically meaningful change in patients with MS not encompassed by physical measures[1]

- On SDMT:
  - Worsening by 4-point or greater was a strong predictor of clinically meaningful changes[1,a]
  - Increase by ~3-point was associated with improved work status in patients with MS[4]

[a]Using relapses and employment as clinical anchors.
SDMT, Symbol Digit Modalities Test; MS, multiple sclerosis.
1. Strober L et al. *Mult Scler*. 2019;25:1781–1790. 2. Sumowski JF et al. *Neurology*. 2018;90:278–288. 3. Amato MP et al. *Mult Scler*. 2010;16:1474–1482. 4. Wojcik C et al. *Mult Scler*. 2022;28:487–491. 5.
Figure adapted with permission from Benedict RH et al. *BMC Neurol*. 2012;12:55.

62

CI on SDMT in newly diagnosed RRMS patients predicts MS progression over 10 years



	Adjusted model		
	OR	95% CI	*P* value
SRT	0.971	0.942–1.002	0.071
SPART	0.964	0.892–1.042	0.360
PASAT3	0.976	0.944–1.009	0.154
SDMT	0.959	0.927–0.993	0.019
WLG	0.983	0.948–1.018	0.349

- Better scores in the SDMT at baseline were associated with lower conversion rates to SPMS

- After adjusting for age and baseline EDSS, the reduced likelihood of reaching EDSS 4.0 with worse baseline NP scores was only confirmed for SDMT

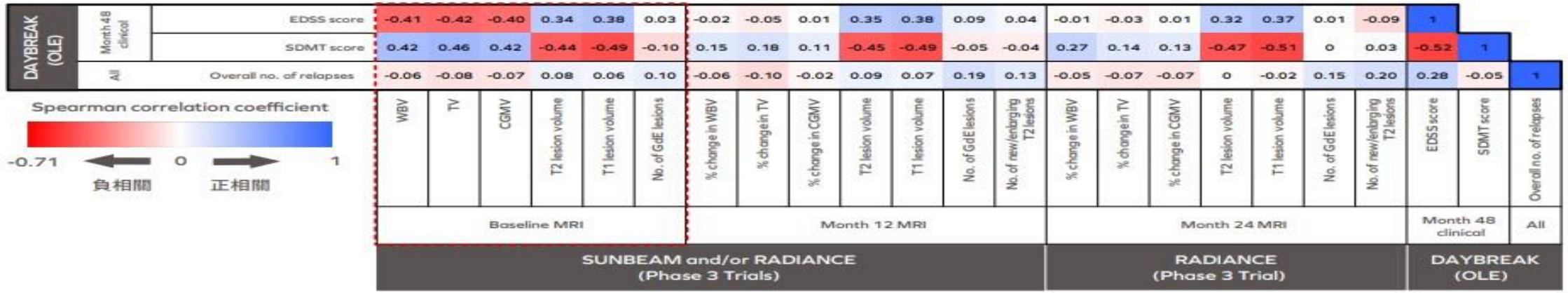
CI, cognitive impairment; EDSS, Expanded Disability Status Scale; HR, hazard ratio; NP, neuropsychological; PASAT3, Paced Auditory Serial Addition Test at 3 seconds; RRMS, relapsing-remitting multiple sclerosis; SDMT, Symbol Digit Modalities Test; SPART, 10/36 Spatial Recall Test; SRT, Selective Reminding Test; WLG, Word List Generation.

Moccia M et al. *Mult Scler*. 2016;22:659-667. Figure and table adapted with permission from *Mult Scler*.

2 SDMT (Symbol Digit Modalities Test) & 疾病活性

- 許多研究已證實 SDMT 檢測出的輕微認知功能障礙與腦容量保存呈正相關，而 SDMT 與 MS 疾病活性的關聯性尚需後續研究加以分析。由於 MS 病人臨床上疾病活性落差大，有些患者病程較快，屬於高度活躍型 (highly-active)，有些則較緩慢失能[2]。

2-2 SDMT 和 EDSS 分數皆與早期 MRI 指標呈現中度相關性 (modest correlation)；其中又以 SDMT 與早期 MRI 指標的關聯性稍高[2]



上表呈現 MRI 與臨床預後的 Speaman 相關係數，數值接近 1 或 -1 代表高度相關（負值指負相關）。

Figure 1. Examples of Clinical Trial Endpoints Used in Multiple Sclerosis[2,4-8]

- MS Quality of Life-54 (MSQOL-54)
- Quality of Life in Neurological Disorders (Neuro-QoL)

- No Evidence of Disease Activity (NEDA)-3
- NEDA-4

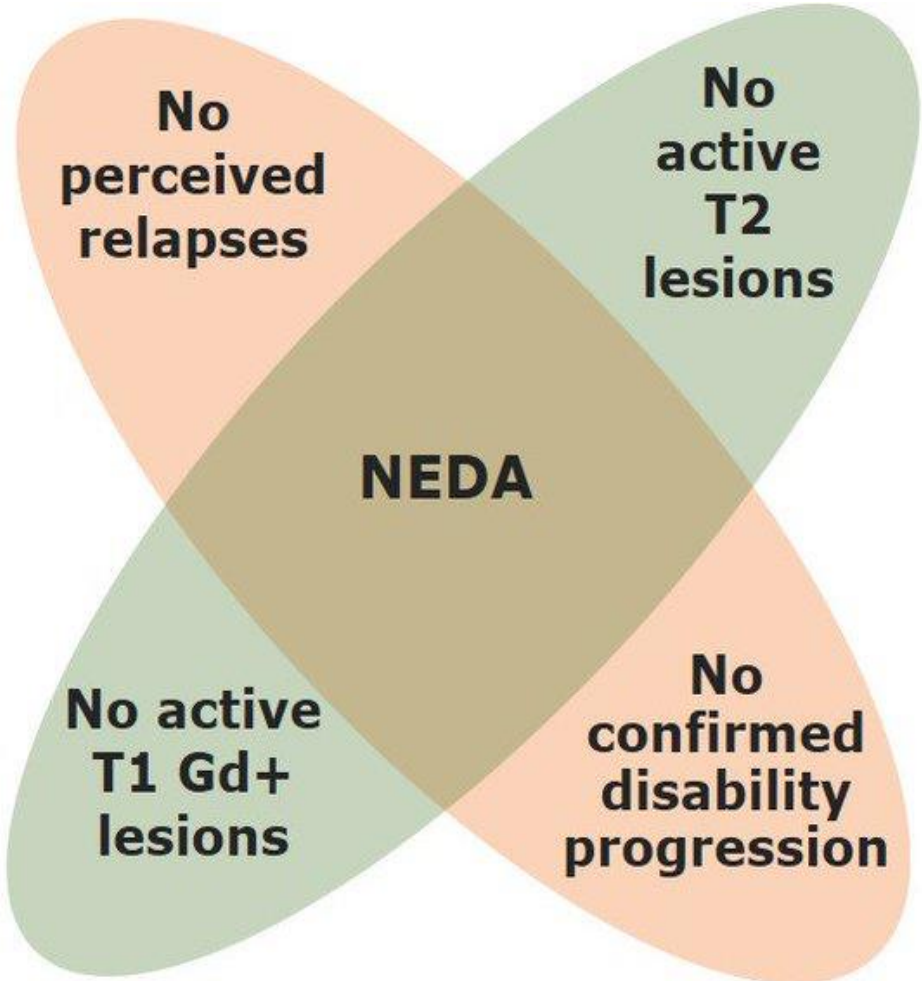
Relapses
- Annualized relapse rate (ARR)
- Relapse rate

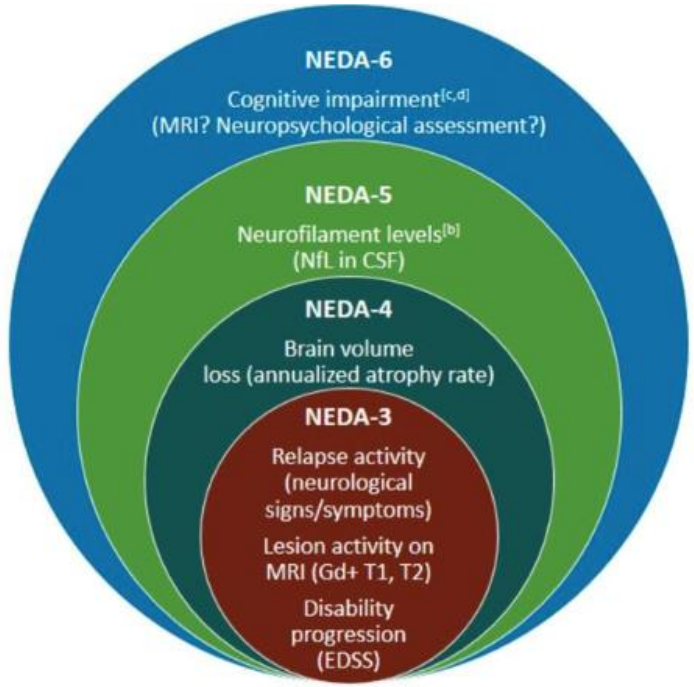
Disability
- Expanded Disability Status Scale (EDSS)
- Multiple Sclerosis Functional Composite (MSFC)
- Timed 25-foot Walk (T25FW)
- 9-Hole Peg Test (9HPT)
- Symbol Digit Modalities Test (SDMT)

Neuroimaging Measures
- Gd enhancing lesions
- T2 lesions
- T1 lesions
- Brain volume loss

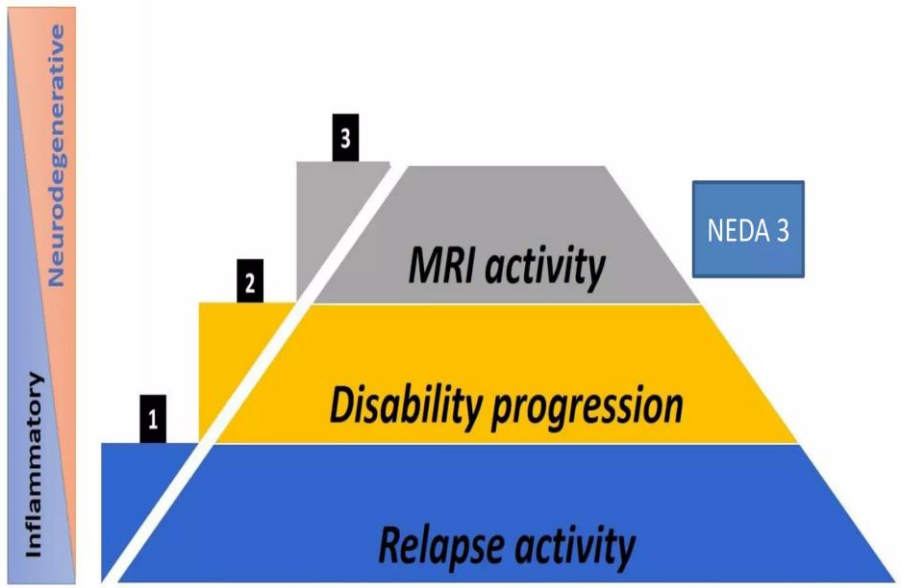
Cerebrospinal fluid (CSF) oligoclonal bands

“No Evidence of Disease Activity” - NEDA





NEDA


Inflammatory
Neurodegenerative
1
2
3
Relapse activity
Disability progression
MRI activity
NEDA 3

NEDA

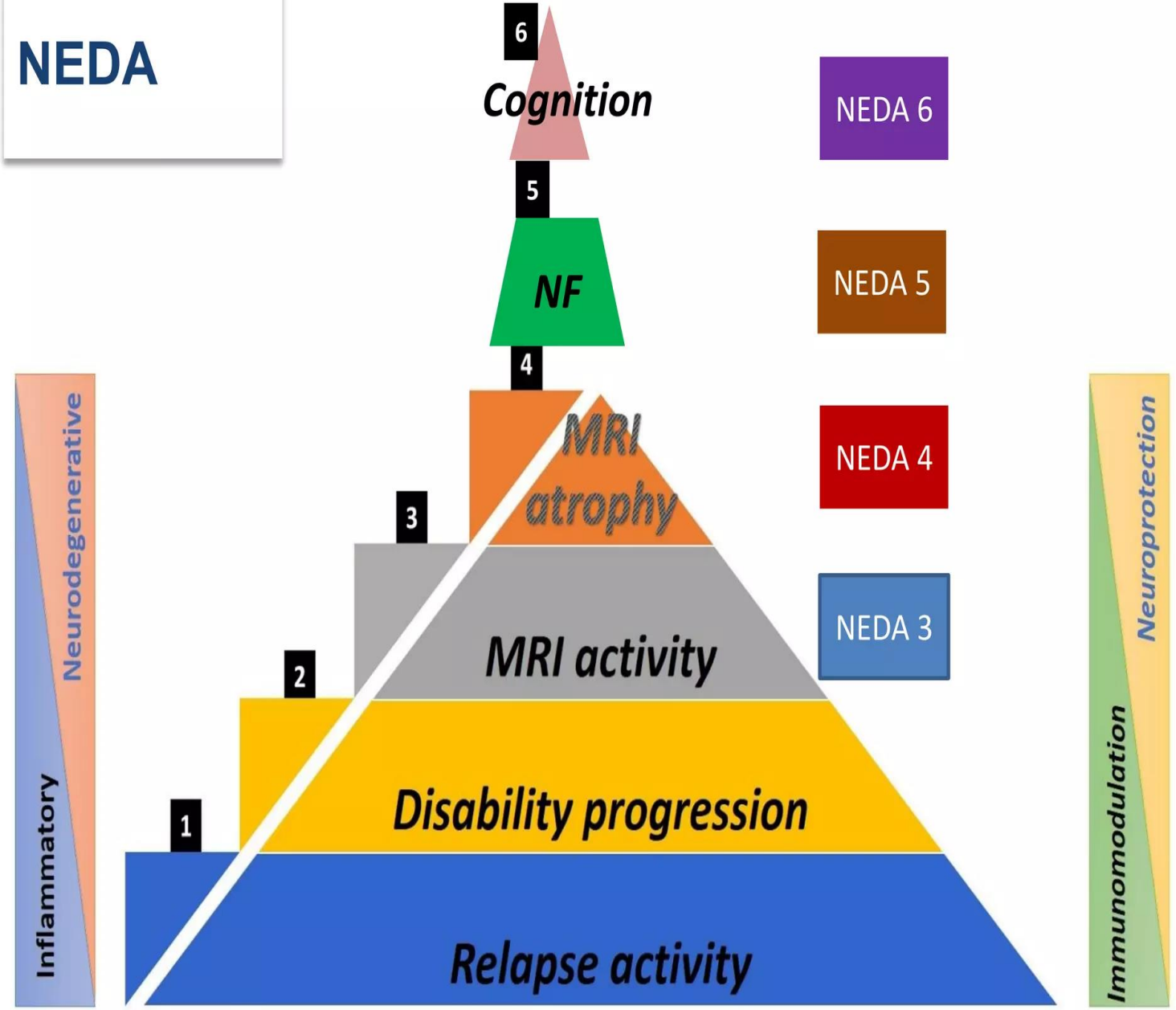
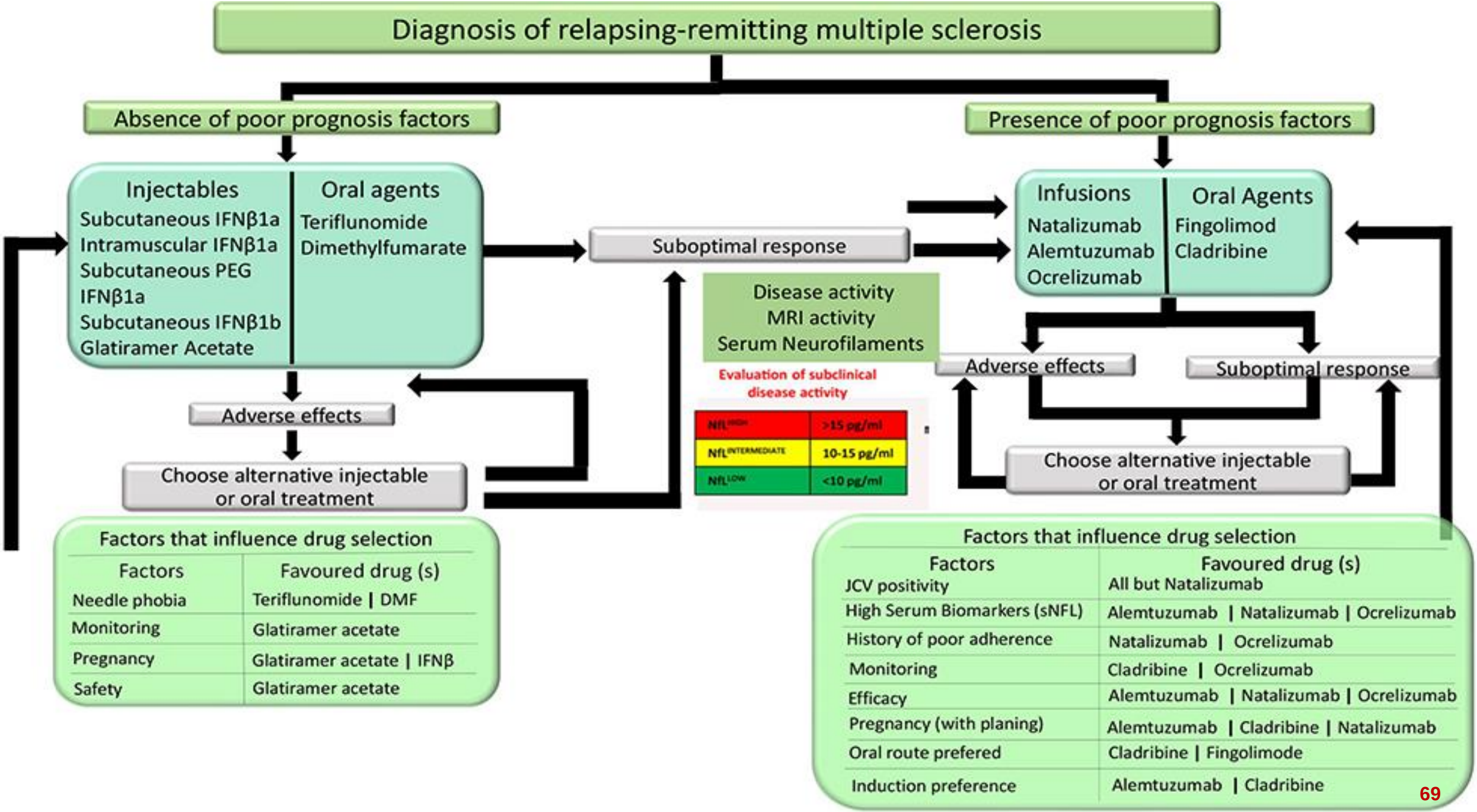
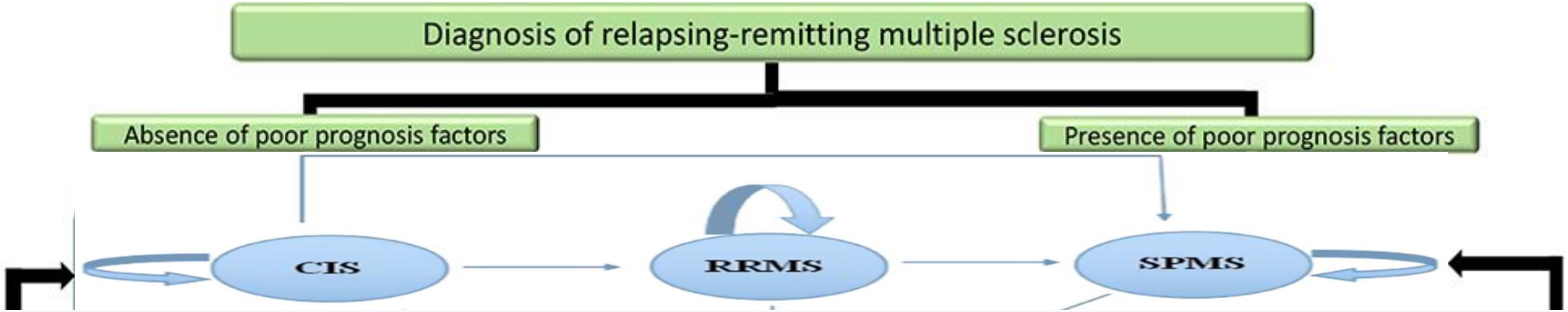

Inflammatory
Neurodegenerative
1
2
3
4
5
6
Relapse activity
Disability progression
MRI activity
MRI atrophy
NF
Cognition
NEDA 3
NEDA 4
NEDA 5
NEDA 6
Immunomodulation
Neuroprotection

Table 2. Validated and promising treatment-response biomarkers and their functions.

Biomarker	Function	References
OCBs	IgG or IgM antibodies synthesized intrathecally by plasma cells	[16–24]
CXCL13	Chemokine expressed in lymphoid organs, essential for the recruitment of lymphocytes	[25–37]
Osteopontin	Pro-inflammatory cytokine secreted by activated immune cells	[38–48]
NAbs against IFN-ß	Serum antibodies against IFNβ	[49–56]
NAbs against natalizumab	Serum antibodies against natalizumab	[57–72]
MxA	Antiviral protein induced by IFNβ	[56,63–65]
Neurofilaments	Axonal cytoskeletal proteins	[66–84]
CHI3L1	Chitinase-like glycoprotein, expressed by astrocytes and macrophages	[85–98]

Ig, Immunoglobulin; OCB, Oligoclonal bands; CXCL13, C-X-C motif chemokine 13; NAbs, Neutralizing antibodies; IFNβ, Interferon-β; MxA, Myxovirus resistance protein A; CHI3L1, Chitinase 3-like protein.


Diagnosis of relapsing-remitting multiple sclerosis
Absence of poor prognosis factors
Presence of poor prognosis factors
Injectables
Subcutaneous IFNβ1a
Intramuscular IFNβ1a
Subcutaneous PEG IFNβ1a
Subcutaneous IFNβ1b
Glatiramer Acetate
Oral agents
Teriflunomide
Dimethylfumarate
Suboptimal response
Infusions
Natalizumab
Alemtuzumab
Ocrelizumab
Oral Agents
Fingolimod
Cladribine
Disease activity
MRI activity
Serum Neurofilaments
Evaluation of subclinical disease activity
NfL HIGH >15 pg/ml
NfL INTERMEDIATE 10-15 pg/ml
NfL LOW <10 pg/ml
Adverse effects
Choose alternative injectable or oral treatment
Adverse effects
Suboptimal response
Choose alternative injectable or oral treatment
Factors that influence drug selection
Factors
Favoured drug (s)
Needle phobia
Teriflunomide | DMF
Monitoring
Glatiramer acetate
Pregnancy
Glatiramer acetate | IFNβ
Safety
Glatiramer acetate
Factors that influence drug selection
Factors
Favoured drug (s)
JCV positivity
All but Natalizumab
High Serum Biomarkers (sNFL)
Alemtuzumab | Natalizumab | Ocrelizumab
History of poor adherence
Natalizumab | Ocrelizumab
Monitoring
Cladribine | Ocrelizumab
Efficacy
Alemtuzumab | Natalizumab | Ocrelizumab
Pregnancy (with planing)
Alemtuzumab | Cladribine | Natalizumab
Oral route prefered
Cladribine | Fingolimode
Induction preference
Alemtuzumab | Cladribine



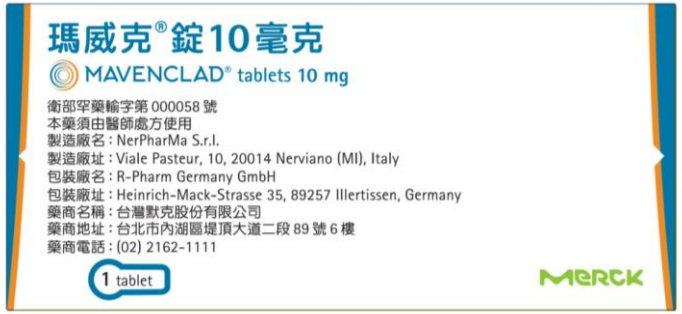
		McDonald MS: Relapsing MS (RMS)			Progressive MS (PMS)	
	CIS	RRMS		SPMS		PPMS
Disease-modifying therapy		(highly-) active[6] first- and second-line therapies	***Pulsed therapies*** • Alemtuzumab • Cladribine • Ocrelizumab ***Continuous therapies*** • Natalizumab[3] • Ofatumumab • S1P-modulators (Fingolimod, Ozanimod, Ponesimod)	**with relapses** • Cladribine • Interferon-b-1b s.c. • Ocrelizumab • Ofatumumab • Ponesimod • Siponimod • (Mitoxantrone[2])	**without relapses, with MRI activity** • Siponimod	**with clinical / MRI activity** • Ocrelizumab
	• Interferon-b-1a i.m. • Interferon-b-1a s.c. • Interferon-b-1b s.c.	mild / moderate	• Dimethyl fumarate • Glatiramer acetate[5] • Interferons[4] • Teriflunomide • (Azathioprine[1])			

「藥品給付規定」修訂對照表
第 8 節 免疫製劑 Immunologic agents

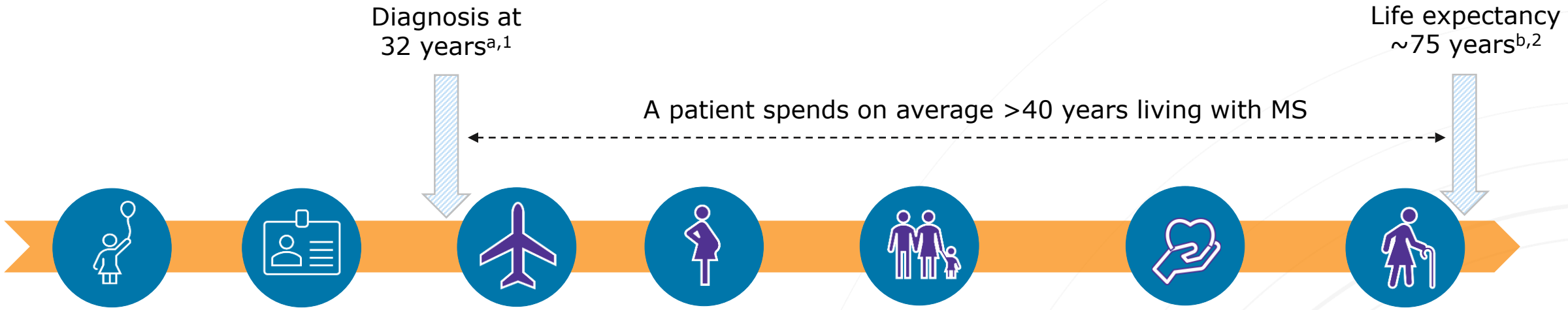
修正後給付規定	
8.2.3.多發性硬化症治療藥品 (91/4/1、92/3/1、92/12/1、93/3/1、94/10/1、96/7/1、97/8/1、99/10/1、100/5/1、100/10/1、101/9/1、102/10/1、107/7/1、107/10/1、108/7/1、109/1/1、109/11/1、112/3/1) 8.2.3.1.Interferon beta-la (如Rebif)、teriflunomide 14mg (如Aubagio)、dimethyl fumarate（如Tecfidera）、peginterferon beta-1a (如Plegridy)、ozanimod(如Zeposia)：(91/4/1、97/8/1、100/10/1、106/10/1、107/7/1、107/10/1、109/11/1、112/3/1) 1.限用於復發型多發性硬化症。 2.初次使用teriflunomide、dimethyl fumarate、peginterferon beta-1a及ozanimod時需經事前審查核准後使用(109/11/1、112/3/1)。	3.不適用於視神經脊髓炎（neuromyelitis optica,NMO），包括：(100/10/1) (1)有視神經及脊髓發作。 (2)出現下列2種以上症狀： i脊髓侵犯大於3節。 ii NMO-IgG or Aquaporin-4抗體陽性。 iii腦部磁振造影不符合多發性硬化症診斷標準。 4.Ozanimod每日限用1粒，若治療無效，第二線治療藥物不得使用fingolimod。(112/3/1) 5.Interferon beta-la、teriflunomide 14mg、dimethyl fumarate、peginterferon beta-1a、ozanimod僅得擇一使用。(112/3/1)

Taiwan NHIA criteria for highly active RRMS

適應症	適用於治療成年病人的復發型多發性硬化症(臨床上有發作，且前二年有二次復發者)
健保給付條件	8.2.3.5.Fingolimod(如Gilenya)、cladribine(如Mavenclad)：(101/9/1、102/10/1、109/1/1、109/10/1) 1.限用於雖已接受乙型干擾素或glatiramer治療，相較於前一年度復發率仍不變或反而上升之高度活躍型復發緩解之多發性硬化症病人(highly active relapsing-remitting multiple sclerosis 即前一年有一次以上復發或是前兩年有兩次以上復發)，但排除使用於： (1)EDSS (Expanded Disability Status Scale)大於5.5之患者。 (2)視神經脊髓炎(neuromyelitis optica,NMO)，包括： Ⅰ.有視神經及脊髓發作。 Ⅱ.出現下列2 種以上症狀： i.脊髓侵犯大於3節； ii.NMO-IgG or Aquaporin-4 抗體陽性； iii.腦部磁振造影不符合多發性硬化症診斷標準。 2.須經事前審查核准後使用，每年需重新申請，併應提出整個用藥期間的復發情形。(102/10/1) 3.Cladribine限給付兩年。(109/1/1) 4.Fingolimod使用兩年後，年度復發率(average annual relapse)無法減少※時應停止本藥品之治療。(102/10/1、109/1/1) 註：年度復發率無法減少之定義為： 採計使用fingolimod藥物後一年至兩年復發次數之數據（以最近一年或兩年之復發次數除以1或2來計算），較諸更先前一年或兩年之年復發率皆無再減少時。(102/10/1) 5.個案在停藥觀察期間復發且為高度活躍型復發緩解之多發性硬化症病人(highly active relapsing-remitting multiple sclerosis可再申請並經事前審查核准後使用。(102/10/1)



Optimizing treatment sequencing is important when considering disease duration and evolving patient needs



Most patients will require more than one DMT throughout the disease course[3]

Treatment should be selected to address the **immediate clinical problem** and to **keep subsequent therapeutic options open**[3,4]

Early treatment with a high-efficacy DMT is important in reducing the risk of neuronal injury[5]

Multiple Sclerosis and Related Disorders 68 (2022) 104220

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journal homepage: www.elsevier.com/locate/msard

Original article

Effectiveness of first generation disease-modifying therapy to prevent conversion to secondary progressive multiple sclerosis

H Tedeholm [a], F Piehl [b], J Lycke [a], J Link [c], L Stawiarz [c], J Burman [d], P de Flon [e], K Fink [f], M Gunnarsson [g], J Mellergård [h], P Nilsson [i], P Sundström [k], A Svenningsson [j], H Johansson [l], O Andersen [a,*]

- **Conclusion:**
- A population-based nationwide study from Sweden identified a lower risk of conversion from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive MS (SPMS) after the introduction of disease-modifying therapies (DMTs) in 1995
- DMT efficiency was confirmed by a downward turn of the annual trajectory of the risk of SPMS conversion, their long-term effect was only moderate

IRTs may be most beneficial when used early in the disease course
Delphi Consensus, France

Objective

To provide a consensus-based expert opinion on the optimal utilization of IRT in the management of relapsing MS using a formal Delphi consensus procedure

14 **neurologists with MS speciality**

100%

Level of expert consensus

IRTs delay the progression of disease in the absence of **continuous immunosuppression**

93%

Level of expert consensus

IRT used as early as possible has an advantage of **reducing inflammation** in the most inflammatory phase of the disease

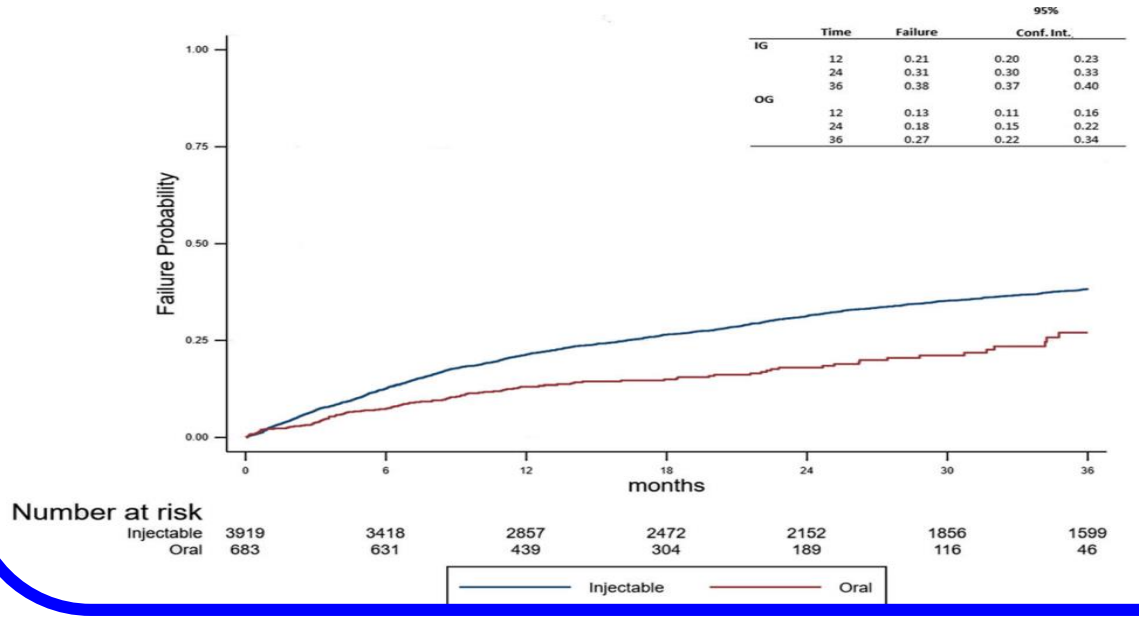
Neurotherapeutics (2021) 18:905–919
https://doi.org/10.1007/s13311-020-01001-6

ORIGINAL ARTICLE

Injectable Versus Oral First-Line Disease-Modifying Therapies: Results from the Italian MS Register

Emanuele D'Amico[1] · Aurora Zanghì[1] · Marzia Romeo[2] · Eleonora Cocco[3] · Giorgia Teresa Maniscalco[4] · Vincenzo Brescia Morra[5] · Damiano Paolicelli[6] · Giovanna De Luca[7] · Simonetta Galgani[8] · Maria Pia Amato[9,10] · Giuseppe Salemi[11] · Matilde Inglese[12,13] · Paolo Agostino Confalonieri[14] · Giacomo Lus[15] · Carlo Avolio[16] · Antonio Gallo[17] · Marika Vianello[18] · Marco Onofrj[7] · Massimo Filippi[19,20] · Maria Trojano[6] · Francesco Patti[1]

Time to first relapse between the two groups



Time to first DMT discontinuation between the two groups

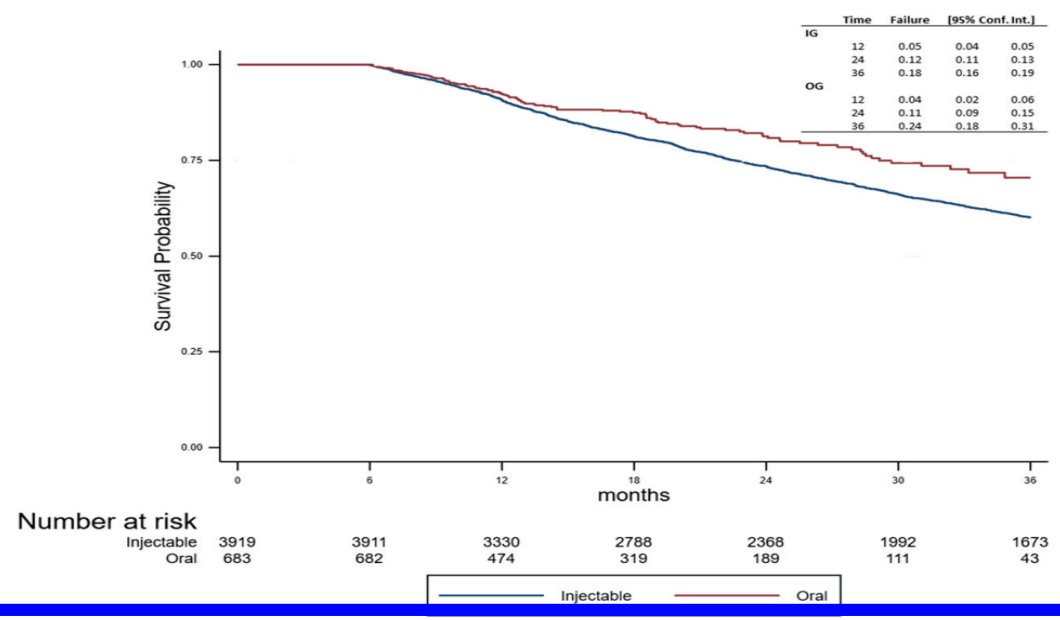
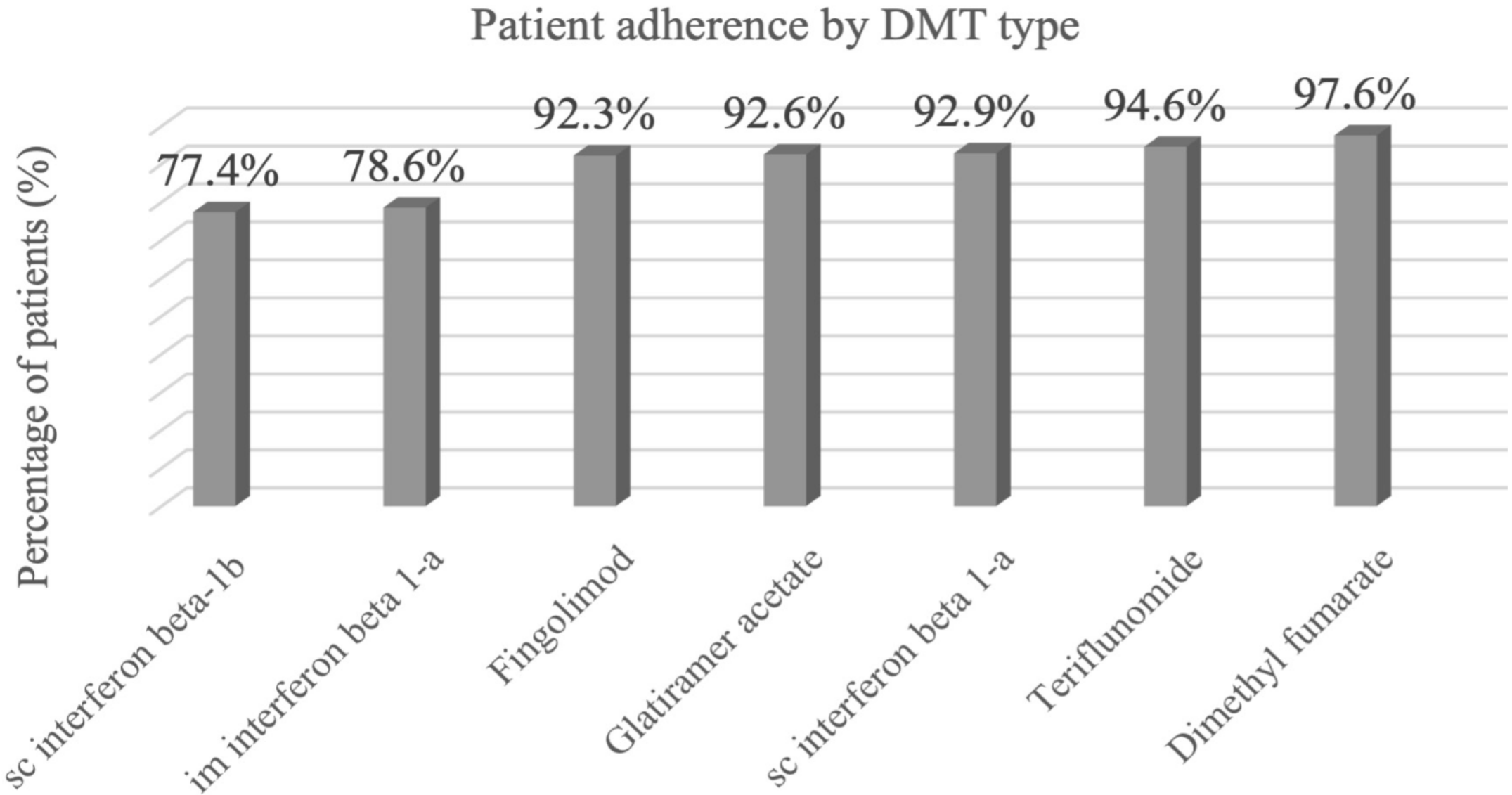


Figure 2. Percentage of adherent patients by type of disease-modifying therapies.



MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: Results from MSBase

Multiple Sclerosis Journal
2023, Vol. 29(2) 221–235
DOI: 10.1177/
13524585221137502

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Table 1

Mechanism of Actions of Oral DMTs

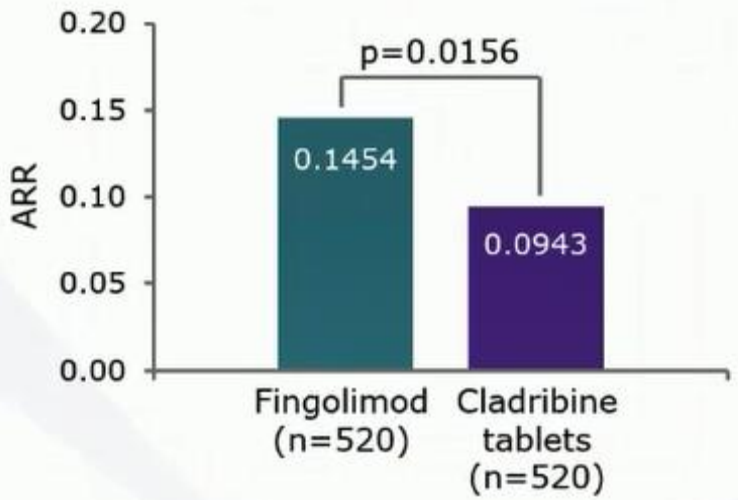
Agent	Mechanism
DNA dimethyl fumarate	Activates erythroid-derived nuclear factor 2–like transcription
Teriflunomide	Inhibits dihydroorotate dehydrogenase
Cladribine	In triphosphate form, inhibits synthesis and repair of DNA
Fingolimod and siponimod	S1P receptor modulators

DMTs: disease-modifying therapies; S1P: sphingosine-1-phosphate.
Source: Reference 4.

ARR compared between oral DMTs

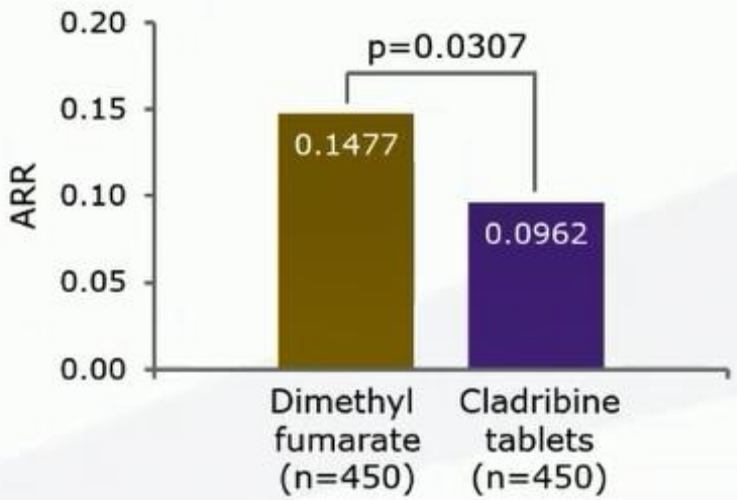
Cladribine tablets vs **fingolimod**

35%
reduction in ARR



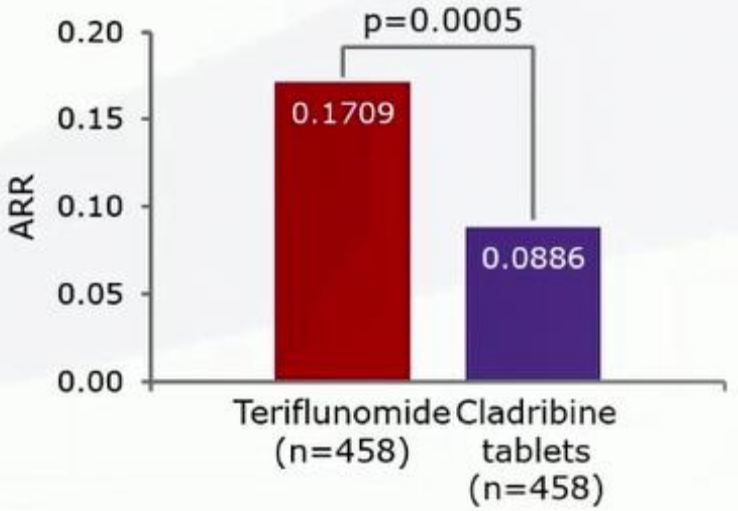
Cladribine tablets vs **dimethyl fumarate**

35%
reduction in ARR



Cladribine tablets vs **teriflunomide**

48%
reduction in ARR



GLIMPSE is an observational real-world study, and several unmeasured confounders could influence the outcomes. Propensity-score matching was applied, which may have reduced selection bias and potential confounding to a certain level. The drop in numbers of evaluated patients over the observation period is a limitation to be considered; no reason for the drop in patient numbers was provided in the reference. Additionally, no safety information from the GLIMPSE study is available

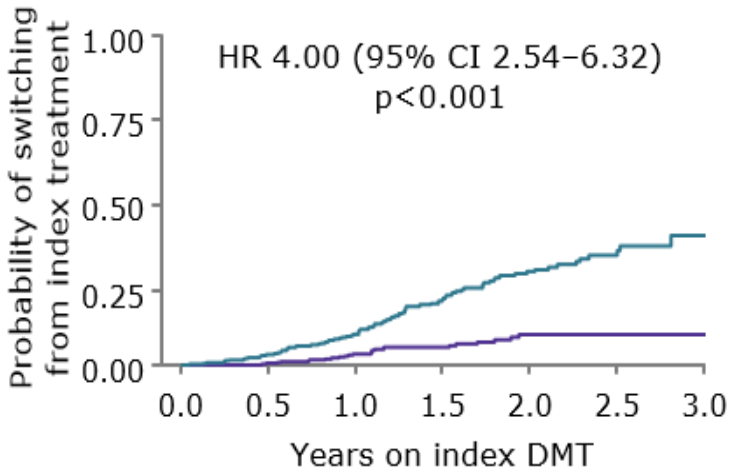
[a]Median follow-up of 11–13 months

ARR, annualized relapse rate; DMT, disease-modifying therapy

Spelman T et al. Mult Scler 2023;29:221–35

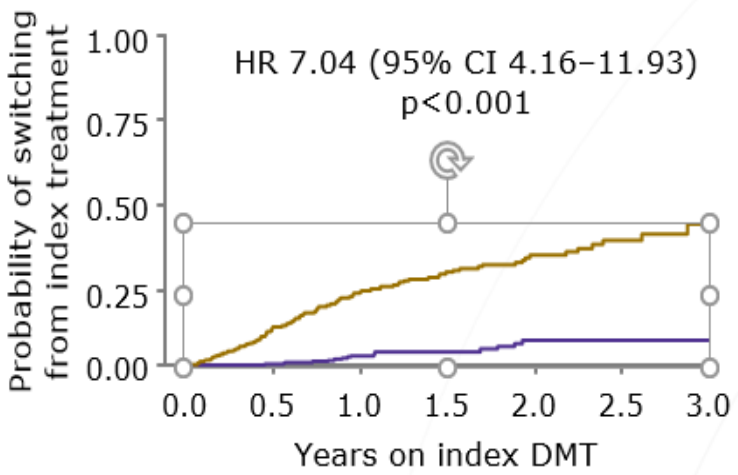
Time to treatment switch compared between oral DMTs

Cladribine tablets vs fingolimod



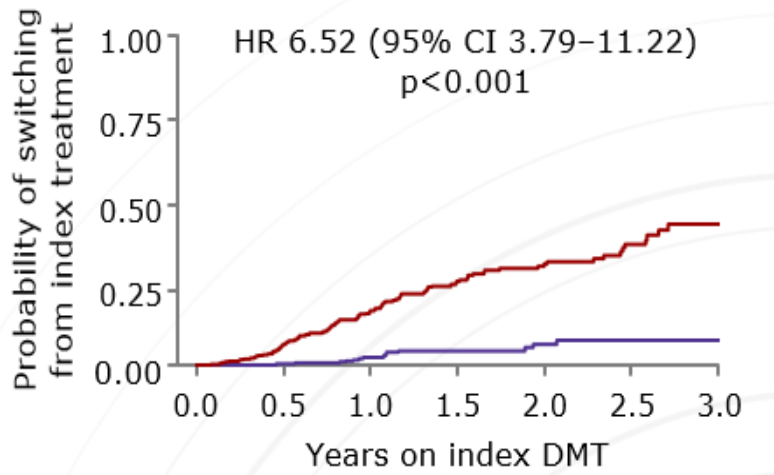
No. at risk							
Cladribine tablets	520	402	297	190	106	42	7
Fingolimod	520	392	300	195	111	47	11

Cladribine tablets vs dimethyl fumarate



No. at risk							
Cladribine tablets	450	346	249	162	81	35	8
DMF	450	311	208	135	92	42	12

Cladribine tablets vs teriflunomide



No. at risk							
Cladribine tablets	458	352	257	166	91	35	7
Teriflunomide	458	361	255	172	105	59	22

GLIMPSE is an observational real-world study, and several unmeasured confounders could influence the outcomes. Propensity-score matching was applied, which may have reduced selection bias and potential confounding to a certain level. The drop in numbers of evaluated patients over the observation period is a limitation to be considered; no reason for the drop in patient numbers was provided in the reference. Additionally, no safety information from the GLIMPSE study is available. Time-to- event analysis used marginal Cox models with HRs and 95% CIs. The entire follow-up period rather than a specific time point was assessed. Attrition in the number of patients over the observation period is reflected in the width of the confidence intervals

[a]Median follow-up of 11–13 months

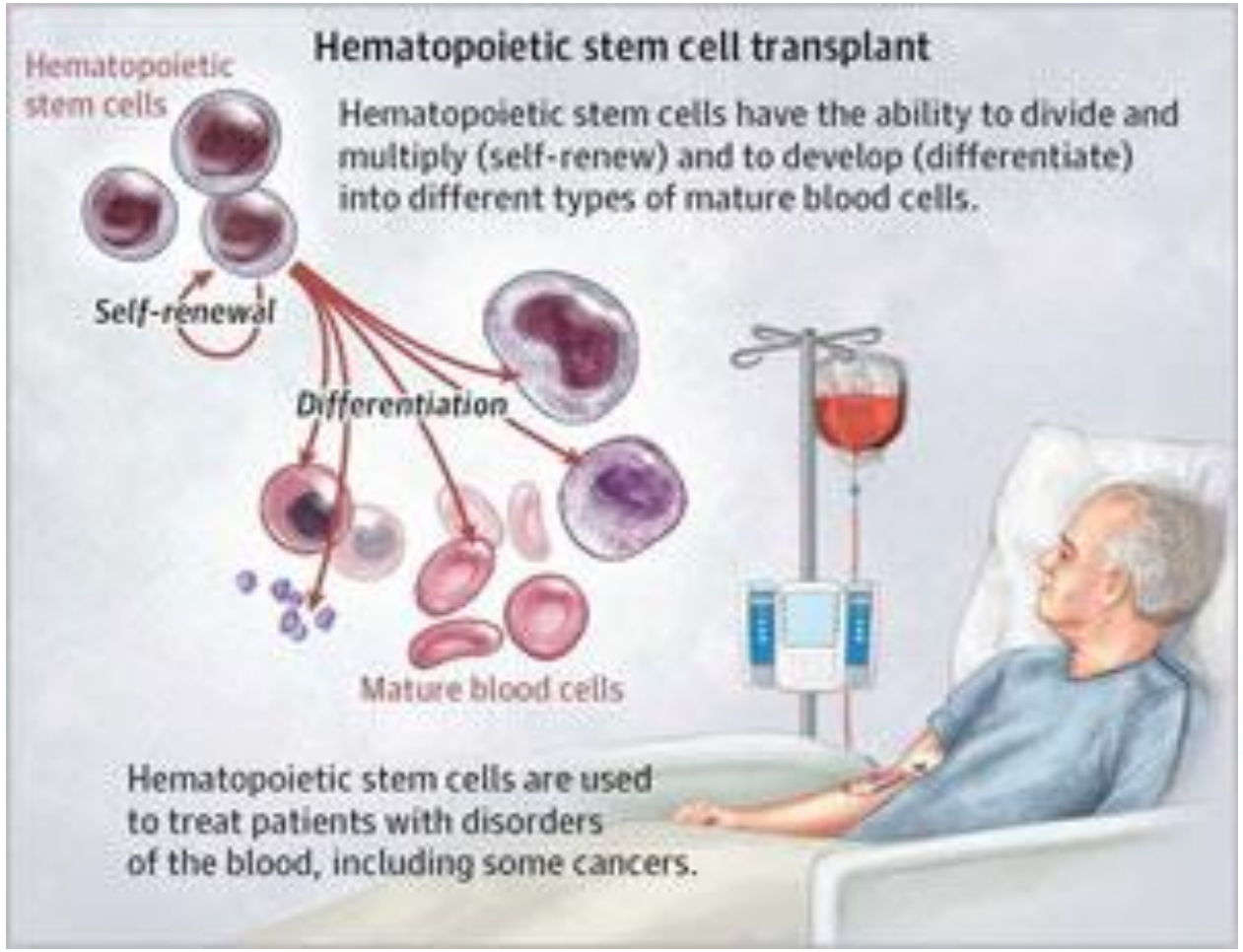
CI, confidence interval; DMF, dimethyl fumarate; DMT, disease-modifying therapy; HR, hazard ratio

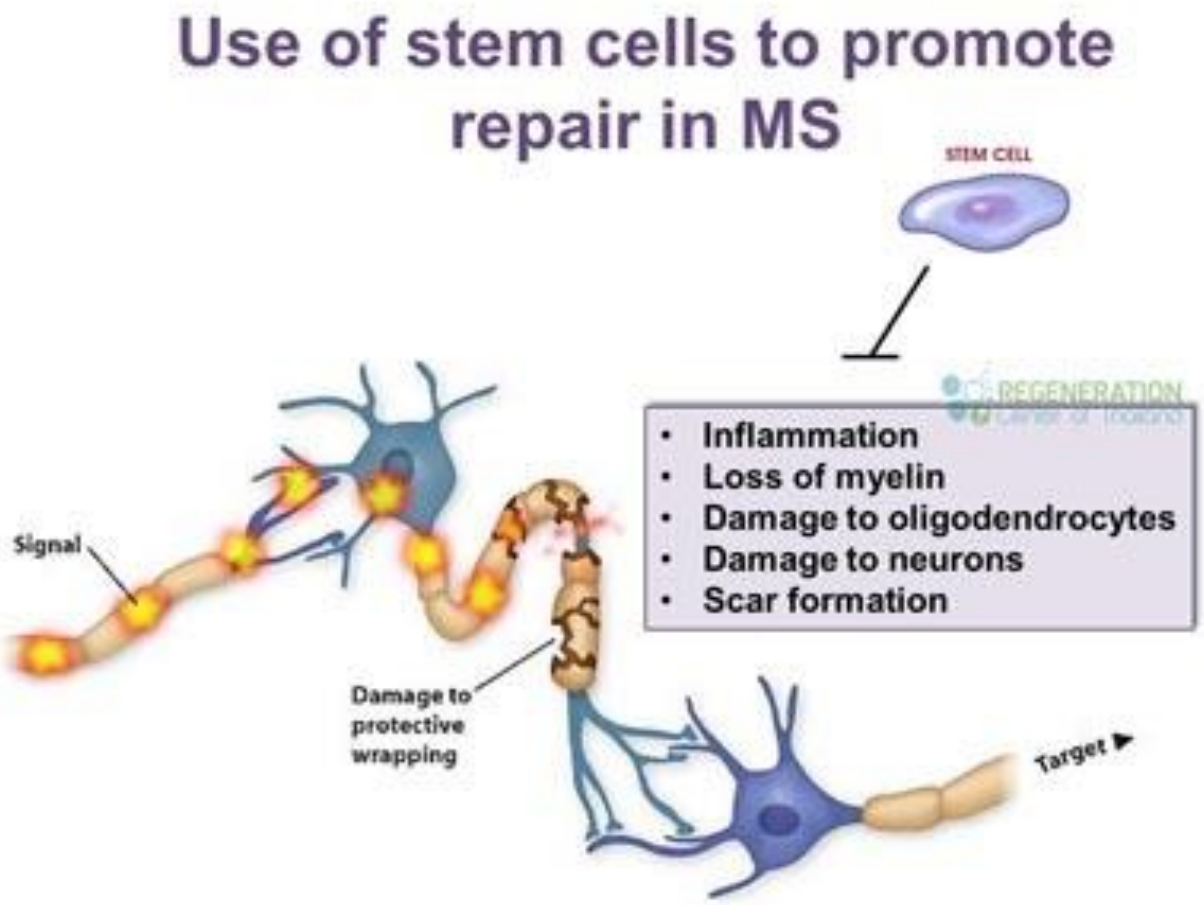
Spelman T et al. Mult Scler 2023;29:221–35

Research and Treatment

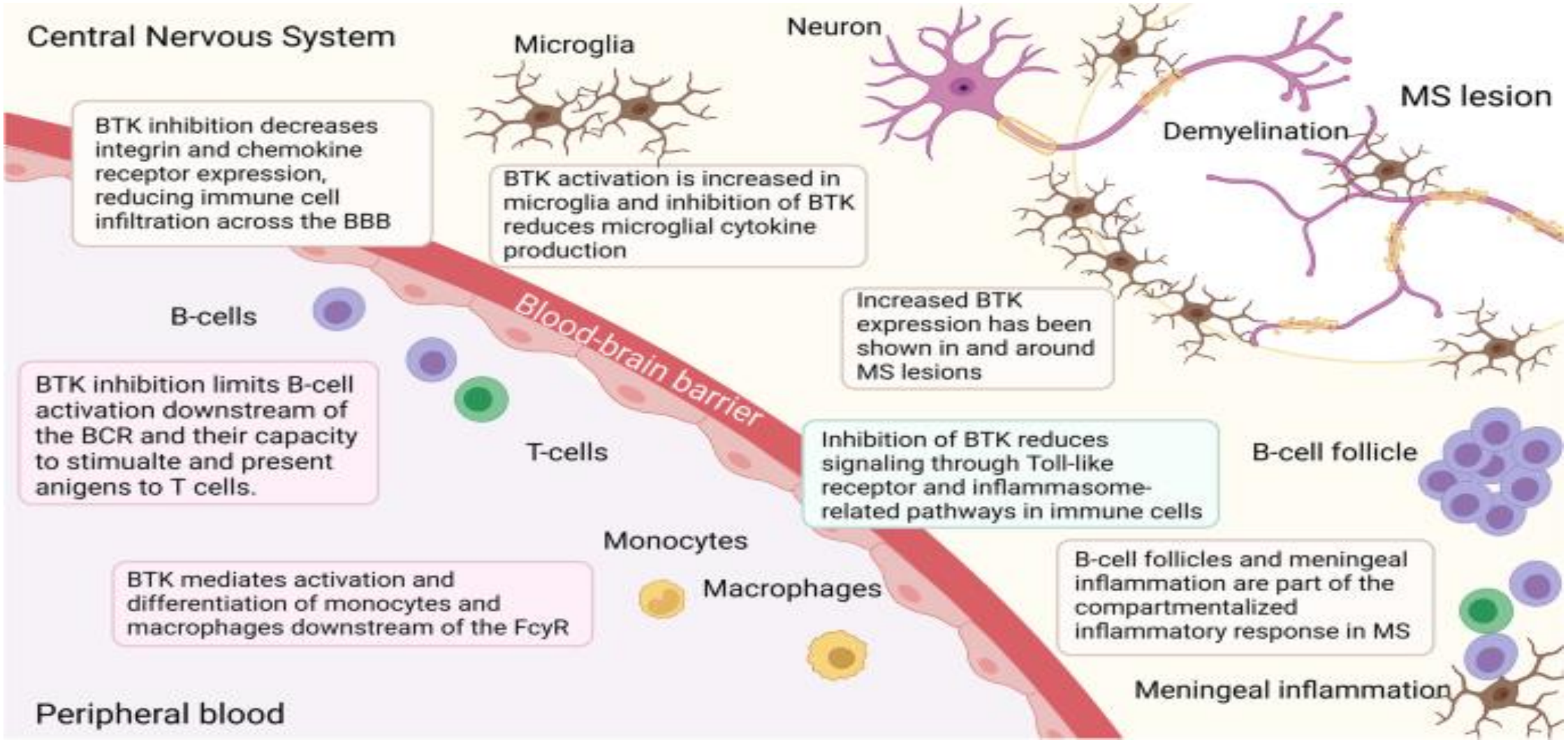
Undergoing Investigation for MS

Hematopoietic stem cell transplant

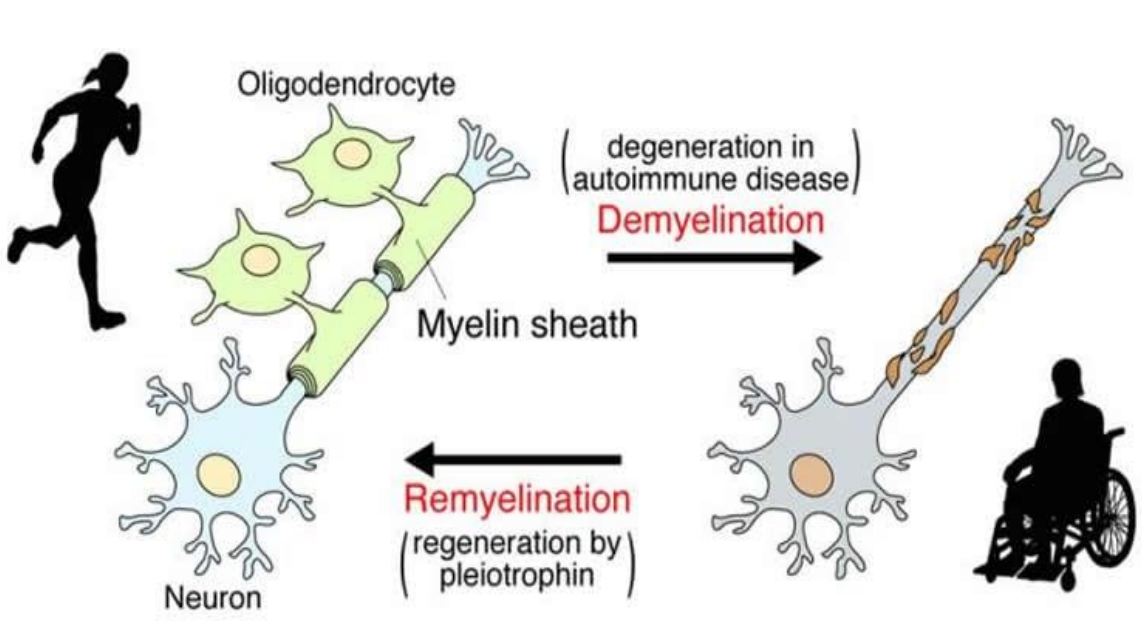


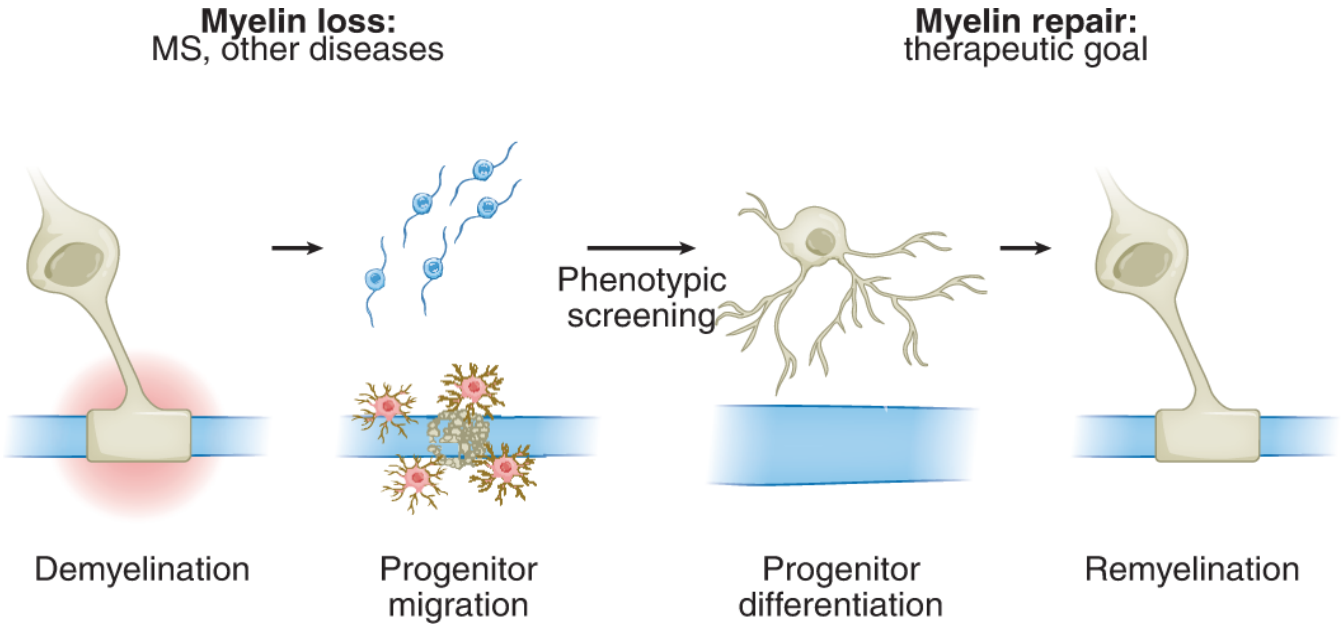


Bruton's tyrosine kinase inhibitors

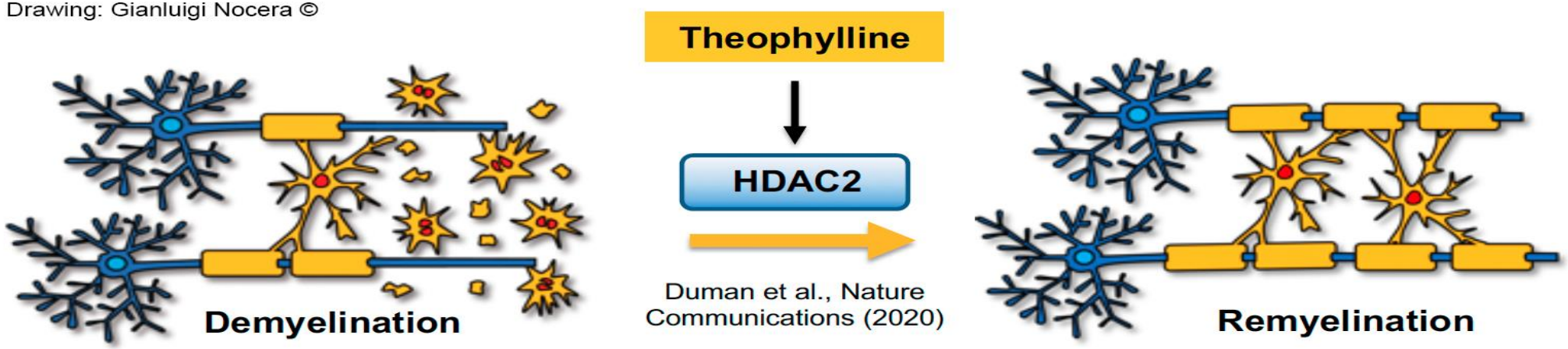


Remyelination





Drawing: Gianluigi Nocera ©



cells

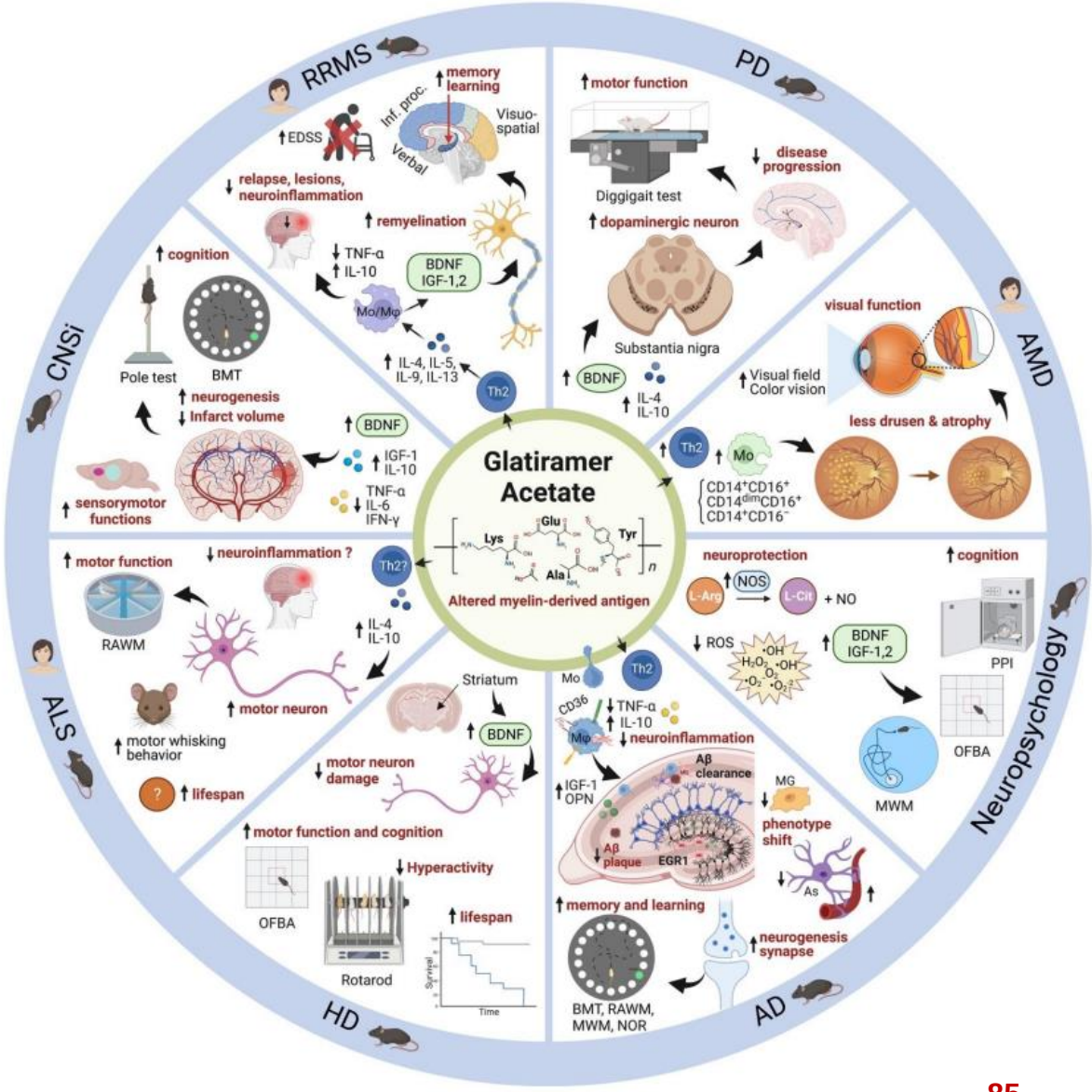
MDPI

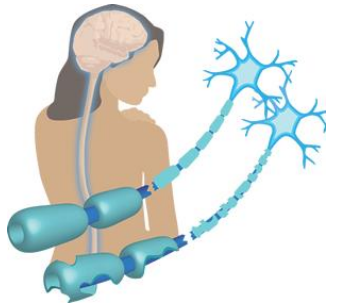
Review

Glatiramer Acetate Immunomodulation: Evidence of Neuroprotection and Cognitive Preservation

Arielle Kasindi [1], Dieu-Trang Fuchs [1], Yosef Koronyo [1], Altan Rentsendorj [1], Keith L. Black [1] and Maya Koronyo-Hamaoui [1,2,*]

- In this systematic review, we examine the potential novel uses of GA across clinical and pre-clinical studies, with evidence for its beneficial impact on cognition
- Future investigation in large-size, double-blind clinical trials is warranted to establish the impact of GA immunomodulation on neuroprotection and cognitive preservation in various neurological conditions





- 近三十年來，多發性硬化症的治療選擇以及提高療效抗復發的新藥物增加
- 仍然存在缺乏針對進展性疾病的有效治療方法
- 新的 DMT 在降低復發率方面具有更高的功效MRI疾病活動性，也可能帶有較高的副作用由於免疫抑製程度增加而導致的情況
- 新的治療方法包括利用免疫保護機制，例如支持調節性 T 細胞功能和修復性小膠質細胞功能
- 需要進一步研究來確定早期危險因子發炎狀態增加、早期神經退化或兩者的結合
- 早期治療幹預神經發炎和神經退化方面串聯使用該疾病的研究可能是進一步研究的關鍵治療進展和真正緩解的最終目標這種病

感謝聆聽 敬請指教