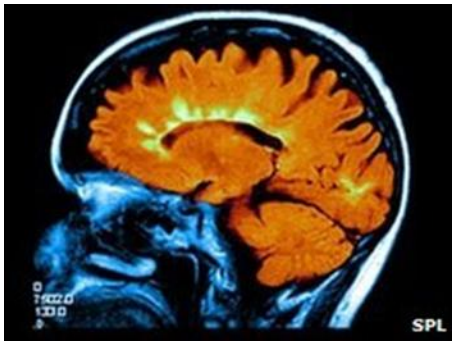
ACCELERATING THE PACE OF CHANGE

WCN 2019
XXIV WORLD CONGRESS OF NEUROLOGY
DUBAI, UNITED ARAB EMIRATES, OCTOBER 27-31 2019

Identifying Prognostic Factors



Ron Milo, M.D.
Department of Neurology
Barzilai Medical Center, Ashkelon
Ben-Gurion University of the Negev
ISRAEL
ronm@bmc.gov.il

Barzilai
University Medical Center
People First

Disclosures

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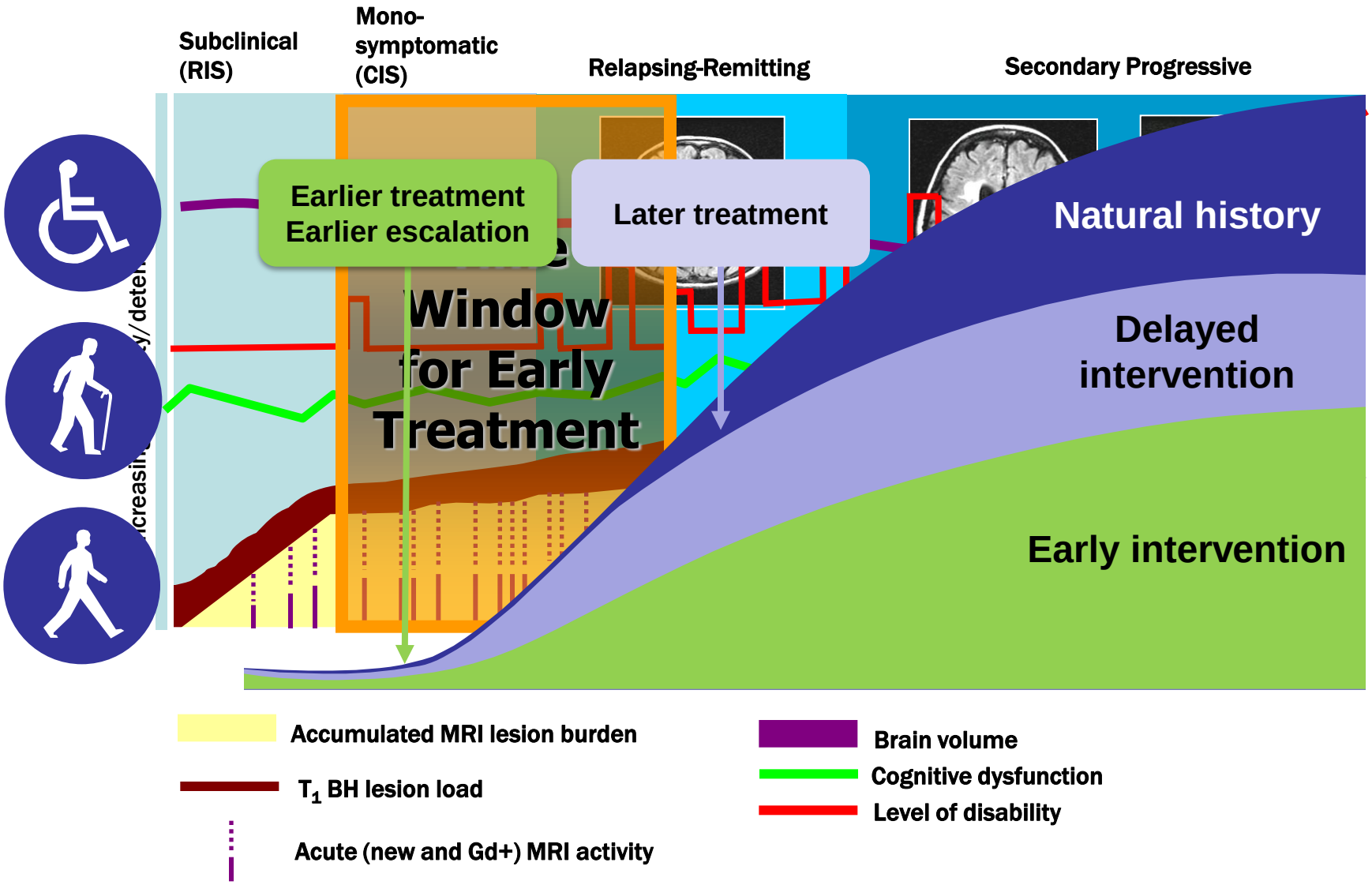
- Research grants: Bayer Healthcare, Medison, Merck-Serono, Novartis and Teva

Learning objectives

- Recognize risk factors for MS
- Identify prognostic factors for poor prognosis early in the course of MS
- Consider prognostic factors in the treatment decision-making process

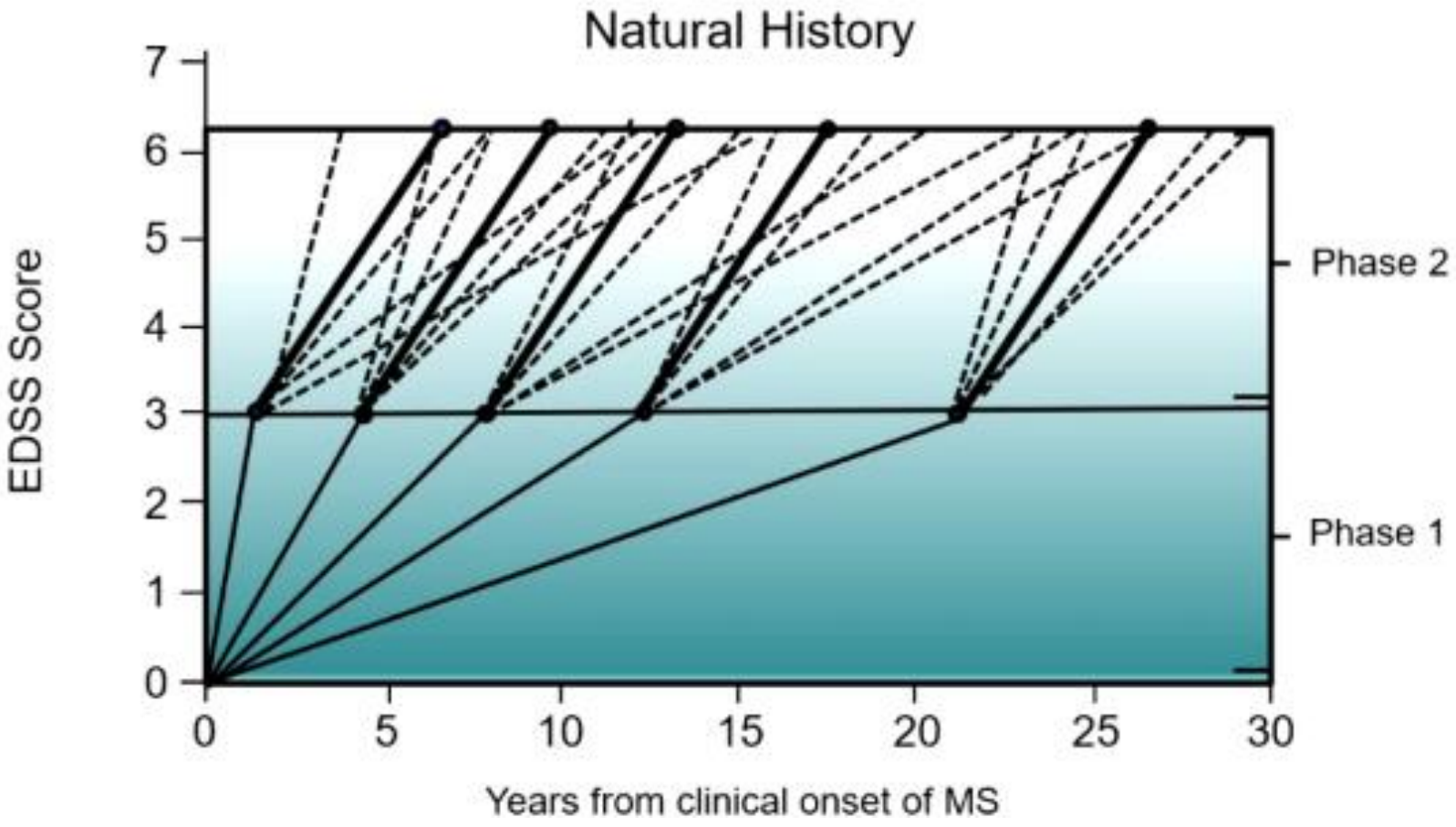
Natural History of MS



BH = black hole; Gd = gadolinium; MRI = magnetic resonance imaging.

Noseworthy et al. *N Engl J Med.* 2000;343:938; Weinshenker et al. *Brain.* 1989;112:133; Trapp et al. *Curr Opin Neurol.* 1999;12:295.

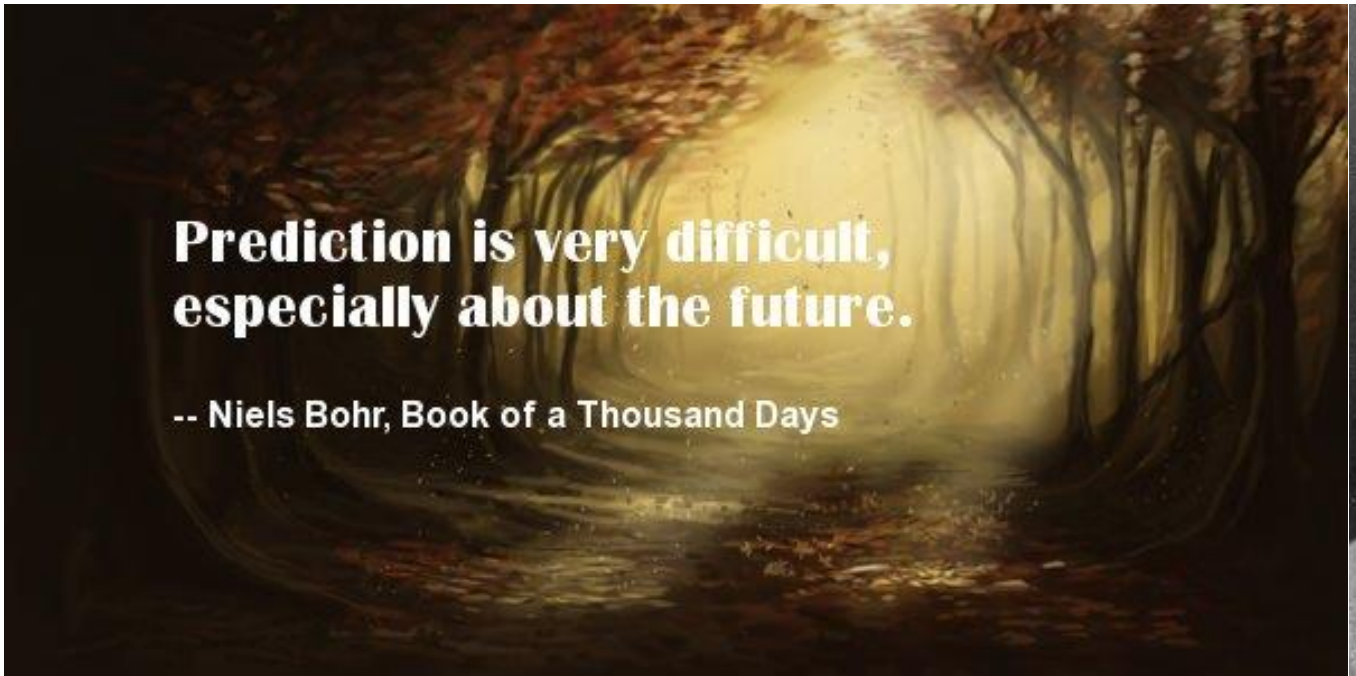
MS takes a highly variable course

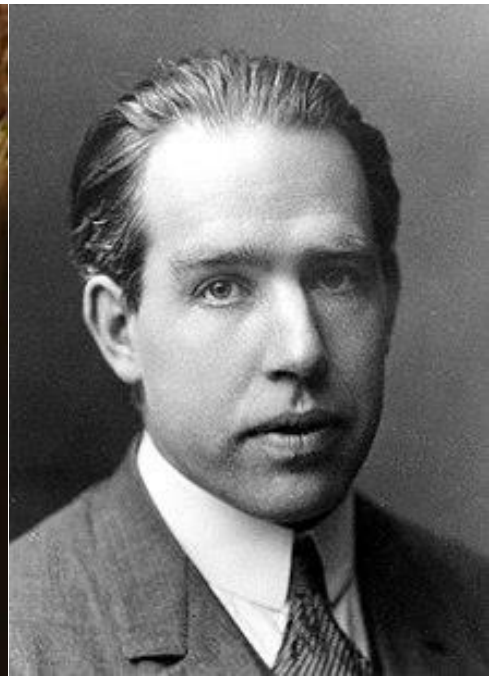


MS takes a highly variable course

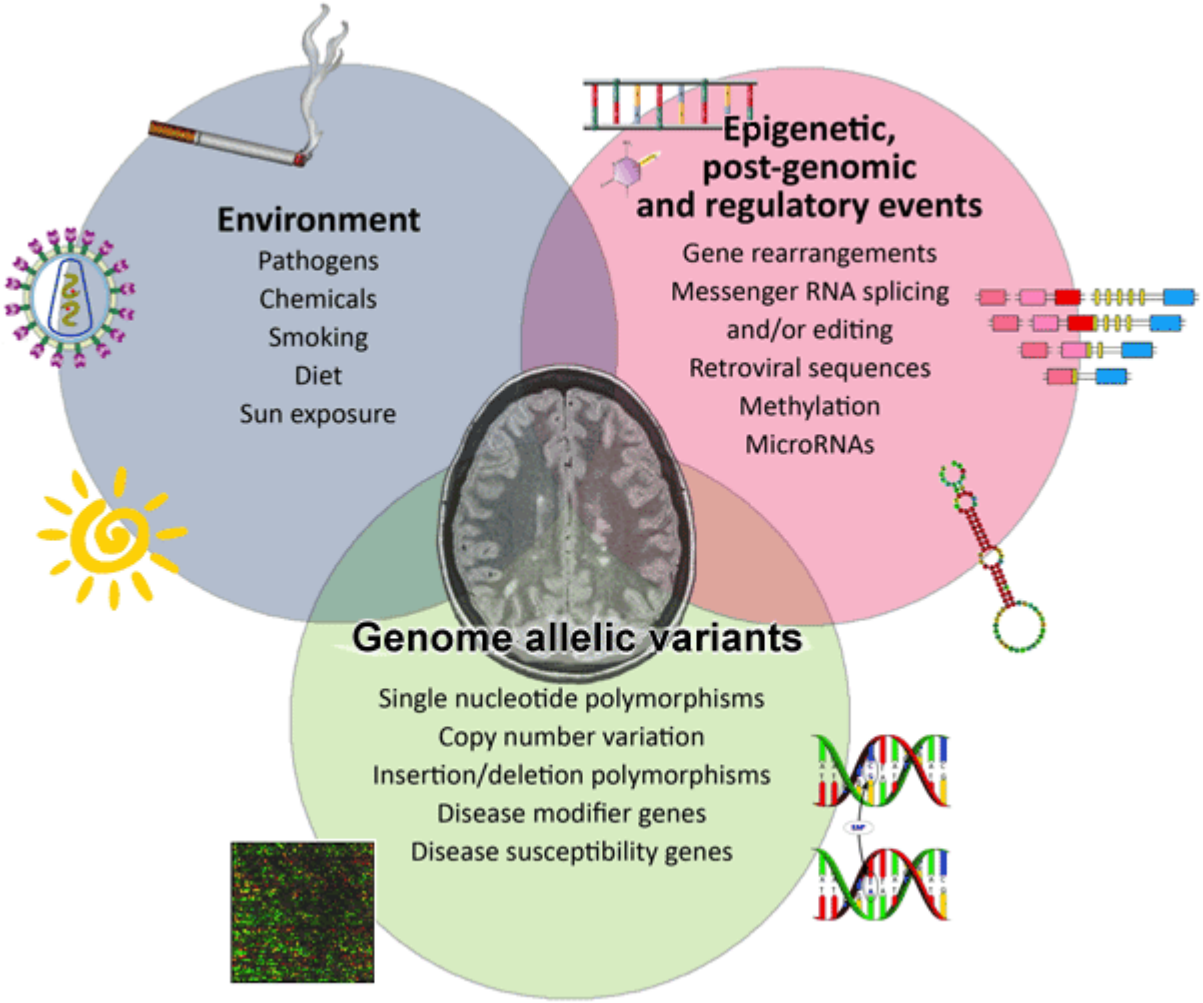
Important to consider:

- **Risk factors** that put individuals at increased risk of developing the disease
- **Prognostic factors** that may predict a patient's disease course (disease progression and disability)





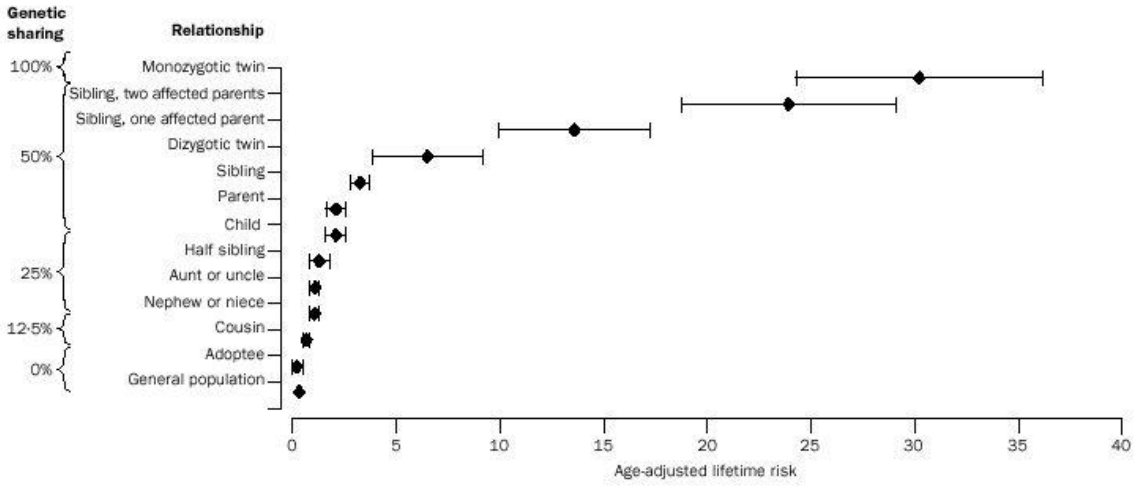
MS is a complex disease

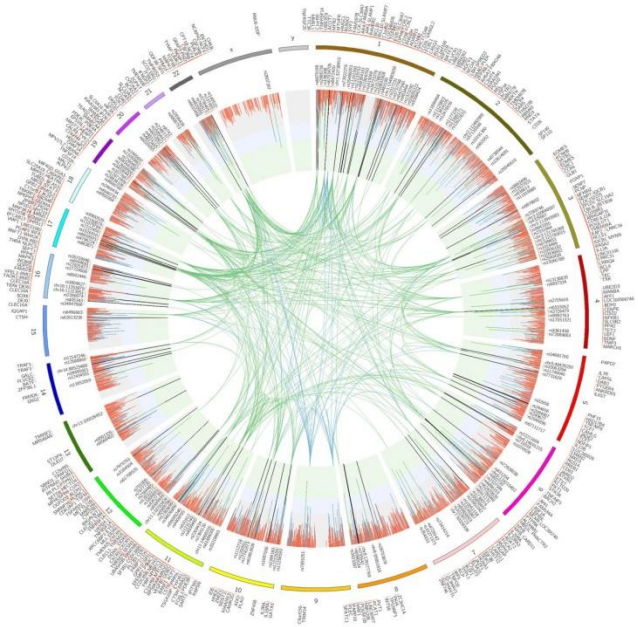


Adapted from: Oksenberg, J. R. & Baranzini, S. E. (2010) Multiple sclerosis genetics—is the glass half full, or half empty? *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2010.91

Genetic risk factors

- worldwide prevalence of familial MS is 12.6%[1]
- Strongest genetic susceptibility factors- HLA DR*2 (in Caucasians)[2] (other HLA loci in Mediterraneans)
- Additional >233 susceptibility alleles, mostly in immune system related loci[3,4]

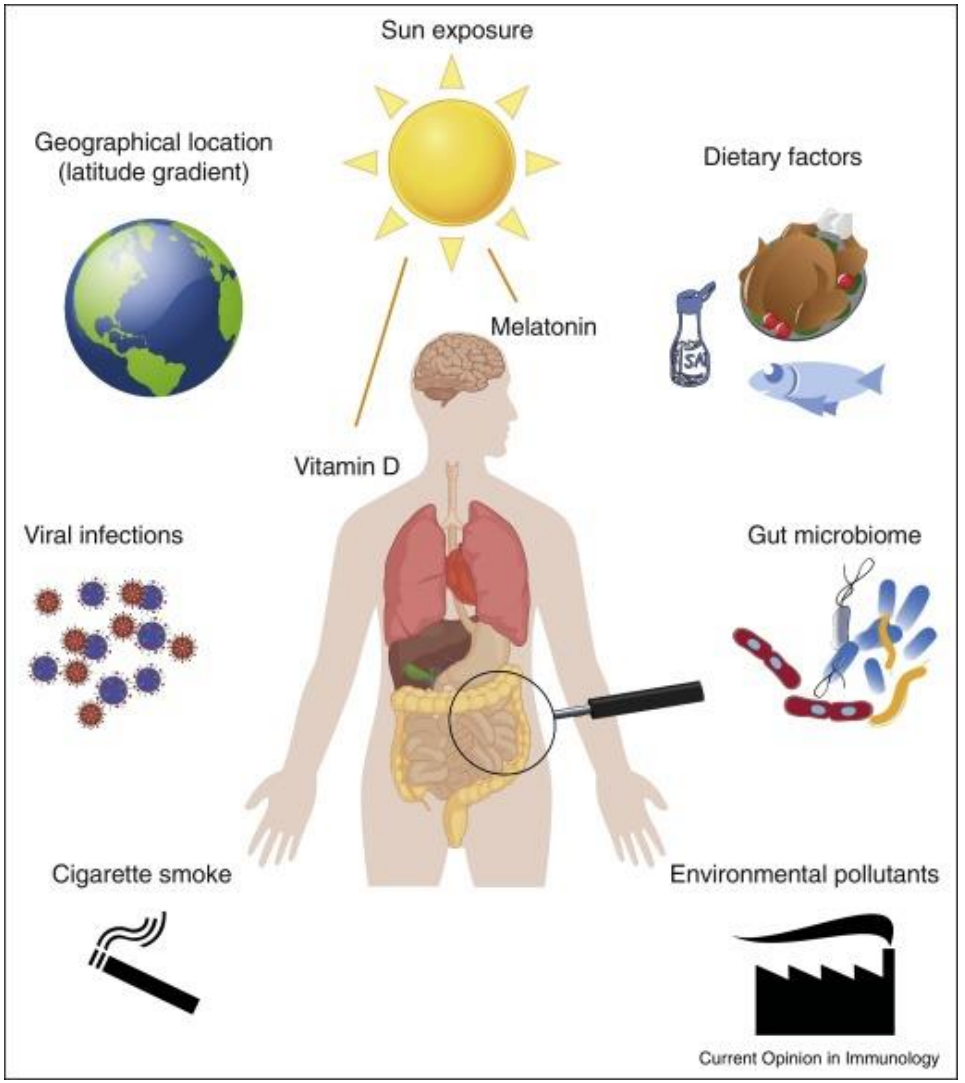




IMSGC, Science 2019;365:eaav7188

Environmental risk factors for MS[5-7]

- EBV infection
- CMV infection
- Low vit. D
- Smoking
- Obesity
- Latitide/UV radiation
- Diet (NaCl, alcohol, coffee…)
- Gut microbiome
- Chemicals/pollutants
- Shift work



Rothhammer & Quintana. Curr Opin Immunol 2016;43:46–53

Most factors seem to have the greatest effect during adolescence

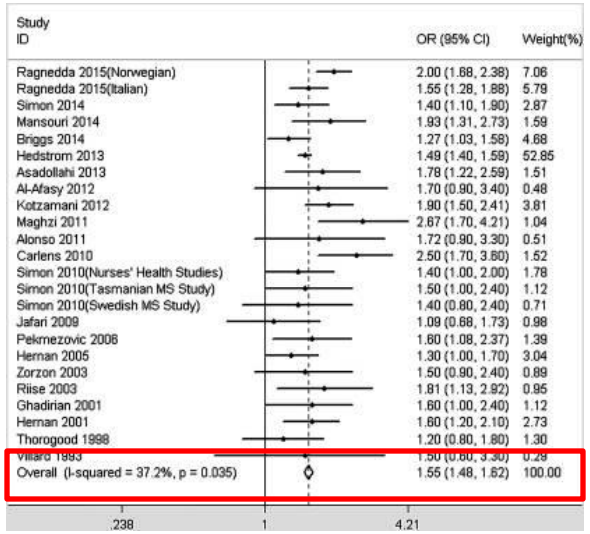
Prognostic factors

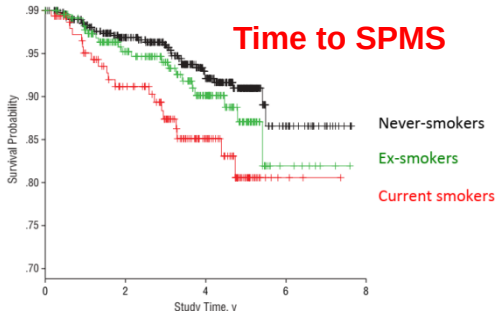
Epidemiologic factors

- **Age**
  - Older age at onset is associated with a more rapid progression[8]
  - Mean time to an EDSS score of 6 decreases as age of onset increases[9]
- **Sex/Sex hormones** (controversial)
  - Male sex might predict worse outcomes in RRMS and SPMS[8]
  - Multiple pregnancies may be protective[10]
  - Oral contraceptives → a milder course in RMS[11]
  - Total free testosterone/Estradiol ratio[12]

Lifestyle factors

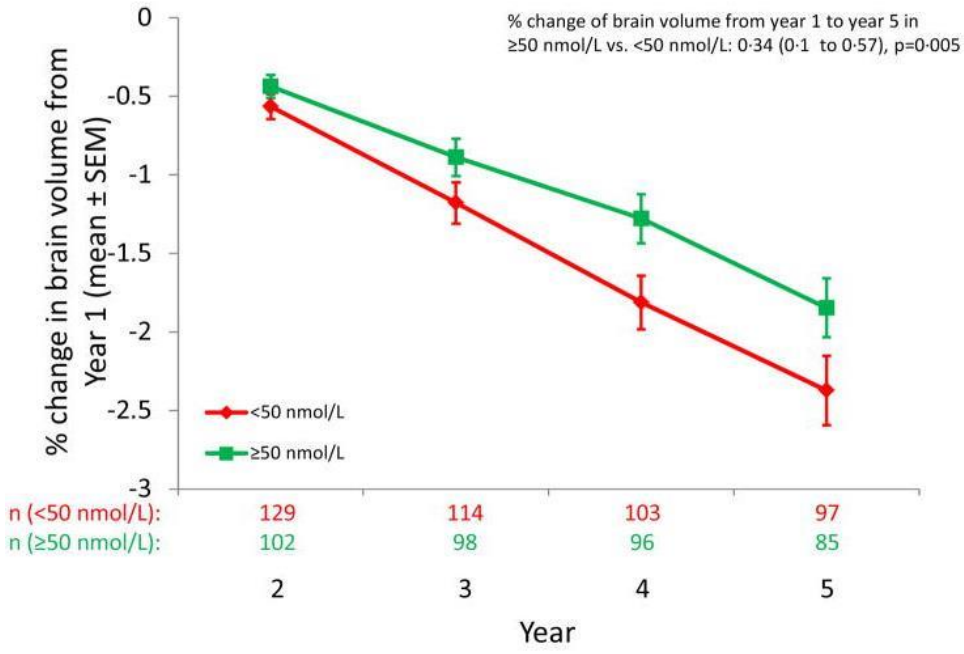
- **Smoking**
  - Heavy smokers have higher chance of developing MS than never smokers[13]
  - Smoking RRMS patients progress faster to SPMS (HR=2.5) than non-smokers[14]
  - Smoking is associated with increased MRI Gd+ number (*P*=0.002) and volume (*P*=0.014)[14]
  - Ex-smokers have slower disease progression than current smokers[15]
- **Other habits**
  - Consumption of alcoholic beverages, coffee, and/or fish is associated with a milder disease course in RMS[16]



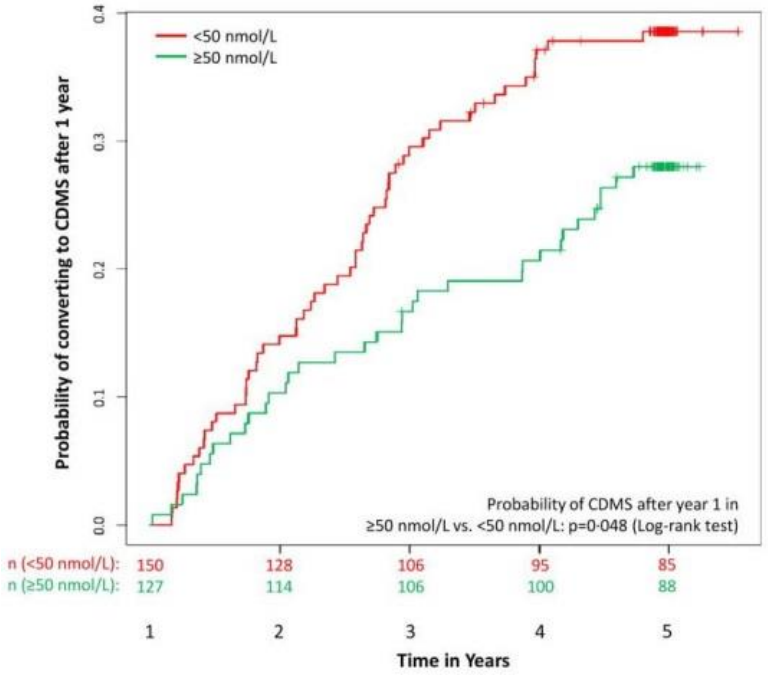


Low vit. D is a risk factor as well as a prognostic factor in MS

% change of brain volume



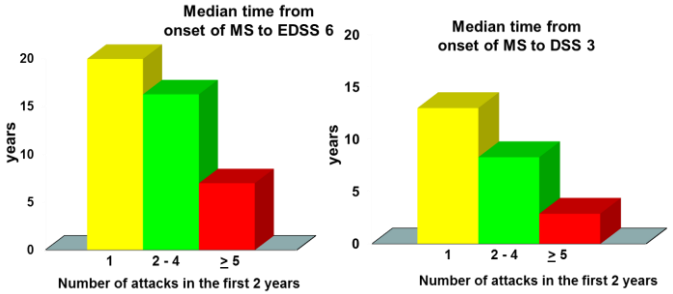
Risk of CDMS after CIS



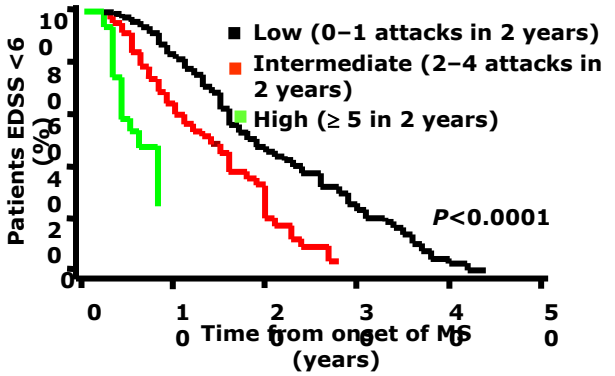
Ascherio A et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA Neurol. 2014;71:306-14

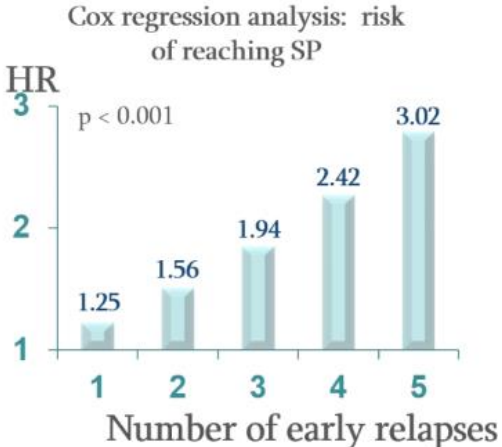
Characteristics of initial attacks

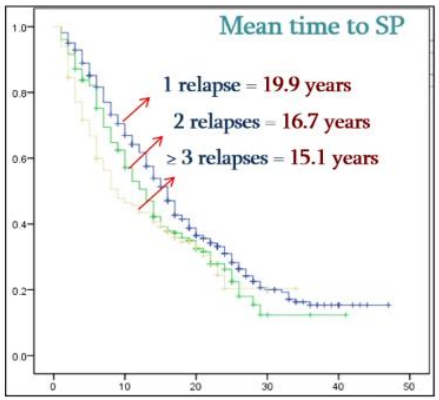
- Type (motor, sphincter or cognitive), location (cerebellum, brainstem, SC) and number of systems involved[8,9,17-19]
- Incomplete recovery[9,18-21]
- Shorter interval between the first and second attack[8,17,18,20,22]
- Frequent attacks years 2-5[8,17,18,22,23]
- Poly-symptomatic (multifocal) relapses[17,21]
- Early vs. late attacks[24]



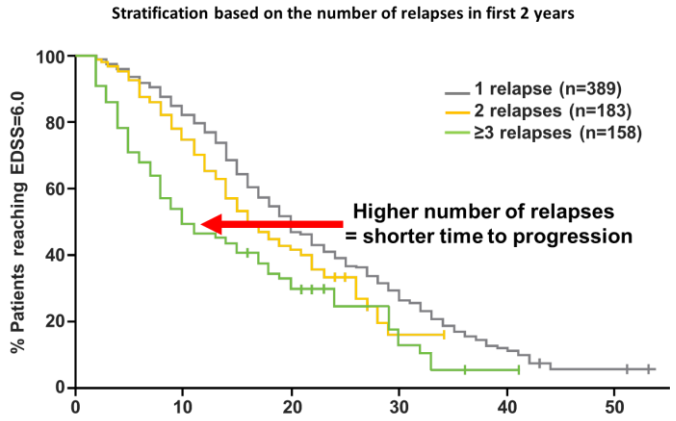
Weinshenker BG, *et al., Brain* 1989







Scalfari et al. 2010



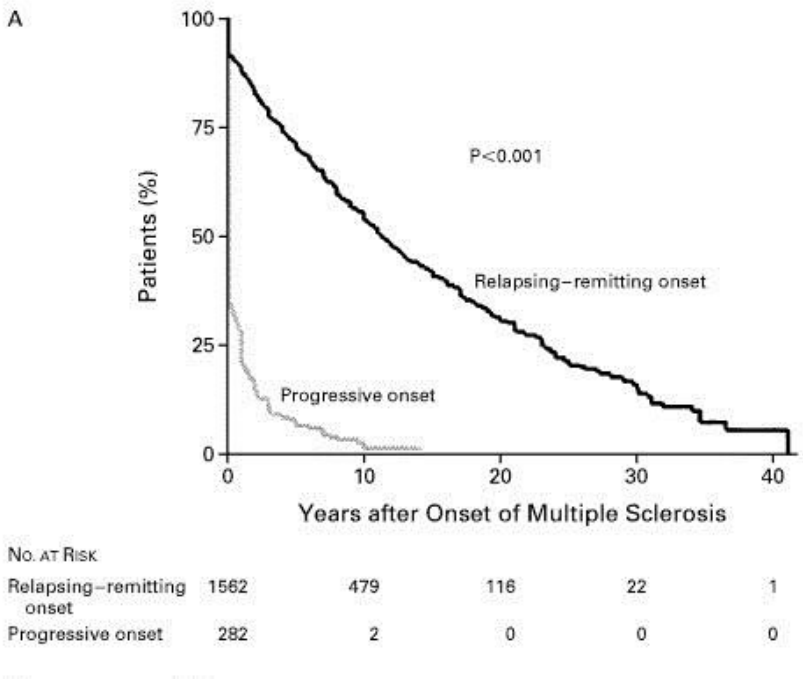
Other clinical predictors

- Early accumulation of disability[8,17,19]
- PPMS course[17,18,25]
- Early secondary progression[26]
- Chronic depression[26]
- Cognitive impairment[26]
- NEDA status[43]
- Vascular risk factors
- Comorbidities
- No previous treatment

Disease course

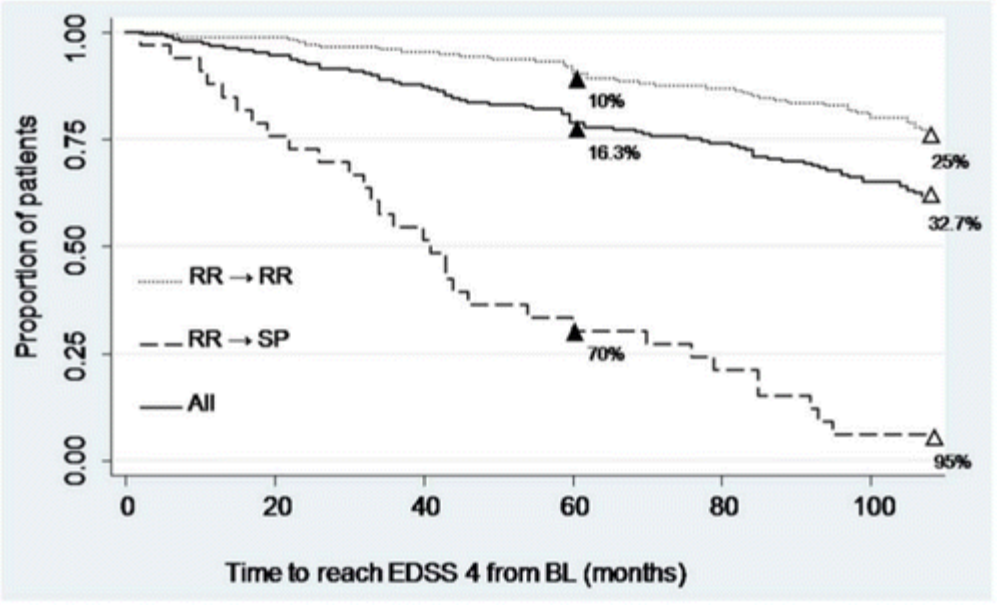
PPMS Course

Time from the Onset of MS to EDSS=4



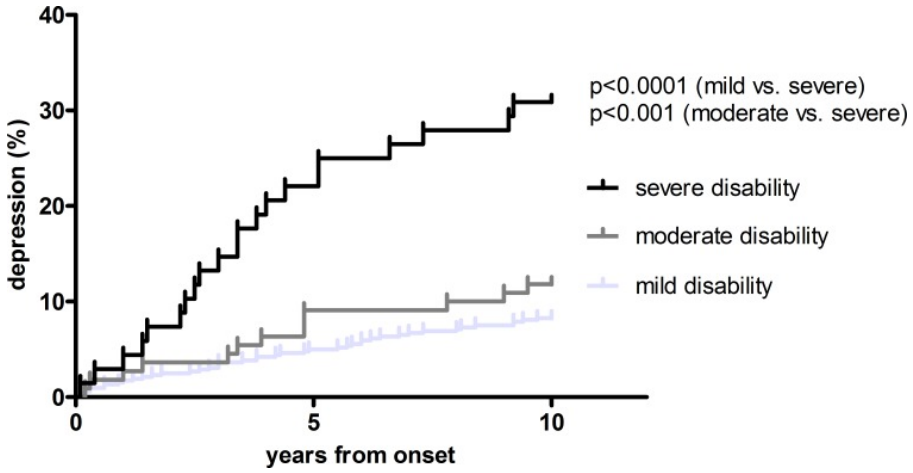
25. Confavreaux C, et al. Relapses and progression of disability in multiple sclerosis. *N Engl J Med*. 2000;343:1430-1438

Early conversion to SPMS

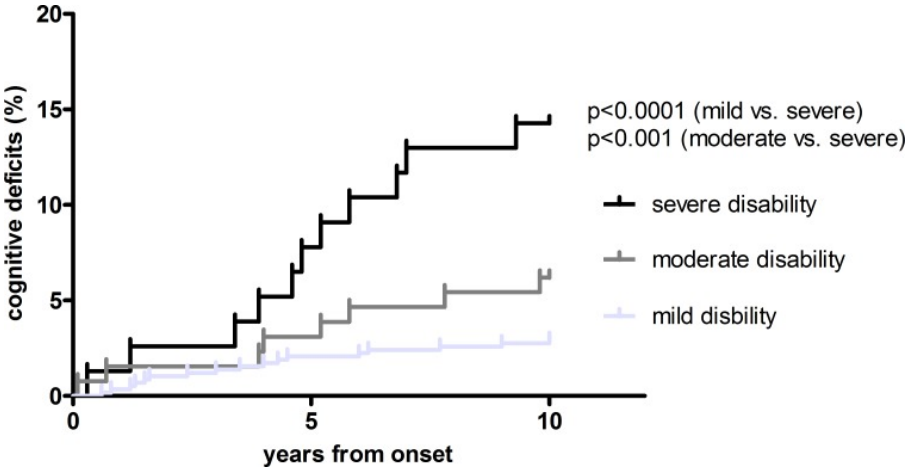


30. Clinical and magnetic resonance imaging predictors of disease progression in multiple sclerosis: a nine-year follow-up study. *Mult Scler*. 2014;20:220-226.

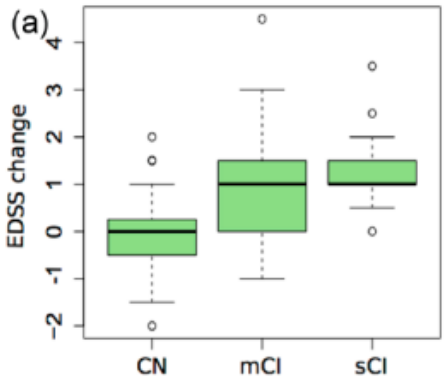
Depression



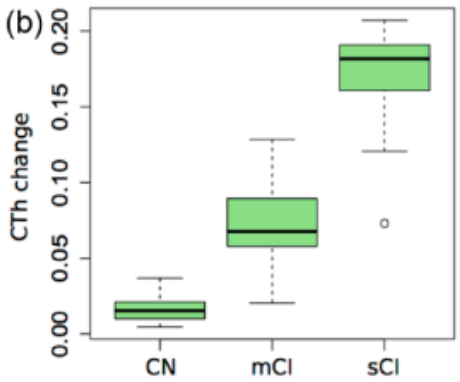
Cognitive impairment



EDSS



Cortical thinning

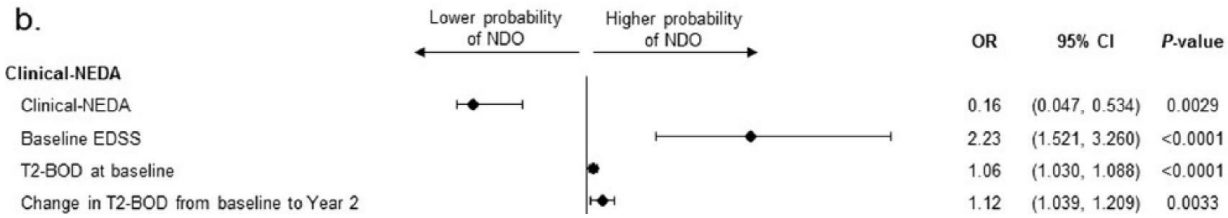


26. Bsteh G, et al. Long term clinical prognostic factors in relapsing-remitting multiple sclerosis. *PLoS One*. 2016;11:e0158978.

Pitteri M et al. Cognitive impairment predicts disability progression and cortical thinning in MS. MSJ 2017;23:848-54

NEDA Status

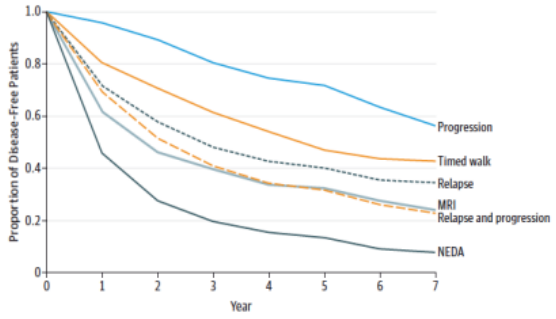
Multifactorial predictors of NDOs 16 years after randomization to the pivotal IFN beta-1b clinical trial in RRMS



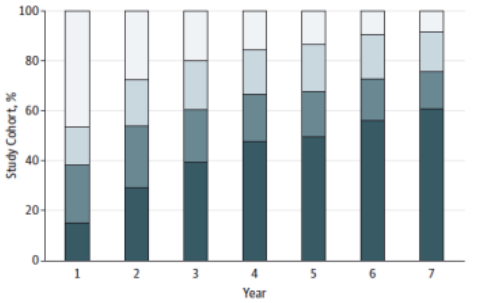
BOD: burden of disease; EDSS: Expanded Disability Status Scale; NDO: negative disability outcome; NEDA: no evidence of disease activity

43. Goodin DS, et al. Predictive validity of NEDA in the 16- and 21-year follow-up from the pivotal trial of interferon beta-1b. Mult Scler. 2019;25:837-847

Figure 1. No Evidence of Disease Activity (NEDA) During 7 Years in the Overall Cohort



NEDA is difficult to sustain long-term even with treatment (only **17 of 216, ≈8%**) maintained NEDA status after 7 years.



RESULTS A total of 99 of 215 patients (46.0%) had NEDA for clinical and MRI measures at 1 year, but only 17 of 216 (7.9%) maintained NEDA status after 7 years. No differences were found in NEDA status between patients with early vs established MS. A dissociation was found between clinical and MRI disease activity. Each year, 30.6% (64 of 209) to 42.9% (93 of 217) of the cohort had evidence of either clinical or MRI disease activity but not both. NEDA at 2 years had a positive predictive value of 78.3% for no progression (Expanded Disability Status Scale score change ≤0.5) at 7 years. Only minor improvement was found in the positive predictive values with additional follow-up of 1 to 3 years.

Rotstein et al JAMA Neurol 2015

fatigue

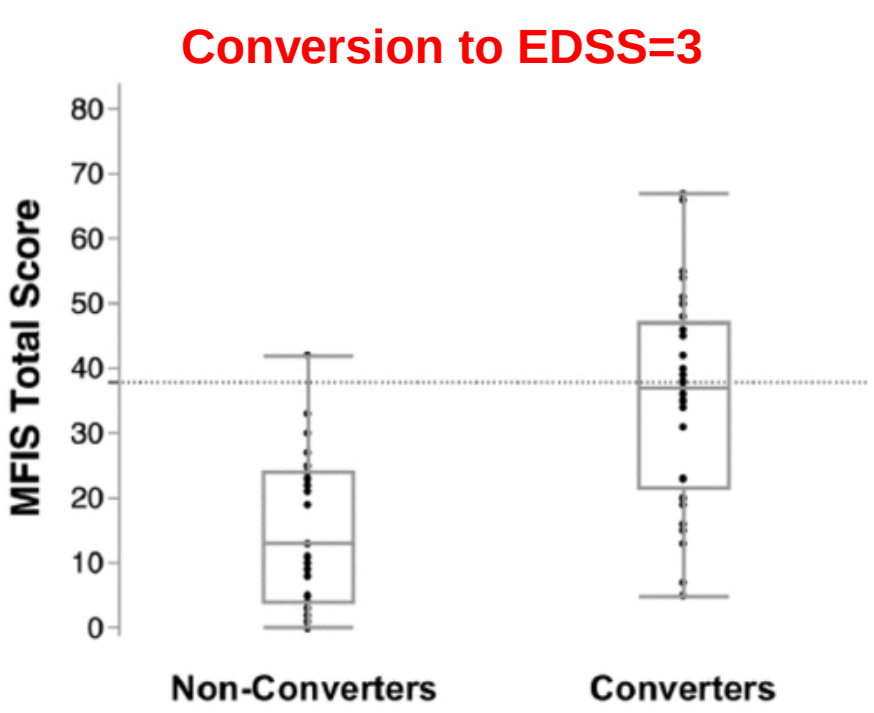


Table 2. Multivariate logistic regression analysis of the association between fatigue and conversion to sustained EDSS ⩾3 (converters = 1, non-converters = 0).

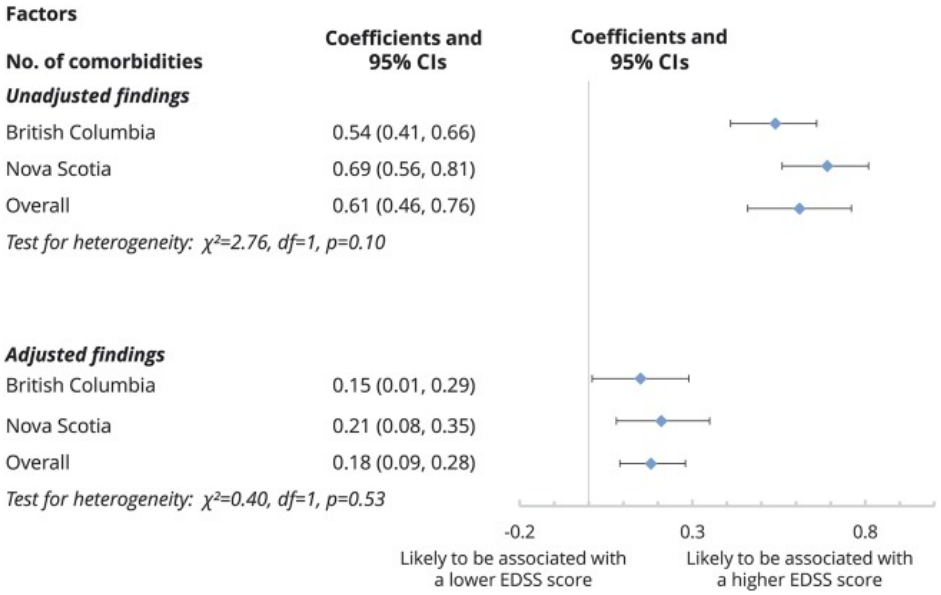
Predictor	Standardized regression coefficient	95% CI	*p*-Value
MFIS	4.34	1.42–16.93	0.009
EDSS	3.58	1.67–9.40	0.001
CES-D	1.43	0.40–5.39	0.568

CI: confidence interval; MFIS: Modified Fatigue Impact Scale; EDSS: Expanded Disability Status Scale; CES-D: Center for Epidemiological Studies Depression scale; SD: standard deviation.
In order to compare the effect of predictors measured by different scales on the conversion to sustained EDSS ⩾3, the coefficient referring to MFIS, EDSS, and CES-D is expressed as standardized regression coefficient, that is, odds ratio per SD increase in the predictor (SD of total MFIS, EDSS, and CES-D scores across all subjects: 17.3, 0.8, and 6.9, respectively).

Canallari M et al. Fatigue predicts disease worsening in relapsing-remitting multiple sclerosis patients. MSJ 2016;22(14):1841-9

Comorbidities

Physical



Zhang T et al. Effects of physical comorbidities on disability progression in multiple sclerosis Neurology 2018;30;90(5):e419-e427

Psychiatric

Table 3 Association between depression, anxiety, and bipolar disorder and neurologic disability, as measured by the Expanded Disability Status Scale in the multiple sclerosis population (British Columbia and Nova Scotia; results combined using meta-analyses)

	Model 1[a]			Model 2[b]			Model 3[c]		
Variable	β	SE	*p* Value	β	SE	*p* Value	β	SE	*p* Value
Depression									
Intercept	1.94	0.12	<0.0001	0.31	0.14	0.0287	0.37	0.18	0.0366
No depression (ref)									
Depression	0.22	0.08	0.0039	0.25	0.08	0.0015	0.24	0.07	0.0010
Anxiety									
Intercept	1.92	0.04	<0.0001	0.36	0.14	0.0134	0.41	0.15	0.0072
No anxiety disorder (ref)									
Anxiety disorder	0.06	0.08	0.4740	0.11	0.09	0.1842	0.11	0.08	0.2055
Bipolar disorder									
Intercept	1.92	0.05	<0.0001	0.38	0.14	0.0085	0.43	0.16	0.0080
No bipolar disorder (ref)									
Bipolar disorder	0.32	0.17	0.0592	0.30	0.17	0.0721	0.29	0.17	0.0808

[a] Adjusted for disease duration.
[b] Adjusted for disease duration, age at onset, sex, socioeconomic status, and disease course.
[c] Adjusted for disease duration, age at onset, sex, socioeconomic status, disease course, disease-modifying therapy use, and physical comorbidity count.

McKay KA et al. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. Neurology 2018;90(15):e1316-e1323

Other clinical predictors

- Early accumulation of disability[8,17,19]
- PPMS course[17,18,25]
- Early secondary progression[26]
- Chronic depression[26]
- Cognitive impairment[26]
- NEDA status[43]
- Comorbidities
- Vascular risk factors

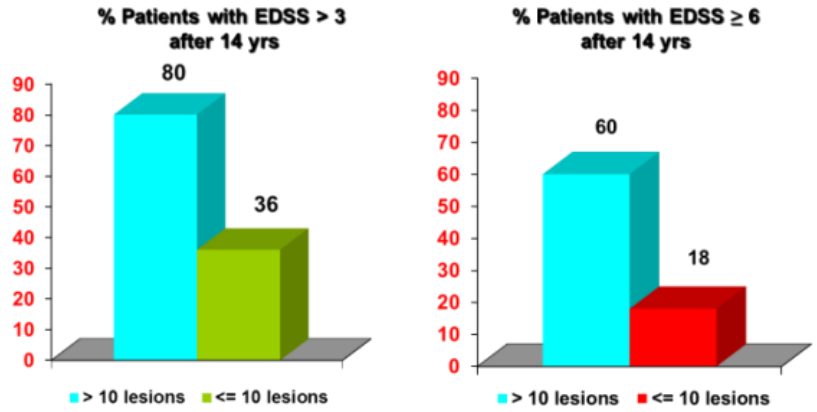
MS = Brain loss
Time = Brain

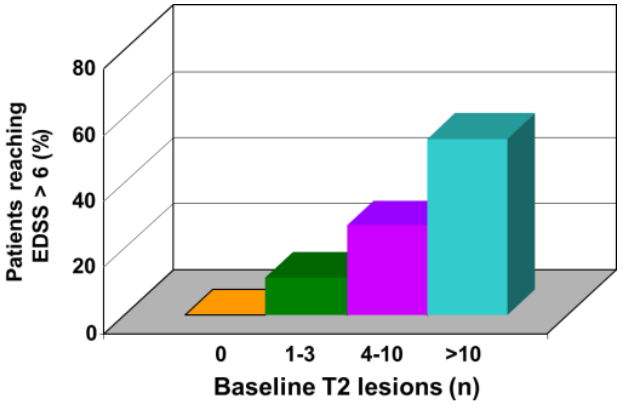
***** MS = Time-dependent brain loss**

Imaging factors

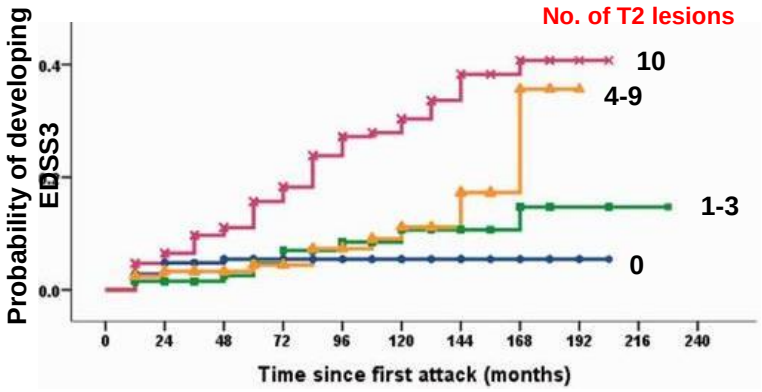
- T2 lesion count and volume in the first 5 years[27-29]
- Location: Cortical, posterior fossa or spinal cord[30-32]
- Gray matter involvement and atrophy[33,34]
- Atrophy: Thalamus, spinal cord, CC, brain[31,35-41]
- Gd enhancement[42]
- Chronic black holes[44]
- OCT[45,46]

T2 lesion count and volume in the first 5 years





Brex, NEJM 2002



29. Tintore M et al. Brain 2015

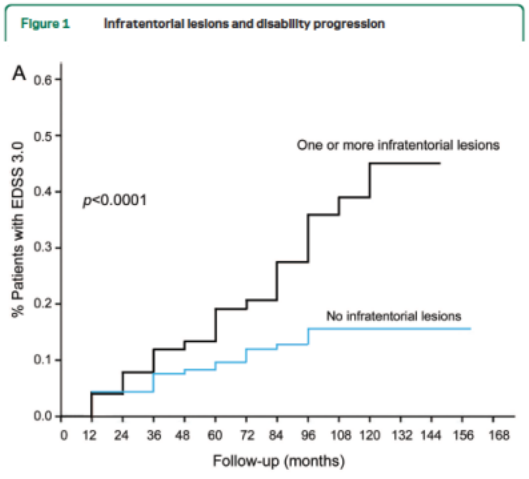
T2 lesion volume: 5Y FU of 84 pts with CIS

MRI at presentation	Conversion to CDMS	EDSS > 3
Normal	2/32 (6%)	0/32
Abn <1.23 cc	17/31 (55%)	7/31 (32%)
Abn >1.23 cc	19/21 (90%)	11/21 (52%)

Filippi M et al. Neurology 1994

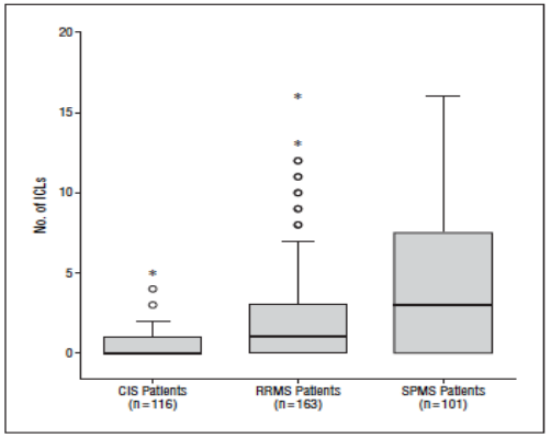
Lesion location

Infratentorial

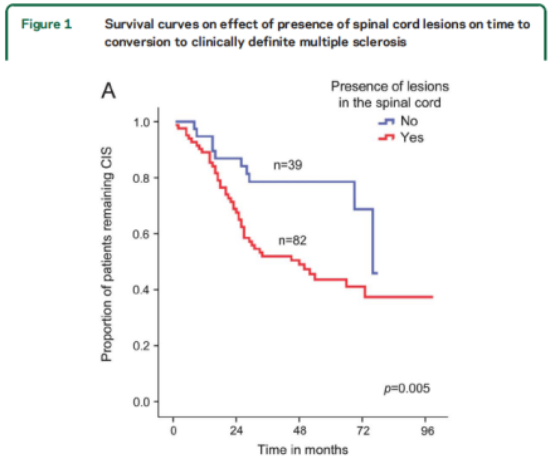


Tintore et al Neurology 2010

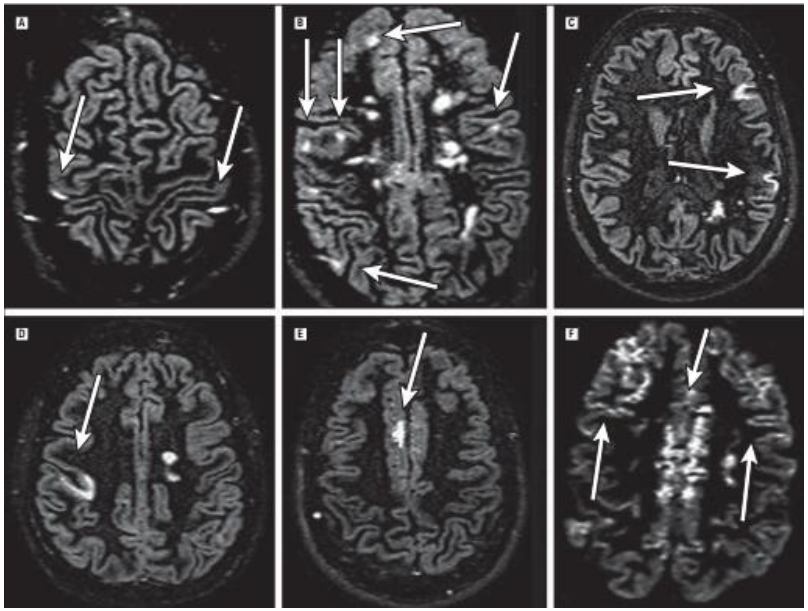
Cortical lesions



Spinal Cord



Sombekke et al Neurology 2013



Calabrese M et al. Arch Neurol. 2007

ORIGINAL CONTRIBUTION

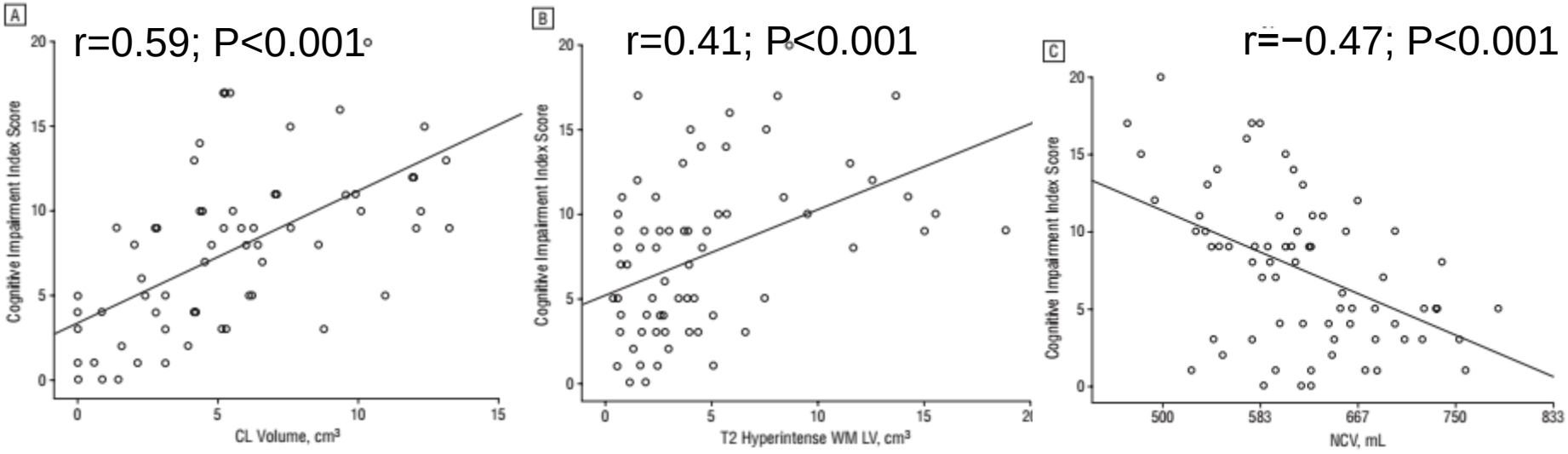
Cortical Lesions and Atrophy Associated With Cognitive Impairment in Relapsing-Remitting Multiple Sclerosis

Massimiliano Calabrese, MD; Federica Agosta, MD; Francesca Rinaldi, MD; Irene Mattisi, MD; Paola Grossi, PhD; Alice Favaretto, MD; Matteo Atzori, MD; Valentina Bernardi, MD; Luigi Barachino, RT; Luciano Rinaldi, MD, PhD; Paola Perini, MD; Paolo Gallo, MD, PhD; Massimo Filippi, MD

Cortical lesion volume

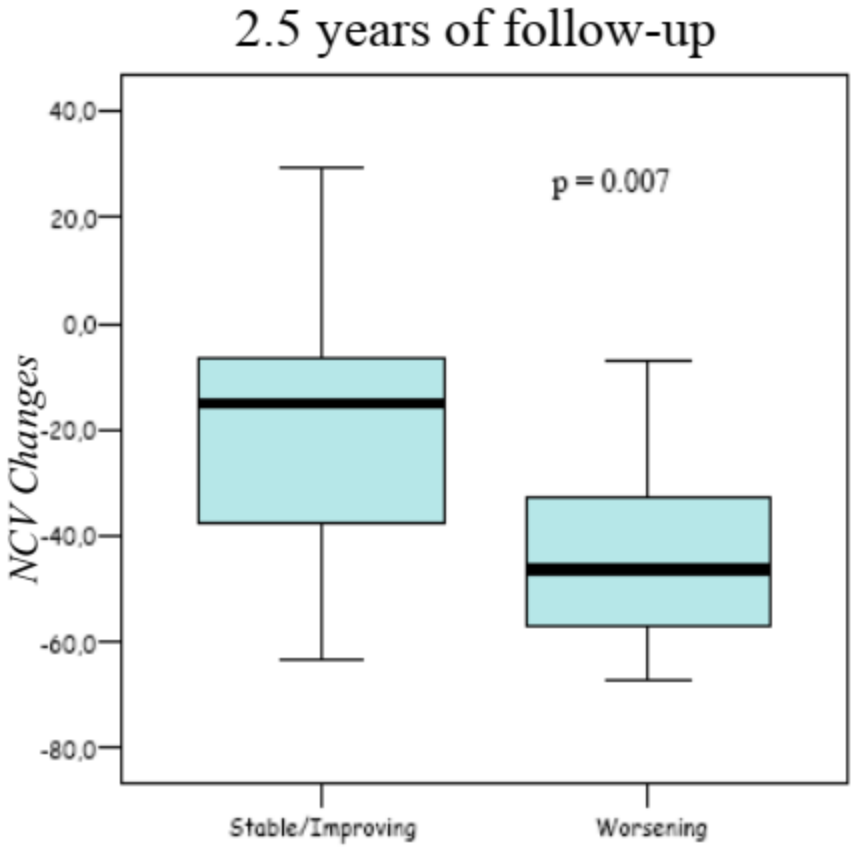
T2 lesion volume

Normalized neocortical gray matter volume



Calabrese M et al. *Arch Neurol. 2009;66(9):1144-50*

Cortical atrophy and cognition in early RRMS



Amato MP et al. Arch neurolo 2007

Gray matter damage

Table 2. Demographic, clinical and adjusted[a] BL MRI volumes (as percentage of whole-brain volume) of 241 RRMS patients, and of the four subgroups: RR→RR, RR→SP, EDSS < 4 and EDSS > 4.

	Mean (range)	SD	Median	RR→RR *n* = 199		RR→SP *n* = 42			EDSS < 4 *n* = 135		EDSS > 4 *n* = 73		
				Median	IQ ranges	Median	IQ ranges	*p*	Median	IQ ranges	Median	IQ ranges	*p*
RR *n* = 241													
Age at FU	44.4 (22–77)	9.1	44	34	28–40	38	30–47	0.021	33	27–39	37	31–44	0.003
Age at onset	27.3 (13–54)	8	26	26	21–33	26	21–35	0.755	25	21–31	26	22–34	0.424
AWM-f	1.2 (0–9.61)	1.6	0.6	0.6	0.2–1.4	1.4	0.3–2.6	0.002	0.6	0.1–1.2	1.2	0.3–2.1	0.005
CSF-f	14.9 (5.8–33.4)	4.7	14.4	13.9	11.2–16.4	17.1	13.3–20.9	< 0.001	13.7	10.9–16.2	16.0	13.6–20.0	< 0.001
GM-f	51.4 (39–58.2)	3.1	51.7	52.1	49.9–53.7	49.8	47.7–51.9	< 0.001	52.4	50.5–54.5	50.3	48.3–52.2	< 0.001
BL EDSS	2.3 (0–4.5)	1	2	2	1.5–2.5	3.3	2.5–3.5	< 0.001	2	1.5–2	2.7	2–3	< 0.001
DD at BL	8.5 (1–35)	6.5	7	6	3–11	7	5–15	0.0613	6	3–10	8	5–16	< 0.001
DD at FU (years)	17.4 (10–44)	6.4	15	15	12–20	16	14–24	0.1021	15	12–19	17	13–22	< 0.001

BL: baseline; MRI: magnetic resonance imaging; RR: relapsing–remitting multiple sclerosis; SP: secondary progressive; SD: standard deviation; FU: follow-up; AWM-f: abnormal white matter fraction; CSF-f: cerebrospinal fluid fraction; GM-f: gray matter fraction; EDSS: Expanded Disability Status Scale; DD: disease duration; IQ: interquartile. [a]Adjusted for age, gender and education.

"Conversion from RR to SP (OR 0.79; CI 0.7–0.9), progression of EDSS (OR 0.85; CI 0.77–0.93), achievement of EDSS 4 (OR 0.8; CI 0.7–0.9), and time to reach EDSS 4 (HR 0.88; CI 0.82–0.94) were all predicted by baseline gray matter volume"

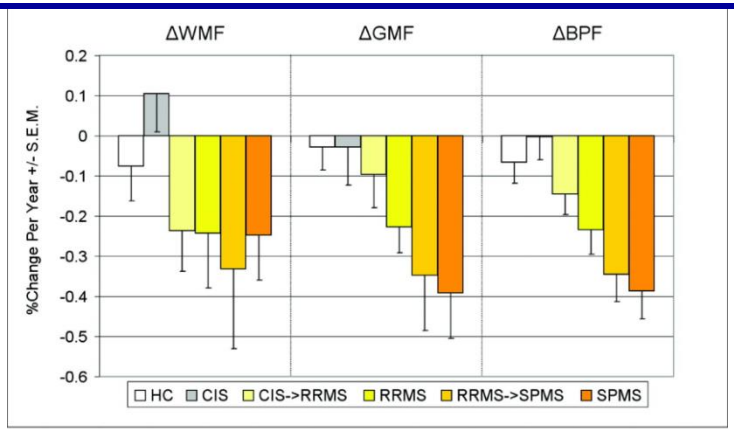
30. Lavorgna L et al. Clinical and magnetic resonance imaging predictors of disease progression in multiple sclerosis: a nine-year follow-up study. *Mult Scler*. 2014;20:220-226

Gray matter atrophy

Correlations of brain volume measurements with clinical features

	rs (p)				
	EDSS (n = 73)[a] (44[b])	MSFC (n = 67)[a] (41[b])	Z-PEG (n = 70)[a] (42[b])	Z-WALK (n = 68)[a] (40[b])	Z-PASAT (n = 68)[a] (42[b])
GMF[a]	**-0.48 (<0.001)**	**0.56 (<0.001)**	**0.59 (<0.001)**	**-0.40 (0.001)**	**0.27 (0.026)**
GMF[b]	-0.41 (0.005)	**0.55 (<0.001)**	0.44 (0.003)	-0.49 (0.001)	0.32 (0.038)
WMF[a]	-0.20 (0.086)	0.03 (0.784)	0.16 (0.176)	-0.11 (0.337)	-0.07 (0.537)
WMF[b]	-0.11 (0.443)	0.10 (0.526)	0.28 (0.071)	-0.09 (0.560)	-0.04 (0.761)

"Gray matter fraction correlated with EDSS and cognitive function, whereas white matter fraction did not"

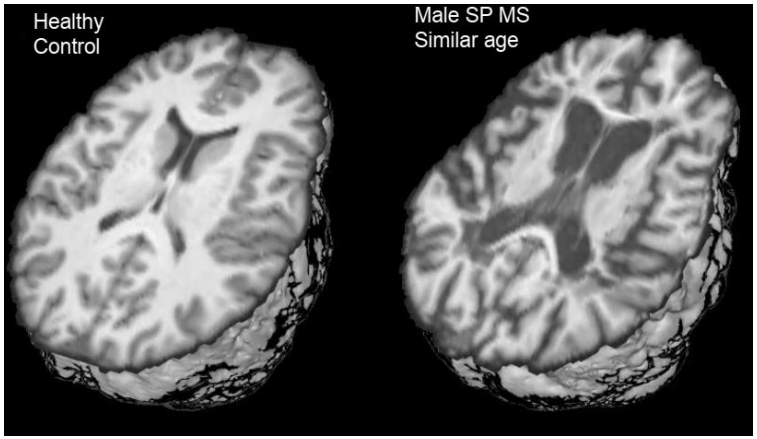


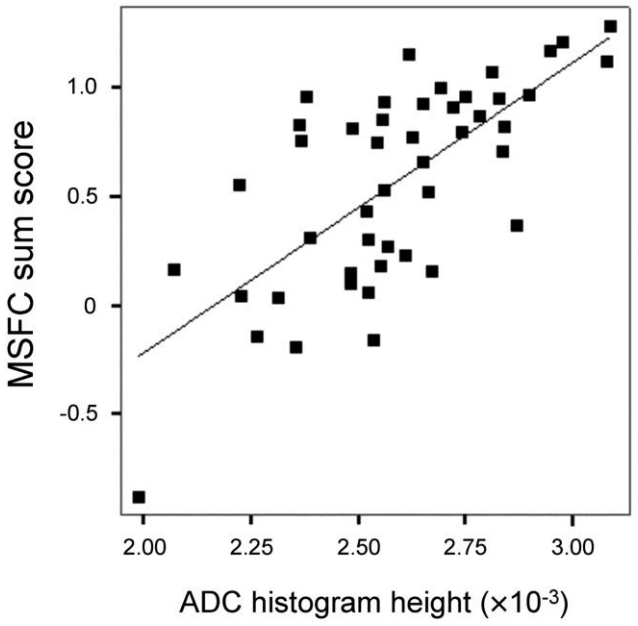
Gray matter atrophy correlated with disability and was more marked with disease progression: atrophy rate was 3.4-fold faster than normal in patients converting from CIS to RRMS and 14-fold faster in patients converting to SPMS

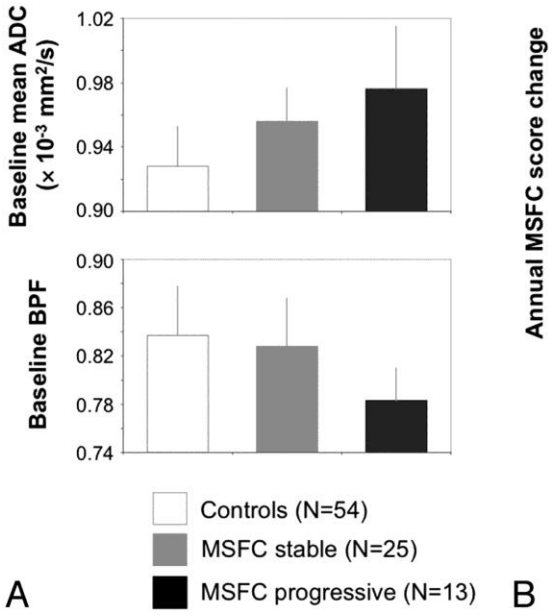
Fisniku LK et al. Gray matter atrophy is related to long term disability in MS. Ann Neurol. 2008;64:247-54

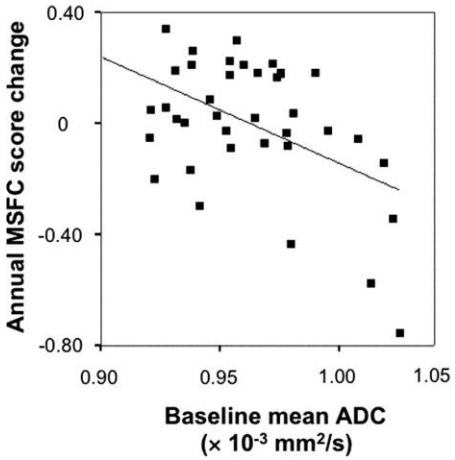
Fisher E, et al. Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol. 2008;64:255-65

Brain atrophy



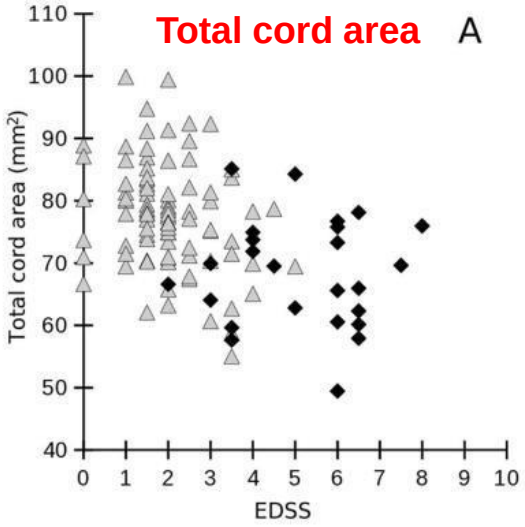






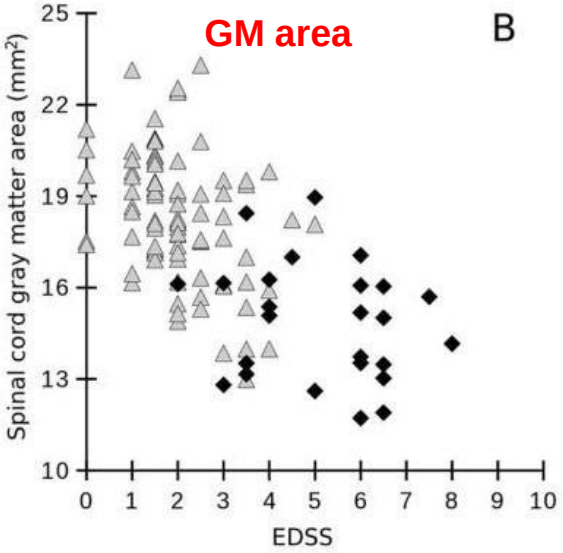
Sämann PG et al. Brain volume and diffusion markers as predictors of disability and short-term disease evolution in multiple sclerosis. AJNR Am J Neuroradiol 2012;33:1356-62

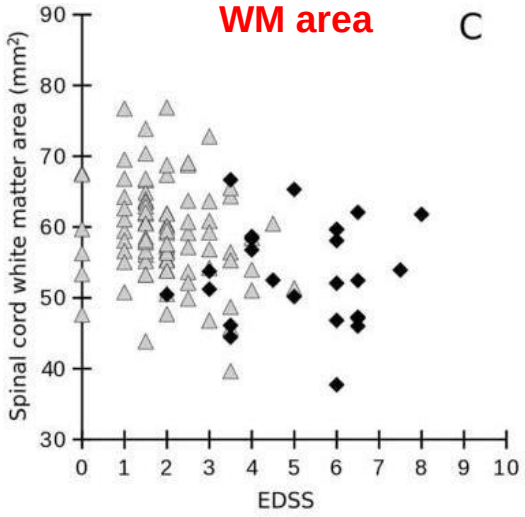
Spinal cord atrophy



RMS

PMS





31. Schlaeger R, et al. Spinal cord gray matter atrophy correlates with multiple sclerosis disability. *Ann Neurol*. 2014;76:568-580

Corpus callosum atrophy

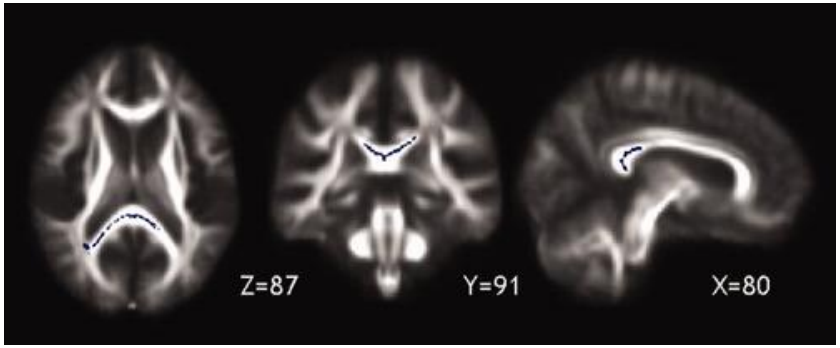


TABLE II. White matter regions showing a significant association between lower baseline FA and neuropsychological scores at 5 years

Clinical and neuropsychological score at follow-up	No. of voxels per significant white matter cluster	MNI Atlas coordinates *x*, *y*, *z*	Significant regions	*P* value
Immediate Story Recall Test	6025	106, 82, 80	Splenium of CC	$P = 0.003$
	1084	74, 171, 59	Anterior part of genu of CC	
Delayed Story Recall Test	4471	105, 84, 80	Splenium of CC	$P = 0.003$
	2466	69, 173, 71	Anterior part of right thalamic radiation and genu of CC	
	651	103, 112, 105	Body of CC	
Symbol Digit Modalities Test	2265	94, 104, 97	Body of CC	$P = 0.05$
	86	99, 84, 86	Splenium of CC	
Hayling Sentence Completion Task	1065	76, 161, 84	Genu of CC	$P = 0.003$
	873	56, 80, 102	Right posterior corona radiata	
	456	107, 71, 121	Left posterior corona radiata	
	243	91, 135, 95	Body of CC	
	177	78, 122, 100	Body of CC	

Corpus callosum damage predicts disability progression and cognitive dysfunction in primary-progressive MS after five year

36. Bodini B, et al. *Hum Brain Mapp*. 2013;34:1163-1172

Deep GM atrophy

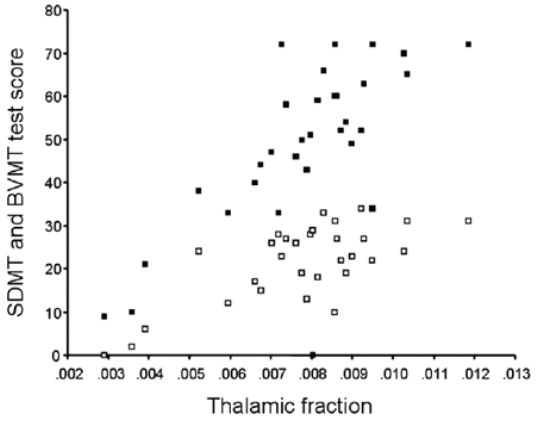
(thalamus, putamen, hippocampus)

Table 3: Univariate logistic regression analysis of the predictive value of thalamic volumetry and DTI findings from the GM with and without the thalamus for patients with EDSS scores worsening during 5 years (dependent variable)[a]

Independent Variables	Units	OR (95% CI)	*P* Values
Baseline NTV	1 mL	1.25 (0.63–2.45)	.53
Baseline thalamic FA	0.01	0.99 (0.97–1.02)	.57
Baseline thalamic MD	0.01 $mm^2/s \times 10^{-3}$	1.02 (0.98–1.06)	.40
Average NTV thalamic volume change	1%	1.00 (0.91–1.11)	.94
Average thalamic FA change	1%	0.87 (0.77–0.97)	.01
Average thalamic MD change	1%	1.04 (0.97–1.11)	.27
Thalamic lesions	n.a.	1.06 (0.66–1.68)	.82
Change in thalamic lesions	Yes vs no	2.23 (0.40–12.5)	.36
Baseline GM without the thalami FA	0.01	1.02 (0.99–1.06)	.22
Baseline GM without the thalami MD	0.01 $mm^2/s \times 10^{-3}$	1.14 (1.02–1.27)	.019
Average GM without the thalami FA change	1%	0.99 (0.93–1.05)	.63
Average GM without the thalami MD change	1%	1.03 (0.92–1.15)	.64

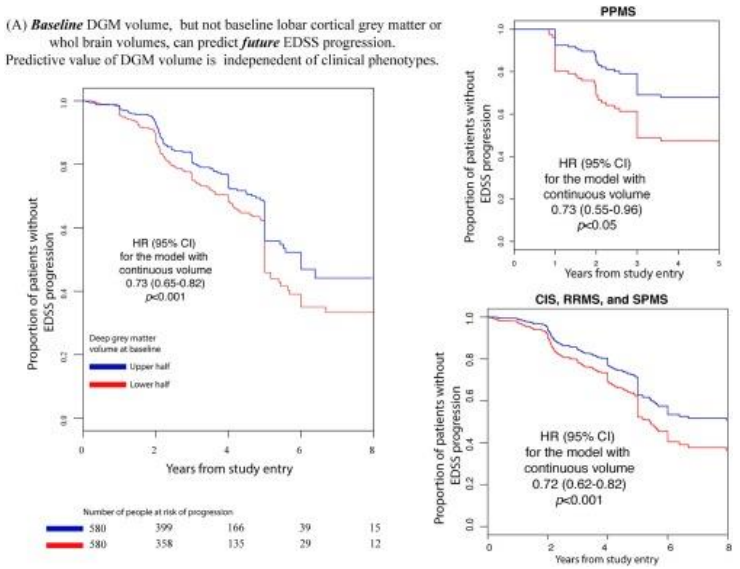
"Short-term accrual of thalamic damage predicts the long-term accumulation of disability in PPMS"

38. Mesaros S, et al. Thalamic damage predicts the evolution of primary-progressive multiple sclerosis at 5 years. AJNR Am J Neuroradiol. 2011;32:1016-20



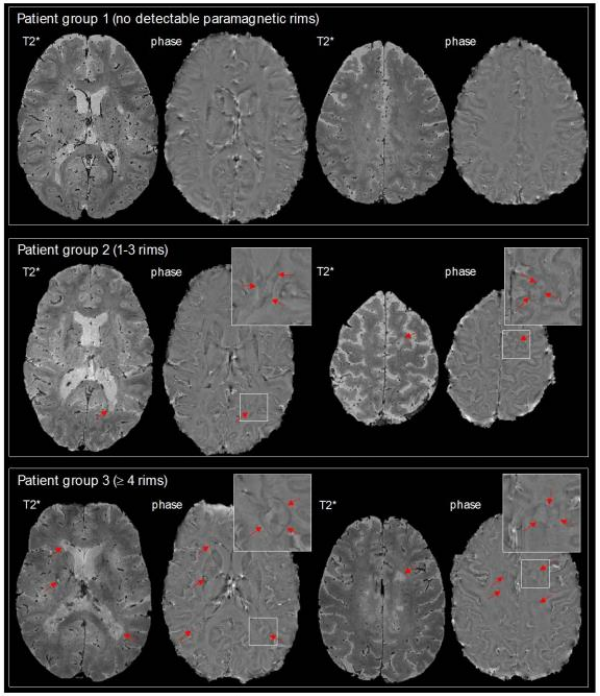
Hutchens MK et al. Thalamic atrophy and cognition in multiple sclerosis. Neurology 2007;69:1212-23

"Deep GM volume loss drives disability accumulation in MS, and temporal cortical GM shows accelerated atrophy in SPMS than RRMS"

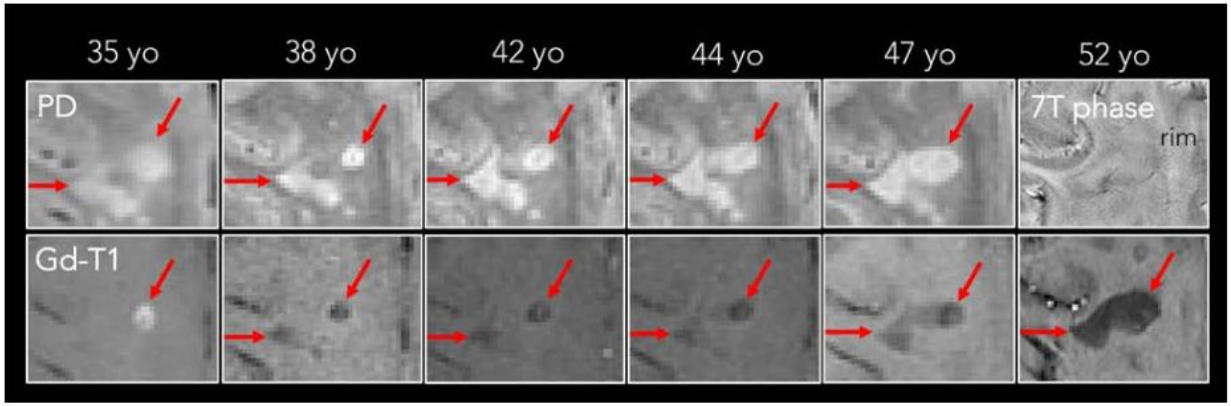


Eshaghi A, et al. Deep gray matter volume loss drives disability worsening in multiple sclerosis. Ann Neurol. 2018;83:210-22

Smoldering chronic active lesions with darkened rims

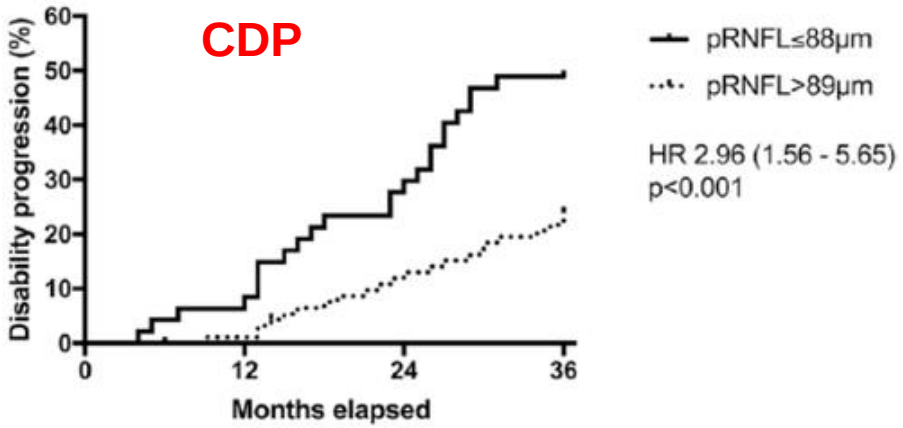


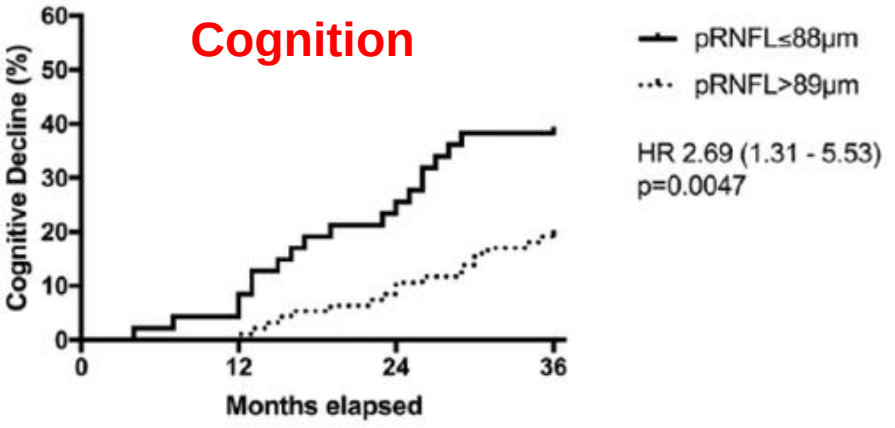
	Spearman Correlation Coefficients	
	EDSS	
	p	r
Log lesion volume	<0.0001	0.423
Log rim-lesion volume	0.0003	0.270
Log number of rim lesions	0.0005	0.248
Normalized brain volume	0.59	0.041
Normalized cortex volume	0.12	-0.120
Normalized WM volume	0.0007	-0.256
Normalized thalamus volume	<0.0001	-0.336
Normalized caudate volume	<0.0001	-0.344
Normalized putamen volume	0.09	-0.128
Normalized ventricular CSF volume	<0.0001	0.369
Normalized sulcal CSF volume	0.0003	0.270

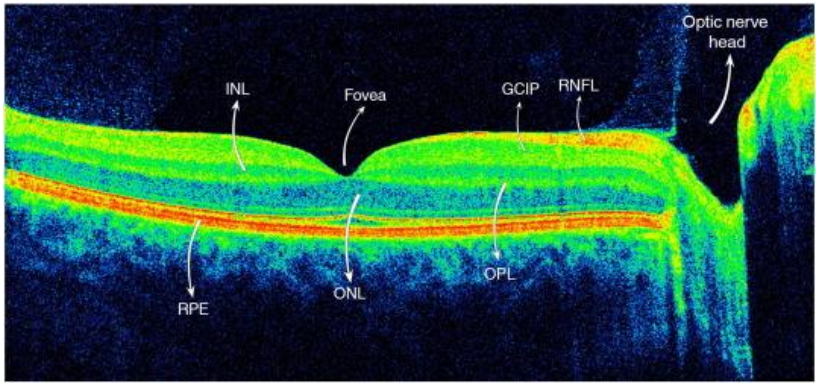


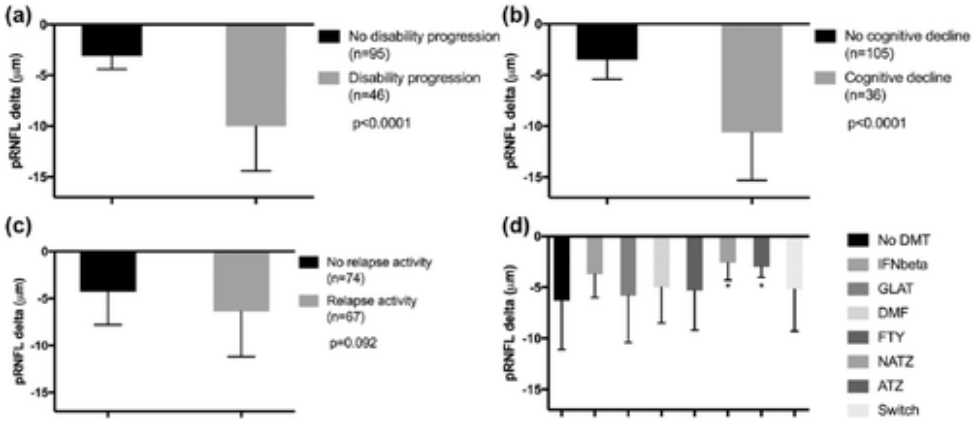
Absinta M et al. Association of Chronic Active Multiple Sclerosis Lesions With Disability In Vivo. JAMA Neurol 2019 Aug 12

Optical Coherence Tomography









"Cross-sectional and longitudinal monitoring of pRNFL is useful as a biomarker for prediction of physical and cognitive disability progression in patients with RRMS in everyday clinical practice"

Bsteh G et al. NSJ 2019;25:196-203

Imaging factors

- T2 lesion count and volume in the first 5 years[27-29]
- Location: Cortical, posterior fossa or spinal cord[30-32]
- Gray matter involvement and atrophy[33,34]
- Atrophy: Thalamus, spinal cord, CC, brain[31,35-41]
- Gd enhancement[42]
- Chronic black holes[44]
- OCT[45,46]

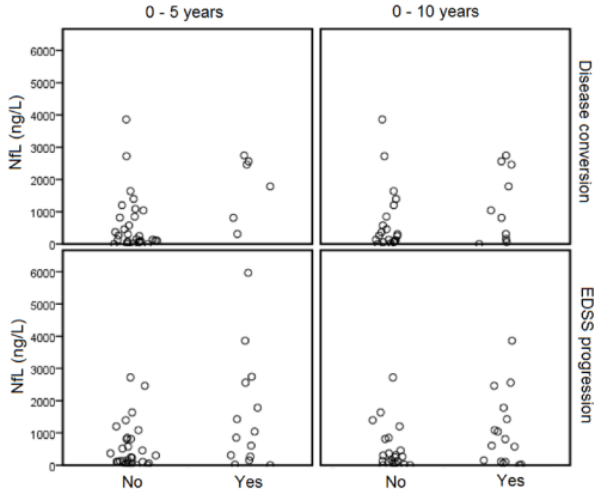
CSF/Serum biomarkers

- OCB (IgM>IgG)[29,47]
- Neurofilament light chain (NFL)[48] (also in serum)[49]
- Chitinase-3-like 1 (CHI3L1)[50]
  inflammatory markers (cytokines, chemokines, MMPs…) of T cells, B cells, monocytes[47,51]
- Other: NO, GFAP, BDNF, anti-viral Ab's…[47]

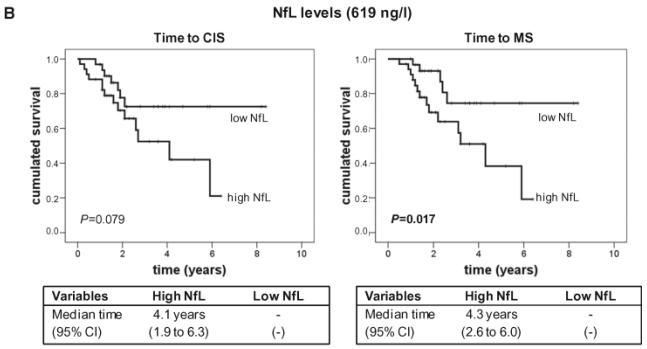
The clinical utility of CSF biomarkers in everyday practice is not well established

Neurofilament light chain (NfL)

CSF



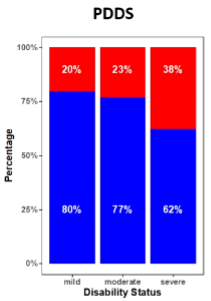
CSF



Variables	High NfL	Low NfL
Median time (95% CI)	4.1 years (1.9 to 6.3)	- (-)

Variables	High NfL	Low NfL
Median time (95% CI)	4.3 years (2.6 to 6.0)	- (-)

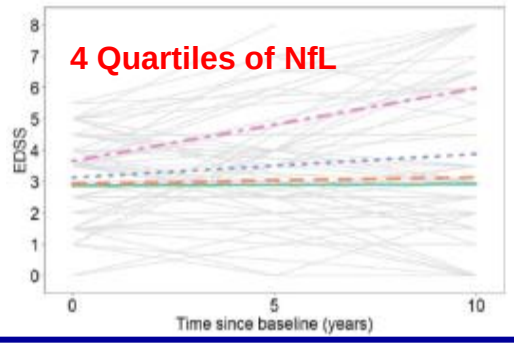
Blood



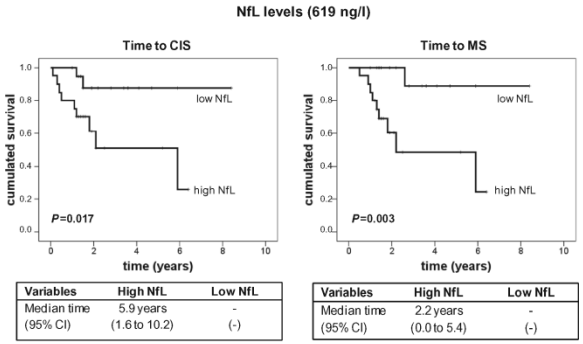
OR* for moderate vs. mild disability:
1.26 (0.96, 1.66)
p=0.09

OR for severe vs. mild disability:
2.50 (1.71, 3.67)
p<0.0001

Prediction for EDSS development

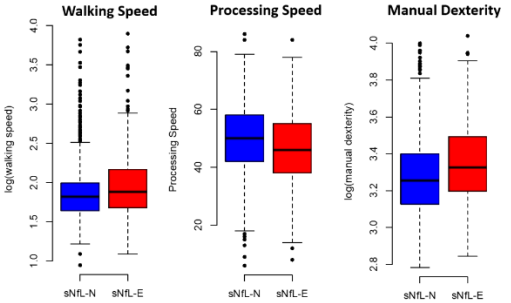


Age ≥37 years



Variables	High NfL	Low NfL
Median time (95% CI)	5.9 years (1.6 to 10.2)	- (-)

Variables	High NfL	Low NfL
Median time (95% CI)	2.2 years (0.0 to 5.4)	- (-)



10.01% (5.97, 14.34) slower; p<0.001

-8.23% (-10.54, 5.86) lower; p<0.001

7.24% (4.91, 9.62). slower; p<0.001

*adjusted for age, race, DMT class, gender, time-lag between sample collection and MSPT, disease subtype and duration

"CSF levels of NfL at the time of diagnosis seems to be an early predictive biomarker of longterm clinical outcome and conversion from RRMS to SPMS"

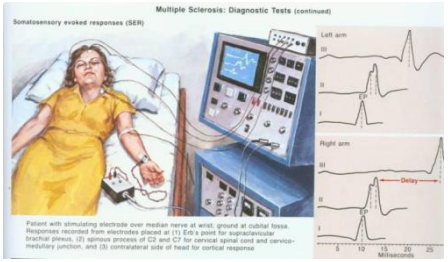
"NfL and OCBs are prognostic biomarkers in RIS and predict conversion to CIS and MS"

"Elevated sNfL was associated with poorer neurologic function and diabetes"

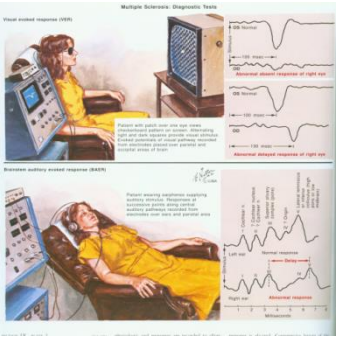
Bhan A et al. MSJ 2018;24:1301-7

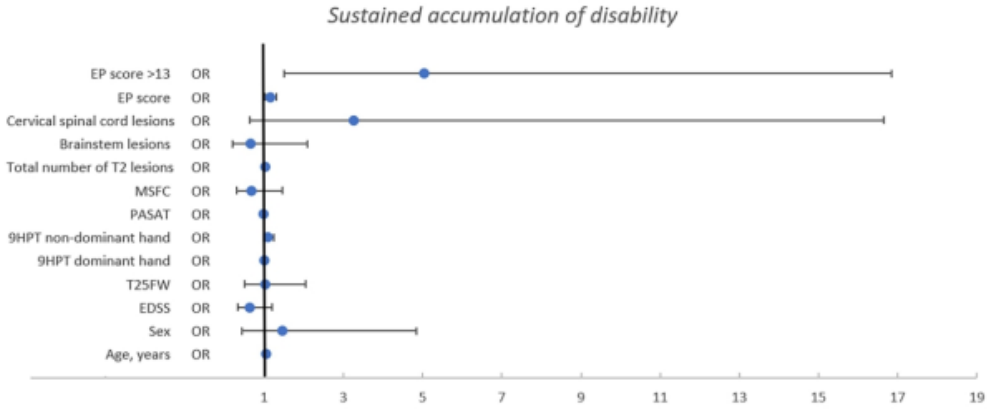
Matute-Blanch C et al. Brain 2018;141:1085-93

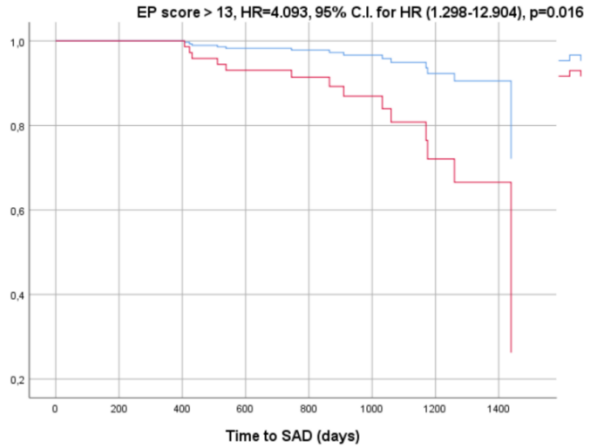
Fitzgerald K et al. ECTRIMS 2019



Evoked potentials







Crnošija L et al. **Evoked potentials can predict future disability in people with clinically isolated syndrome**. J Neurol 2019

Table 2
Longitudinal correlations between evoked potentials and EDSS ($n = 45$).

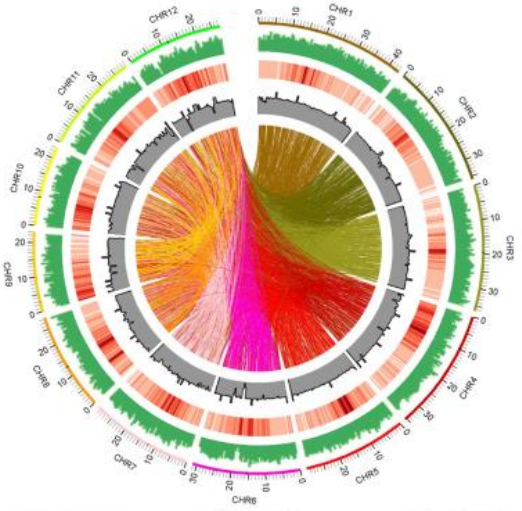
Variable	Correlation coefficient[a]	*p*-Value
Σ(*s*-P100, *s*-CMCT$_{UE}$, *s*-CMCT$_{LE}$, *s*-N13–N20, *s*-N22–P40)$_{T1}$ versus EDSS$_{T7}$	0.70	<0.001
Number of pathological EP results$_{T1}$ versus EDSS$_{T7}$	0.71	<0.001
$\Delta\Sigma$(*s*-P100, *s*-CMCT$_{UE}$, *s*-CMCT$_{LE}$, *s*-N13–N20, *s*-N22–P40)$_{T7-T1}$ versus ΔEDSS$_{T7-T1}$	0.51	0.001
ΔNumber of pathological EP results$_{T7-T1}$ versus ΔEDSS$_{T7-T1}$	0.34	0.035
Σ(*s*-P100, *s*-CMCT$_{UE}$, *s*-CMCT$_{LE}$, *s*-N13–N20, *s*-N22–P40)$_{T1}$ versus ΔEDSS$_{T7-T1}$	0.35	0.017
Number of pathological EP results$_{T1}$ versus ΔEDSS$_{T7-T1}$	0.35	0.016
EDSS$_{T1}$ versus ΔEDSS$_{T7-T1}$	0.22	0.144

Abbreviations: T1, baseline; T7, 3 years follow-up; UE, upper extremities; LE, lower extremities; *s*-latency value, *z*-score of latency value (right) + *z*-score of latency value (left).
[a] Spearman rank correlation.

52. Schlaeger R, et al. **Combined evoked potentials as markers and predictors of disability in early multiple sclerosis.** Clin Neurophysiol. 2012;123:406-410

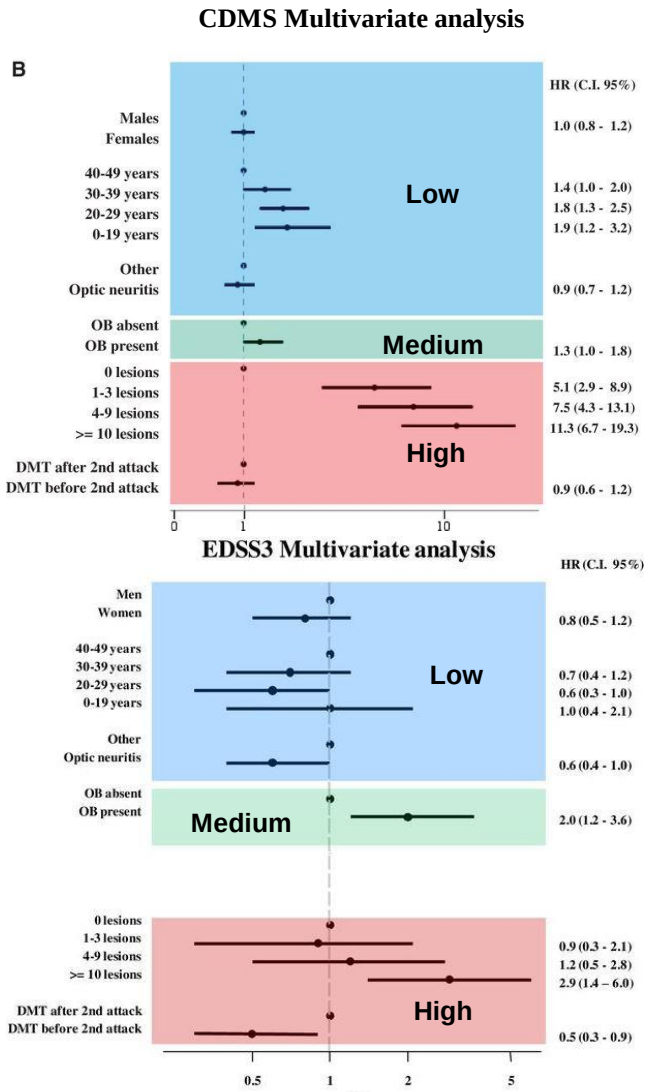
Genomic factors

- HLA genotypes[3]
  - HLA-DRB1, DRB*07, DRB*44, -DQB1*0301,-DQB1*0302,-DQB1*0602, and-DQB1*0603[53,54]
- *NLRP3* and *NLRC4* (inflammasome components) variants[55]
- Other MS susceptibility polymorphisms[56]

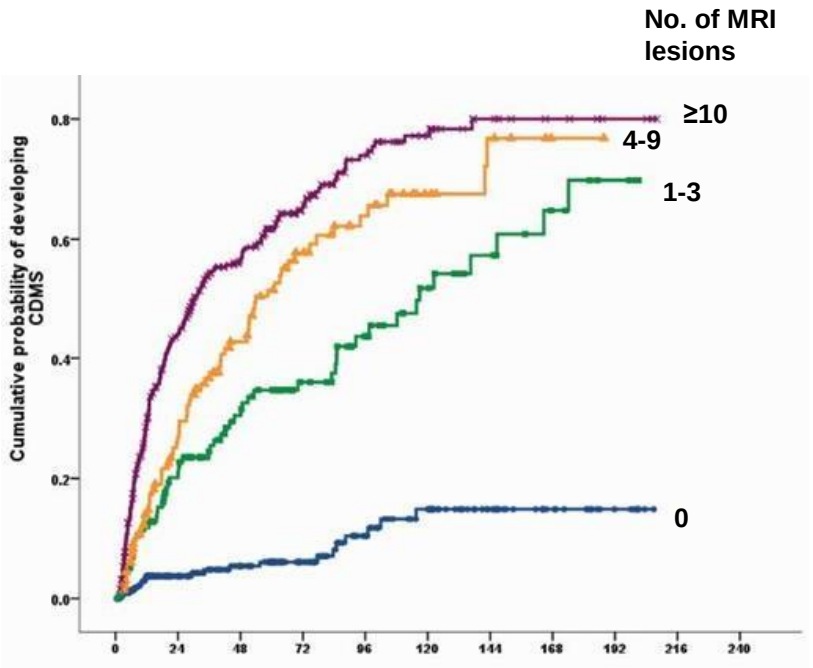


55. Soares JL, et al. Variants in NLRP3 and NLRC4 inflammasome associate with susceptibility and severity of multiple sclerosis. *Mult Scler Relat Disord.* 2019;29:26-34

Risk of MS and disability accumulation after CIS



Conversion to CDMS is associated with baseline no. of MRI lesions



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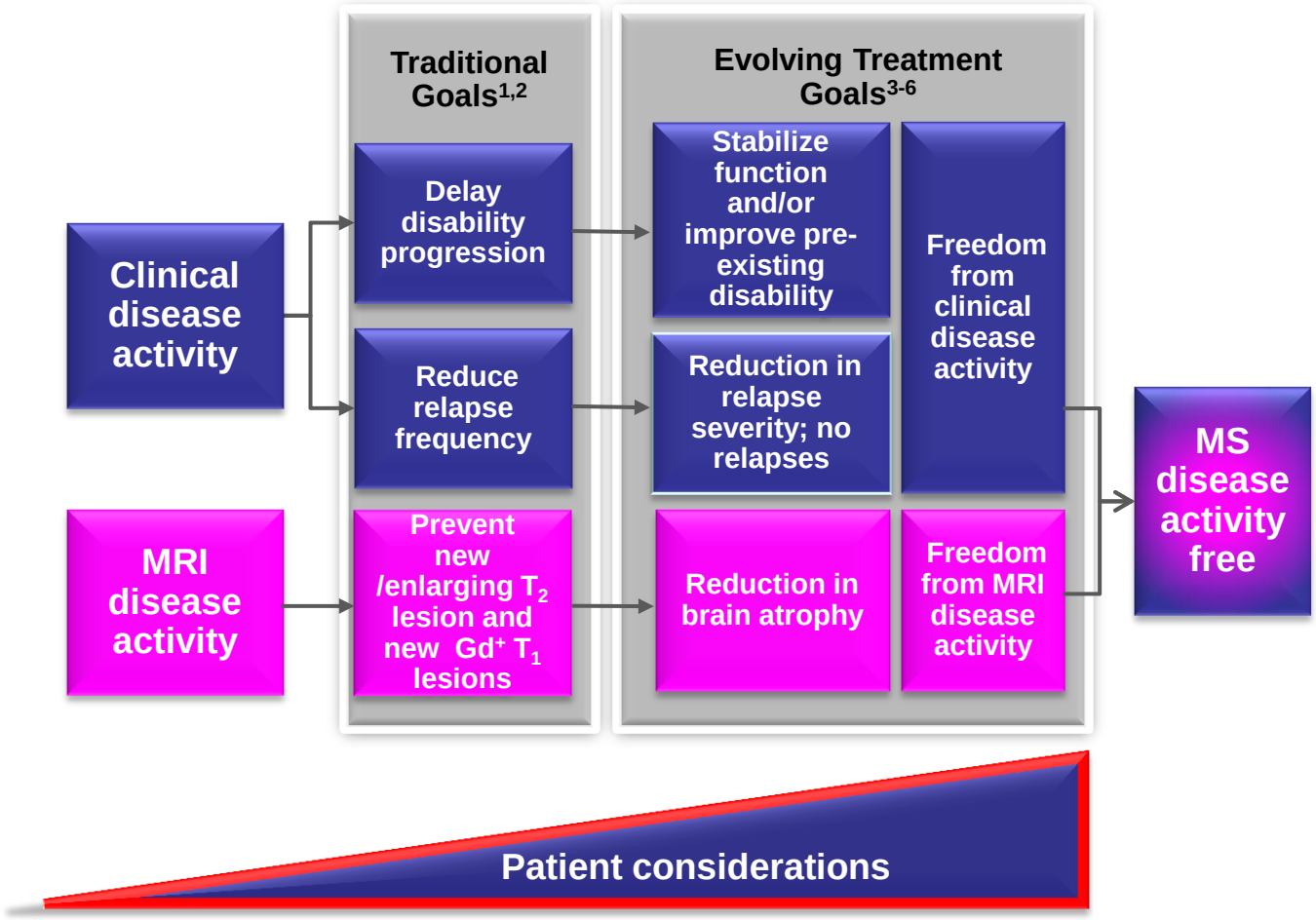
Making treatment decisions[57]

I. Define your treatment goals

T2T: Treat to Target



Gd=gadolinium; MRI=magnetic resonance imaging

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II. Determine the risk of your patient

Factors at disease onset associated with poor prognosis

Epidemiologic	Envioronmental / Life Style	Clinical	Paraclinical/ Biologic	Imaging
Age at onset>40	EBV infection	Type (motor, cerebellar, sphincter or cognitive) and no. of systems involved	IgG or IgM OCB (CSF)	Location: Intracortical, posterior fossa or spinal cord lesions
Gender (male)	Low Vit. D	Topography: cerebellum, brainstem, spinal cord	Biomarkers (CSF, blood CHI3L1, neurofilament)	High lesion load
Ethnic origin (Asian or African)	Smoking	Polyregional (multifocal) symptoms	Abnormal evoked potentials	Contrast enhancement
Latitide (?)	Obesity	Partial or no recovery from initial attacks	Genomic factors (e.g. ApoE4, HLA-DRB1*15)	Brain, thalamic or spinal cord atrophy
Ageing	Diet (e.g. high salt, sweetened drinks, mediterranean)	Frequent attacks during the first years	Inflammatory markers in CSF	Smoldering chronic active lesions with darkened rims
	Organic solvents	Short interval between the first two attacks	High plasma ceramides	Chronic T1 black holes
	CMV infection (↑ in the ME, ↓ in Europe)	Rapid disability progression during the first years		Cortical pathology
	Exercise (protective)	Progressive dis. from onset		Gray matter damage
	Sun exposure	NEDA status		OCT
	Alcohol, coffee, fish, oral tobacco (protect.)	Cognitive impairment, Depression		
	Microbiome	Fatigue		
	Night work	Comorbidities		
		Vascular risk factors		

Risk Calculator?

Total Risk Score	Risk Level
0 -5	Low
6 - 10	Moderate
11 -15	High
16 -20	Very High
≥ 21	Extreme

Tailoring initial treatment

- **Prognostic factors can help determine likely outcomes and guide treatment decisions**

Multiple poor prognostic factors: More likely to do poorly, likely greater benefit from high efficacy therapy	**All other patients:** Patient and clinician choice after weighing potential risks and benefits	**Few poor prognostic factors and/or positive prognostic factors:** More likely to do well, potentially less accepting of 'risk' with high-efficacy therapy

- **In clinical practice, it can be difficult to identify patients not at the extremes**

III. Consider additional factors

- Efficacy
- Safety
- Tolerability
- Clinical or MRI disease activity
- Cognitive dysfunction
- Response to previous DMTs
- Drug properties, metabolism, MoA
- Comorbidities
- Concomitant medications
- Current immunity or immunization status
- Previous immunosuppressive therapy
- Monitoring
- Adherence to treatment and monitoring
- Physician experience
- Patient's preferences (convenience, route and frequency of administration, side effects, individual tolerability)
- Patient’s expectations
- Patient's life style
- Childbearing potential, pregnancy and family planning
- Cost
- Treatment access and logistics
- Regulatory status
- Social and family support systems

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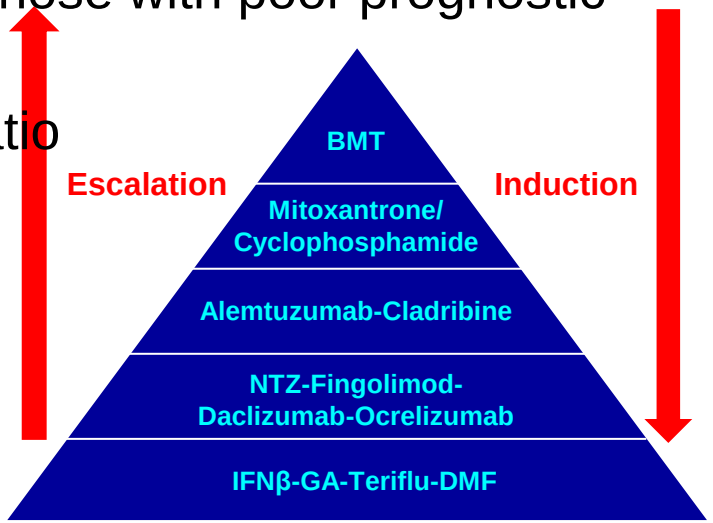
IV. Select a treatment strategy

- **Escalation therapy**
  - Standard but “failure-based” approach
  - Appropriate for patients with inactive disease, good prognostic factors
  - High-quality supportive evidence is limited
  - Questions: definition of treatment failure, sequence of escalation, washout, additive risks of immunosuppression
- **Induction therapy**
  - Appropriate for highly active patients or those with poor prognostic factors at disease onset
  - Short course may improve risk-benefit ratio
  - Long-term benefit still unclear
- **Combination therapy**
  - Limited evidence
  - Future strategy?



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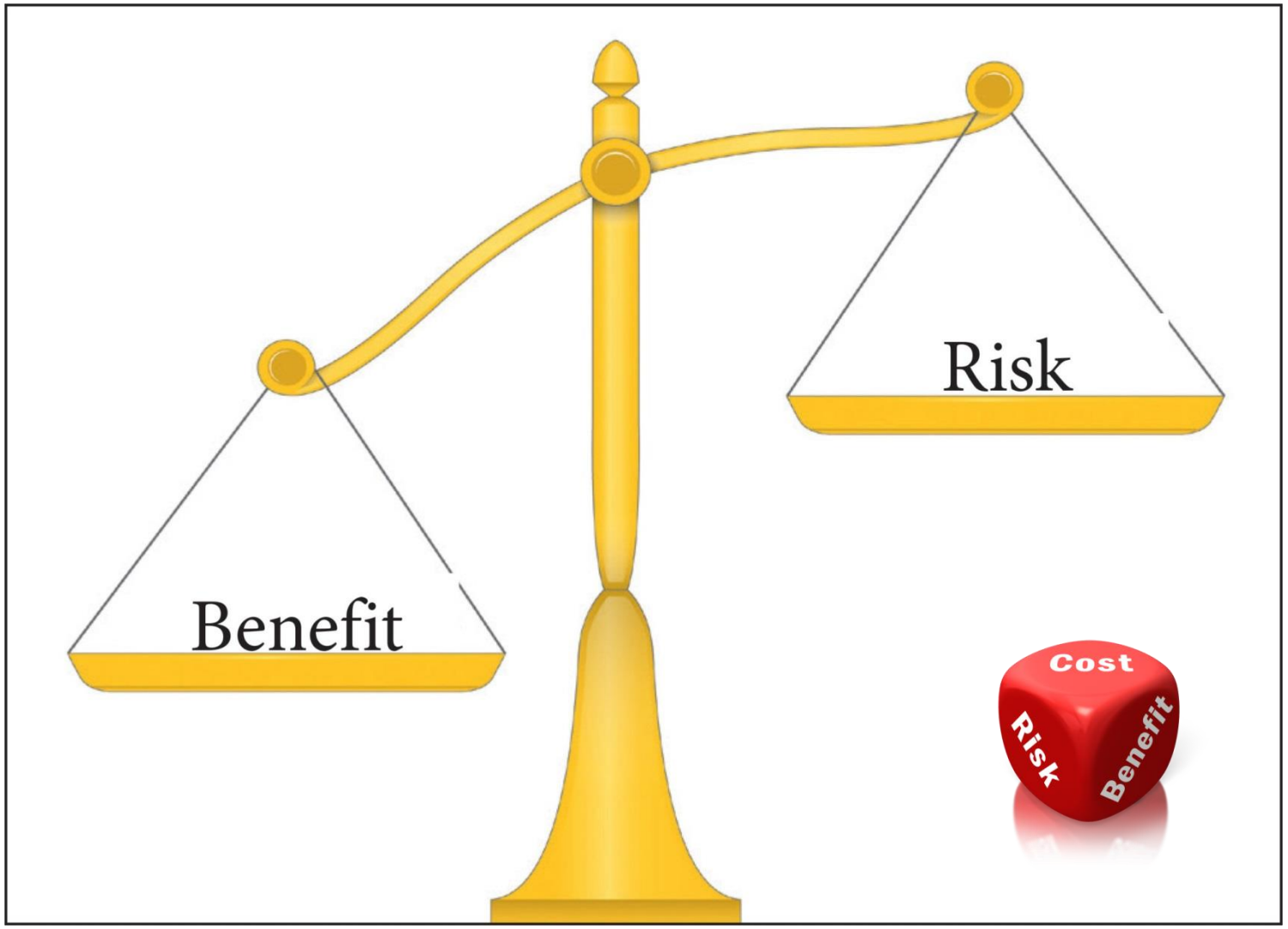
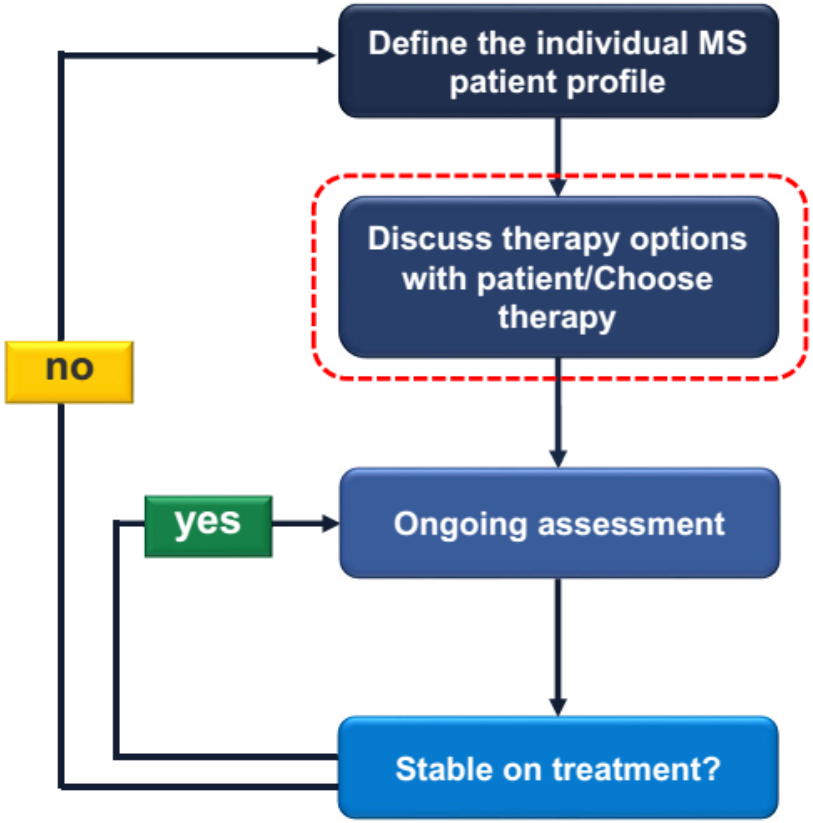
V. Assess Benefit/Risk ratio



VI. Share decisions, Monitor and assess for disease activity/treatment failure



"If it weren't for the great variability of individuals, medicine might as well be a science and not an art"
Sir William osler, M.D. 1892

Conclusions

- **MS is highly variable and unpredictable, however, several factors have emerged as predictive of the course and prognosis of the disease**
- **Some genetic and environmental risk factors that affect the likelihood of developing MS may also predict its course**
- **There are multiple epidemiological, environmental, clinical, imaging and biological prognostic factors to be considered**
- **Prognostic factors are important for decision making and selecting the most appropriate treatment for the individual patient with MS**

Ashkelon

Thank You

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