RIUNIONI REGIONALI

Approccio multidisciplinare nella gestione delle terapie ad alta efficacia

Emanuele D'Amico
Università degli Studi di Foggia

Disclosures

Honoraria speaking from Merck-Serono, Sanofi-Genzyme, Roche, Biogen, Novartis, Bristol.

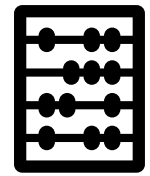
Agenda

- **Evidence**
- **Evolving the MS therapeutic paradigm**
- **The Holistic MS management:**

  -Unmet needs

  -Warnings

- **Take home messages**

EVIDENCE

MS: a devastating disease

Cognitive Dysfunction

- Prevalence: 43% to 65%[1,2]
- Affects employment, activities of daily living, and social functioning[2]

Life Shortening

- 5- to 11-year decrease in life expectancy[3–7]
- 2- to 7-fold increase in suicide risk[5,8]
- ~50% MS patients die of disease-related causes[5,6,8]

MS has a negative impact on…

QOL
EDSS and utility[a] have shown a significant inverse relationship[9]

Mortality
Mortality ratio of patients with MS exceeds CV disease,[b,10] stroke,[c,11] and early breast cancer[12]

Employment
~50% of patients with MS are unemployed as of EDSS 3.0 and/or after 10 years from diagnosis[13]

Healthcare costs
Bulk of cost attributed to services (28.5%) and long-term sick leave and early retirement (30%)[d,14]

Relationships
Compared with general population, patients with MS have a higher probability of separating/divorcing and doing so sooner[13]

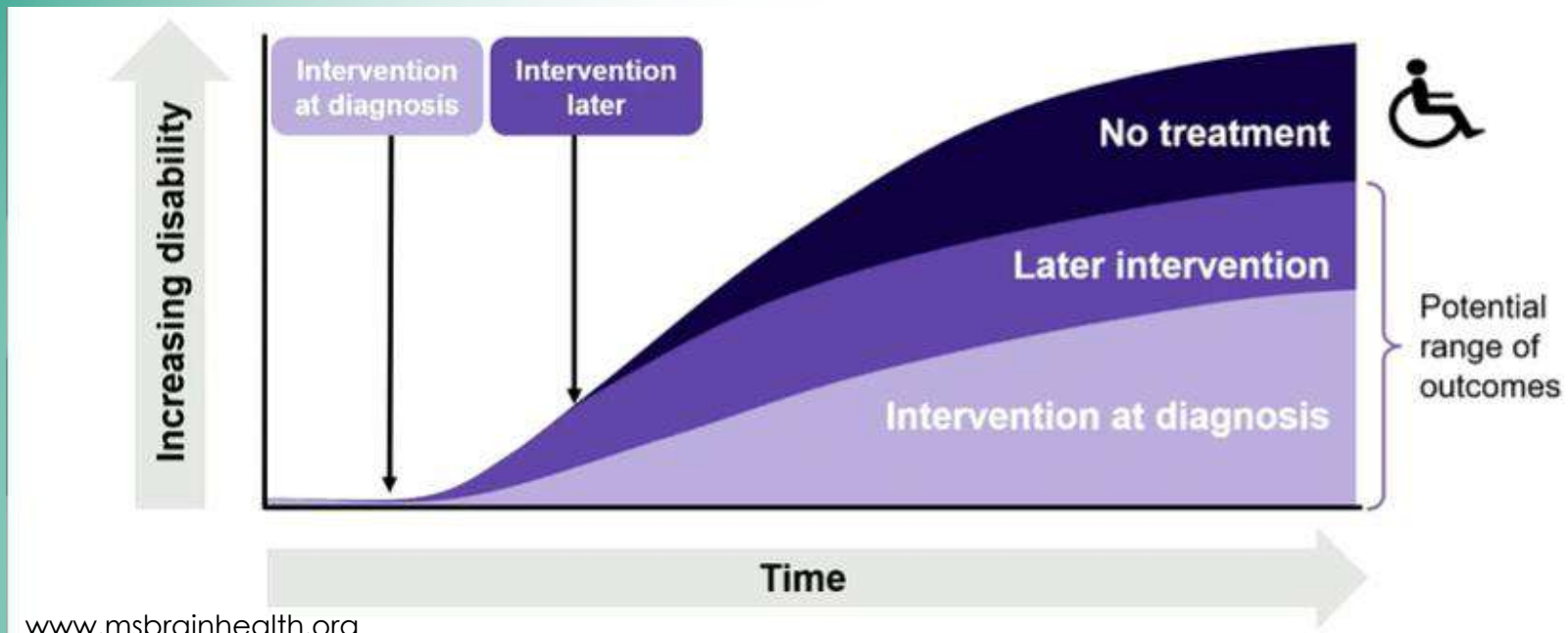
[a]In this study, utility measures were derived from EQ-5D using the EuroQoL instrument;
[b]In patients with type 2 diabetes; [c]In patients with valvular heart disease in Olmsted County, Minnesota; [d]MS patients with EDSS ≥6

EDSS, Expanded Disability Status Scale; QOL, quality of life; CV, cardiovascular; EQ-5D, European Quality of Life-5 Dimensions

1. Rao et al. *Neurology*. 1991;41:685–691. 2. Rao et al. *Neurology*. 1991;41:692–696. 3. Sadovnick et al. *Neurology*. 1992;42:991–994.
4. Ebers. *J Neurol Neurosurg Psychiatry*. 2001;71:16–19. 5. Torkildsen et al. *Mult Scler*. 2008;14:1191–1198. 6. Smestad et al. *Mult Scler*. 2009;15:1263–1270. 7. Kingwell et al. *J Neurol Neurosurg Psychiatry*. 2012;83:61–66. 8. Sadovnick et al. *Neurology*. 1991;41:1193–1196.
9. Orme et al. *Value Health*. 2007;10:54–60. 10. De Marco et al. *Diabetes Care*. 1999;22:756–761. 11. Petty et al. *Mayo Clin Proc*. 2005;80:1001–1008. 12. Hoorning et al. *Int J Radiat Oncol Biol Phys*. 2006;64:1085–1091. 13. Pfleger et al. *Mult Scler*. 2010;16:121–126.
14. Beg et al. *Eur J Health Econ*. 2006;7(Suppl 2):S75–S85.

Slide provided courtesy of Prof G.Giovannoni

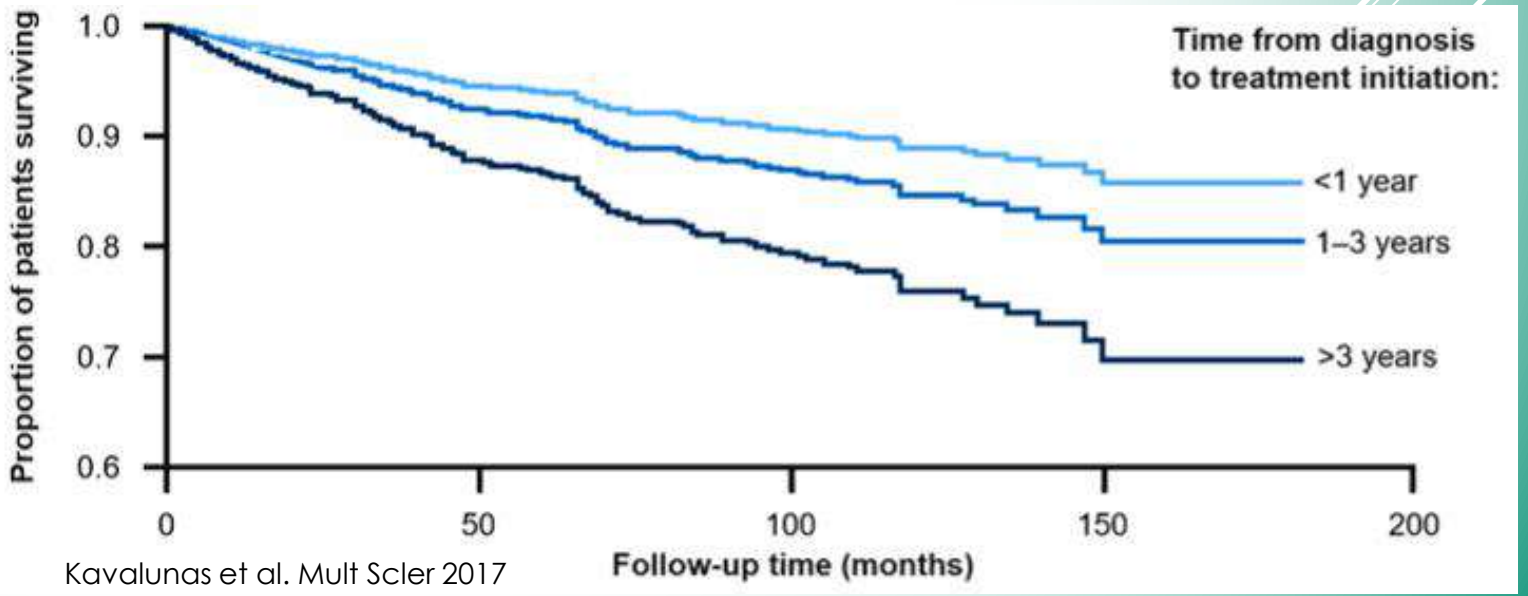
Early treatment and prognosis



www.msbrainhealth.org

Single centre study in newly diagnosed patients with MS (N=639), median follow up= 99 months

The risk of increasing irreversible EDSS 4.0 increased by 7.4 (95% CI 4.8-10.1) for each year of treatment delay.



Kavalunas et al. Mult Scler 2017

Early intensive treatment vs escalation

Therapeutic Advances in Neurological Disorders — *Original Research*

Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies

Pietro Iaffaldano, Giuseppe Lucisano, Francesca Caputo, Damiano Paolicelli, Francesco Patti, Mauro Zaffaroni, Vincenzo Brescia Morra, Carlo Pozzilli, Giovanna De Luca, Matilde Inglese, Giuseppe Salemi, Giorgia Teresa Maniscalco, Eleonora Cocco, Patrizia Sola, Giacomo Lus, Antonella Conte, Maria Pia Amato, Franco Granella, Claudio Gasperini, Paolo Bellantonio, Rocco Totaro, Marco Rovaris, Marco Salvetti, Valentina Liliana Adriana Torri Clerici, Roberto Bergamaschi, Davide Maimone, Elio Scarpini, Marco Capobianco, Giancarlo Comi, Massimo Filippi, and Maria Trojano; on behalf of the Italian MS Register

Ther Adv Neurol Disord
2021, Vol. 14: 1–10
DOI: 10.1177/17562864211019574

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Maria Trojano
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Pietro Iaffaldano

EIT strategy was more effective than ESC strategy in controlling disability progression over time.

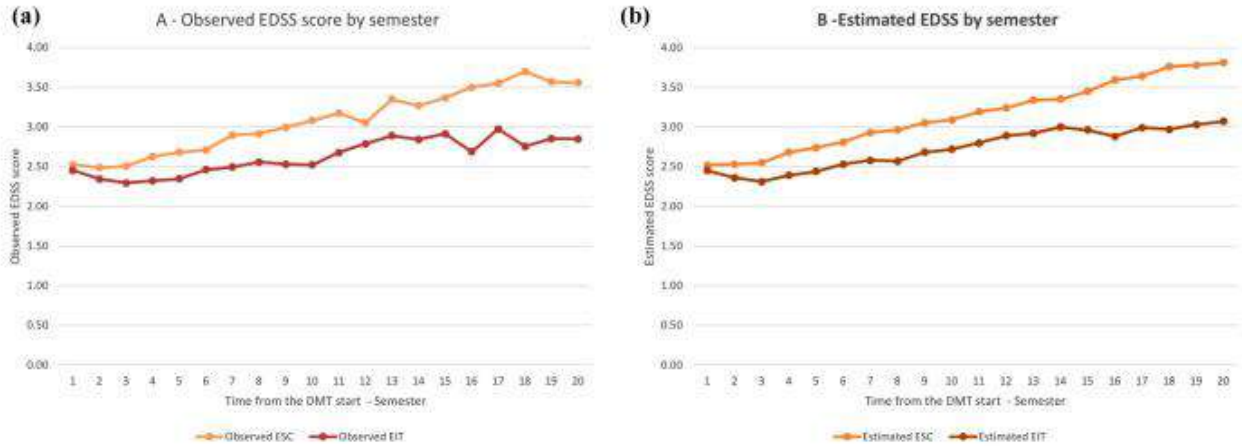


Figure 2. Comparison of disability trajectories of the observed (a) and of the estimated (b) EDSS scores by semester between the ESC and EIT groups.
EIT, early intensive treatment; EDSS, Expanded Disability Status Scale; ESC, escalation approach.

The study cohort included 2702 RRMS patients.

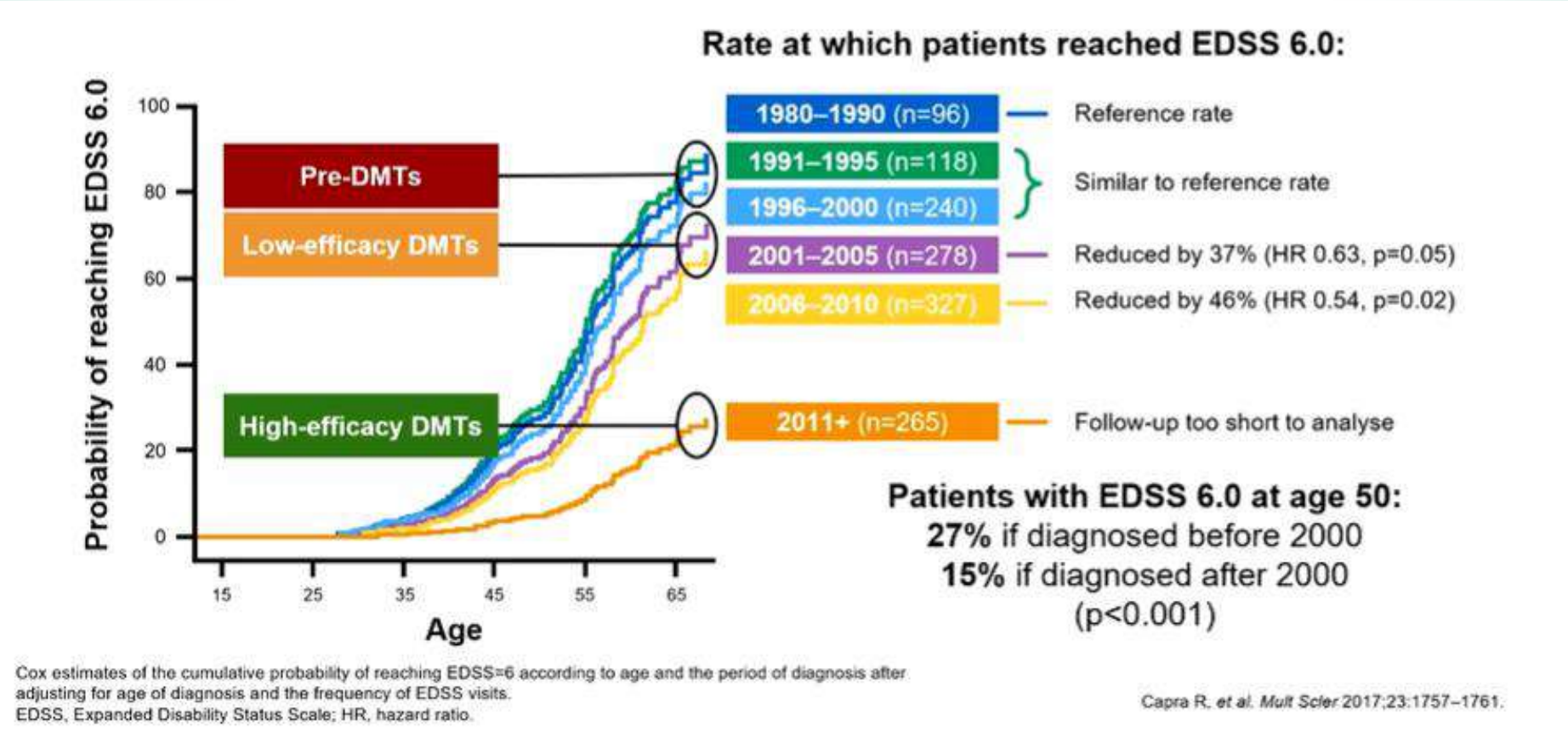
The PS matching procedure produced 363 pairs, followed for a median (interquartile range) of 8.5 (6.5–11.7) years.

Mean annual delta-EDSS values were all significantly ($p<0.02$) higher in the ESC group compared with the EIT group.

The mean delta-EDSS differences between the two groups tended to increase from 0.1 (0.01–0.19, p=0.03) at 1year to 0.30 (0.07–0.53, p=0.009) at 5 years and to 0.67 (0.31–1.03, p=0.0003) at 10 years.

Early treatment and prognosis

THE COMPARISON OF THERAPEUTIC ERA

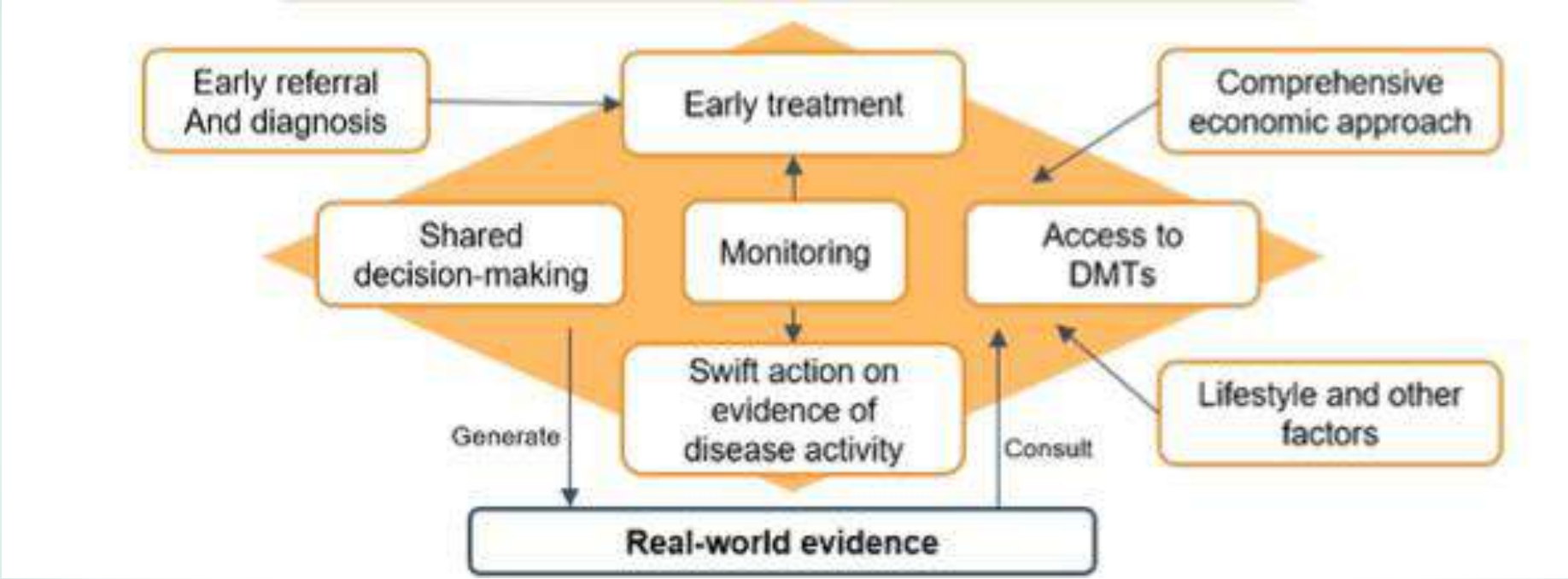


Cox estimates of the cumulative probability of reaching EDSS=6 according to age and the period of diagnosis after adjusting for age of diagnosis and the frequency of EDSS visits.
EDSS, Expanded Disability Status Scale; HR, hazard ratio.

Capra R, *et al. Mult Scler* 2017;23:1757–1761.

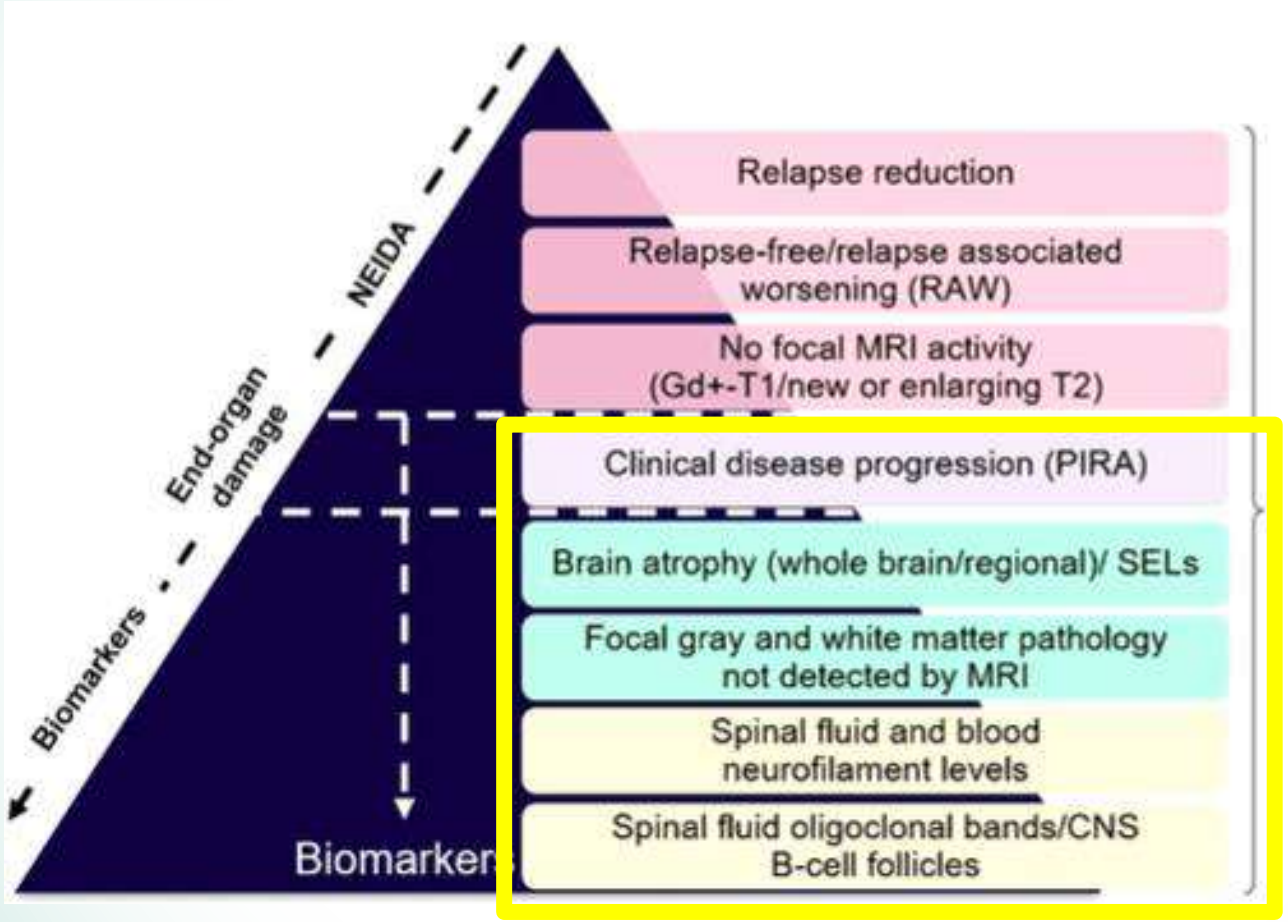
EVOLVING THE MS THERAPEUTIC PARADIGM

MAXIMIZE THE LIFELONG BRAIN HEALTH:



G,Giovannoni. Time matters in Multiple Sclerosis. 2015.

BEYOND NO EVIDENCE OF INFLAMMATORY ACTIVITY (NEIDA)



Beyond MS

- **Disability improvement**
- **Brain Health**

Slide provided courtesy of Prof G.Giovannoni

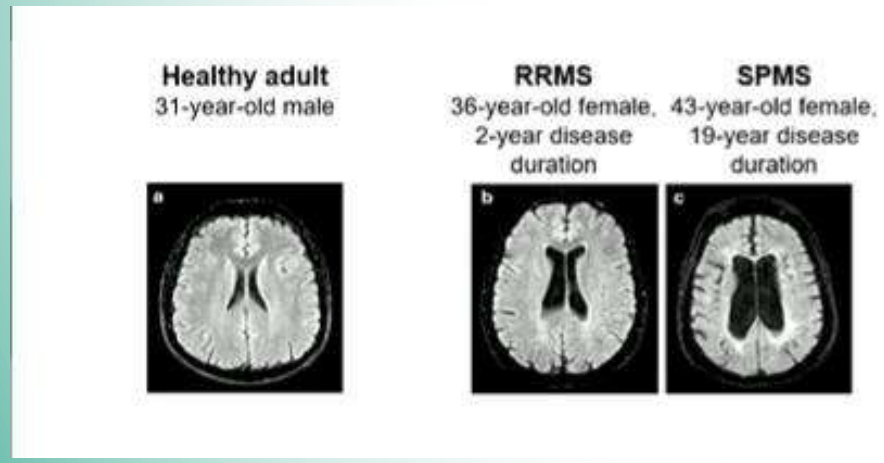
BEYOND NEIDA

➢ BRAIN VOLUME LOSS IN MS

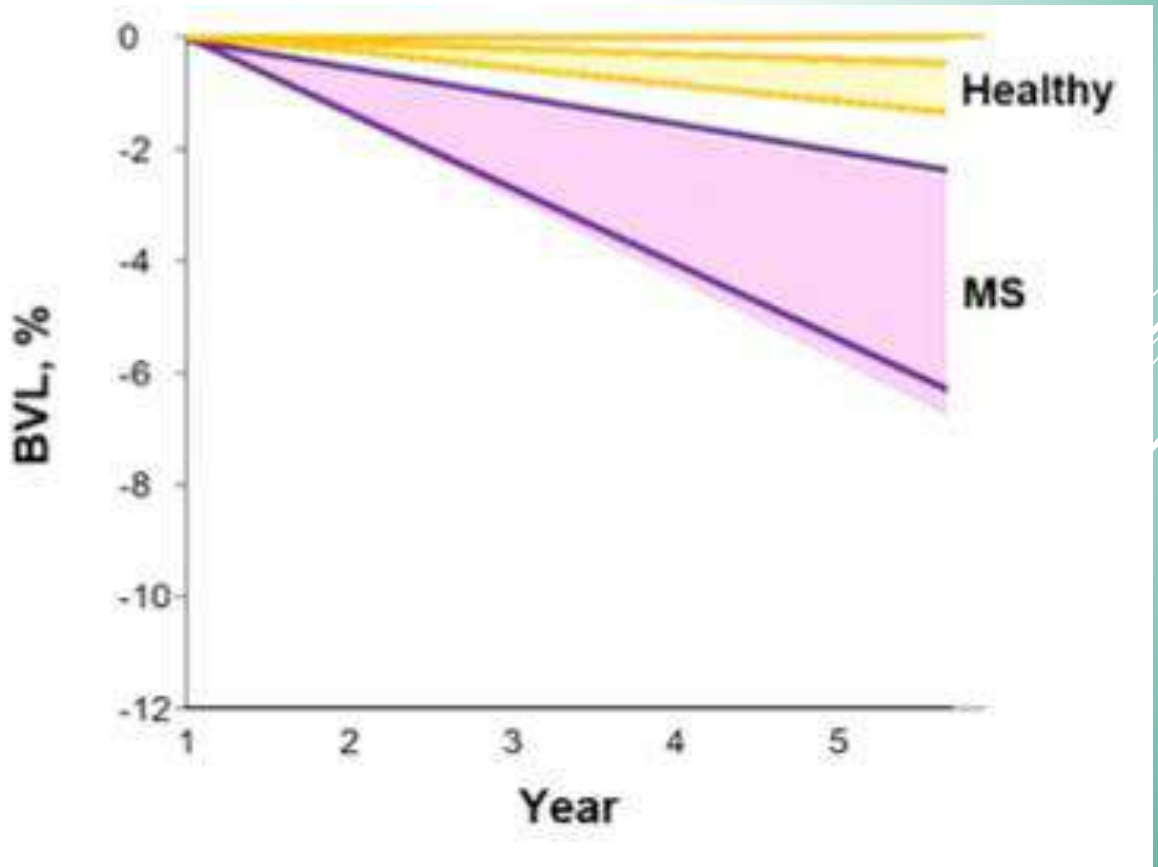
Brain volume loss begins early in MS and progresses more rapidly then in healthy individuals:

Healthy individuals: 0.1%-0.3%/year

MS: 0.5%-1.3%/year



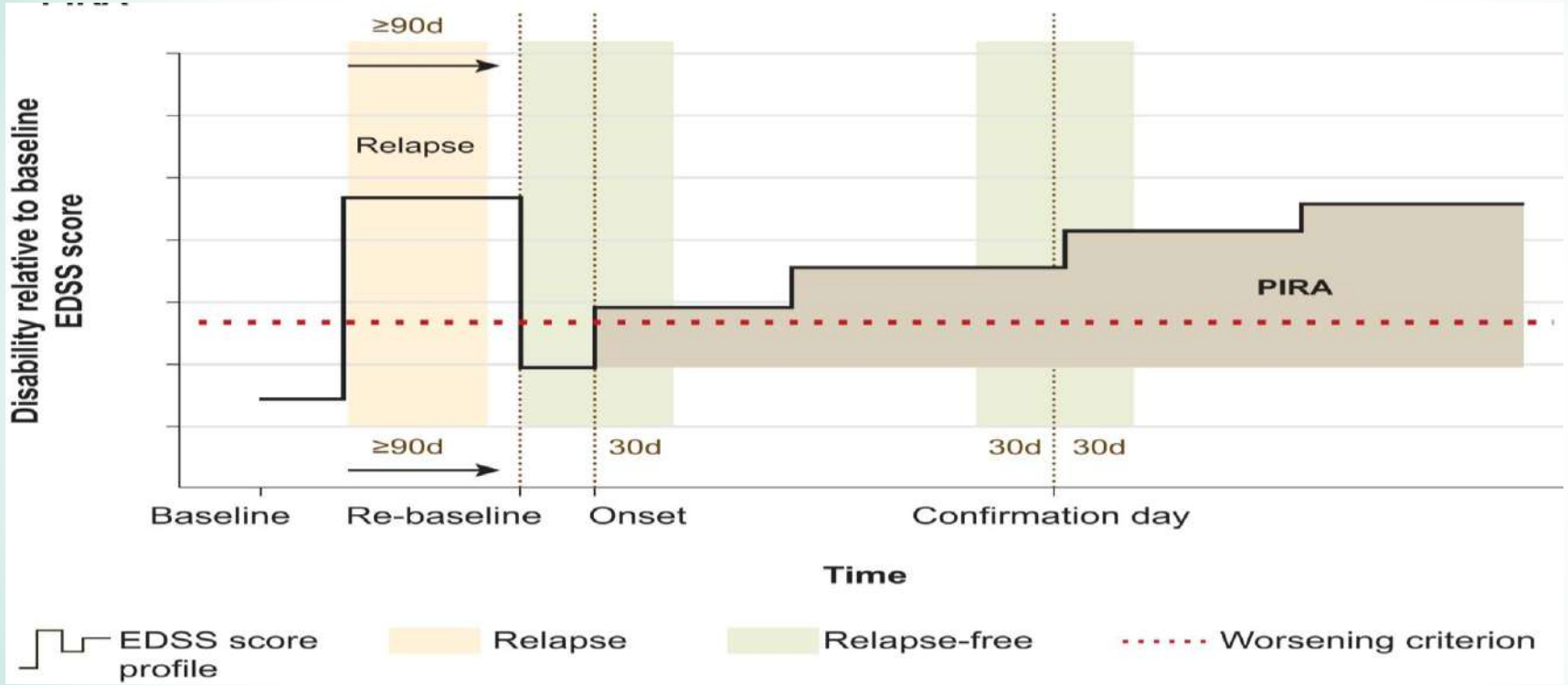
Rate of BVL: Healthy Adults vs Adults with MS



De Stefano et al. CNS Drugs. 2014; Images A-C used under permission from Rudick RA et al. Neurology 1999

BEYOND NEIDA

- **PROGRESSION INDEPENDENT OF RELAPSE ACTIVITY**

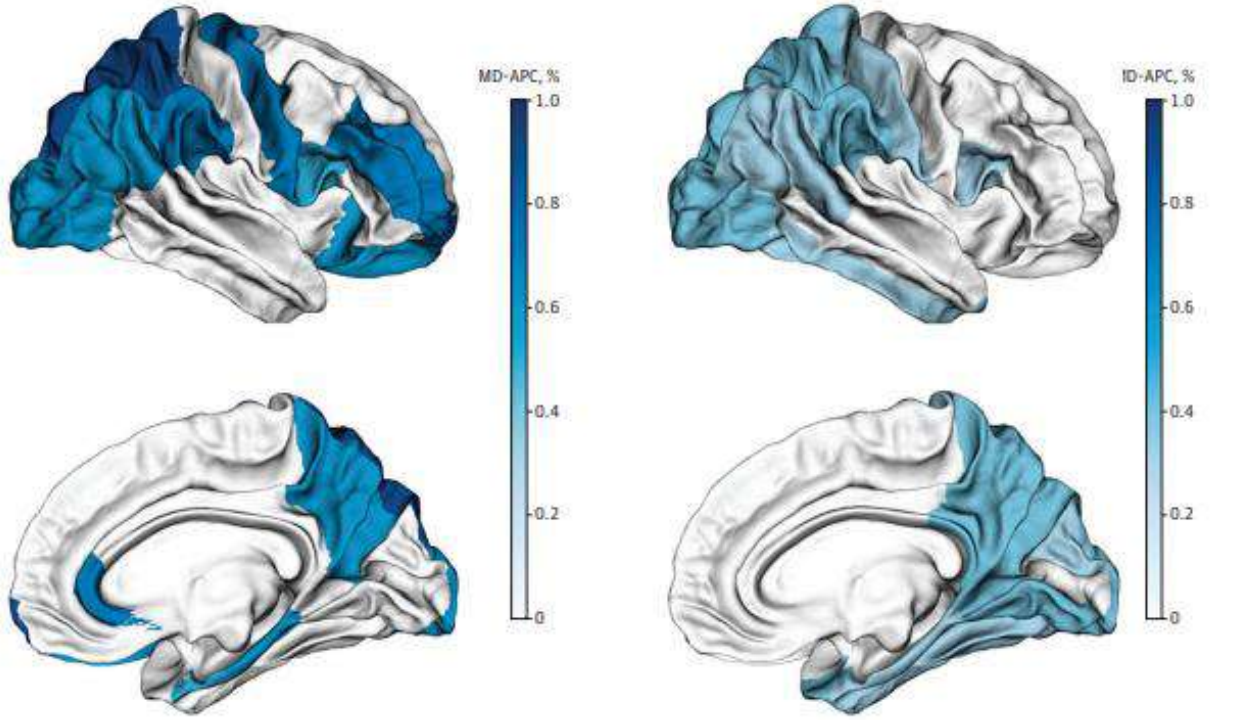


Lublin et al, *Brain*, 2022

BEYOND NO EVIDENCE OF INFLAMMATORY ACTIVITY (NEIDA)

➢ PROGRESSION INDEPENDENT OF RELAPSE ACTIVITY

Figure 3. Differences in Rates of Regional Cortical Thinning Comparing Stable Patients vs Patients With Only Progression Independent of Relapse Activity (PIRA) or Patients With Only Relapse Activity

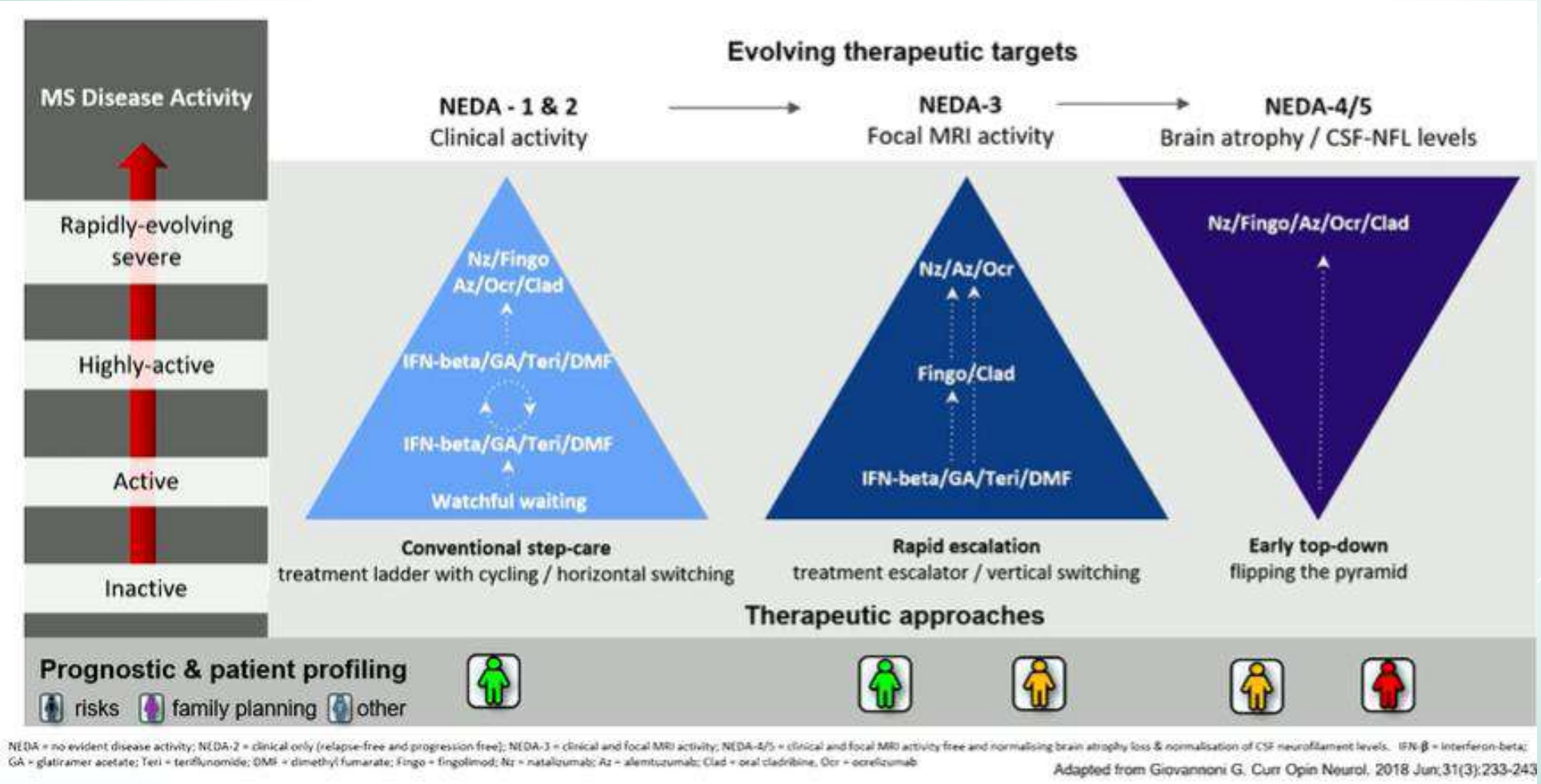


The effect size, expressed as mean difference in annual percentage cortical thickness change (MD-APC), is graphically displayed in different shades of blue for each of the Desikan-Killiany atlas[25] regions presenting significant differences between groups after correction for multiple comparisons.

Cagol et al, *JAMA Neurology*, 2022

HOLISTIC MS MANAGEMENT

Holistic management of the disease

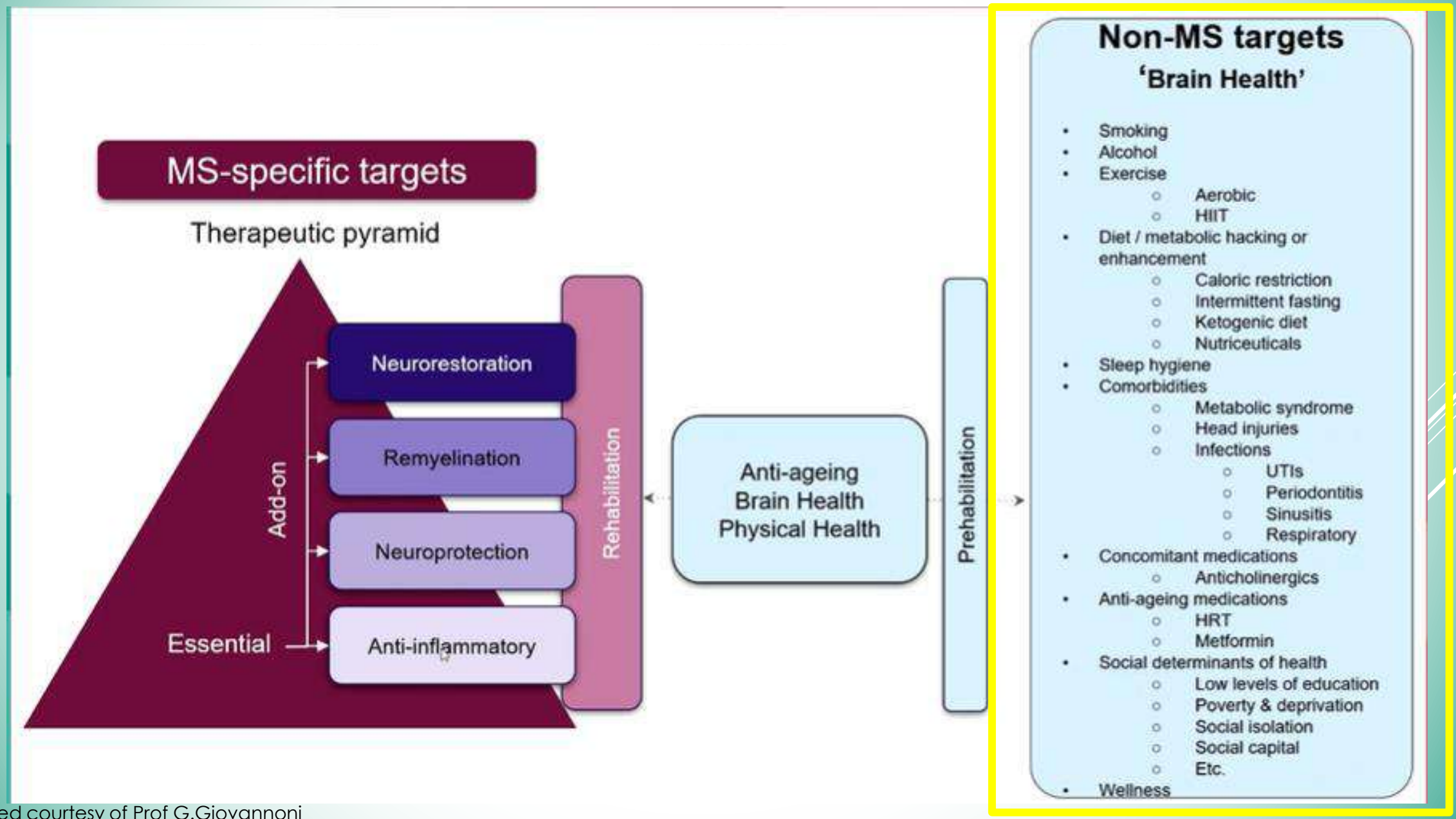


NEDA = no evident disease activity; NEDA-2 = clinical only (relapse-free and progression free); NEDA-3 = clinical and focal MRI activity; NEDA-4/5 = clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. IFN-β = interferon-beta; GA = glatiramer acetate; Teri = teriflunomide; DMF = dimethyl fumarate; Fingo = fingolimod; Nz = natalizumab; Az = alemtuzumab; Clad = oral cladribine, Ocr = ocrelizumab

Adapted from Giovannoni G. Curr Opin Neurol. 2018 Jun;31(3):233-243

Slide provided courtesy of Prof G.Giovannoni

Holistic management of the disease



Slide provided courtesy of Prof G.Giovannoni

Holistic management of the disease

- Biology underlying the recovery of function is complex and involve many biological processes
  - Synaptic
  - Axonal
  - Cortical
  - Interacts with systems biology (ageing, comorbidities, concomitant medications, exercise and lifestyle factors)
- Can we afford not develop combination therapies?

1#Comorbidities and polypharmacy

2#Physical activity and dietary habits

3# Neurorestoration and neuroprotection

1#Comorbidities, and Polypharmacy

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

The Framingham cardiovascular risk score and 5-year progression of multiple sclerosis

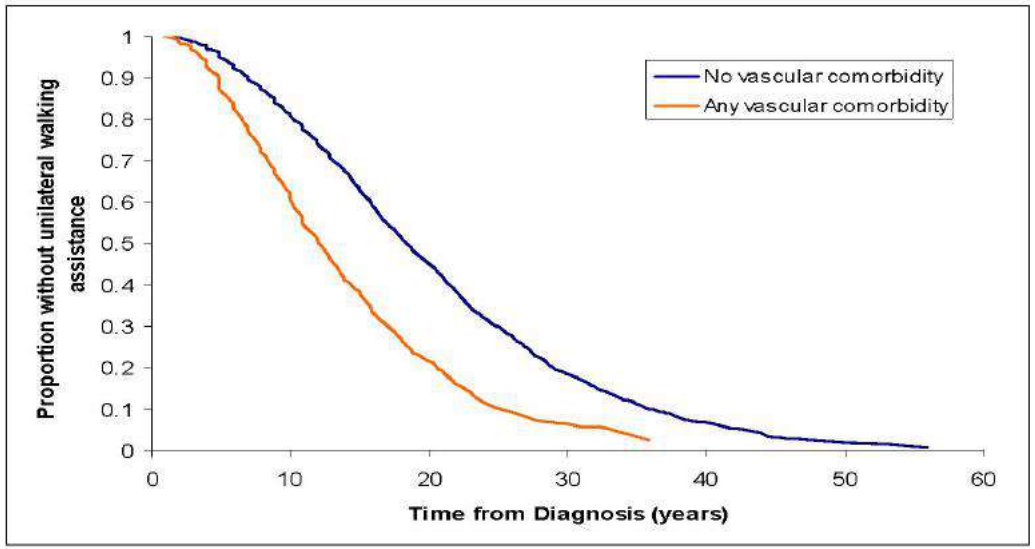
Martina Petruzzo, Antonio Reia, Giorgia T. Maniscalco, Fabrizio Luiso, Roberta Lanzillo, Cinzia Valeria Russo, Antonio Carotenuto, Lia Allegorico, Raffaele Palladino, Vincenzo Brescia Morra, Marcello Moccia

First published: 22 October 2020 | https://doi.org/10.1111/ene.14608 | Citations: 2

Martina Petruzzo and Antonio Reia contributed equally as co–first authors.

Cardiovascular comorbidities accelerate disability progression

Higher cardiovascular risk was associated with higher risk of relapses, disability, and DMT escalation in MS.
Early identification, correction, and treatment of cardiovascular comorbidities should be carefully considered within MS management.



Marrie et al. Neurology 2010;74:1041–1047.

1#Comorbidities, and Polypharmacy

Therapeutic Advances in Chronic Disease

Original Research

Exploring polypharmacy phenomenon in newly diagnosed relapsing–remitting multiple sclerosis: a cohort ambispective single-centre study

Aurora Zanghi, Emanuele D'Amico, Salvatore Lo Fermo and Francesco Patti

Ther Adv Chronic Dis

2021, Vol. 12: 1–12

DOI: 10.1177/2040622320983121

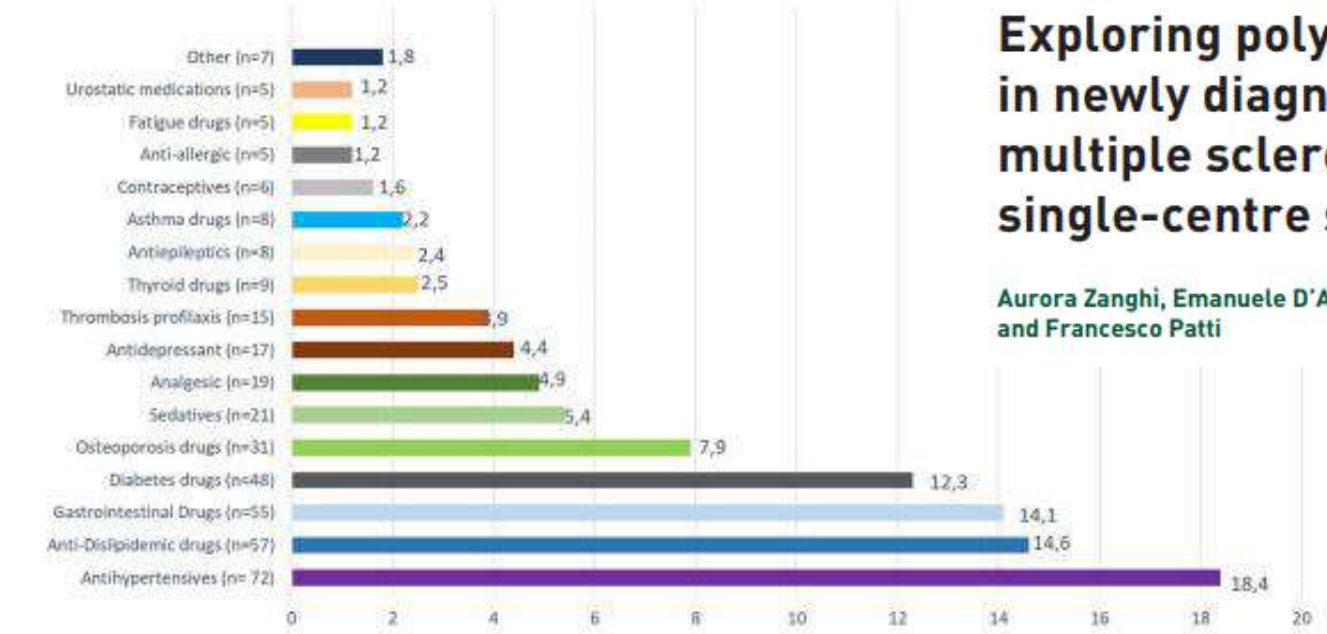


Figure 2. Proportion of categories of medications used by poly RRMS patients.
Groups were calculated according to the total number of drugs taken by poly RRMS patients.

2# Physical activity and dietary habits

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Obesity worsens central inflammation and disability in multiple sclerosis

Mario Stampanoni Bassi, Ennio Iezzi, Fabio Buttari, Luana Gilio, Ilaria Simonelli, Fortunata Carbone, Teresa Micillo, Veronica De Rosa, Francesco Sica, Roberto Furlan, Annamaria Finardi, Roberta Fantozzi, Marianna Storto, Paolo Bellantonio, Pamela Pirollo, Sonia Di Lemme, Alessandra Musella, Georgia Mandolesi, Diego Centonze and Giuseppe Matarese

Springer | CURRENT NUTRITION REPORTS

springer.com

Curr Nutr Rep. 2018; 7(3): 150–160.

Published online 2018 Aug 16. doi: 10.1007/s13668-018-0236-z

PMCID: PMC6132382

PMID: 30117071

The Role of Diet in Multiple Sclerosis: Mechanistic Connections and Current Evidence

Ilana Katz Sand

Clinical Rehabilitation 2005; **19**: 165–169

A pilot study of the effect of aerobic exercise on people with moderate disability multiple sclerosis

J Kileff and **A Ashburn** Rehabilitation Research Unit, School of Health Professions and Rehabilitation Sciences, University of Southampton, Southampton, UK

Received 21st October 2003; returned for revisions 24th December 2003; revised manuscript accepted 25th July 2004.

MULTIPLE SCLEROSIS JOURNAL | MSJ

Controversies in Multiple Sclerosis

Specific dietary interventions to tackle obesity should be a routine part of recommended MS care – Yes

Mario Stampanoni Bassi and Diego Centonze

Multiple Sclerosis Journal

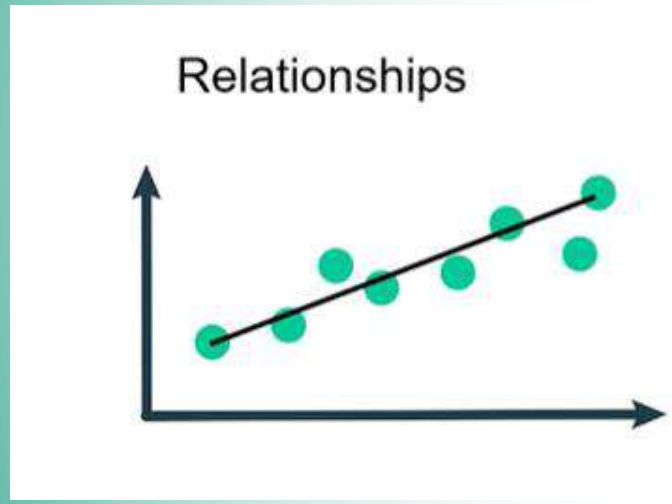
2020, Vol. 26(13) 1627–1629

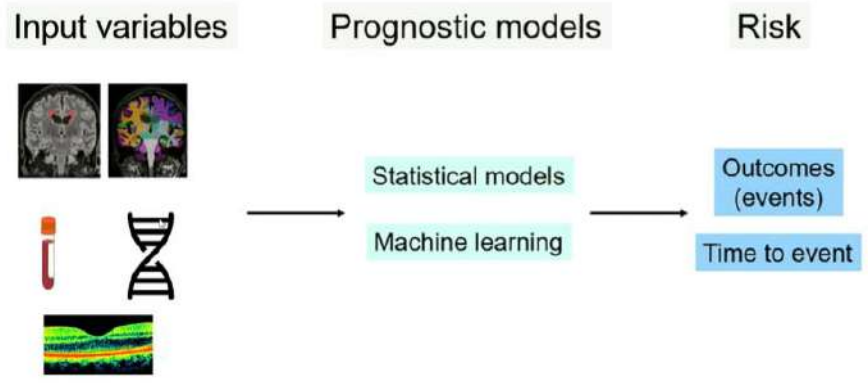
DOI: 10.1177/1352458520916701

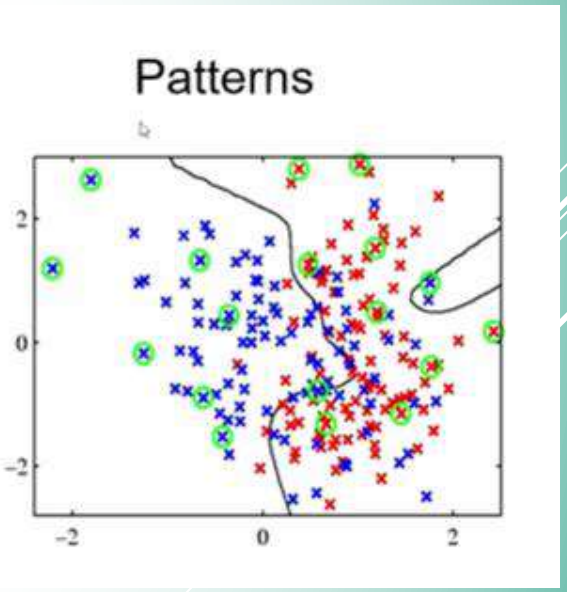
Holistic management of the disease

Learning from Statistics

MOVING FROM RELATIONSHIPS TO PATTERNS



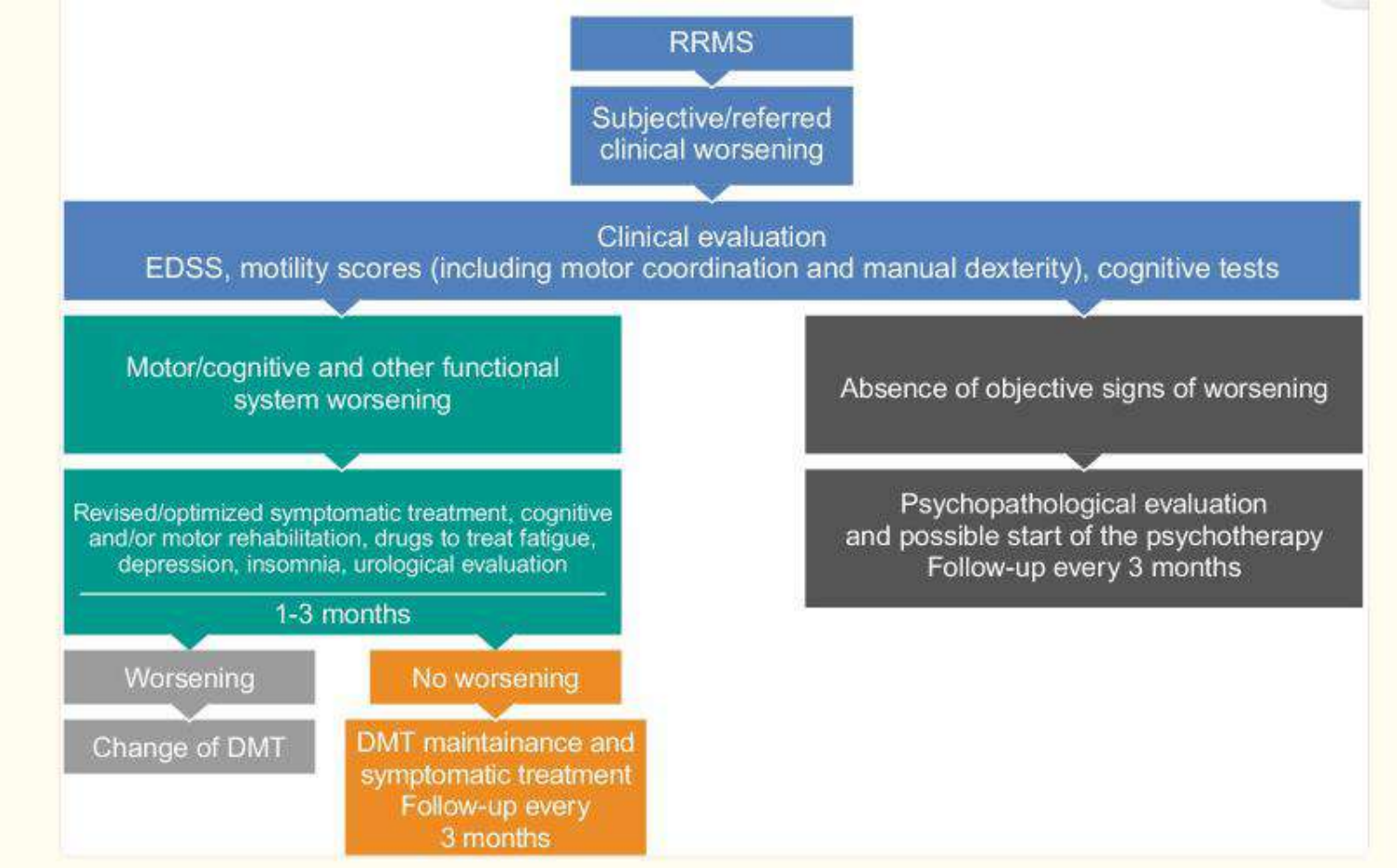




UNMET NEEDS

Holistic management of the disease

A symptoms related algorithm in unclear transitional phases

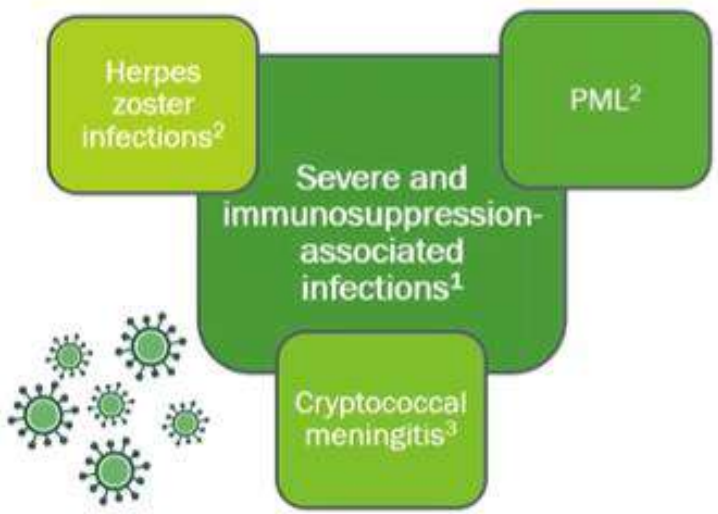


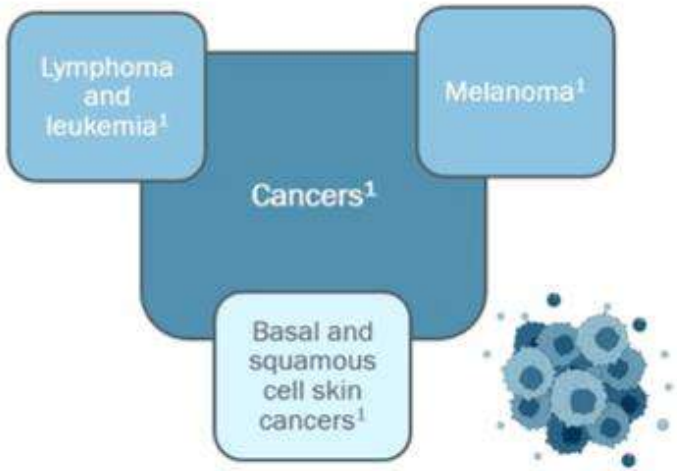
Lus et al. Mult Scler Rel Dis 2022

WARNINGS

WARNINGS

Long term DMTs Safety





Post-approval studies with real-world data (in red patiens from Msbase)

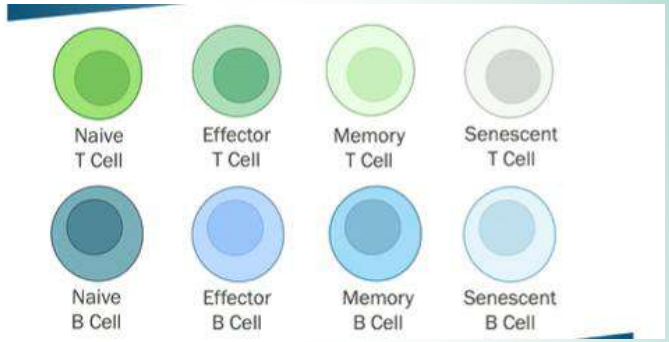
CLARION[1,2] 2018–2034**	MANUSCRIPT[2] 2019–2029**	TYSABRI SWITCH[2,3] 2017–2024**
patients newly initiating: ○ fingolimod (n=~4,000; n=658) or ○ cladribine (n=~4,000; n=546)	patients exposed to: ○ ocrelizumab (n=~5,000; n=1,897) or ○ other DMTs (n=~3,500; n=3,303)	patients (80,327) receiving natalizumab after: ○ IFN or GA (n=1,069) ○ fingolimod (n=500) ○ DMF (n=142) or ○ teriflunomide(n=58)

1. Butzkueven et al. Curr. ,Med Res Opin. 2022.38.1167:76. 2, Eupas Register number EUPASS24484. 3. eupass reister number 28619; 4 EUPAS regster number 19800; NCT03399981

1.Jalk G. et al. Vaccines (Basel) 2020; 9:12. 2.Pianas R et al. Patient related outcome Meas 2014; 25-33:3. 3Wienemann T. et al. BMC Neurol. 2020;20.158.

Warnings

MS changes across the lifespan
Real world evidence and treatment decision later in LIFE



Increasing FOCUS

- Long term efficacy and safety of newer high More patients are ageing on long-terms MS therapy efficacy DMTs
- Optimal approaches for aging patients who has controlled MS but increasing comorbidities.
- De escalation of therapy may provide equivalent efficacy and fewer risks than continuing EIT in patients reaching immunosenescence

Adaptive immunity and age

- The benefit/risk profile changes as people with MS age:
- Less need for immunosuppressant to manage disease activity
- Increased risk of infection with immunosenescence
- Potential dor more severe infection outcomes

1. Schweltzer et al. Curr Opin Neurol 2019; 2. Volmer BL et al Front Neurol 2022; 3 Marrie RA et al. Neurology 2016

Warnings
Efficacy and AGE

frontiers in Neurology

ORIGINAL RESEARCH
published: 10 November 2017
doi: 10.3389/fneur.2017.00577

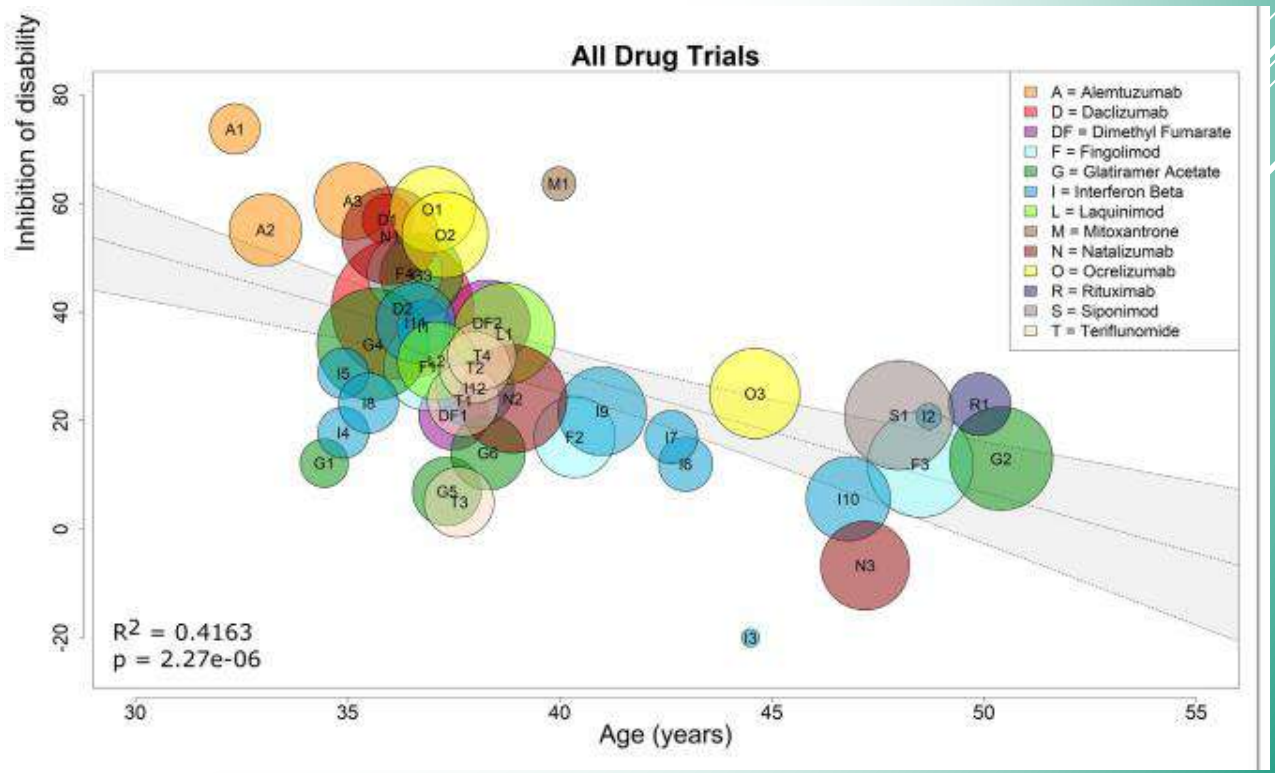
Meta-analysis of the Age-Dependent Efficacy of Multiple Sclerosis Treatments

Ann Marie Weideman[1†], Marco Aurelio Tapia-Maltos[1,2†], Kory Johnson[3], Mark Greenwood[4] and Bibiana Bielekova[1]*

Efficacy of immunomodulatory disease-modifying therapies (DMTs) on MS disability progression is strongly dependent on age.

The efficacy of immunomodulatory DMTs on MS disability strongly decreased with advancing age ($R2 = 0.6757$, $p = 6.39e{-}09$).

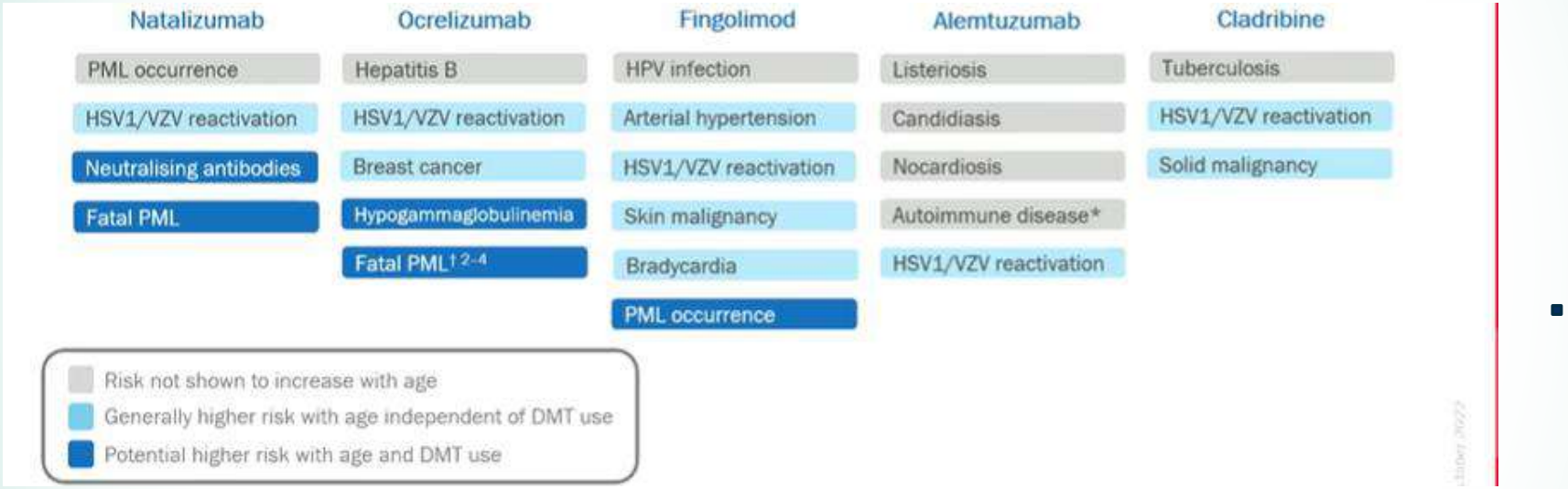
The regression predicts zero efficacy beyond approximately age 53 years.
The comparative efficacy rank derived from the regression residuals differentiates high- and low-efficacy drugs.
High-efficacy drugs outperform low-efficacy drugs in inhibiting MS disability only for patients younger than 40.5 years



Warnings

Do Severe adverse events with high efficacy DMTs correlate with patient age?

Selected AEs observed during DMTs and correlation with age in PwMS



- **Increased risk of infection with immunosenescence**
- **Potential or more severe infection outcomes**

1. Schwietzer F et al. Curr Opin Neurol. 2019. 2. OCREVUS (USA). 2022; 3 Petel et al. JAMA neurology 2021. 4. GENENTECH 6 monthly report OCREVUS and PML June 2022

Take home messages

Take home messages

- **Treatment target needs to go beyond NEDA**
- Normal brain volume loss
- Holistic management of MS-marginal gains

- **Early high efficacy DMTs treatment markedly reduces long term disability in people with MS and preserve brain health.**

- **Neurologists can make the difference:**
- ***Sentinel events occur early in the course of MS***
- ***Time is brain and spinal cord***
- ***Flipping the pyramid***

- **Clinical trials are short; life is long.**