

For HCPs

Brain Health: Time Matters

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Barts and The London

BartsMS

Disclosures

Professor Giovannoni has received personal compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Abbvie, Bayer-Schering Healthcare, Biogen-Idec, Canbex, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.

Regarding www.ms-res.org survey results in this presentation: please note that no personal identifiers were collected as part of these surveys and that by completing the surveys participants consented for their anonymous data to be analysed and presented by Professor Giovannoni.

Professor Giovannoni would like to acknowledge several companies and colleagues for making available data slides for this presentation.

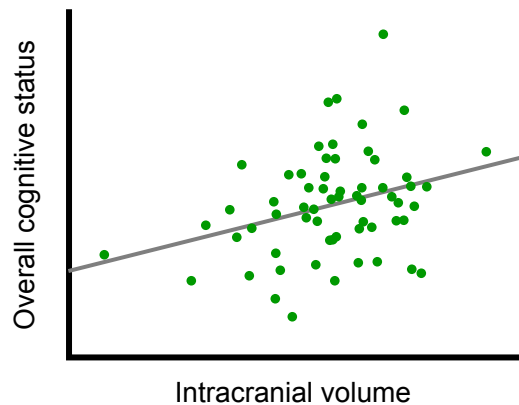
Who should take responsibility?



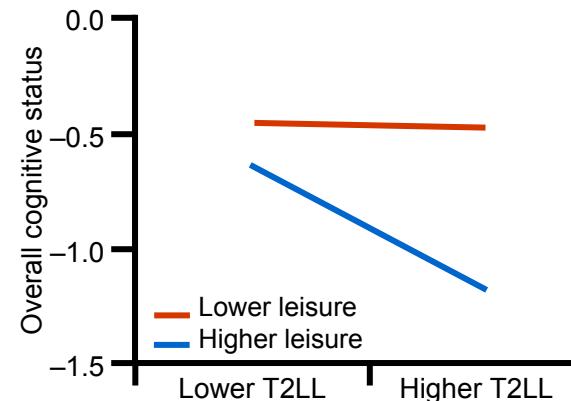
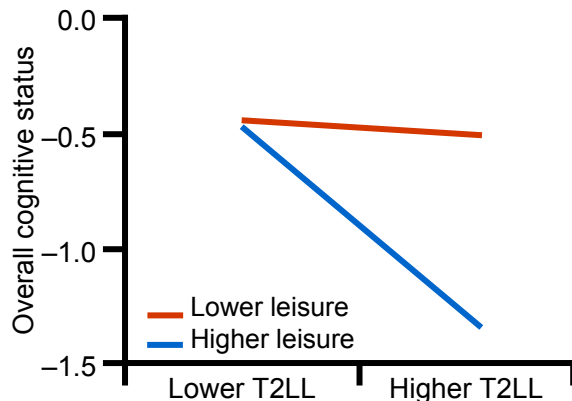
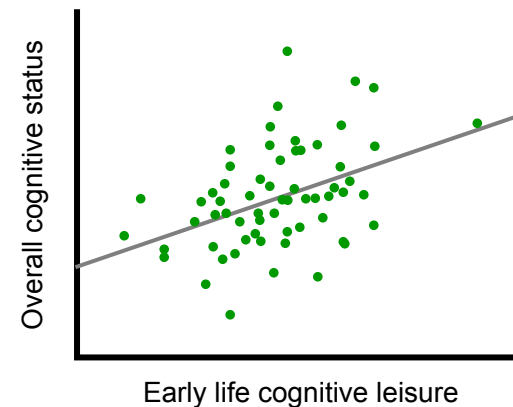
- The person with MS?
- The HCP or neurologist?
- The healthcare system?
- The regulators?
- Society?

Brain reserve and cognitive reserve in MS

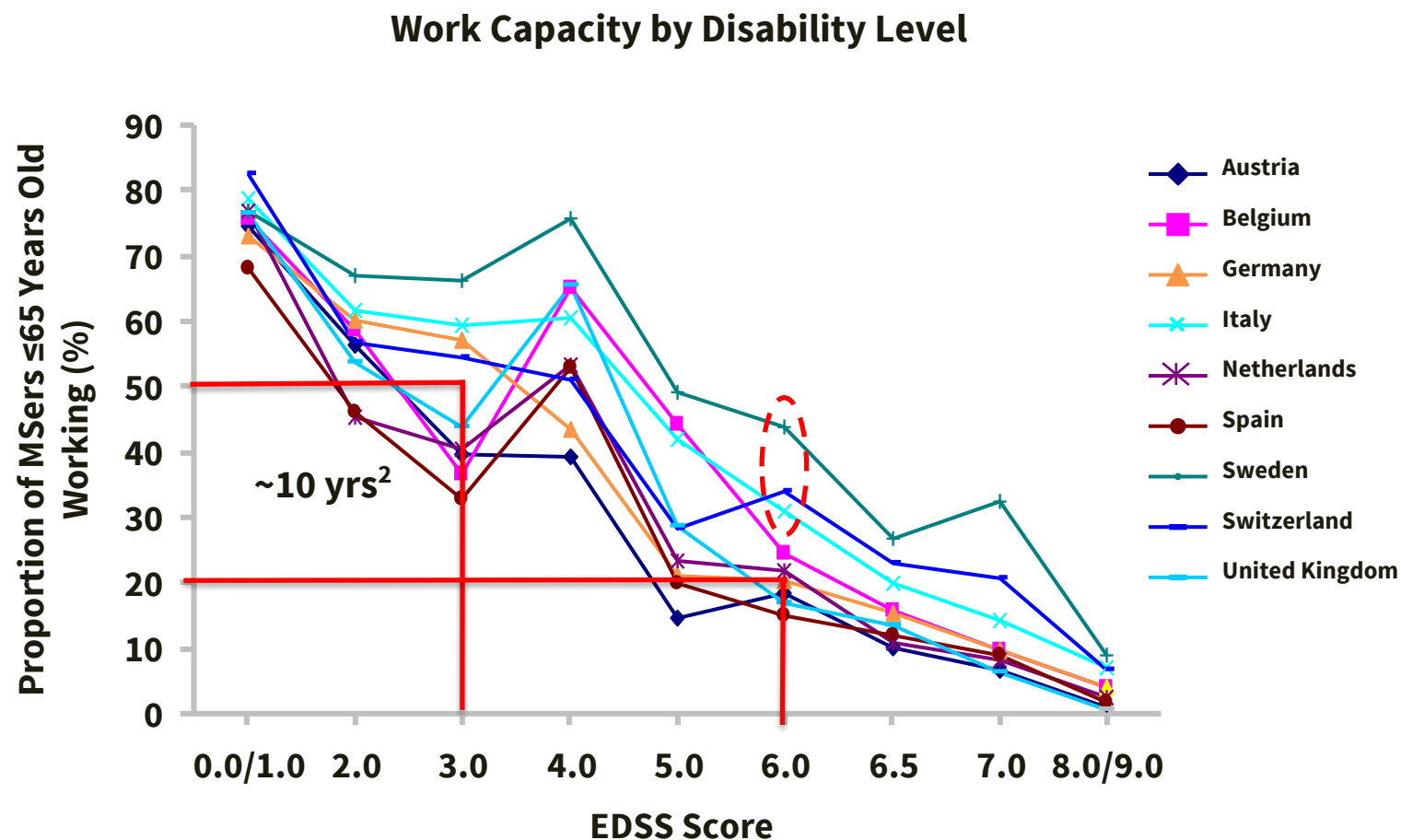
Brain reserve protects against disease-related cognitive decline



Cognitive reserve independently protects against disease-related cognitive decline over and above brain reserve



Consequences of increasing EDSS scores: loss of employment¹

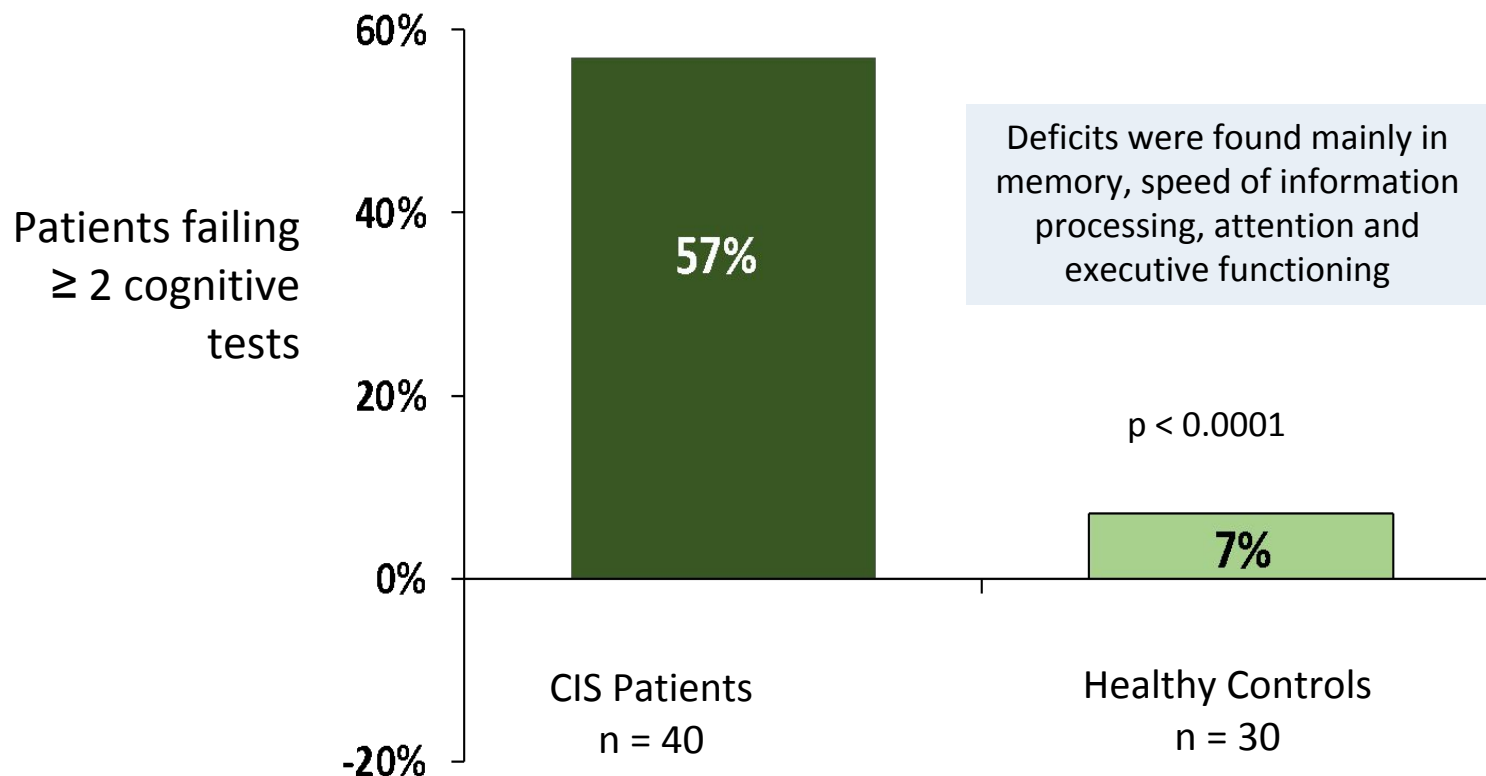


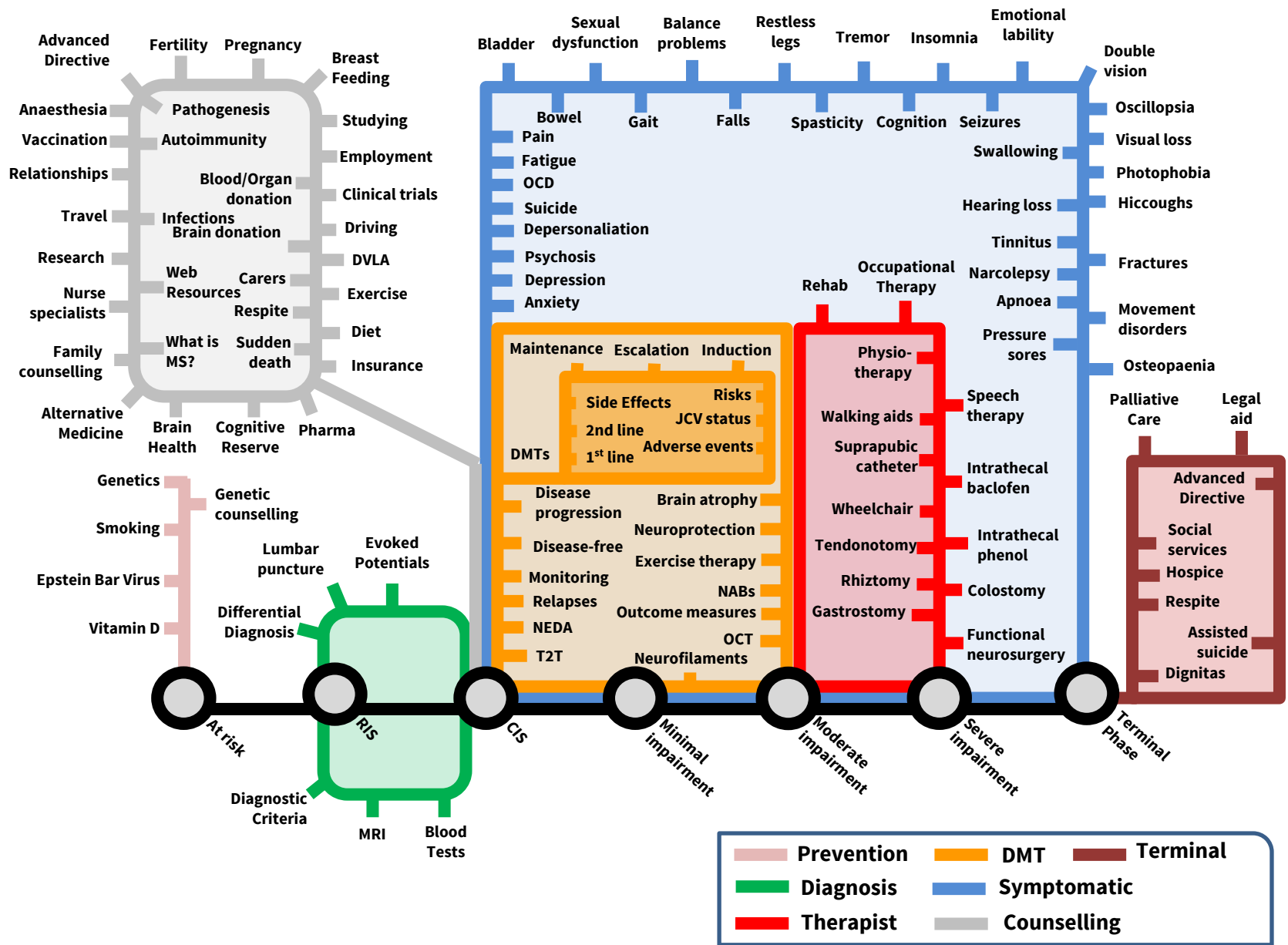
The proportion of MSers employed or on long-term sick leave is calculated as a percentage of MSers aged 65 or younger.

1. Kobelt G et al. *J Neurol Neurosurg Psychiatry*. 2006;77:918-926;

2. Pflieger CC et al. *Mult Scler*. 2010;16:121-126.

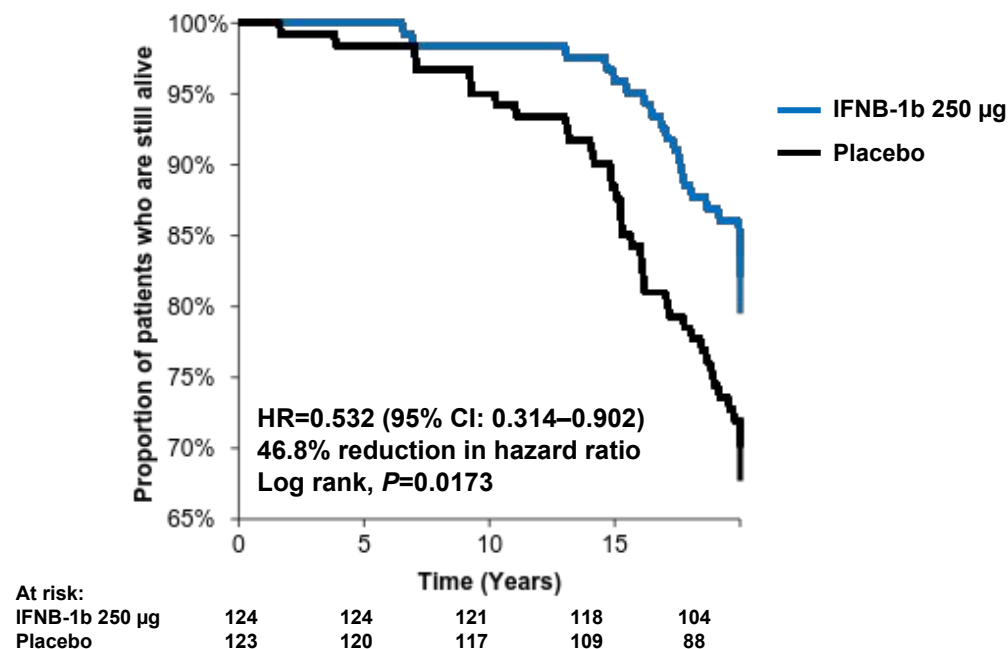
Impact of MS: cognitive functioning in the CIS stage





IFN-beta long term follow up: Time from Study Randomization to Death

Early treatment with IFNB1b: associated with 46.8% reduction in the hazard rate for mortality-NNT 8



Pathological substrate for brain atrophy: 11,000 to 1

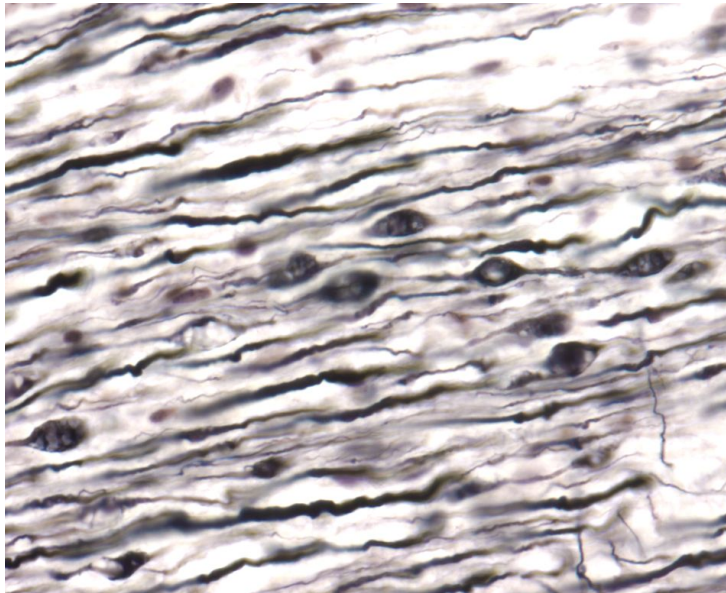
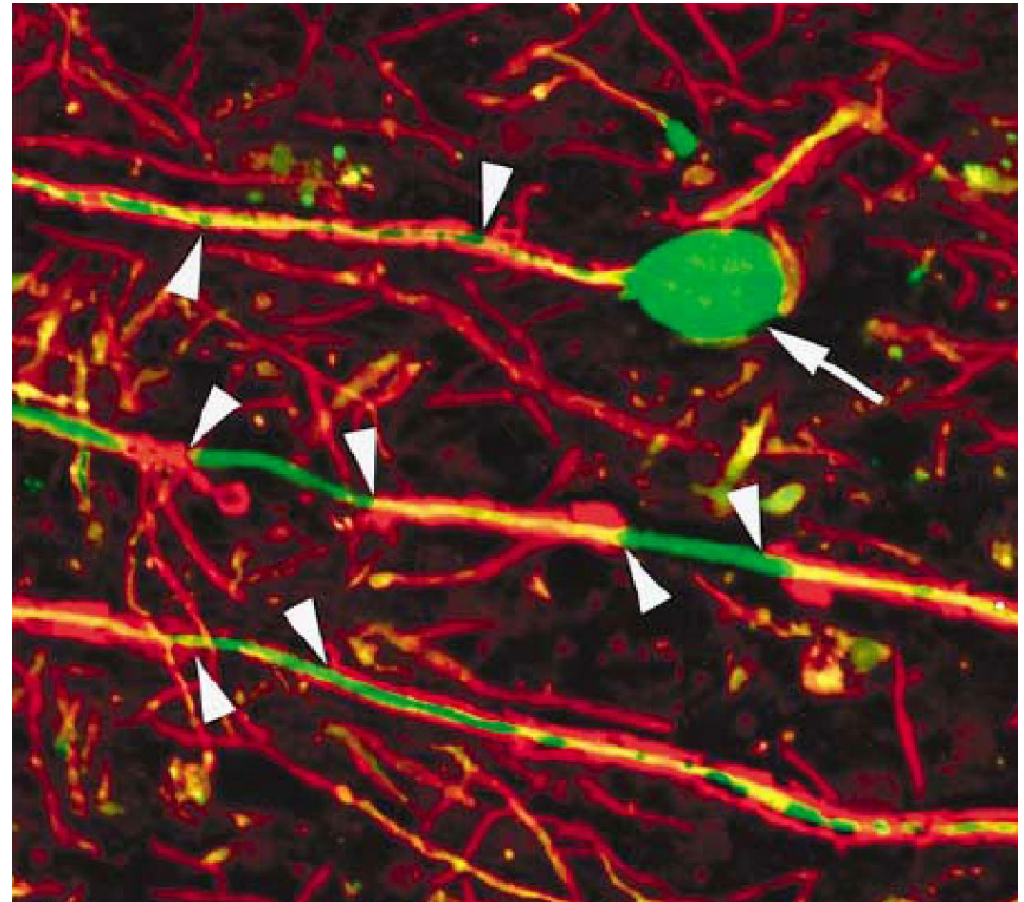


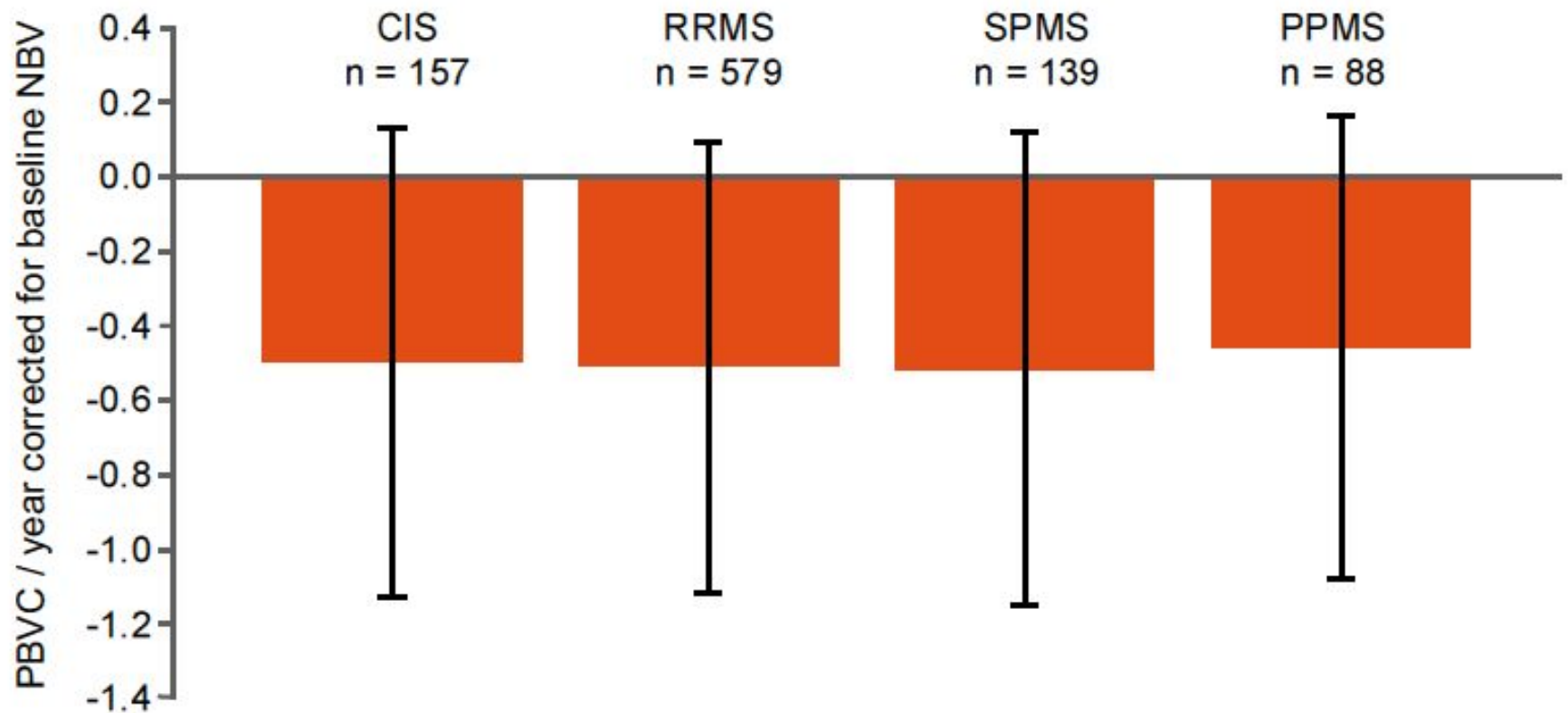
TABLE 2. DISTRIBUTION AND NUMBER OF TRANSECTED AXONS IN MULTIPLE-SCLEROSIS LESIONS.

TISSUE (NO. OF PATIENTS)	NO. OF LESIONS ANALYZED	NO. OF TRANSECTED AXONS/mm ³ *
Active lesions (3)	5	11,236±2775
Chronic active lesions (4)	13	
Edge		3138±688
Core		875±246
Nonlesion white matter (5)	11	17±2.8
Control white matter (4)	5	0.7±0.7

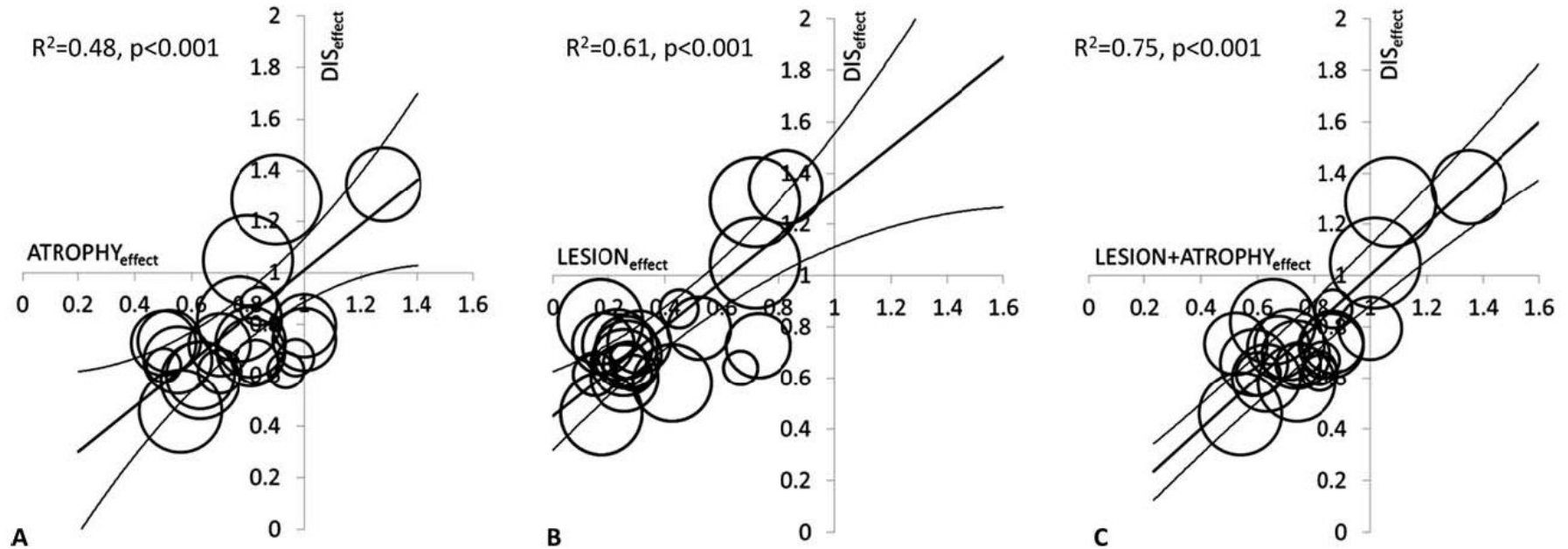


Brain atrophy occurs across all stages of the disease

n= 963 MSers



Treatment effect on disability predicted by effect on T2-lesion load and brain atrophy



Meta-analysis of treatment effect on EDSS worsening (y) vs effects on MRI lesions and brain atrophy, individually or combined, in 13 placebo-controlled RRMS trials (13,500 patients)

No evident disease activity: NEDA

Treat-2-target



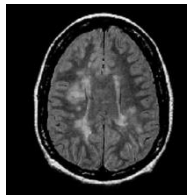
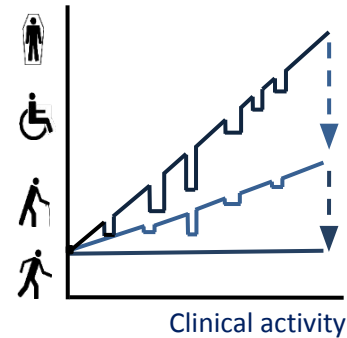
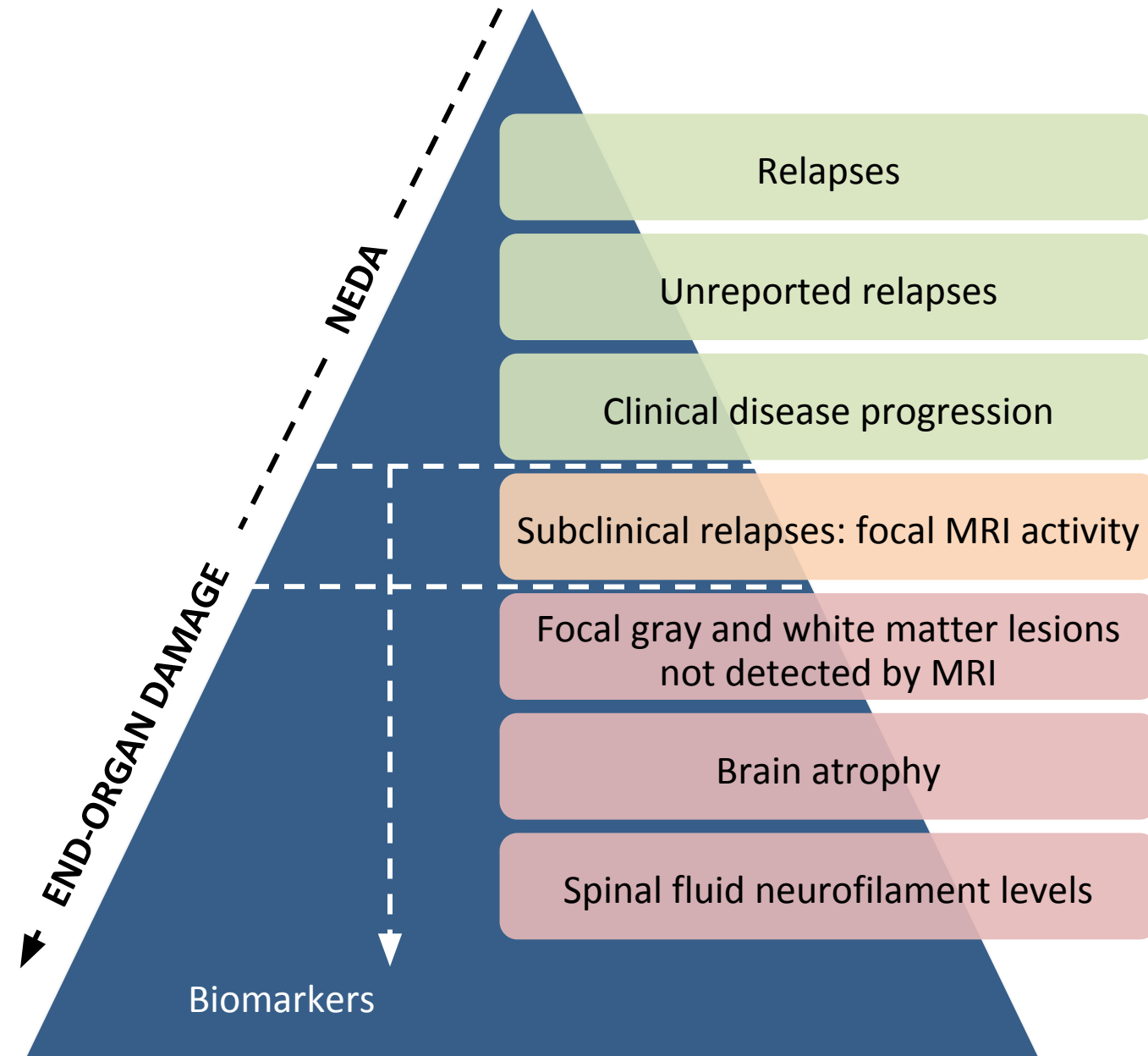
What is NEDA?

- × No relapses
- × No sustained disability progression (EDSS)
- × No MRI activity
 - × No new or enlarging T2 lesions
 - × No Gd-enhancing lesions

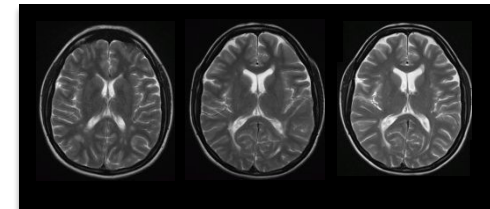
DAF^{1,2}

What about MEDA (minimal evident disease activity)?

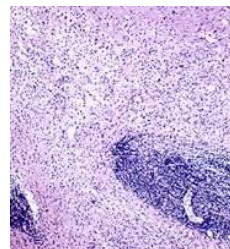
MS Iceberg



Focal MRI activity

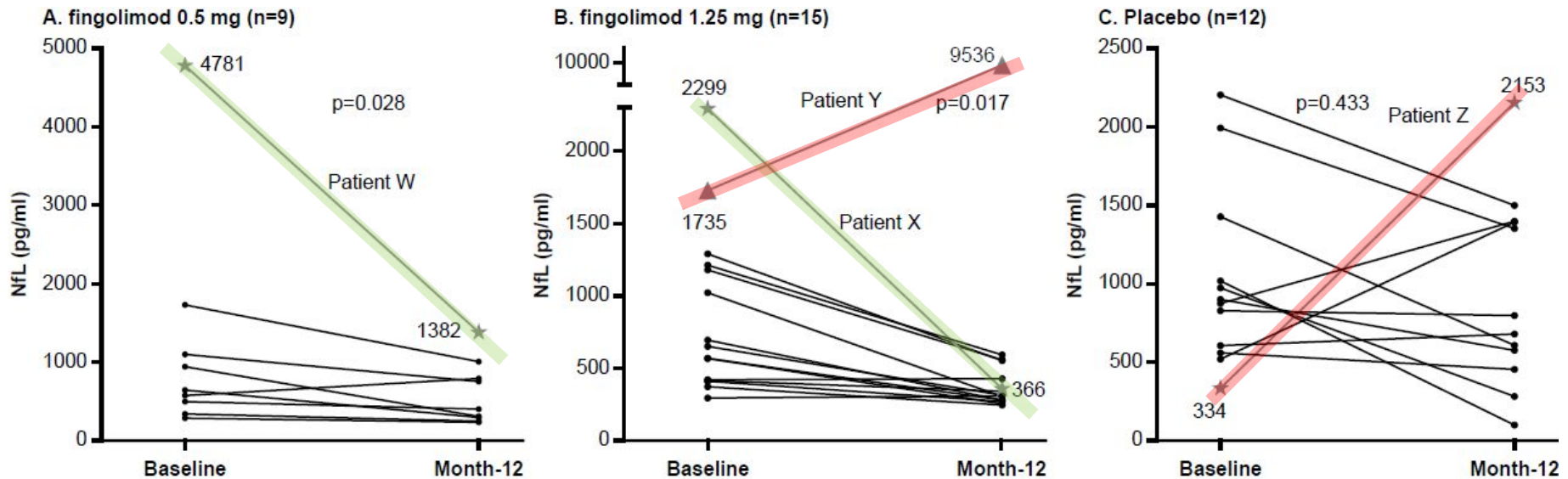


Hidden focal and diffuse MRI activity



Microscopic or biochemical pathology

Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis



Clinical and MRI outcomes at baseline and Month-12 for outlier patients

Patient W: EDSS decreased from 2 to 1.5; reduction in Gd+ lesions from 5 to 0; decrease in T2 lesion volume (12309 mm³ to 11828 mm³) and no relapses.

Patient X: stable EDSS score of 1.5; no Gd+ lesions (both timepoints); stable T2 lesion volume (5153 mm³ to 5159 mm³) and no relapses.

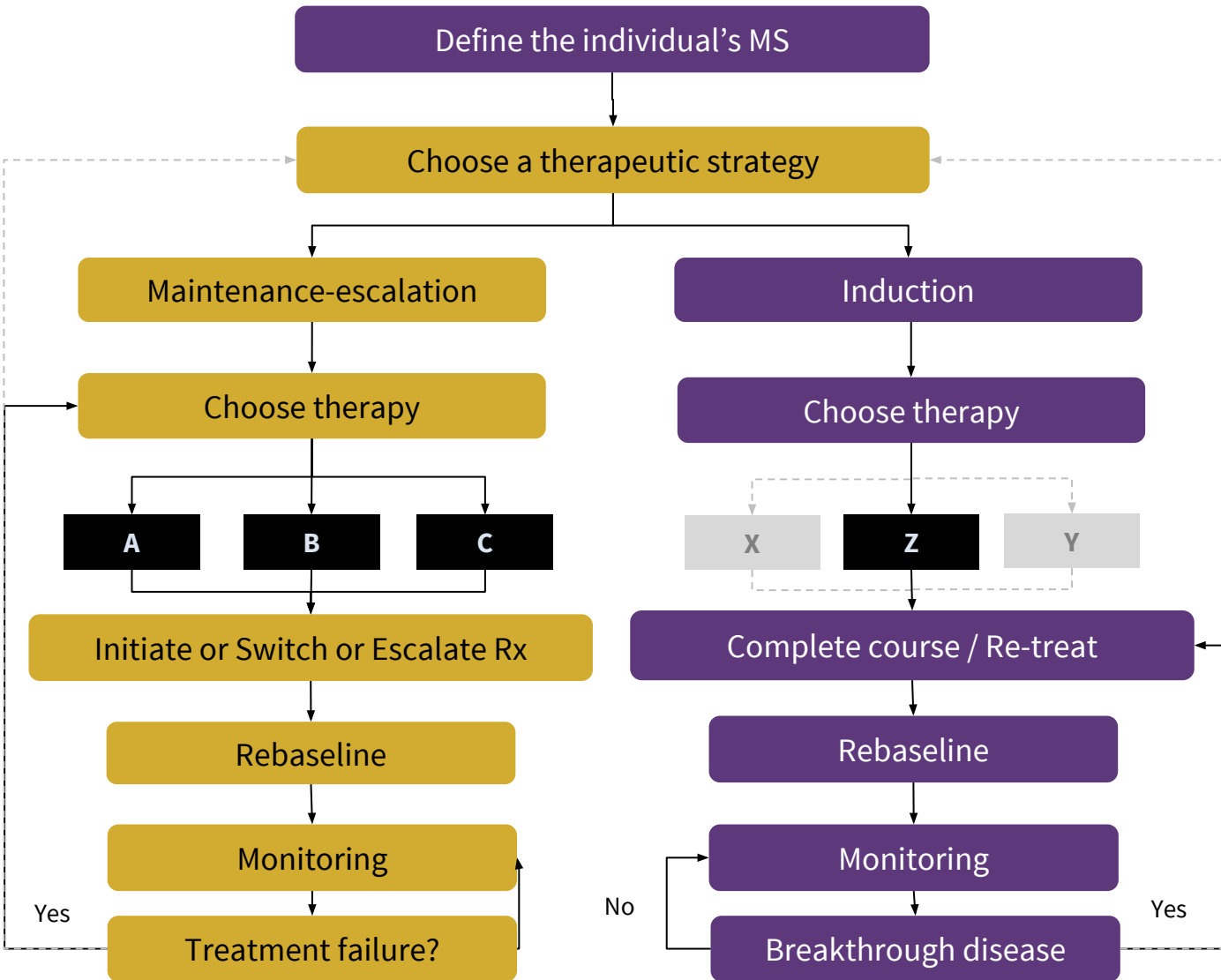
Patient Y: EDSS from 1.5 to 4.5; reduction in Gd+ lesions from 1 to 0; increase in T2 lesion volume (6512 mm³ to 23794 mm³); two relapses.

Patient Z: increase in EDSS (3 to 4.5); increase in Gd+ lesions from 1 to 7; increase in T2 lesion volume (5888 mm³ to 6569 mm³); two relapses.

Fingolimod → PPMS (INFORMS STUDY)
 ClinicalTrials.gov ID: NCT00731692
 Siponimod → SPMS (EXPAND STUDY)
 ClinicalTrials.gov ID: NCT01665144

BARTS-MS T2T-NEDA ALGORITHM

T2T = treating-to-target; NEDA = no evident disease activity



- MS prognosis based on clinical and MRI indices
- Life style and goals
- Shared goals for therapy

- Patient's preferences?
- Your choice?

- Patient's preferences?
- Your choice?

- Only one licensed induction therapy at present

Rebaselining:

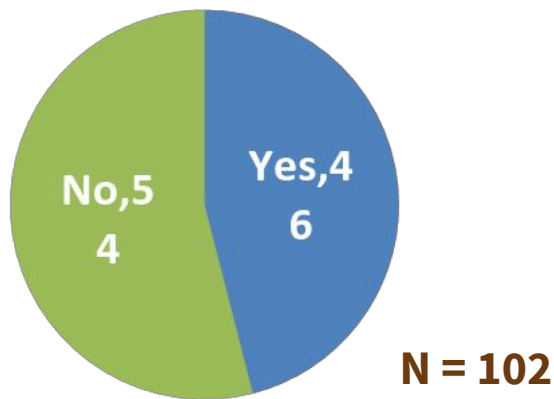
- ifn- β , natalizumab, fingolimod, teriflunomide, dimethyl-fumarate=3-6 months
- glatiramer acetate=9 months
- alemtuzumab=24 months

Individual measures:

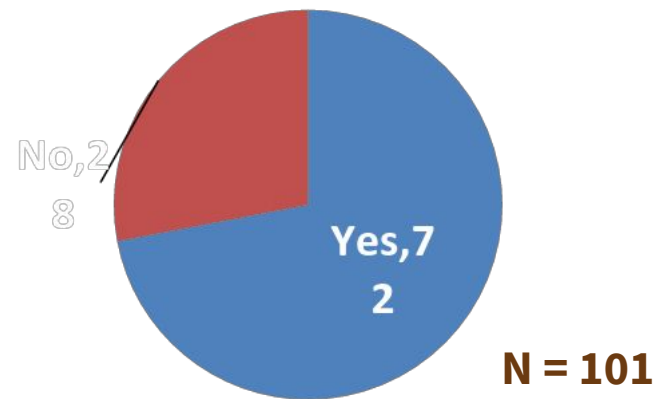
- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Drug or inhibitory markers, e.g. NABs?

Relapse reporting

Patients who have ever experienced an MS relapse and not contacted a healthcare professional

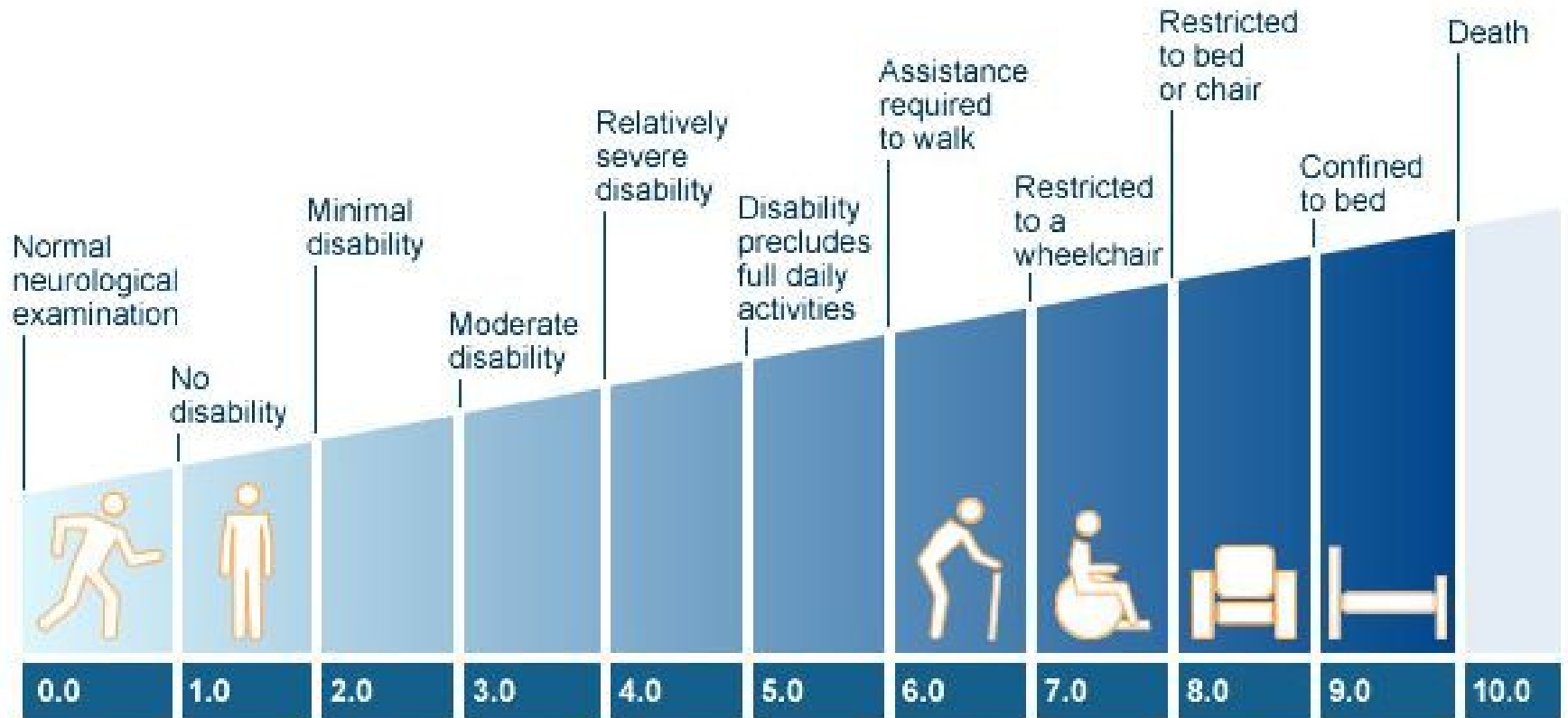


Patients reporting most recent relapse to a specialist MS team



- Most common reasons for not reporting their most recent relapse to a specialist MS team were:
 - ‘Mild relapse so not felt necessary’ 5/28 (18%)
 - ‘Saw or spoke to their GP’ 4/28 (14%)
- Most common reasons for not seeking healthcare support were:
 - ‘Felt I could manage’/mild relapse 18/42 (43%)
 - ‘Nothing that they can do to help’ 8/42 (19%)

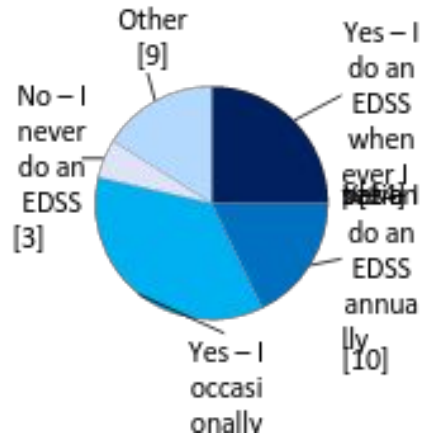
EDSS



Adapted from <http://www.msdecisions.org.uk/>. Accessed 15 April 2014.
Previously adapted from Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).
Neurology 1983; 33:1444–1452.

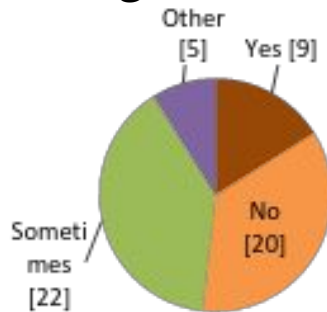
Survey of UK MSologists

Clinical – In your routine MS clinical practice, do you use the EDSS?



Yes – I do an EDSS whenever I see a patient	14	25%
Yes – I do an EDSS annually	10	18%
Yes – I occasionally do an EDSS	20	36%
No – I never do an EDSS	3	5%
Other	9	16%

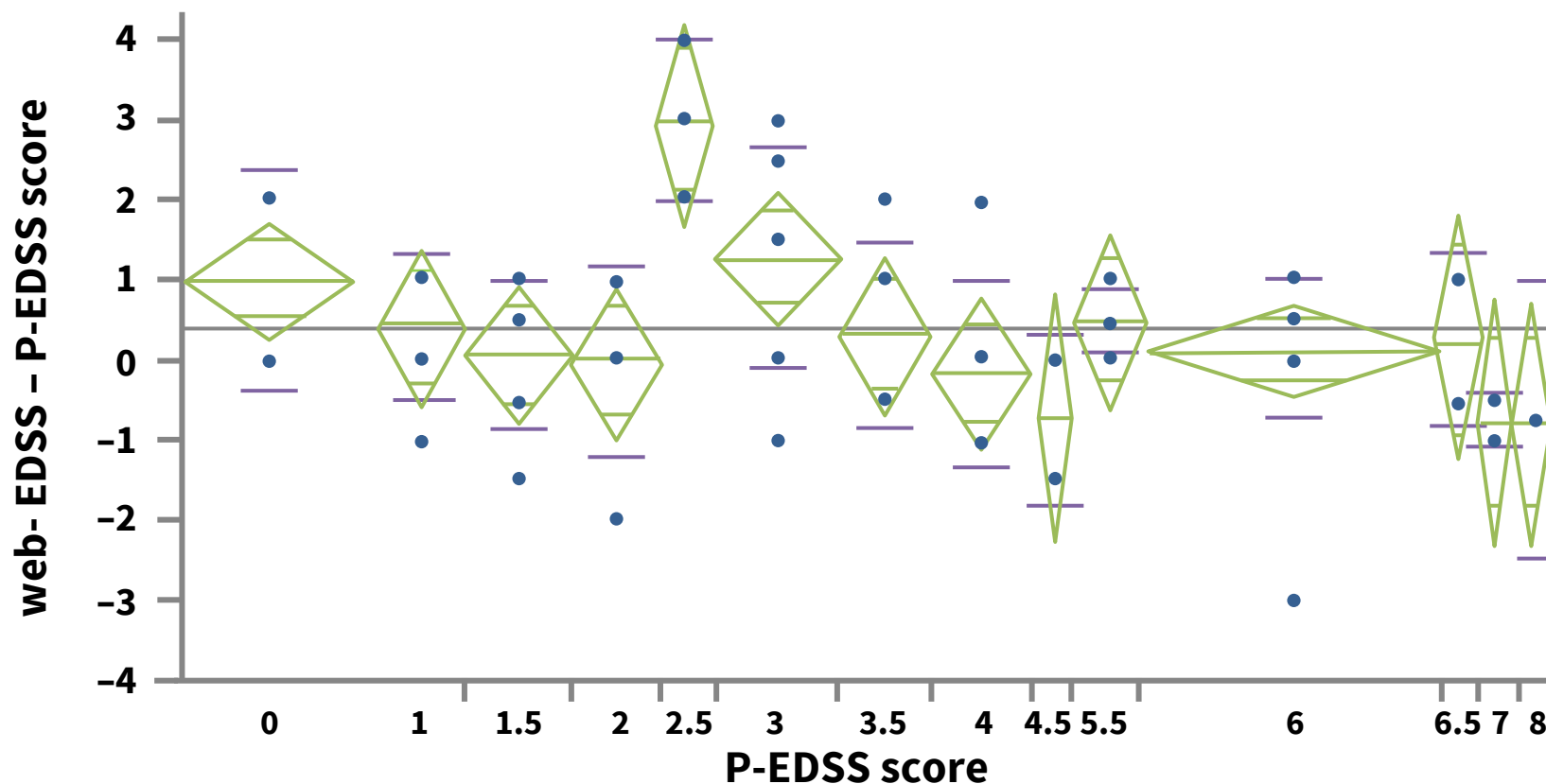
Clinical – If you do an EDSS in your routine clinical practice, do you walk the patients to assess their walking distance?



Yes	9	16%
No	20	36%
Sometimes	22	39%
Other	5	9%

Validating a novel web-based method to capture disease progression outcomes in MS

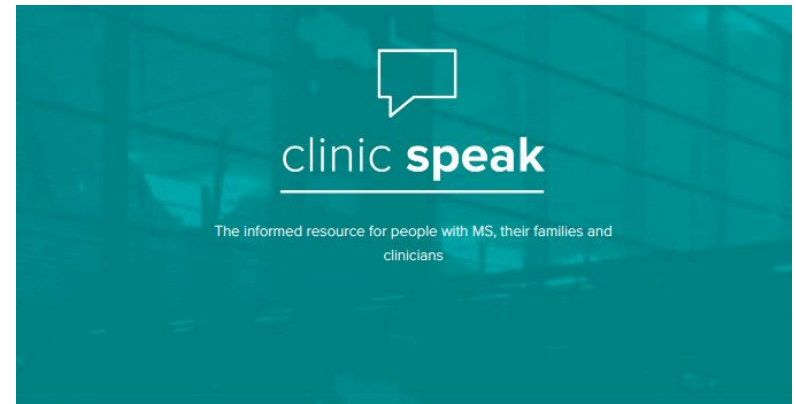
ORIGINAL COMMUNICATION



P-EDSS, physician or actual EDSS.

The midpoint of the diamonds is the mean difference between the two EDSS scores, the upper and lower lines within the diamonds are the 95% CI. The width of the diamond indicates the sample size, the dots the actual values. The horizontal line at 0.46 indicates the mean difference between the two scores. The graph indicates the greater variation at lower EDSS scores, with greater agreement at scores > 5.

clinicspeak.com



9 hole peg test

The 9 hole peg test is the gold standard for monitoring arm and hand function in clinical trials. This cardboard version gives you independence from your neurologist, empowering you to test and monitor your own disease progression.

🕒 2 minute instructional video

[Visit Website](#)

EDSS online assessment

Calculate, track and understand your MS disease status.

This is version 1 of the system and will be updated once we have new tools for assessing the neurological systems and walking distance more accurately.

🕒 5-10 minute online assessment

[Visit Website](#)

What is the 9 hole peg test?

The 9 hole peg test is the gold standard for monitoring arm and hand function in clinical trials. This cardboard version gives you independence from your neurologist, empowering you to test and monitor your own disease progression.

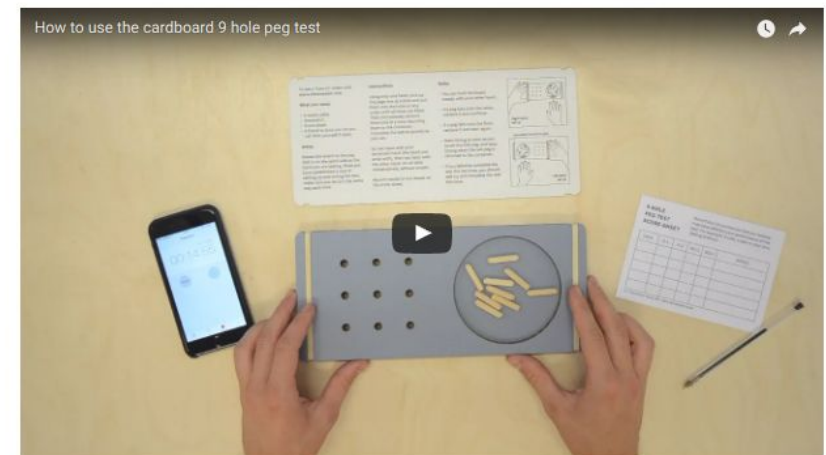
Why is the 9 hole peg test important?

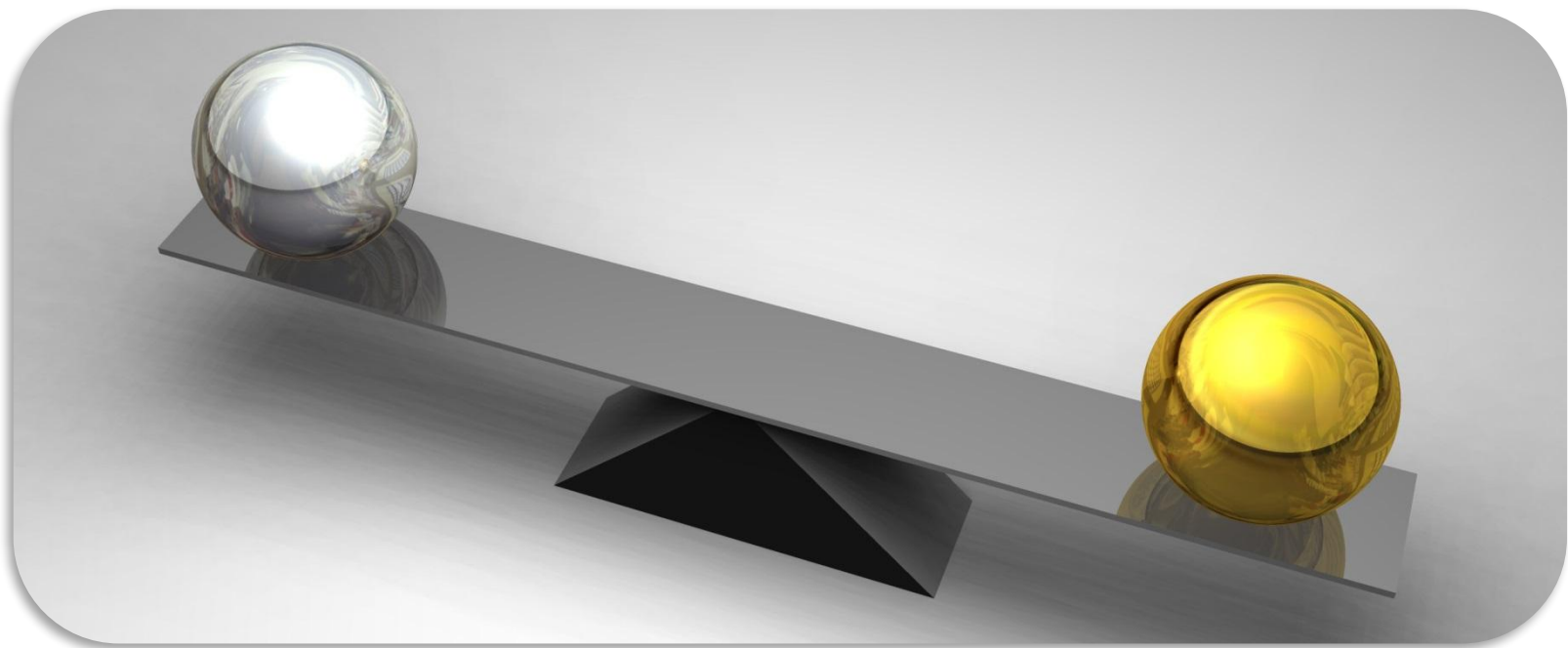
Preserving arm and hand function is critical for people with MS to remain independent and to preserve their quality of life. Over 90% of people with Multiple Sclerosis valued arm and hand function as being more important to them than leg function.

Although disease-modifying therapies (DMTs) may not be able to preserve lower limb function in people with MS who already have pre-existing walking problems, we hypothesise that some DMTs may be able to preserve arm and hand function.

Therefore, we are striving for future trials of new and existing DMTs to focus on arm and hand function.

How do I use the 9 hole peg test?





Disability Accumulation in MS Has a Negative Impact on Multiple Aspects of Life

20:50:80

Employment

1. Approximately **20%** of MSers with MS for <5 years are unemployed¹
2. More than **50%** of MSers are unemployed 10 years after diagnosis²
3. Approximately **80%** of MSers with an EDSS of 6.0 are unemployed³

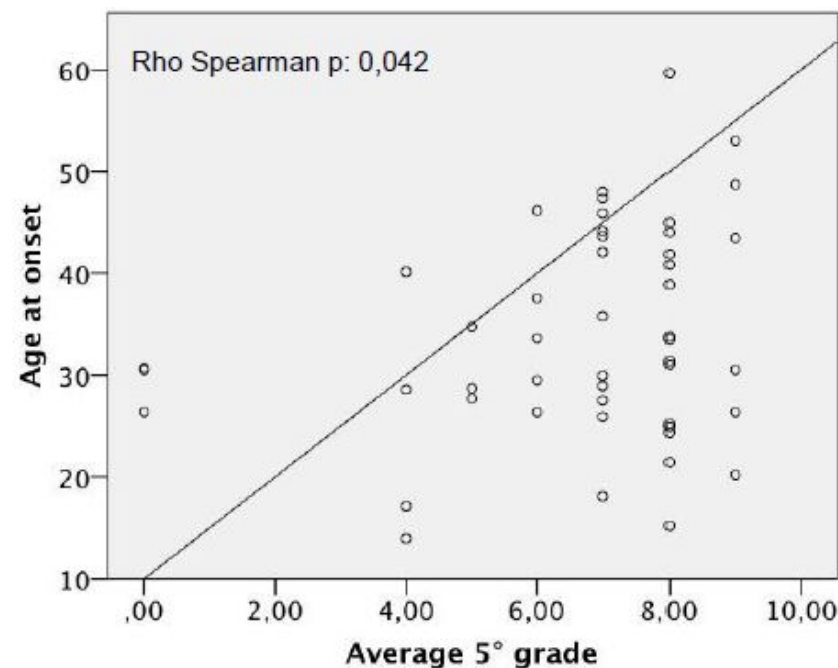
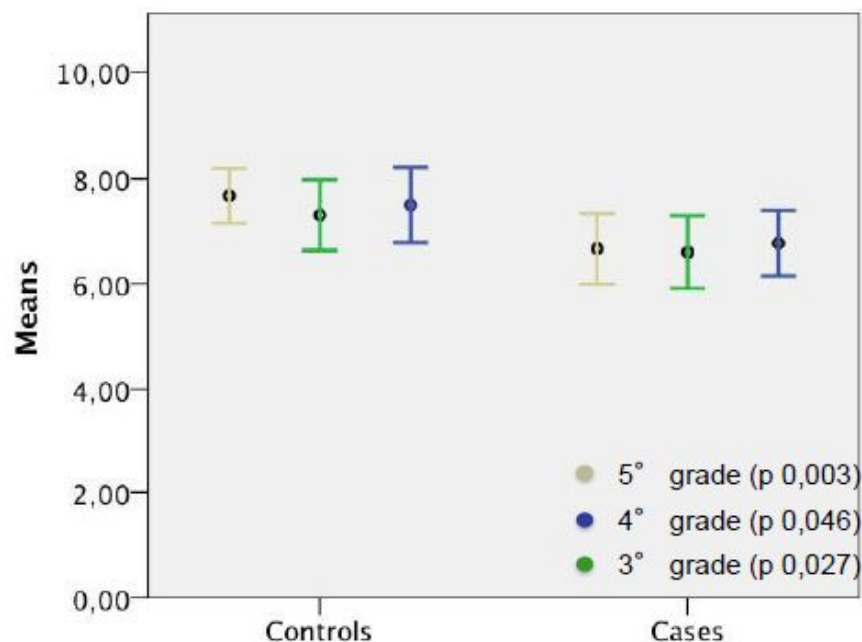
**MS disability
impacts life roles
and reduces
quality of life¹**

EVALUATION OF SCHOOL PERFORMANCE AS AN INDIRECT MARKER OF COGNITIVE DECLINE PRIOR TO DIAGNOSIS OF MULTIPLE SCLEROSIS

Pérez Akly, M.¹; Zanga, G.¹; Ciardi, C.¹; Racosta, J.^{2,3}; Sinay, V.^{2,3}.

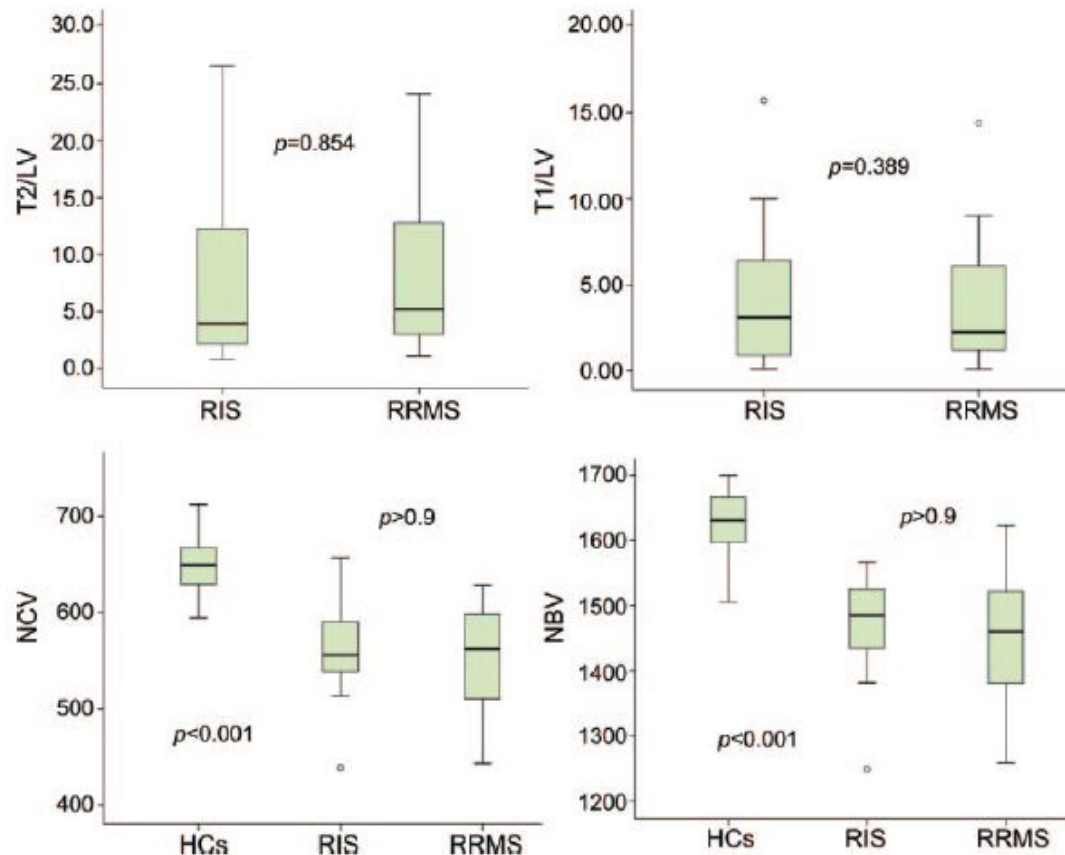
¹ Hospital Dr. César Milstein, ² Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina / ³ Institute of Neurosciences at Favaloro Foundation

This study was supported by an IVAX Argentina research grant



Association of MRI metrics and cognitive impairment in radiologically isolated syndromes

Figure Magnetic resonance data expressed in cm^3 in radiologically isolated syndrome (RIS), relapsing-remitting multiple sclerosis (RRMS), and healthy control subjects (HCs)



NBV = normalized brain volume; NCV = normalized cortical volume; T1/LV = T1 lesion volume; T2/LV = T2 lesion volume.

Reduced head and brain size for age and disproportionately smaller thalami in child-onset MS

Figure 2 Thalamus, globus pallidus, putamen, and caudate segmentation

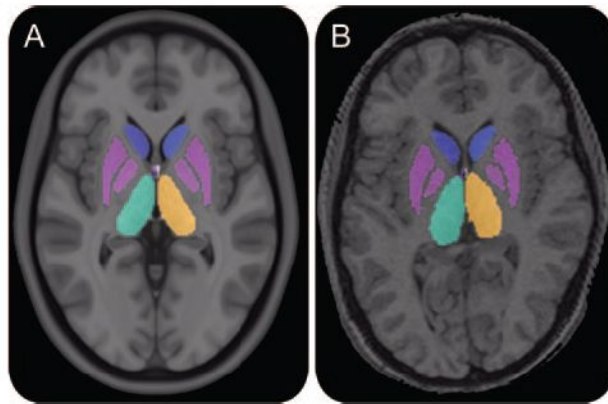


Table 1 Comparison between the HC population and the NIHPD population for each z score used in the study^a

z scores	HC, mean \pm SD	p Value (uncorrected)
Scaling factor	-0.25 ± 1.18	0.1
ICV	0.25 ± 0.98	0.1
NBV	-0.05 ± 1.23	0.8
NWMV	0.22 ± 1.03	0.2
NGMV	-0.28 ± 1.40	0.1
NGPV	0.28 ± 0.95	0.1
NPV	-0.13 ± 0.82	0.4
NTV	0.26 ± 0.99	0.1
NCV	0.34 ± 1.01	0.046
Ratio GPV/BV	0.24 ± 1.02	0.2
Ratio PV/BV	-0.21 ± 1.12	0.2
Ratio TV/BV	0.15 ± 1.34	0.4
Ratio CV/BV	0.22 ± 1.31	0.2

Abbreviations: CV/BV = absolute caudate volume divided by absolute brain volume; GPV/BV = absolute globus pallidus volume divided by absolute brain volume; ICV = intracranial volume; NBV = normalized brain volume; NGMV = normalized grey matter volume; NGPV = normalized for head size globus pallidus volume; NIHPD = NIH pediatric database; NTV = normalized for head size thalamus volume; NWMV = normalized white matter volume; PV/BV = absolute putamen volume divided by absolute brain volume; TV/BV = absolute thalamus volume divided by absolute brain volume.



Why Grey Matter matters

Gavin Giovannoni, Barts and The London, g.giovannoni@qmul.ac.uk

Brain atrophy in MS: what are its consequences?

MS BRAIN

BRAIN ATROPHY



Brain atrophy, or shrinkage, occurs in the majority of MSers at all stages. Grey matter atrophy accelerates over time and with disease progression.

Siman BJ. *Multi Scler* 2006; Fischer T et al. *Ann Neurol* 2008.

SOCIAL

DIVORCE



Compared with the general population, MSers are 40% more likely to separate, or divorce, and do so sooner.

Phleger CC et al. *Multi Scler* 2010;16(12):1326.

OCCUPATIONAL

JOBS



10 years after diagnosis 50% of MSers are unemployed. By the time you need a wheelchair, over 80% of MSers are unemployed.

Kobelt et al. *Neuro Neurosurg Psychiatry* 2006;77(9):918-926.

COGNITIVE

MEMORY



At the time of the first clinical attack over 50% of CISers have cognitive impairment in at least two cognitive areas.

Faulstich et al. *Multi Scler* 2007;13(1):124-127.

EMOTIONAL

SUICIDE



MSers have a 2-7x higher chance of committing suicide.

Torkelson G et al. *Multi Scler* 2008;14(11):1191-1198; Sadovnick AD et al. *Neurology* 1991;41(11):1193-1196.

PHYSICAL

DISABILITY



The average time from MS onset to needing a walking stick is 20 years, and for a wheelchair 30 years.

Conference, Compton. *Multiple Sclerosis*, 4th Edition, 2005.

SOCIETY

QUALITY OF LIFE



Society rates the quality of life of someone with MS who is bed bound as being worse than death.

Crone M et al. *Value in Health* 2007;10(5):465.

MORTALITY

SURVIVAL



MS reduces life expectancy by approximately 8 years and half of MSers die of MS-related complications.

Torkelson G et al. *Multi Scler* 2008;14(11):1191-1198; Siman BJ et al. *Multi Scler* 2006;12(11):1283-1290; Kingwell E et al. *J Neurol Neurosurg Psychiatry* 2012;83(1):68.

MS LESION

OPTIC NEURITIS

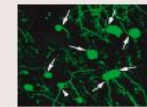


After a single attack of optic neuritis approximately 20% of the nerve fibres are lost in the optic nerve.

Hicks M et al. *Neurology* 2001;57(1):134-136.

MS LESION

INFLAMMATION

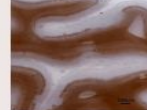


In each cubic millimetre of an acute MS lesion there are over 11,000 transected axons, or nerve fibres, compared to less than one in normal brains.

Trapp B et al. *N Engl J Med* 1996;334(12):1278-1285.

MS LESION

GREY MATTER



In MS there is extensive demyelination, neuronal transection and death, and loss of neurons, in the cerebral cortex or grey matter.

Petersen A et al. *Ann Neurol* 2001;50(5):689-696; Prineas S et al. *Ann Neurol* 2001;50(5):689-696.

MS BRAIN

ATROPHY

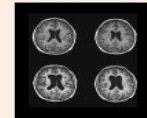


The brains of MSers shrink at a rate of 0.5-1.0% per year compared to a rate of between 0.1-0.4% in normal brains.

Barkhof F et al. *Ann Neurol* 2009;65(1):100-108; Siman BJ. *Multi Scler* 2006;12(11):1283-1290; Potkin M et al. *Arch Neurol* 2008;65(1):100-108.

MS BRAIN

BRAIN VOLUME



Brain atrophy, or brain shrinkage, in MS, as measured by MRI, is associated with disability and cognitive impairment.

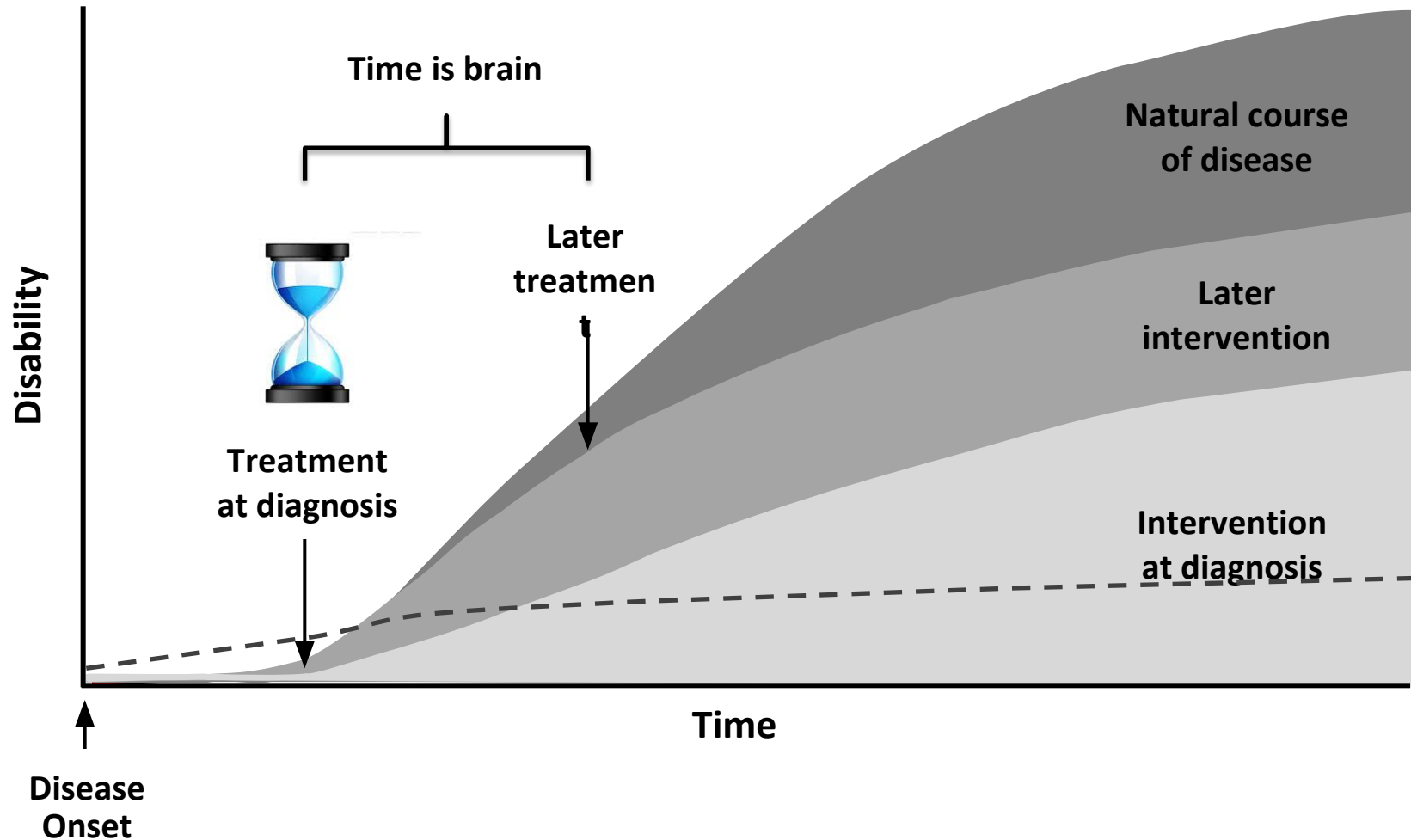
Rudick R et al. *J Neurol Sci* 2009;228(1-2):106-111; Calabrese M et al. *Arch Neurol* 2008;65(1):100-108; Goodwin G et al. *Neurology* 2011;76(1):100-108.

Save your Grey Matter it really does matter.

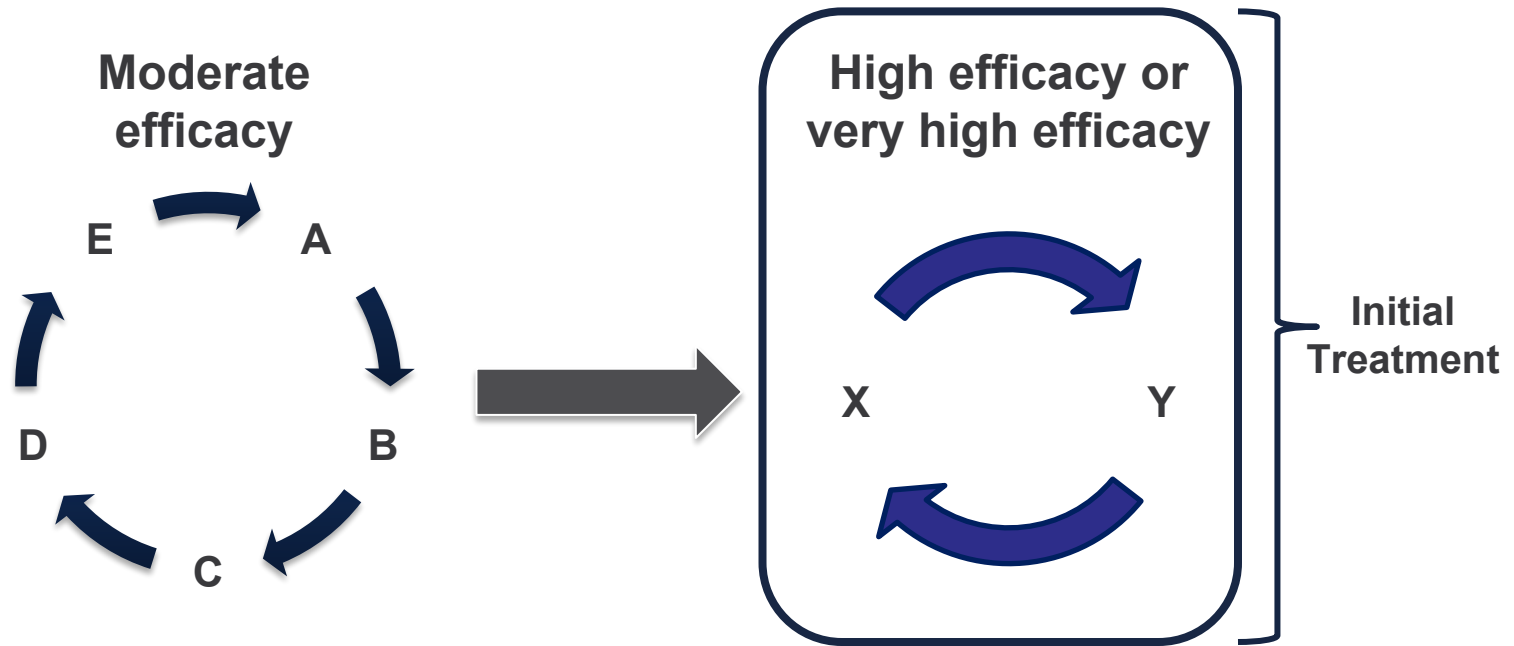
Version 4.0, 29 September 2013.

Early treatment

Theoretical model: treat early and effectively

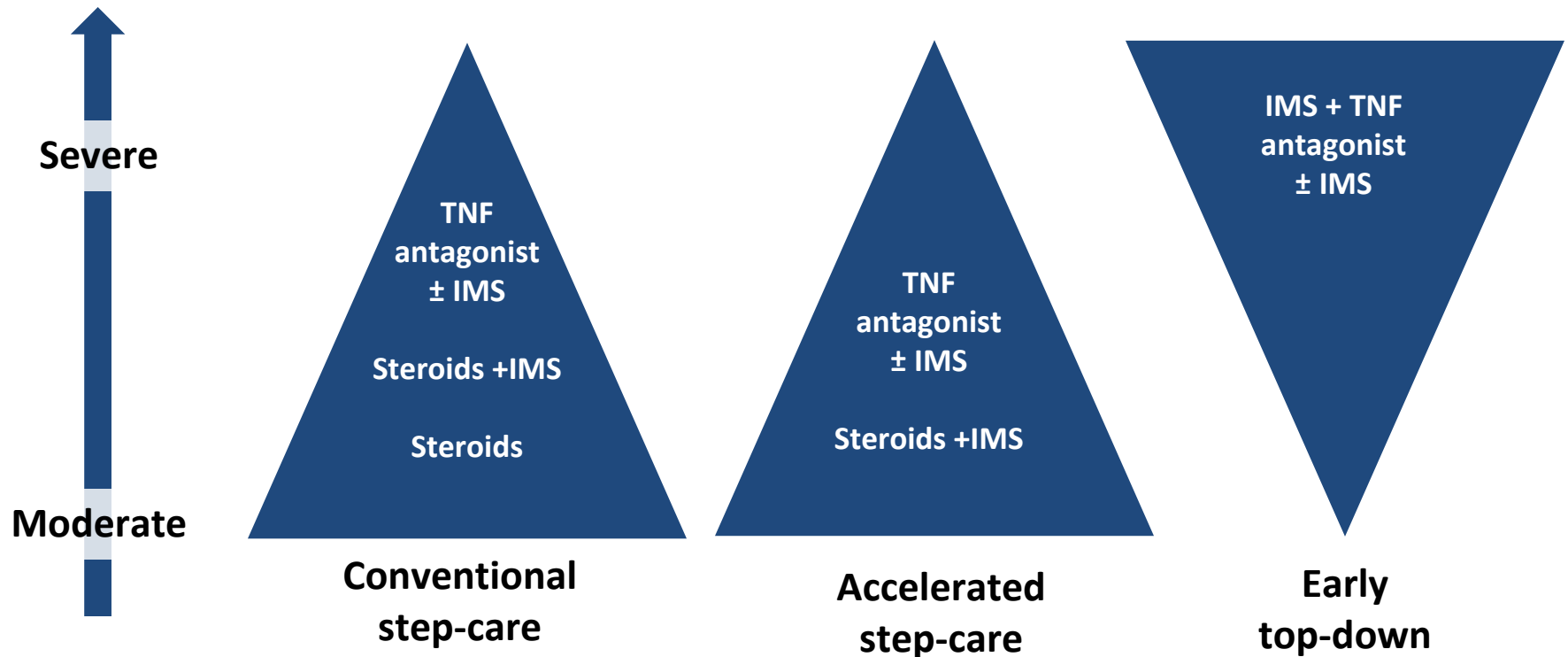


The Traditional Approach to MS Treatment



- Heterogeneity of disease course across different MSers and over time can affect treatment response¹⁻³
- Depending on the definition used, up to 49% of MSers treated with a first-line injectable therapy (IFNB) still have clinical disease activity¹

Treating beyond symptoms with a view to improving IBDer outcomes in inflammatory bowel diseases



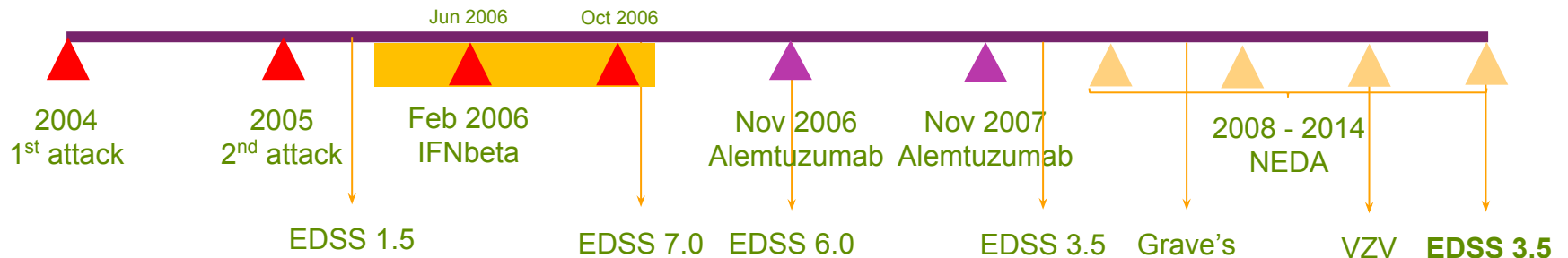
“FLIPPING THE PYRAMID”

The cost of delayed access to highly active treatment



EDSS = 0.0: fully functional

20 month vs. 32 month delay or 2 relapses



EDSS = 3.5: unable to run, play tennis or walk down stairs quickly without the use of a handrail


Making a difference

BMJ Case Reports 2015; doi:10.1136/bcr-2014-208960

CASE REPORT

Timing is everything in the treatment of multiple sclerosis

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Accepted 19 March 2015

Published 15 April 2015

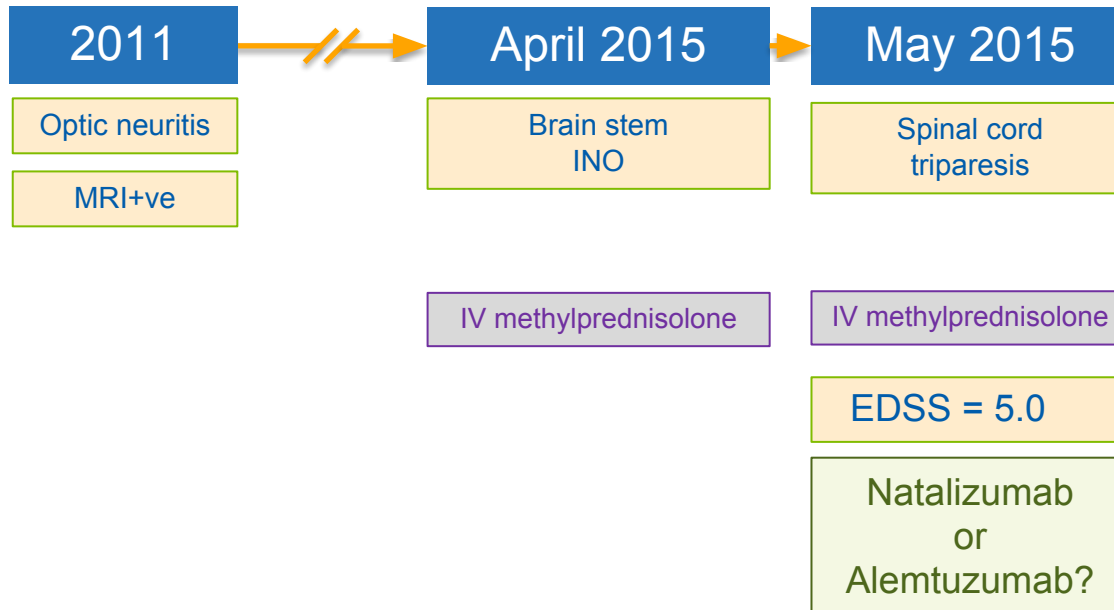
Summary

We present two similar cases of relapsing–remitting multiple sclerosis, both of whom received treatment with the monoclonal antibody alemtuzumab, but had significantly different long-term outcomes. Patient A is 12 years into his illness and was treated early in his disease course, he has no disability and continues to perform at a high level as a professional golfer. Patient B was initially started on interferon- β 1a therapy and went on to have two disabling relapses on this treatment which resulted in a degree of fixed disability prior to the start of alemtuzumab. 10 years into his disease course he has moderate disability and daily symptoms of spasticity in his legs which impair his quality of life. These two contrasting cases highlight the difficult decision of when to start potent immune modulating therapies for multiple sclerosis in young adults who appear well early in their disease but have the potential to rapidly accrue irreversible disability from future relapses.



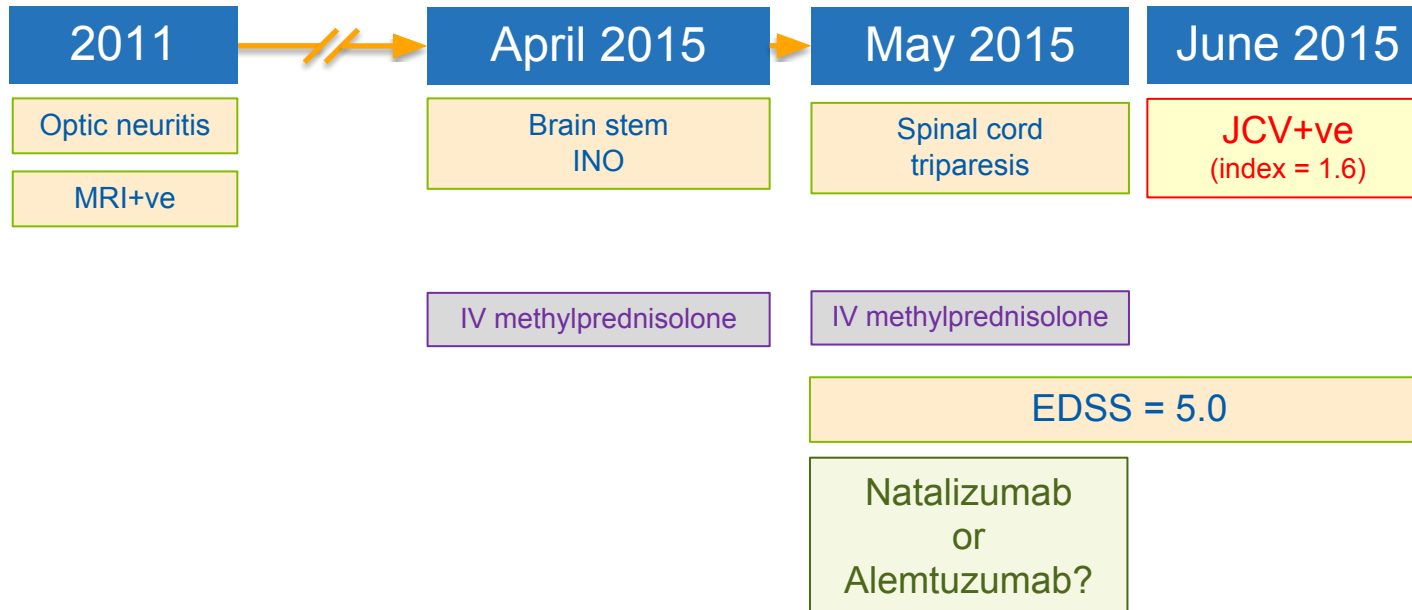
Case 3

Case scenario: 25-year-old woman with RRMS



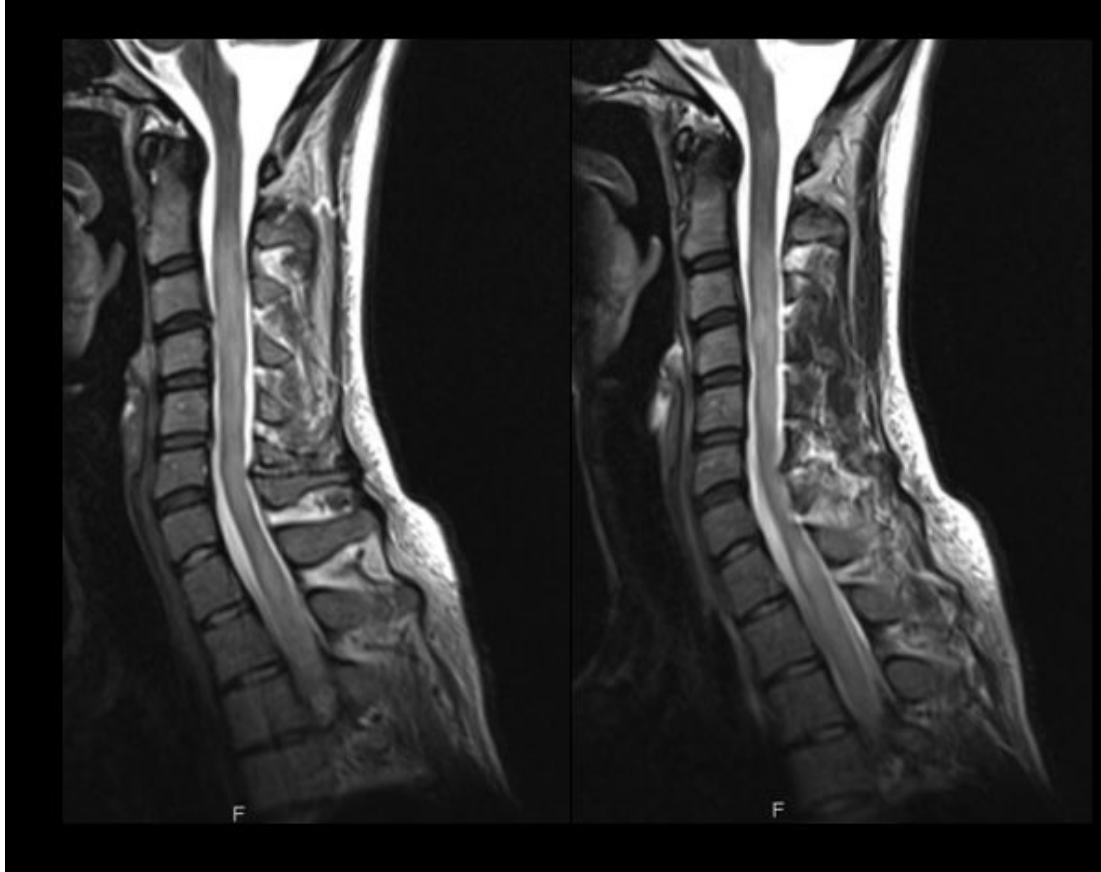
Case 3

Case scenario: 25-year-old woman with RRMS



Case 3

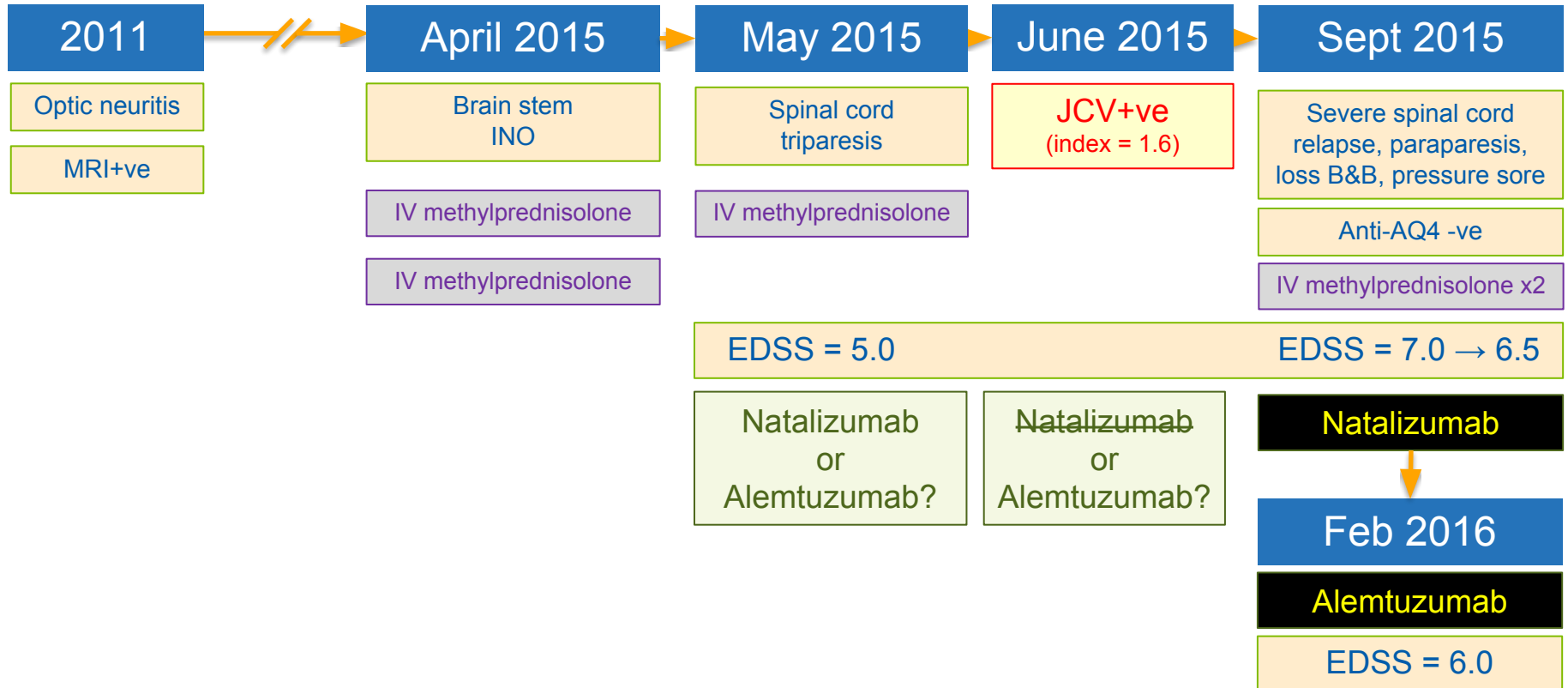
Case scenario: 25-year-old woman with RRMS



Patient case scenario provided by Professor Gavin Giovannoni.

Case 3

Case scenario: 25-year-old woman with RRMS

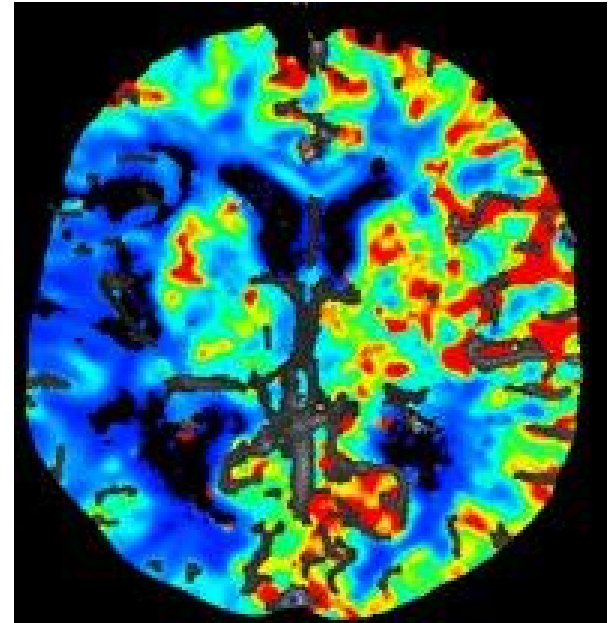


Patient case scenario provided by Professor Gavin Giovannoni.

AQ4=Aquaporin-4

1. Haines JD et al. *Mt Sinai J Med.* 2011;78:231-243; 2. Münzel EJ et al. *Drugs.* 2013;73:2017-2029.

Stroke or brain attack: *'time really is brain'*



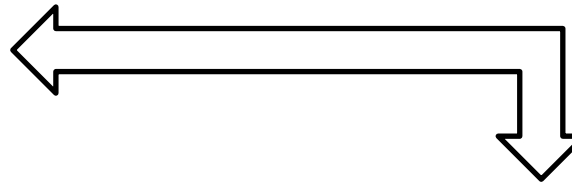
Passive



Active

Therapeutic hierarchy

Therapeutic pyramid



Brain Health Initiative

Neuro-restoration

Remyelination

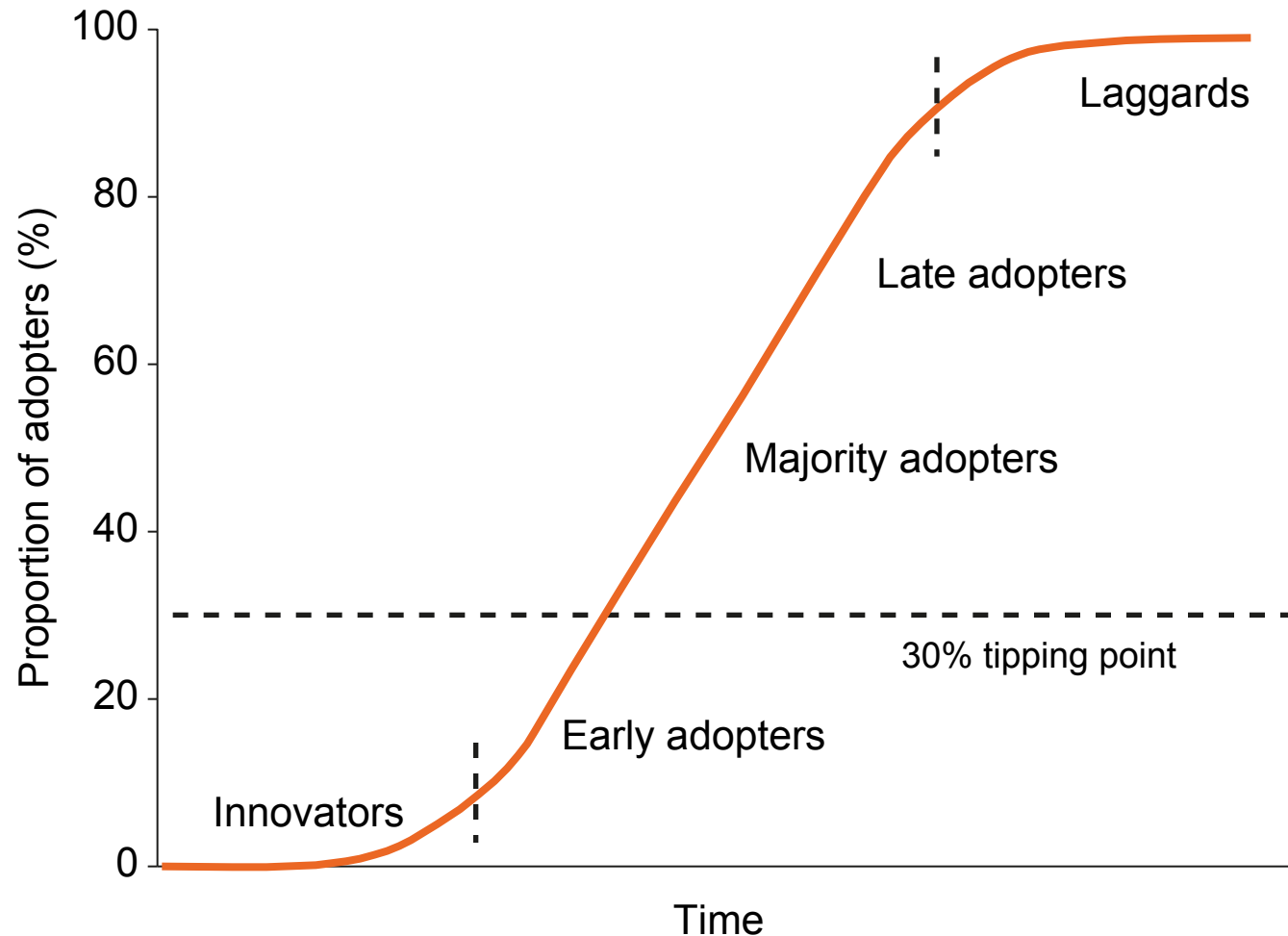
Neuroprotection

Anti-inflammatory

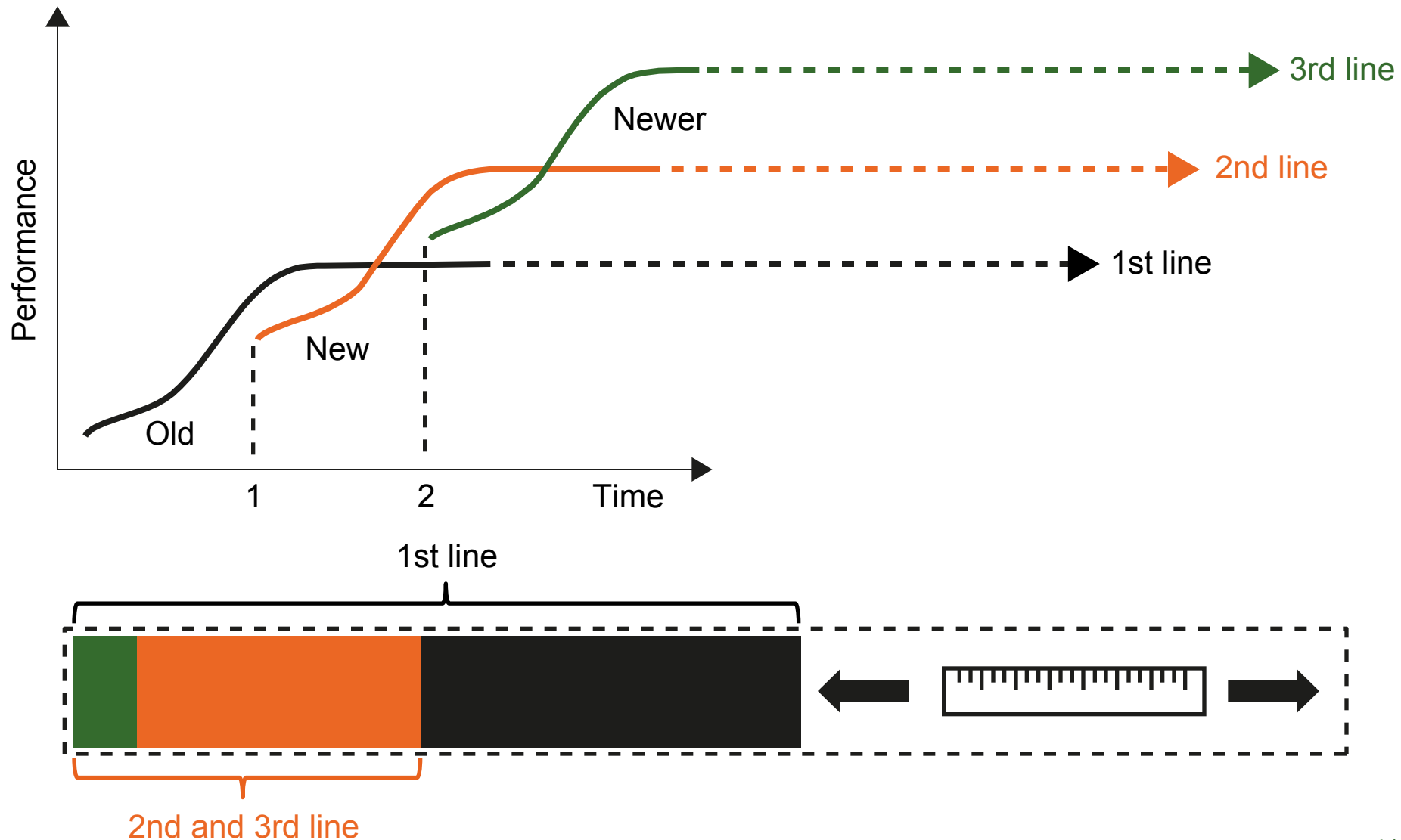
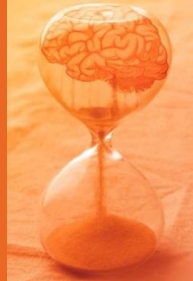
Anti-ageing

- Smoking
- Exercise
- Diet
- Sleep
- Co-morbidities
- Infections
- Concomitant medications

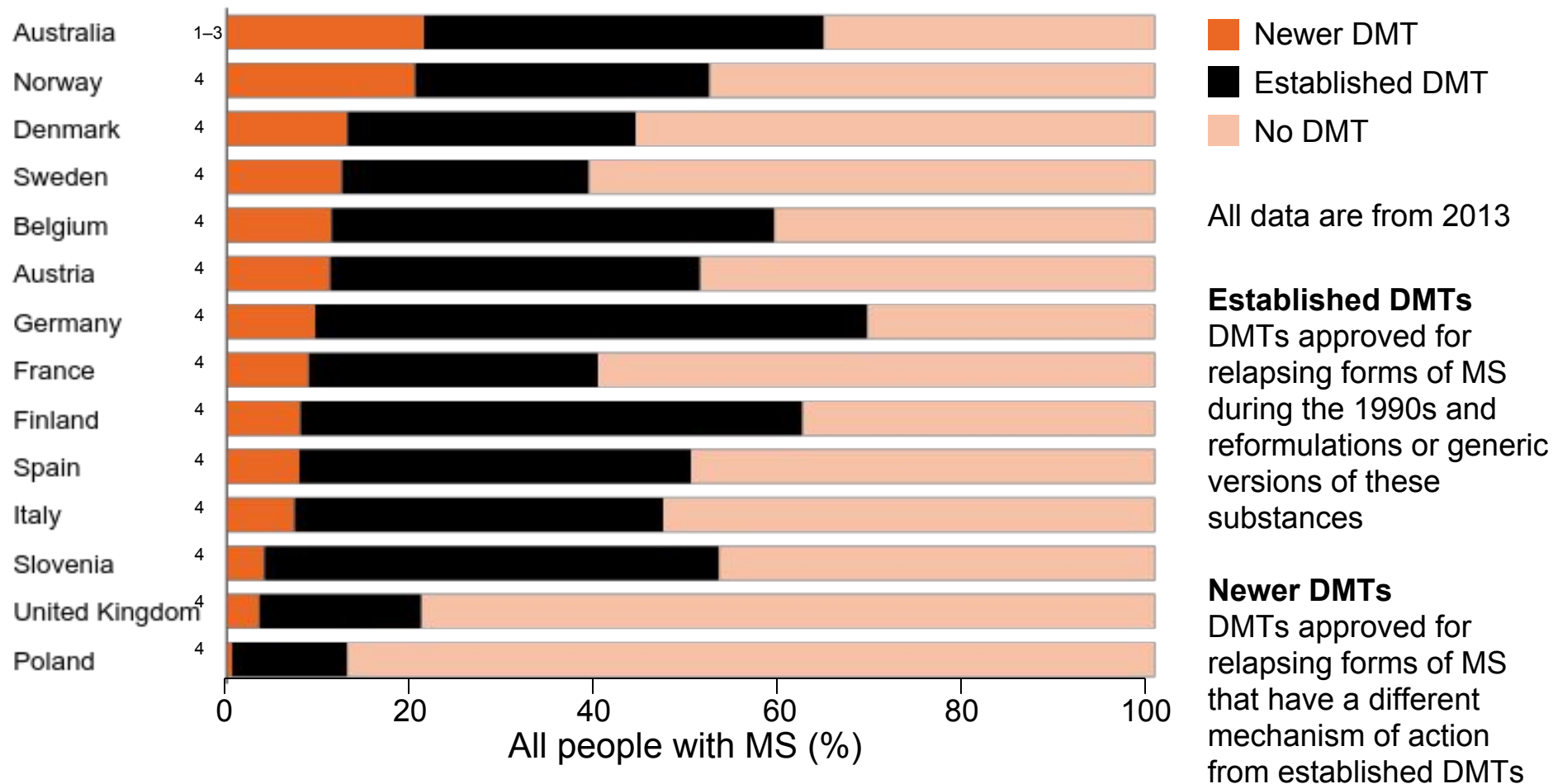
Rapid adoption of innovations has the potential to improve MS care



Slow adoption of innovations results in healthcare inequity

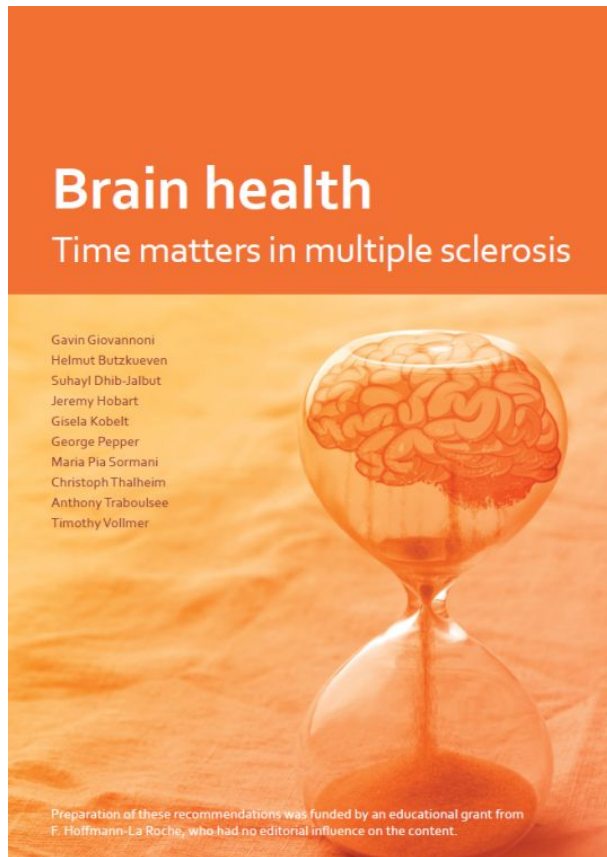


Large disparities exist in access to disease-modifying therapies

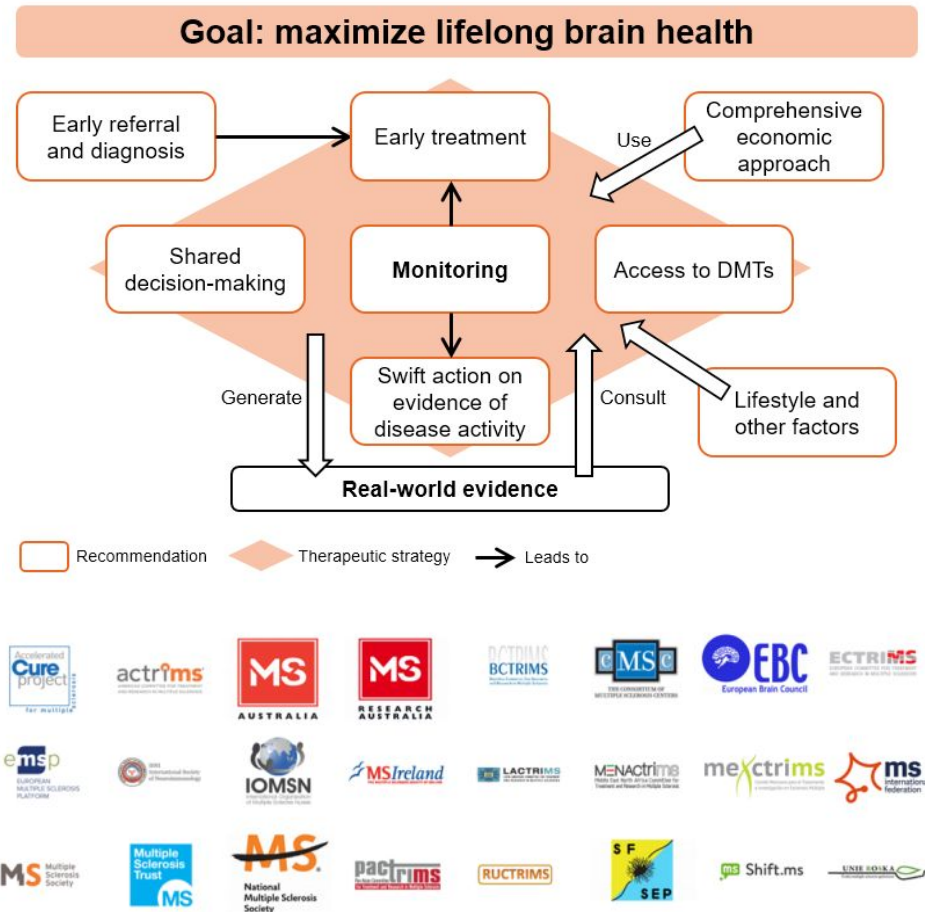


DMT, disease-modifying therapy. 1. Hollingworth S *et al.* *J Clin Neurosci* 2014;21:2083-7; 2. World Bank, 2015. <http://data.worldbank.org/indicator/SP.POP.TOTL>; 3. MSIF, 2013. <http://www.atlasofms.org>; 4. Wilsdon T *et al.* 2013. <http://crai.com/sites/default/files/publications/CRA-Biogen-Access-to-MS-Treatment-Final-Report.pdf>. Figure reproduced from Giovannoni G *et al.* *Brain health: time matters in multiple sclerosis*. Available at: www.msbrainhealth.org

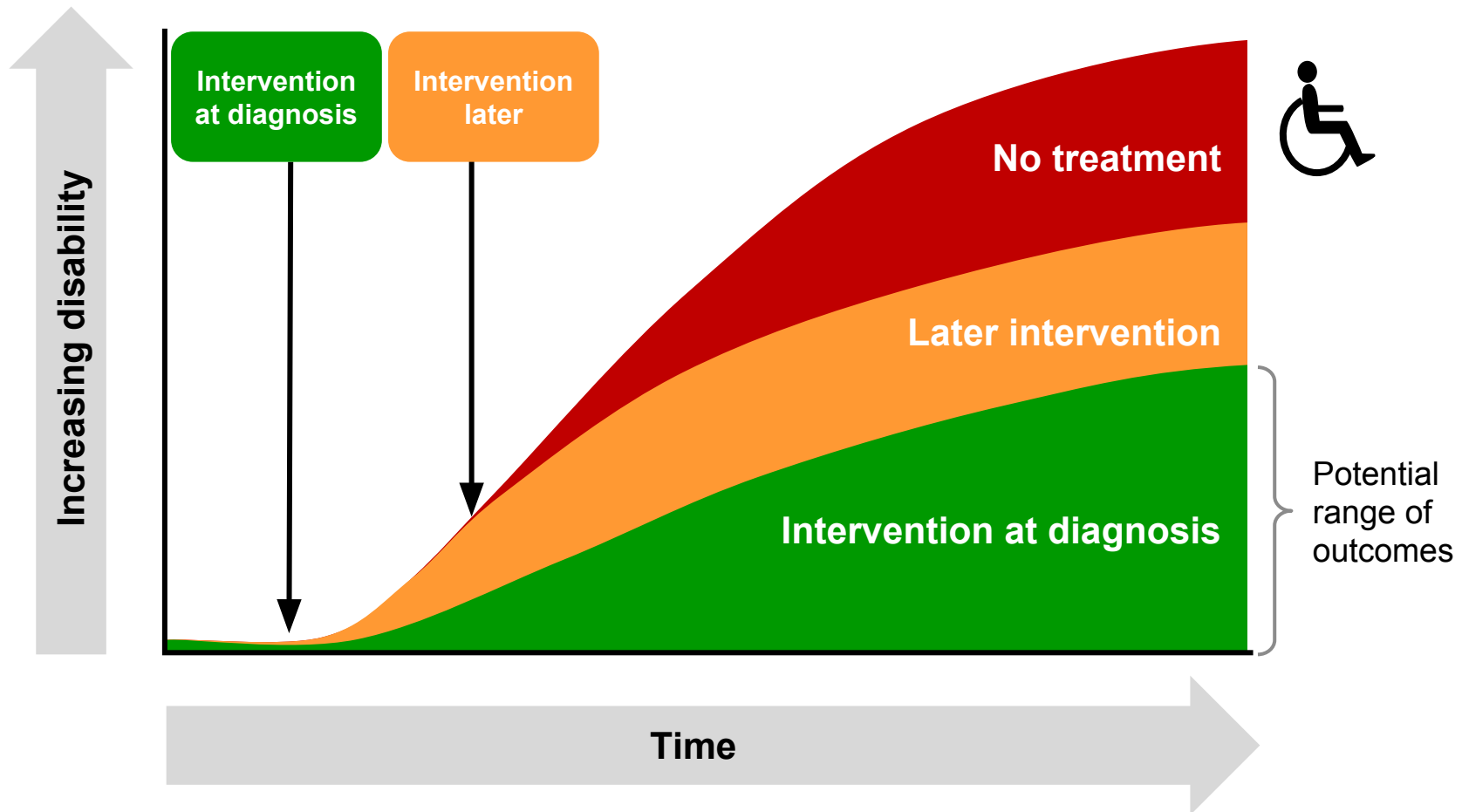
International policy initiative



www.msbrainhealth.org



Early intervention and long-term prognosis



Barts-MS: 2016 Brain Health Challenge

Treat-2-Target

Lifestyle

Comorbidities

Wellness

Barts-MS



***2016
Brain Health
Challenge***

Barts-MS: 2016 Brain Health Challenge

Treat-2-Target

Lifestyle

Comorbidities

Wellness

- Prognosis
- Active MS
- Treatment
- Re-baselining
- Monitoring
- NEDA



Barts-MS: 2016 Brain Health Challenge

Treat-2-Target

Lifestyle

Comorbidities

Wellness

- Diet & supplements
- Exercise
- Smoking
- Alcohol
- Sleep
- Stress



Barts-MS: 2016 Brain Health Challenge

Treat-2-Target

Lifestyle

Comorbidities

Wellness

- Obesity
- Hypertension
- Glucose
- Cholesterol
- Smoking
- Sleep disorders
- Infections
- Falls
- Depression & anxiety
- Concomitant medications



Barts-MS: 2016 Brain Health Challenge

Treat-2-Target

Lifestyle

Comorbidities

Wellness

- Intellectual
- Emotional
- Physical
- Social
- Spiritual
- Occupational
- Environmental





ESRF

end-stage renal failure



Rheumatoid arthritis

End-stage joint disease

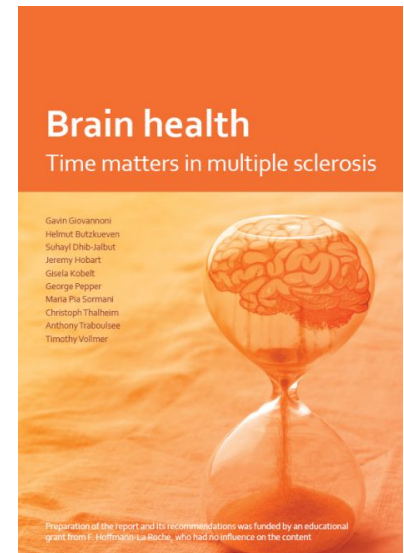




From initial impact to lasting improvement – the logical next step!



The MS Brain Health report has united the global MS community in support of its messages and recommendations. This unity is a precious resource and one to be nurtured.



Representative from
a major patient
organization that
has endorsed and
promoted the report

We need to look for ways to describe the collective aims that recognize and allow for the variation or diversity between systems.

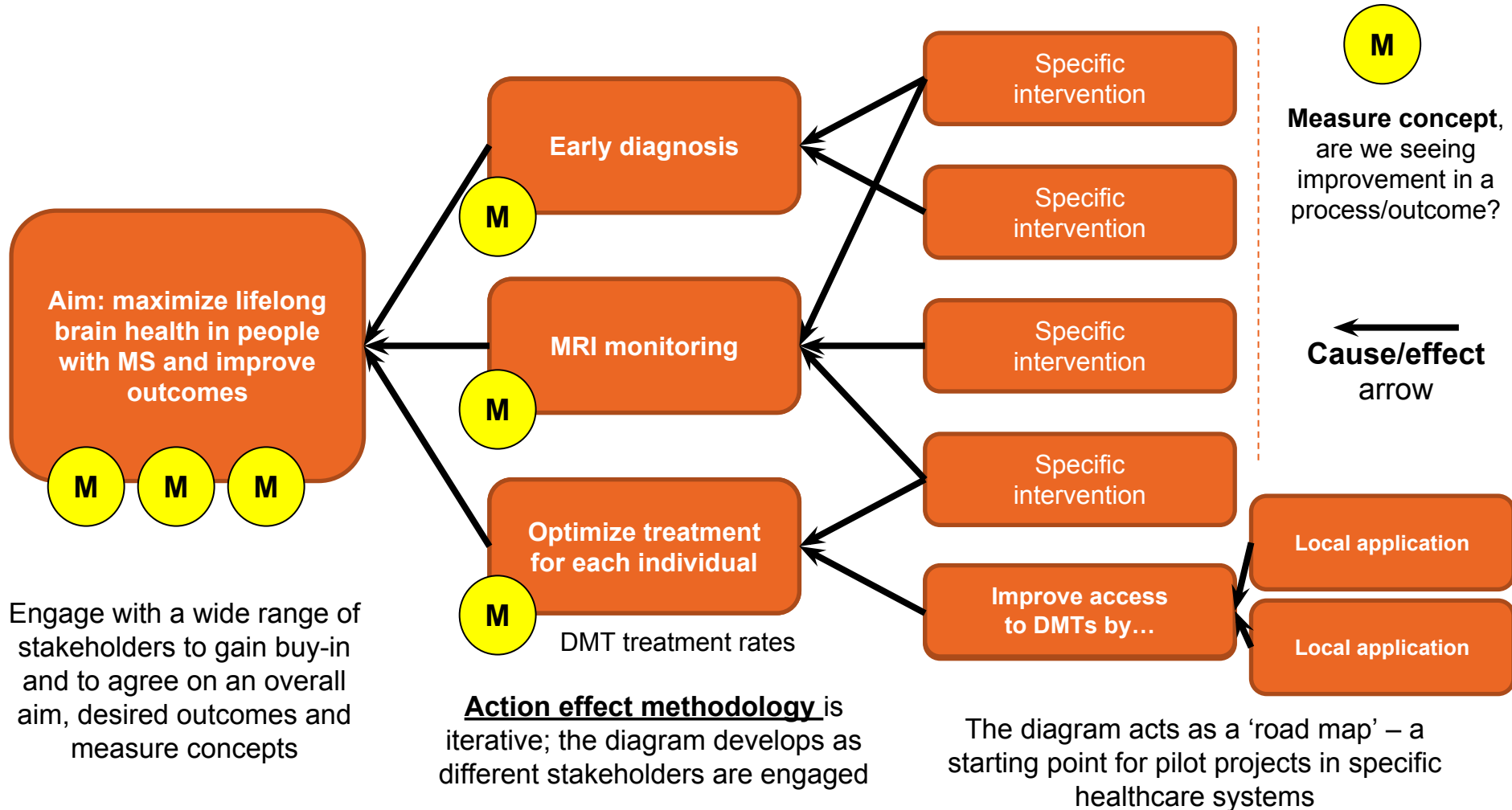
A quality improvement approach to measure local adoption of the recommendations



Agree on the **overall aim**, aspirations and scope

Agree on **factors that contribute** to the aim

Interventions are changes made to achieve the aim



MS Brain Health – a potential 'tripadvisor' for MS ...



tripadvisor®



msAdvisor



msAdvisor

Barts-MS, Royal London Hospital
Whitechapel, London E1 1BB

[Contact](#)[Staff](#)[Services](#)[For you](#)

Overall

62 reviews



Diagnosis

38.6 days



Monitoring

868 MSers



DMTs

54%



Relapses

8.3 days



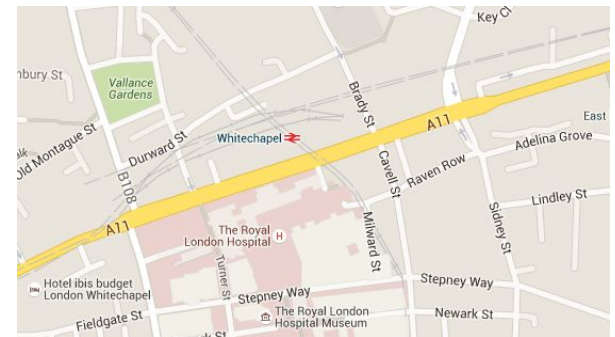
Co-morbidities

1211 MSers



Education

187 reviews



Our vision is to create a better future
for people with MS and their families



Your voice will help to effect this change

Be an early adopter

Pledge your support of the report's
recommendations at www.msbrainhealth.org



MS Brain Health
Time Matters

www.msbrainhealth.org

Summary



1. Disability accumulation and health status deterioration occur early in MS, suggesting an **early therapeutic window** of opportunity
2. Heterogeneity of treatment response supports that **treatment decision-making should be individualised**, rather than taking a step-wise “treatment ladder” approach for all MSers
3. Evaluation of the **benefits and risks** of treatment vs the risk of MS disease progression requires consideration of both the physician’s and **MSers’ perspectives**
4. **Optimising therapy** requires ongoing assessment to identify MSers who are experiencing suboptimal response to current therapy
5. **Treatment adherence** is an important consideration both at treatment initiation and in the face of **suboptimal treatment response**



Questions?