Translating information into evidence

examples from multiple sclerosis

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MSBase
Neuro-Immunology Registry

>68,000 patients

>350,000 patient-years

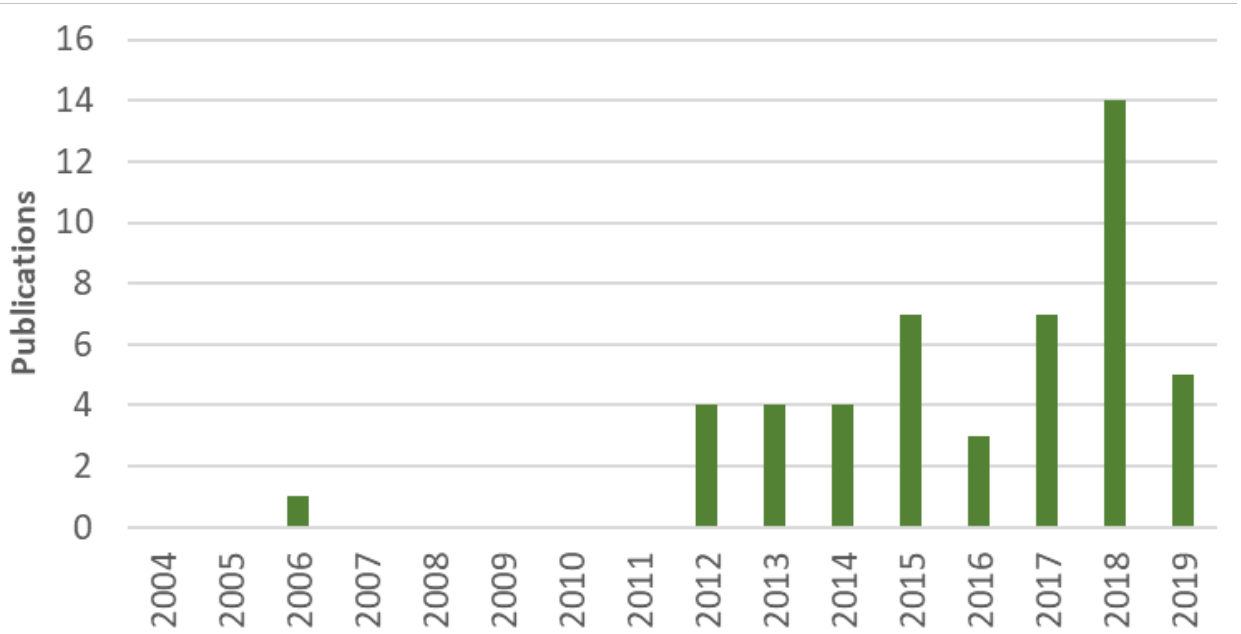
129 centres

34 countries

http://www.msbase.org

Butzkueven et al., Mult Scler 2006;12:769

Published output



49 papers

Including:

JAMA
Lancet Neurol
Brain
Ann Neurol
Neurology
JAMA Neurology
JNNP
Mult Scler J

Summary of the research output

MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

The MSBase registry: Informing clinical practice

Tomas Kalincik and Helmut Butzkueven

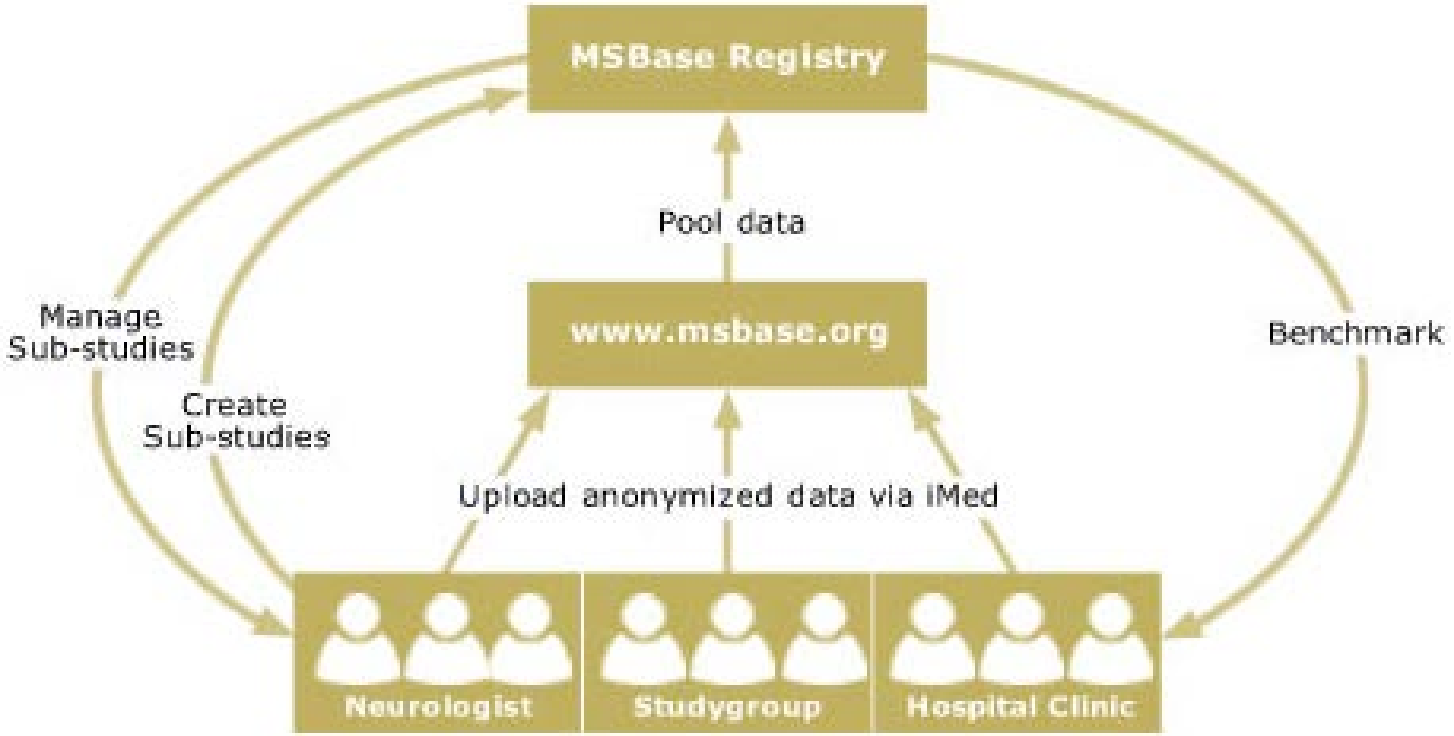
Abstract: Over the last decade, clinical registries have significantly contributed to the pool of evidence that supports management decisions in patients with multiple sclerosis. Being the largest international registry of multiple sclerosis and neuroimmunological disorders, MSBase collects demographic, clinical and limited paraclinical information from patients managed in different regions and under various circumstances. In this review, we will provide an overview of its published output, with focus on the information with impact on the management of multiple sclerosis.

Kalincik & Butzkueven, Mult Scler in press

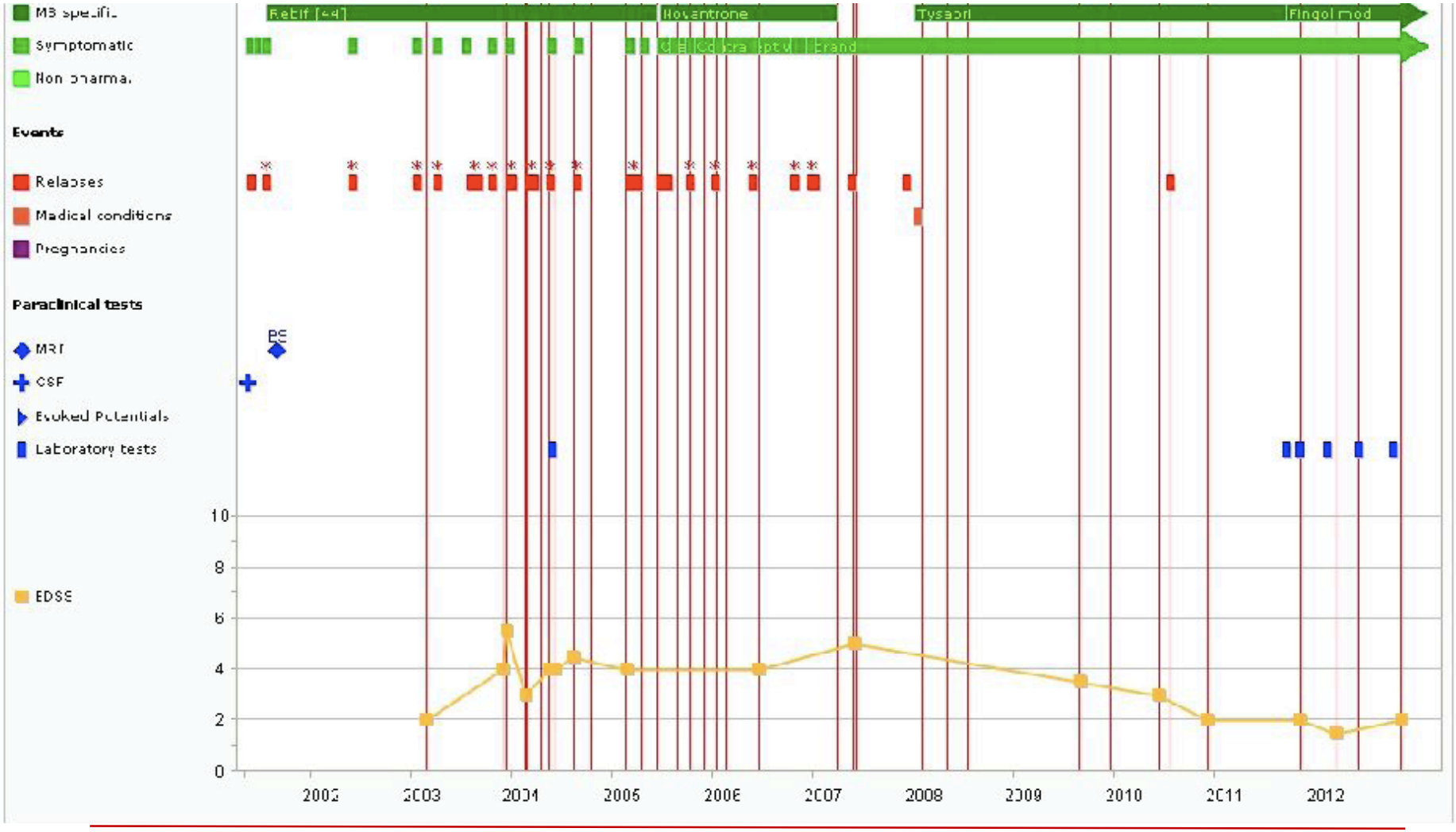
MSBase themes (research)

- epidemiology of MS
- symptomatology
- prognostics
- therapy: efficacy, management strategies, safety
- diagnosis and outcome measures
- data quality

Structure

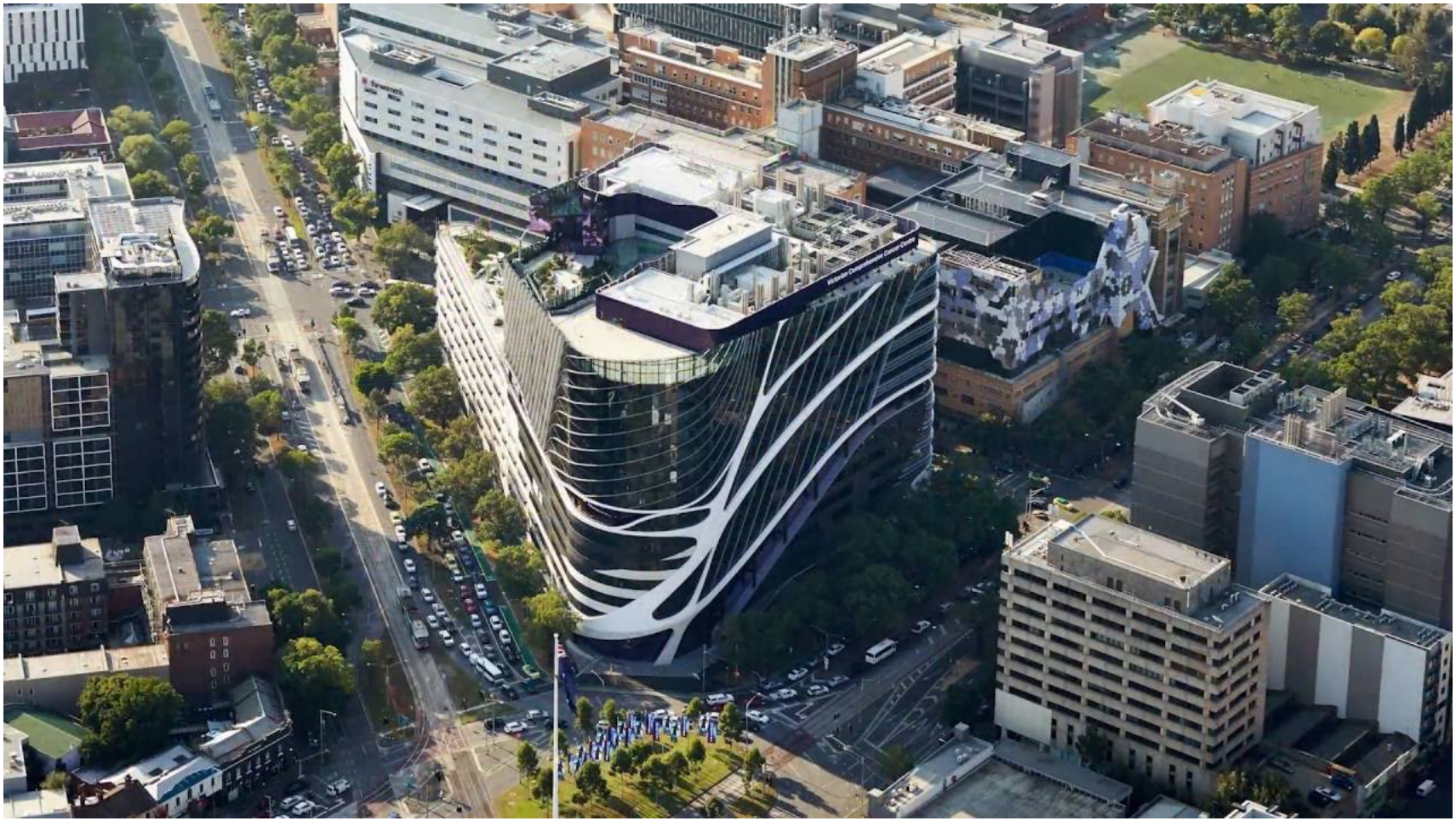

MSBase Registry
Pool data
www.msbase.org
Manage
Sub-studies
Create
Sub-studies
Upload anonymized data via iMed
Benchmark
Neurologist
Studygroup
Hospital Clinic

MSBase: data entry system



MSBase
Neuro-Immunology Registry

CORe at UoM & RMH



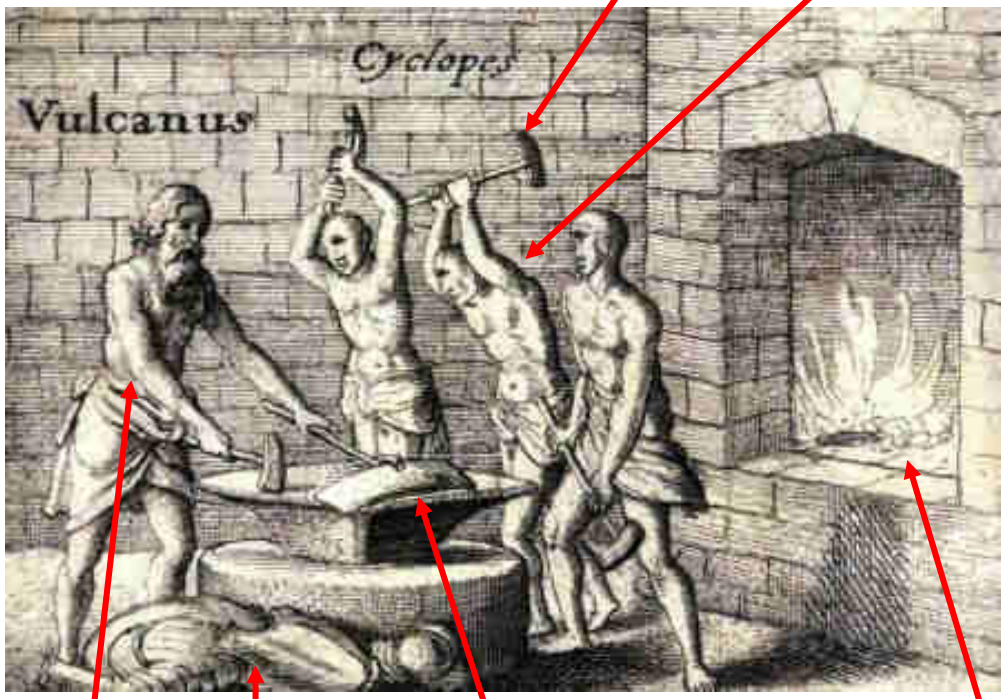
Predicting the Future — Big Data, Machine Learning, and Clinical Medicine

Ziad Obermeyer, M.D., and Ezekiel J. Emanuel, M.D., Ph.D.

By now, it's almost old news: big data will transform medicine. It's essential to remember, however, that data by themselves are useless. To be useful, data must be analyzed, interpreted, and acted on. Thus, it is algorithms — not data sets — that will prove transformative. We believe, therefore, that attention has to shift to new statistical tools from the field of machine learning that will be critical for anyone practicing medicine in the 21st century.

First, it's important to understand what machine learning is not. Most computer-based algorithms in medicine are "expert systems" — rule sets encoding knowledge on a given topic, which are applied to draw conclusions

Obermeyer, NEJM 2016, 375:1216



analytics

fellows

your best friend

ideas

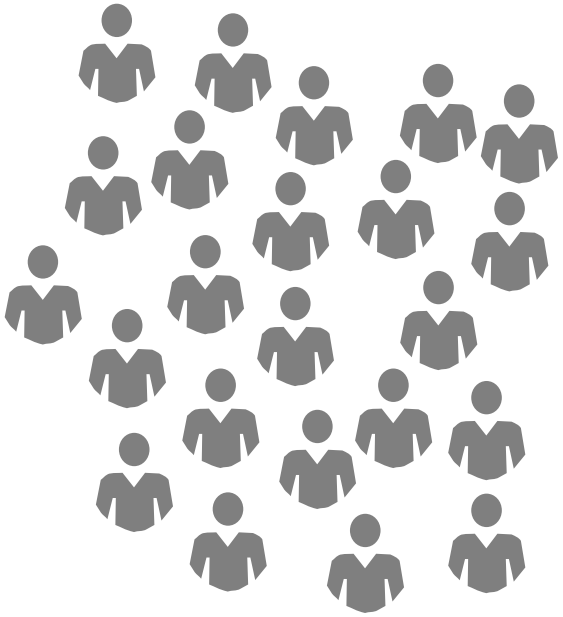
data

quality procedures

evidence

Towards the evidence to guide clinical practice

EFFECTIVENESS ≈ EFFICACY IN THE REAL WORLD



Efficacy: ”Does the treatment work?”
Effectiveness: “In what situations does the treatment work?”

Heterogeneity of the disease: Inherent characteristic of MS and of treatment response.

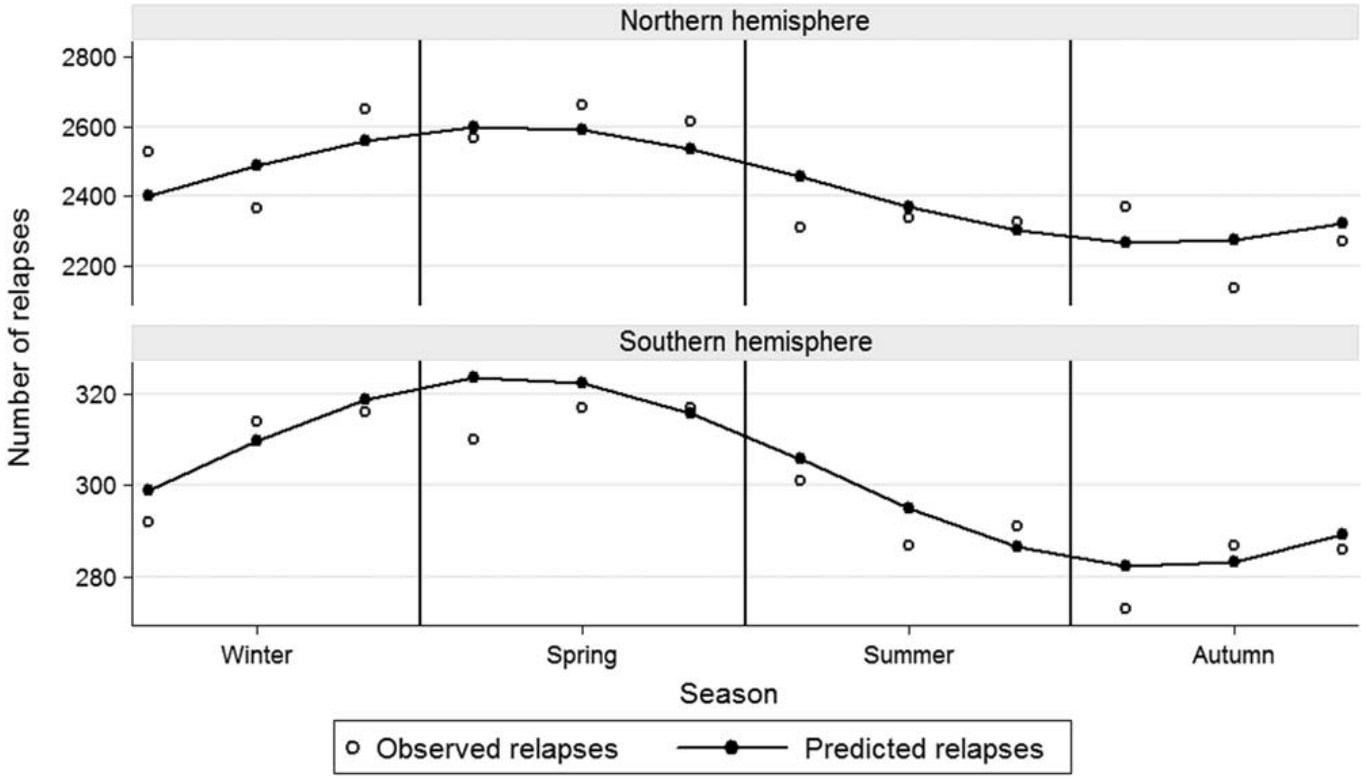
NB: Heterogeneity in the data introduces noise.

Personalised therapy: The path to overcome heterogeneity of the disease.

From efficacy to effectiveness:

1. establish general principles
2. define dependence of these general principles on context
3. identify the context in individual patients in a timely manner

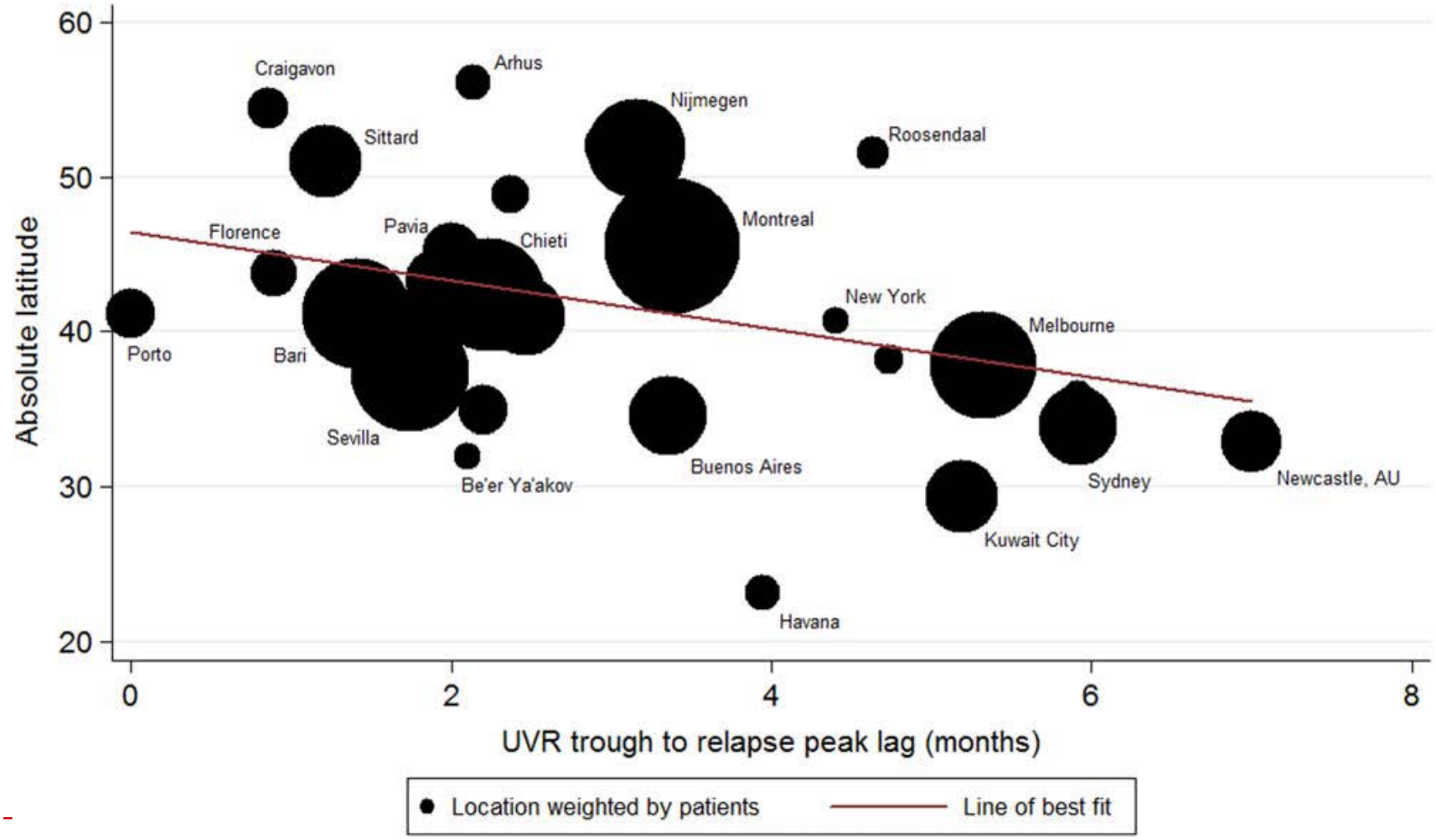
Seasonality, latitude & relapses



MSBase Neuro-Immunology Registry

Spelman et al., Ann Neurol 2014, 76:880

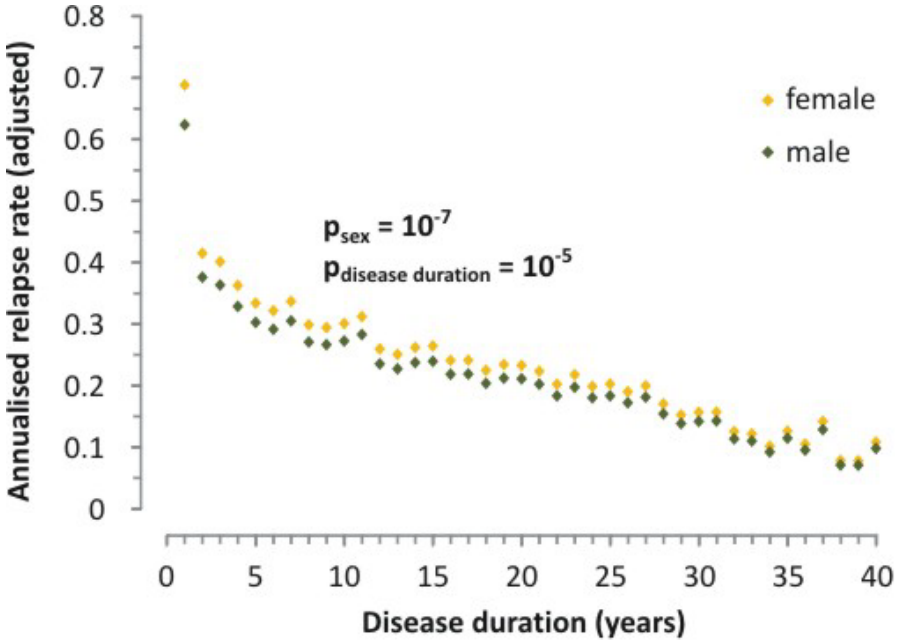
Seasonality, latitude & relapses

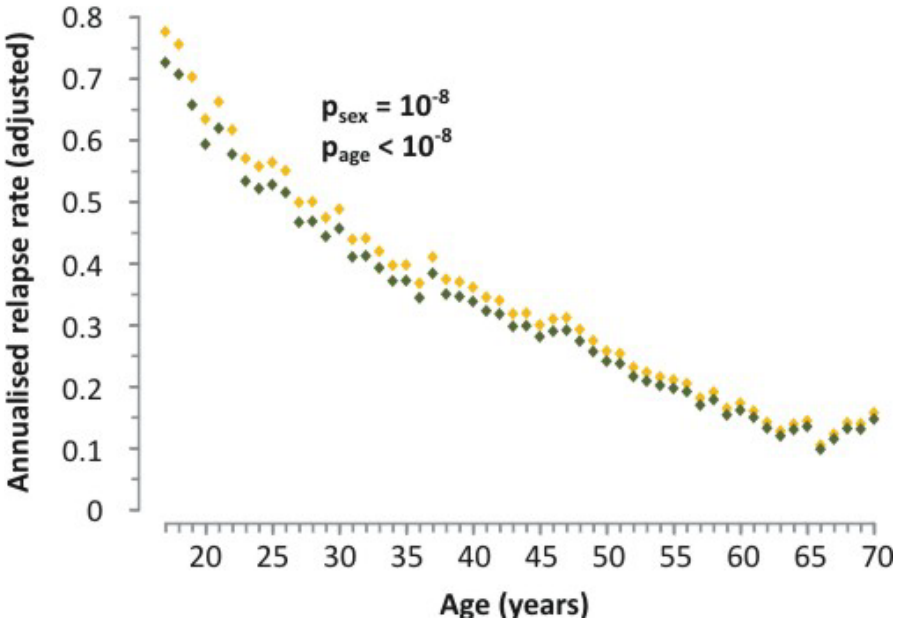


MSBase Neuro-Immunology Registry

Spelman et al., Ann Neurol 2014, 76:880

Sex and relapses

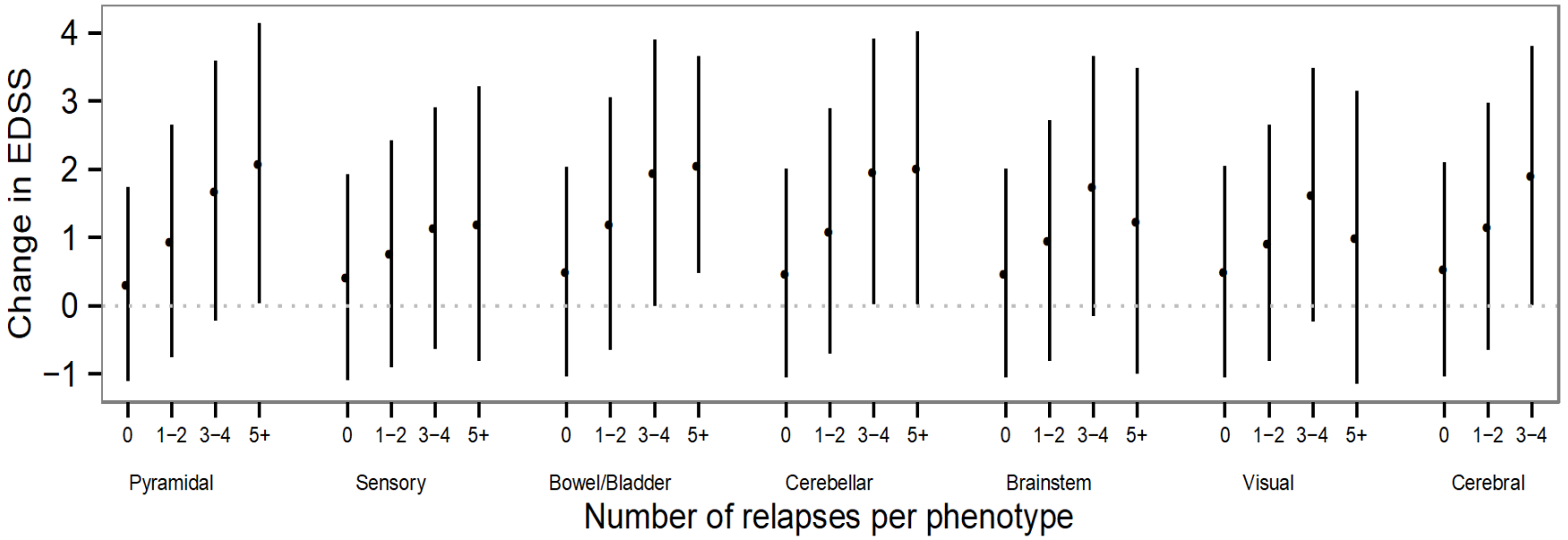




MSBase Neuro-Immunology Registry

Kalincik et al., Brain 2013, 127:301

Relapses & disability

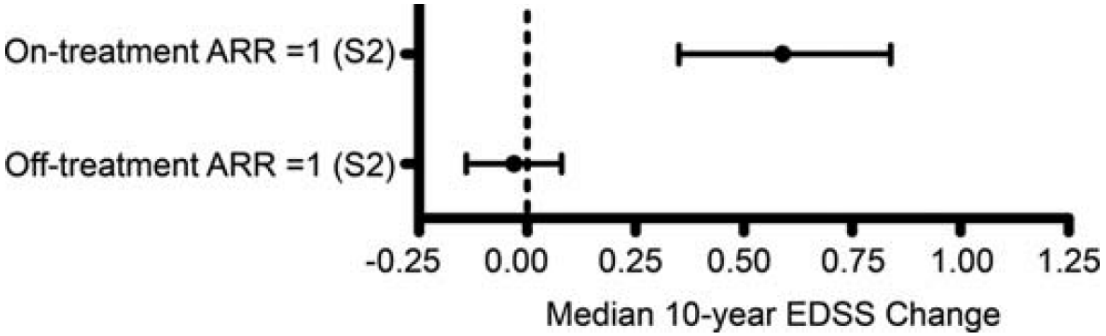


median follow-up: 5.9 years

MSBase Neuro-Immunology Registry

Stewart et al., Mult Scler 2017, 23:266

Relapses & disability

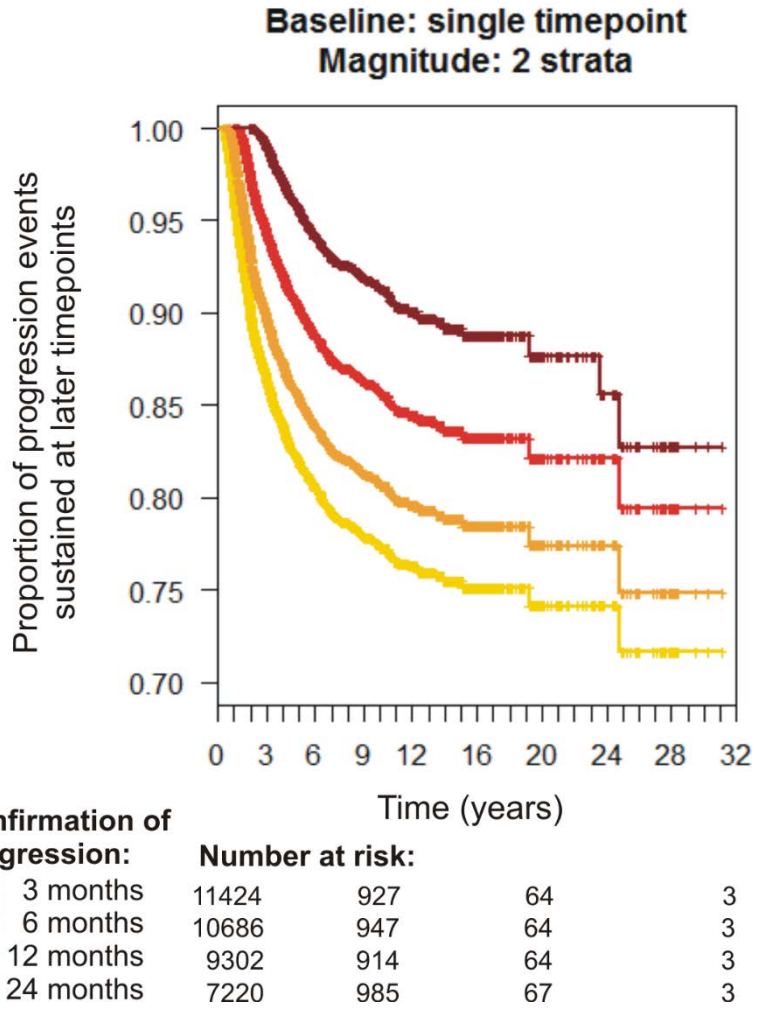


follow-up: 10 years

MSBase Neuro-Immunology Registry

Jokubaitis et al., Ann Neurol 2016, 80:89

EDSS progression metrics



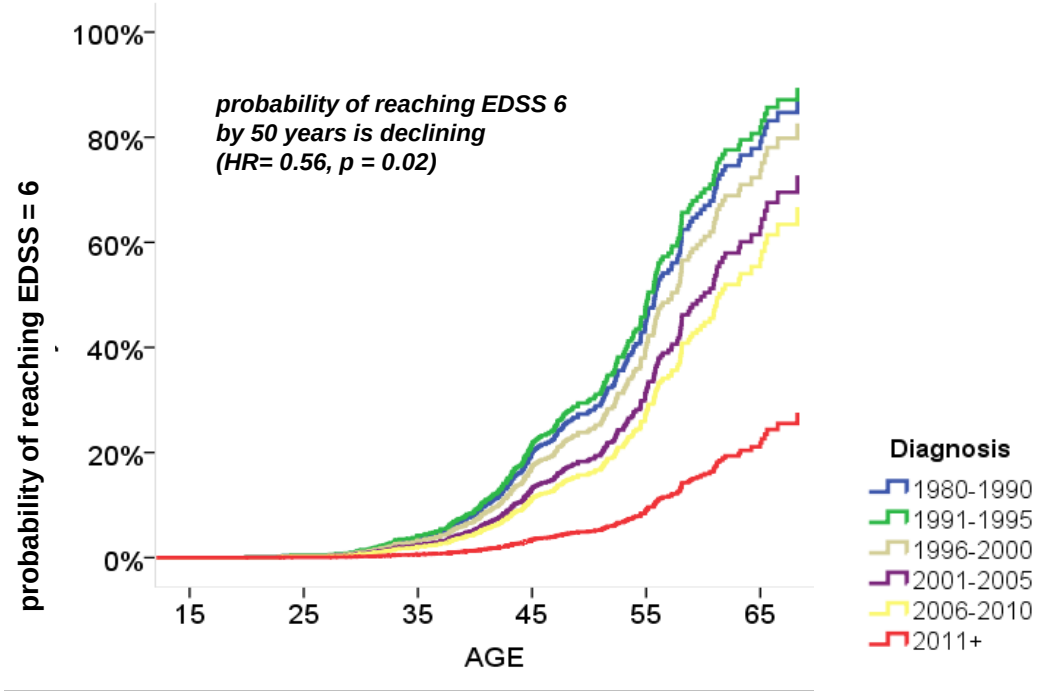
Kalincik et al., Brain 2015, 138:3287

Changing long-term outcomes in MS

Simple questions – difficult answers

long-term effect of immunotherapy on disability

Secular trends



age at EDSS=6 is increasing

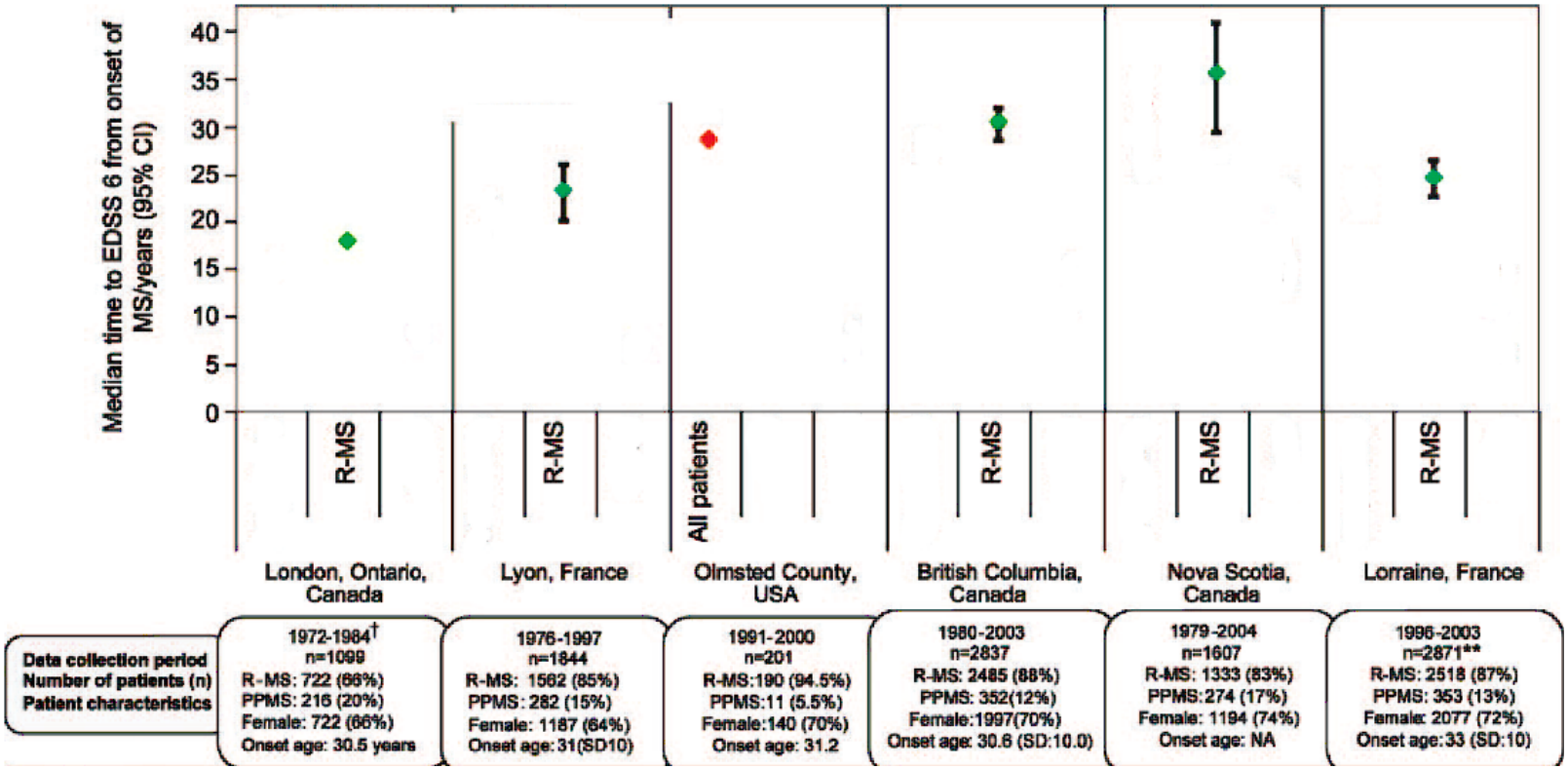
(after adjusting for the mean age at diagnosis and intervals between EDSS visits)

Cox proportional hazards model

Capra et al., Mult Scler 2017;23:1757

Secular trends

time to EDSS 6



UCSF
2004-2014
n=517

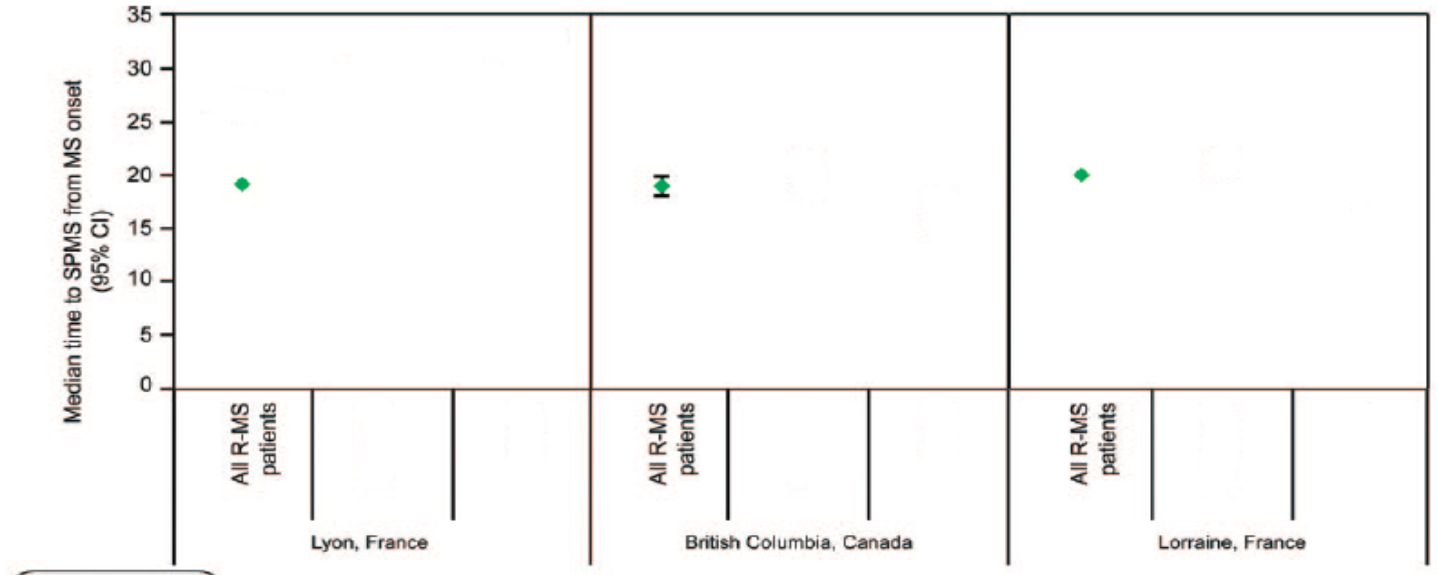
Cree et al., Ann Neurol 2016, 80:499

Kaplan-Meier analysis (median survival time)

Tremlett et al., Neurology 2010, 74:2004

Secular trends

time to SPMS



	Lyon, France	British Columbia, Canada	Lorraine, France
Data collection period Number of R-MS patients (n) Number of patients reaching SPMS (%)	1976-1997 n=1562 496 (32%)	1980-2003 n=2485 1445 (58%)	1996-2003 n=2518* 933 (37%)
➤ Method of assigning SPMS ➤ Definition of SPMS	➤ Retrospective ➤ Initial RR phase followed by a progressive phase whether superimposed relapses present or not (Lublin & Reingold)	➤ Date assigned retrospectively by neurologist at clinic visits ➤ Initial RR course followed by progression with or w/out occasional relapses, minor remissions or plateaus (Lublin & Reingold)	➤ Not specified* ➤ Not specified*

UCSF

2004-2014
n=517
Cree et al., Ann Neurol 2016, 80:499

increase in EDSS over ≥1-year independent of relapses in patients with RMS

MSBase

1996-2016
n=15,717
Fambiatos et al., ECTRIMS 2017

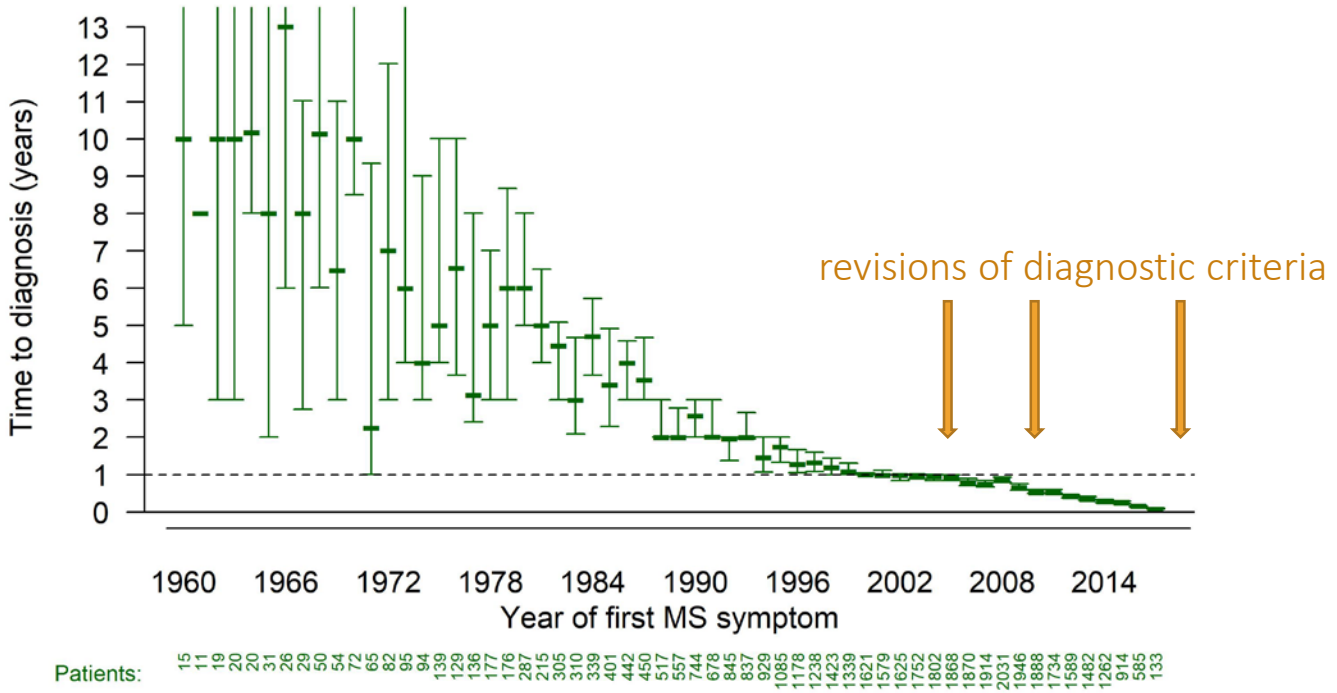
objective definition as per Lorscheider et al., Brain 2017, 139:2395

Kaplan-Meier analysis (median survival time)

Tremlett et al., Neurology 2010, 74:2004

Secular trends

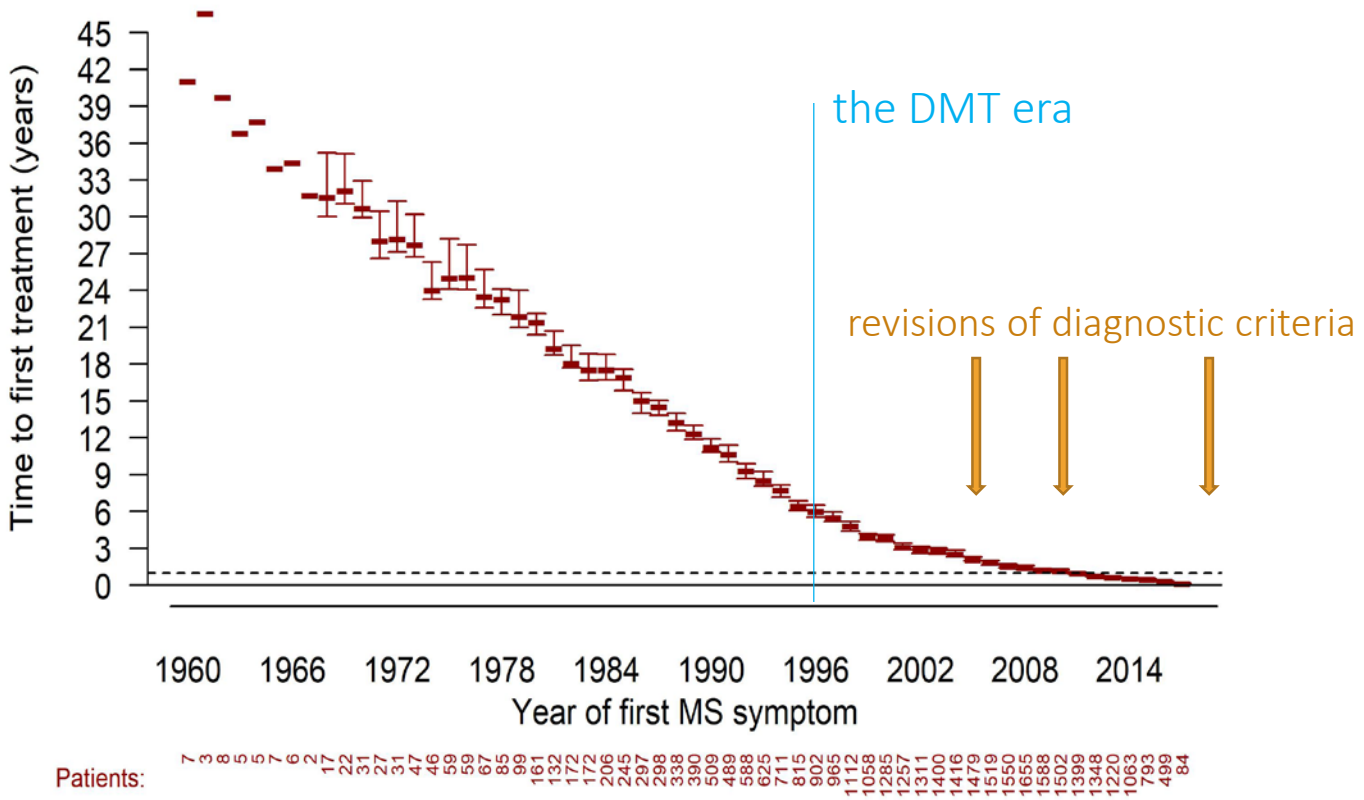
time to diagnosis



Kaplan-Meier analysis (median survival time ± 95% confidence interval)

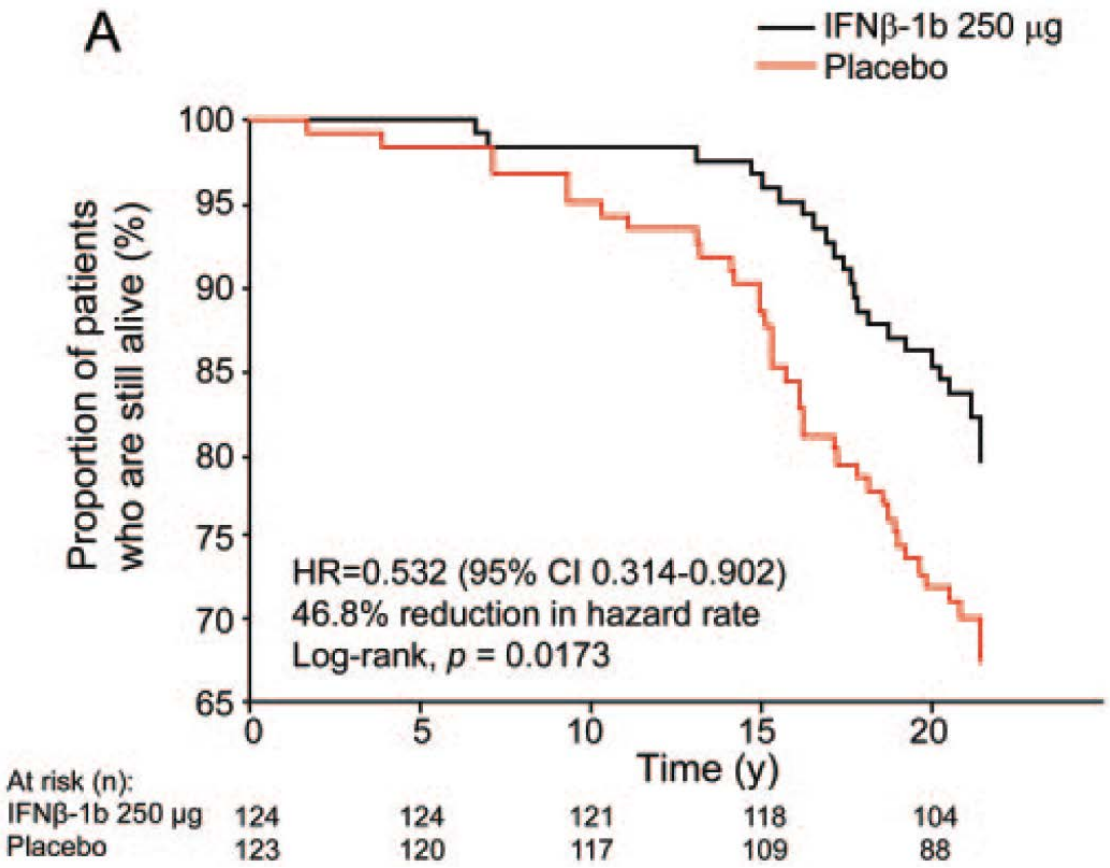
Secular trends

time to first immunotherapy



Kaplan-Meier analysis (median survival time ± 95% confidence interval)

Long-term association of early treatment decisions with mortality

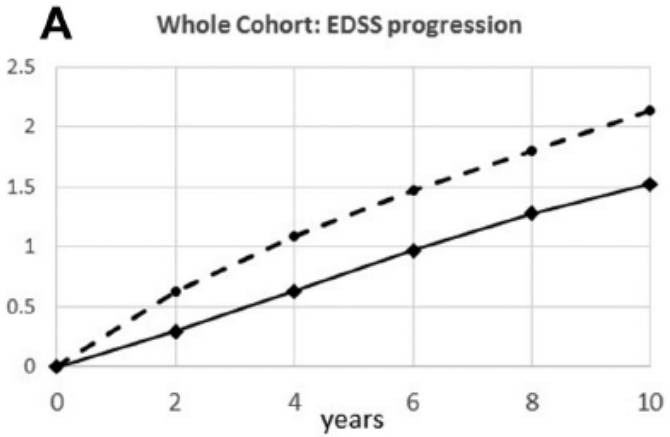


Kaplan-Meier analysis

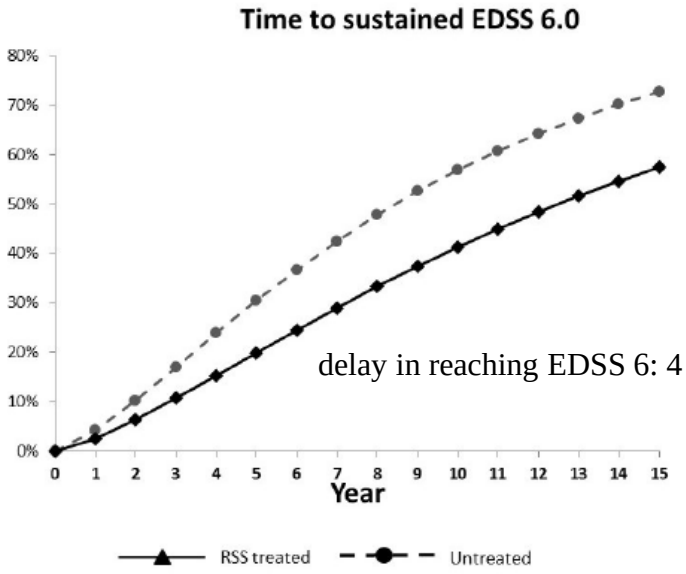
Goodin et al., Neurology 2012, 78:1315

Long-term effect of immunotherapy on disability

UK Risk Sharing Scheme (2002-2016), injectable therapies, n=4862
British Columbia MS Cohort (1980-1995), natural history, n=978



absolute [relative] treatment effect:
Markov model: 0.12 EDSS [93% (90-96)]
multilevel model: 0.61 EDSS [72% (69-74)]



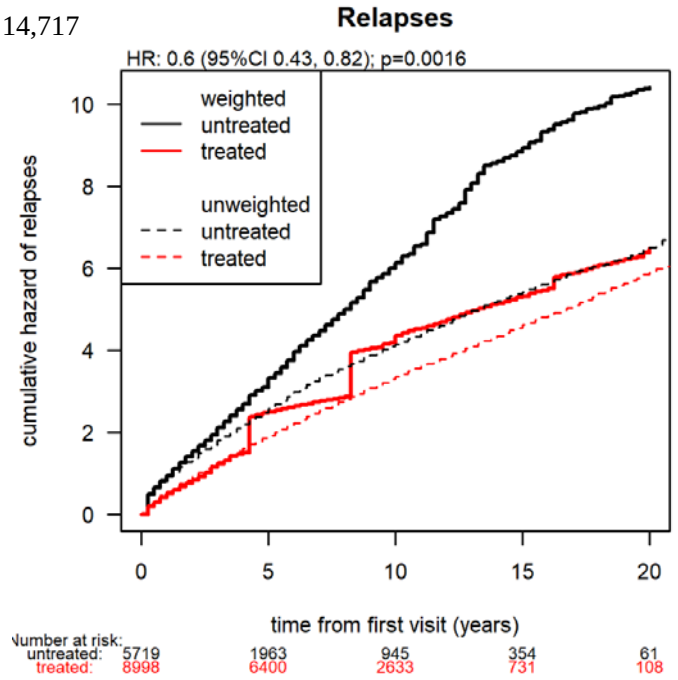
delay in reaching EDSS 6: 4 years (2.7-5.3)

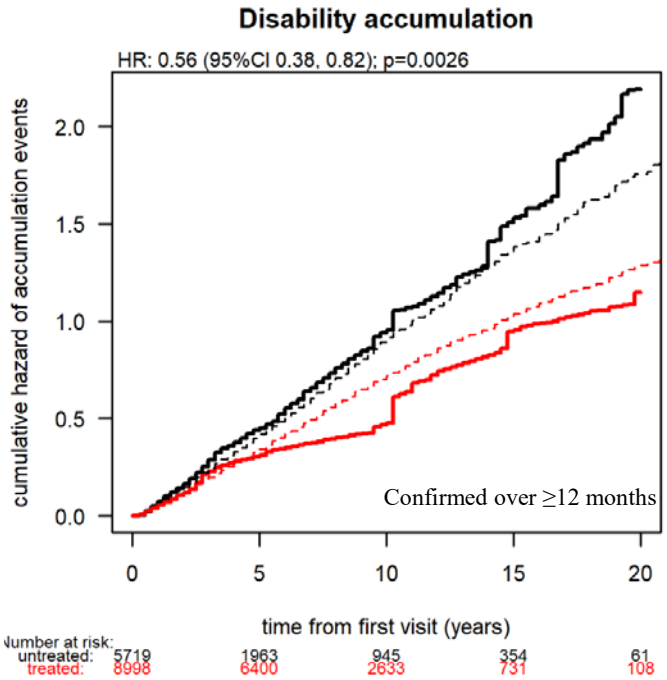
Markov model
multilevel model
accelerated failure time model (Weibull)

Palace et al., JNNP *in press*

Long-term effect of immunotherapy on disability

n = 14,717





marginal structural model

Kalincik et al., ECTRIMS 2017

Effect of immunotherapy on SPMS onset

definition of SPMS

- EDSS step ≥4
- EDSS progression (1 step if EDSS 4-5.5 or 0.5 if EDSS ≥6)
- confirmation of progression over ≥3 months
- confirmation of increase in the lead functional system score
- in the absence of a relapse
- pyramidal functional system score ≥2

benchmark: relentless progression of neurological disability

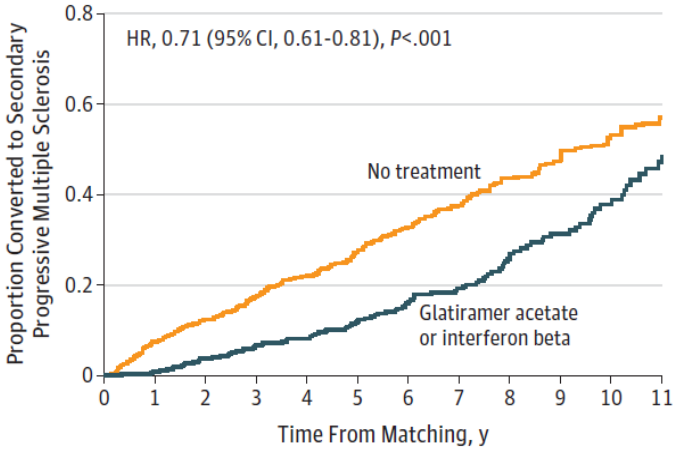
87% agreement with a consensus SPMS diagnosis

accuracy (at individual level): 2x2 tables

Lorscheider et al., Brain 2016, 139:2395

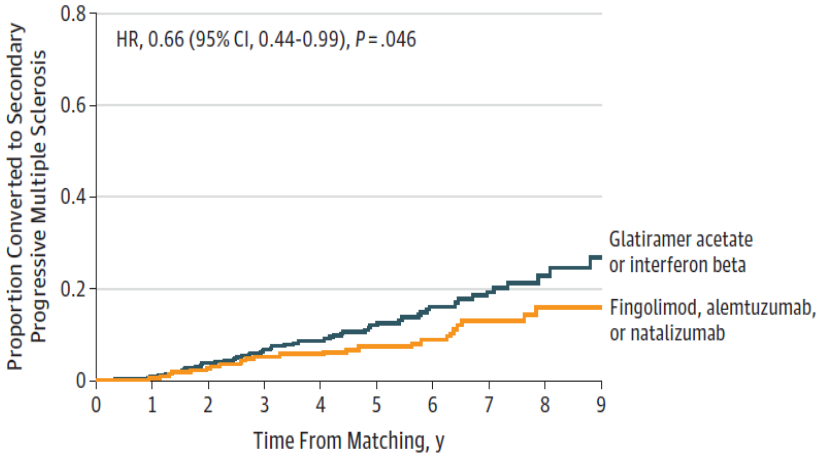
Effect of immunotherapy on SPMS onset

Early injectables vs. no treatment



No. with follow-up data												
No treatment	213	213	213	213	213	180	153	126	96	74	51	33
Glatiramer acetate or interferon beta	407	407	407	407	407	355	300	251	191	142	98	62

Early injectables vs. higher-efficacy therapy



No. with follow-up data										
Initial treatment										
Glatiramer acetate or interferon beta	380	380	380	380	380	252	182	142	93	44
Fingolimod, alemtuzumab, or natalizumab	235	235	235	235	235	148	103	80	54	30

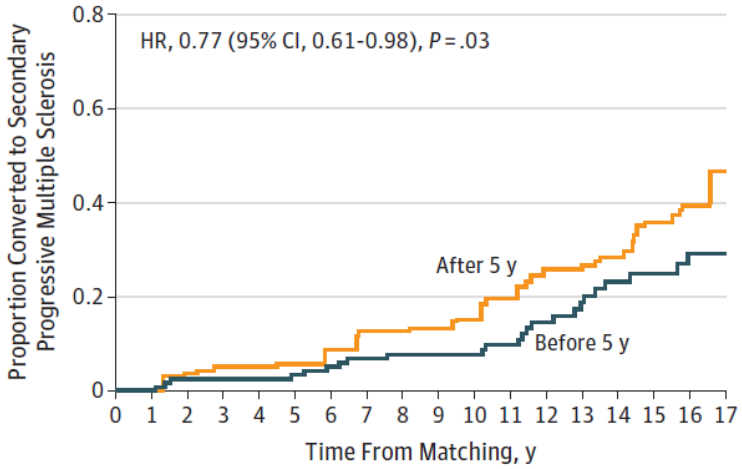
propensity score matching + pairwise censoring
Cox proportional hazards model

MSBase Neuro-Immunology Registry

Brown et al., JAMA 2019; 321:175

Effect of immunotherapy on SPMS onset

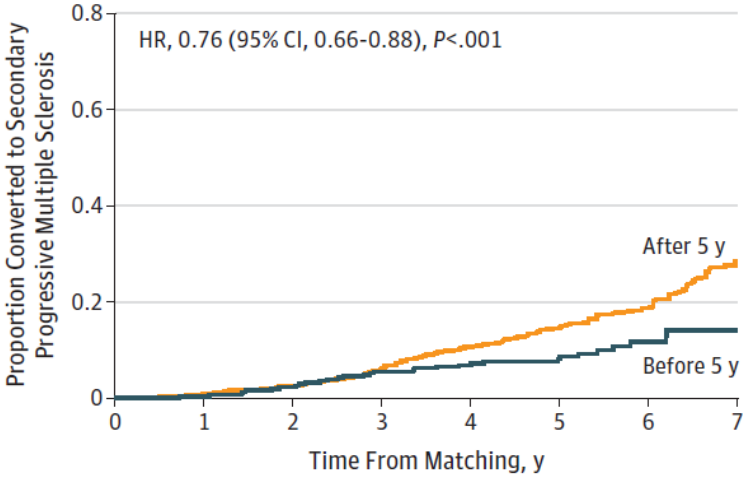
Early vs. delayed injectables



No. with follow-up data

Glatiramer acetate or interferon beta									
>5 y	38	38	38	38	36	31	23	15	11
≤5 y	120	120	120	119	115	102	77	60	44

Early vs. delayed higher-efficacy therapies



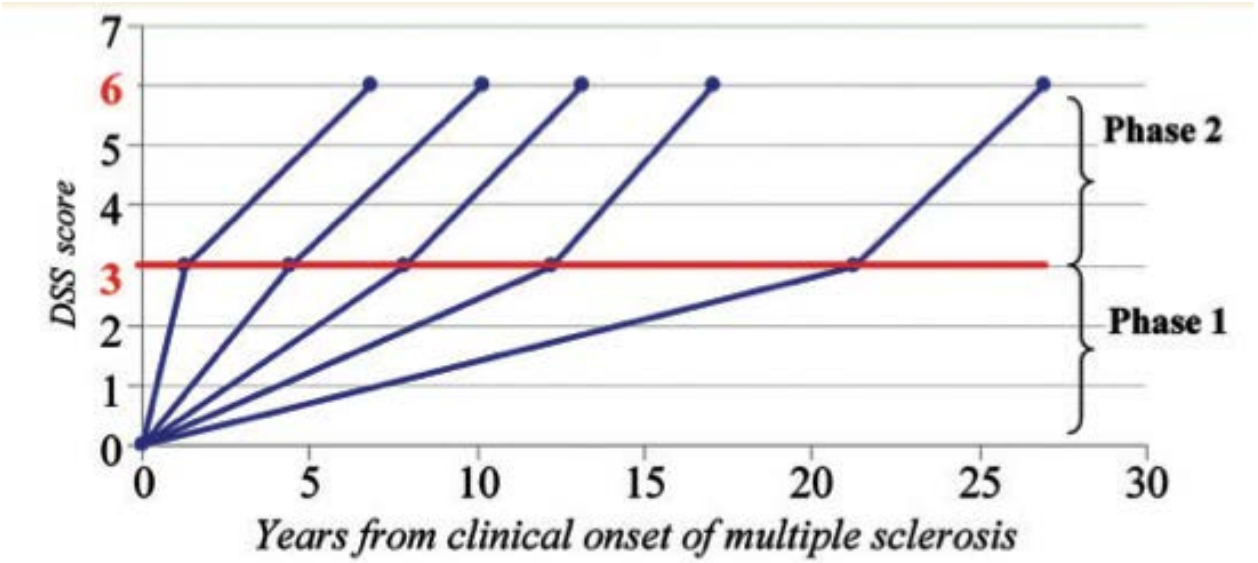
No. with follow-up data

Escalation to fingolimod, alemtuzumab, or natalizumab								
>5 y after onset	331	331	331	331	331	204	106	49
≤ 5 y after onset	307	307	307	307	307	191	97	47

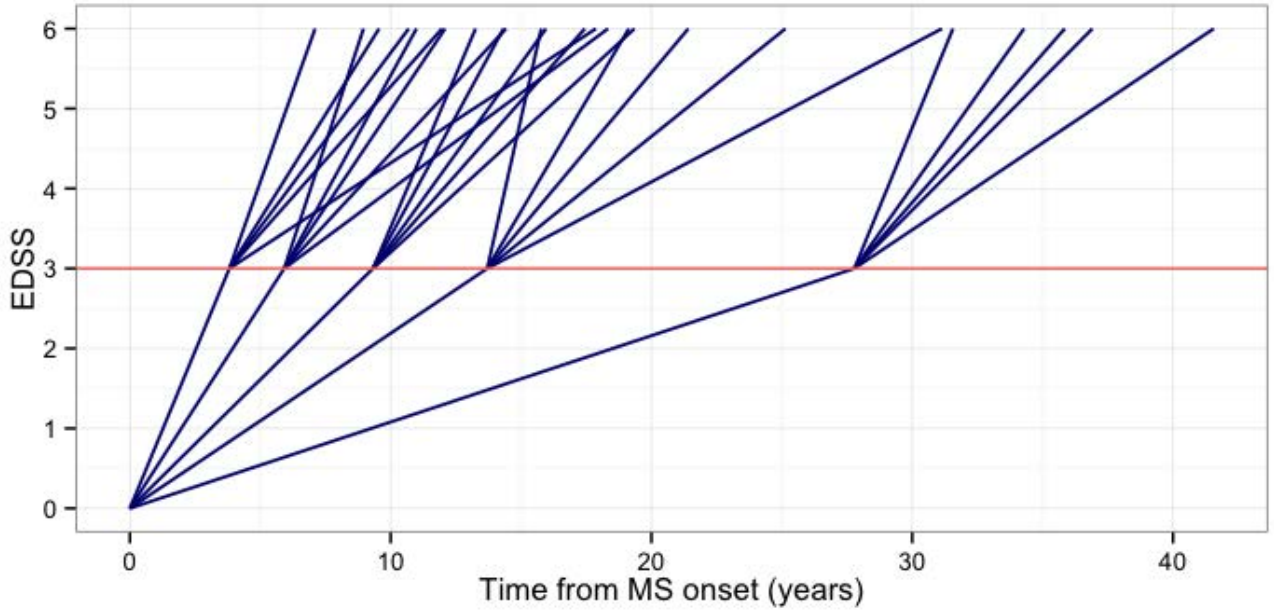
propensity score matching + pairwise censoring
Cox proportional hazards model

MSBase Neuro-Immunology Registry

Brown et al., JAMA 2019; 321:175



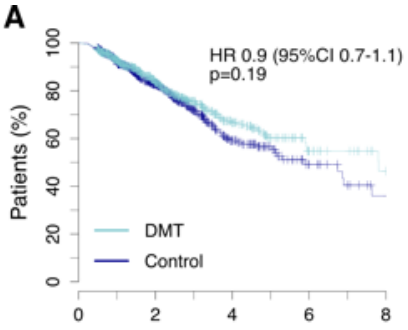
Leray et al., Brain 2010, 133:1900

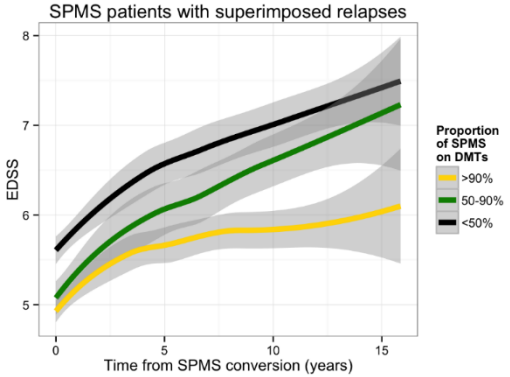


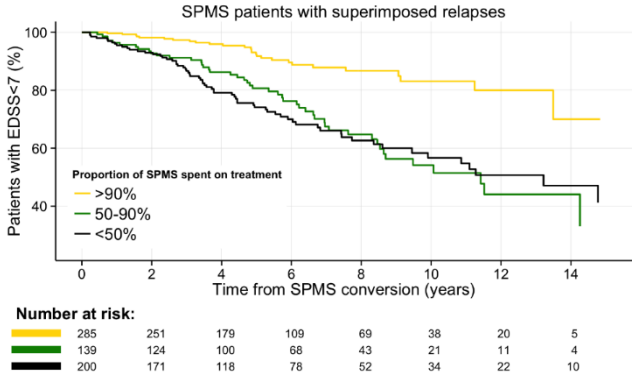
Lizak et al., JNNP 2017; 88: 196

Treating secondary progressive MS in context

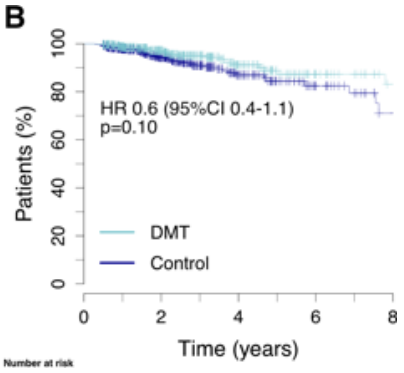
Confirmed disability progression

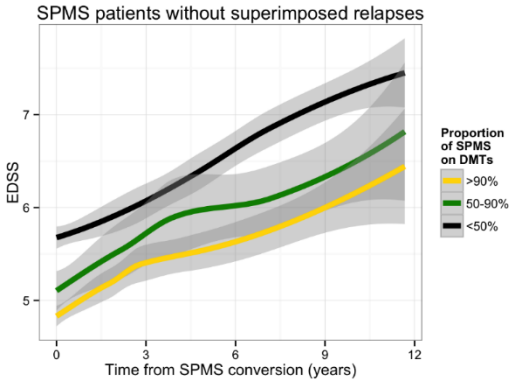


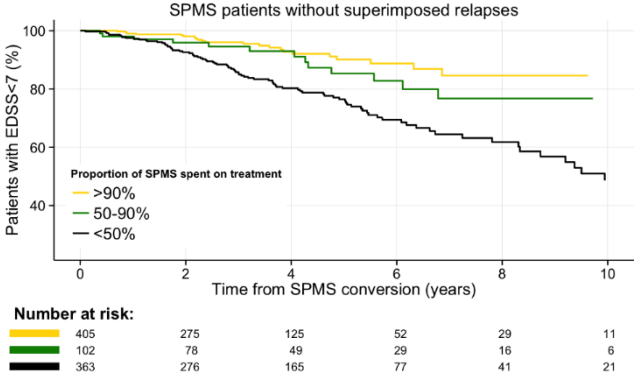




EDSS≥7







propensity score matching + pairwise censoring
Cox proportional hazards model

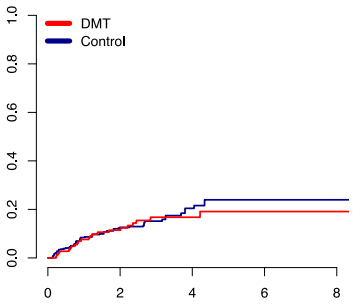
Lorscheider et al., Neurology 2017, 89:1050

multivariable linear regression model
multivariable Cox proportional hazards model

Lizak et al., ECTRIMS 2018

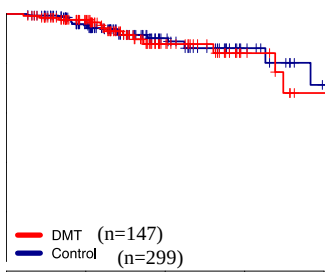
Treating primary progressive MS in context

Confirmed disability progression



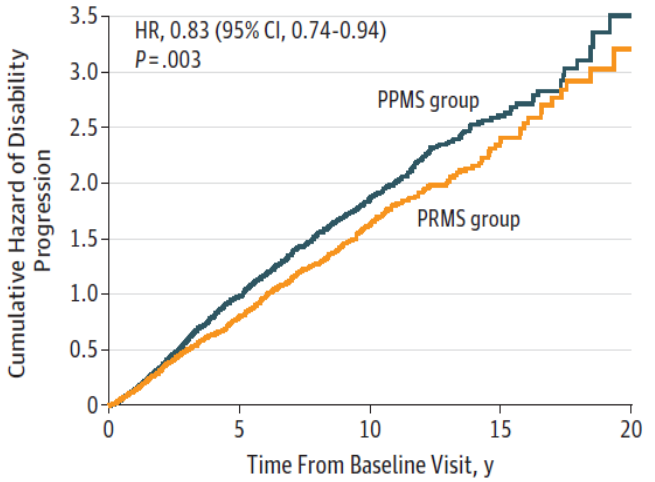
HR 1.1, 95%CI 0.6-2.0, p=0.79

EDSS≥7



HR 1.1, 95%CI 0.6-2.3, p=0.71

3-month confirmed disability progression



No. at risk

PPMS group	866	429	189	67	9
PRMS group	553	321	152	47	10

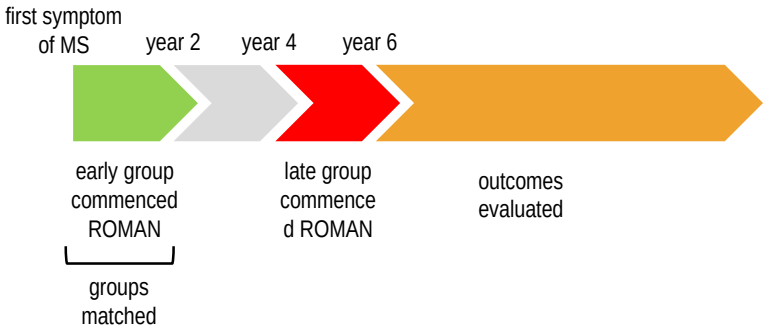
propensity score matching + pairwise censoring
Cox proportional hazards model

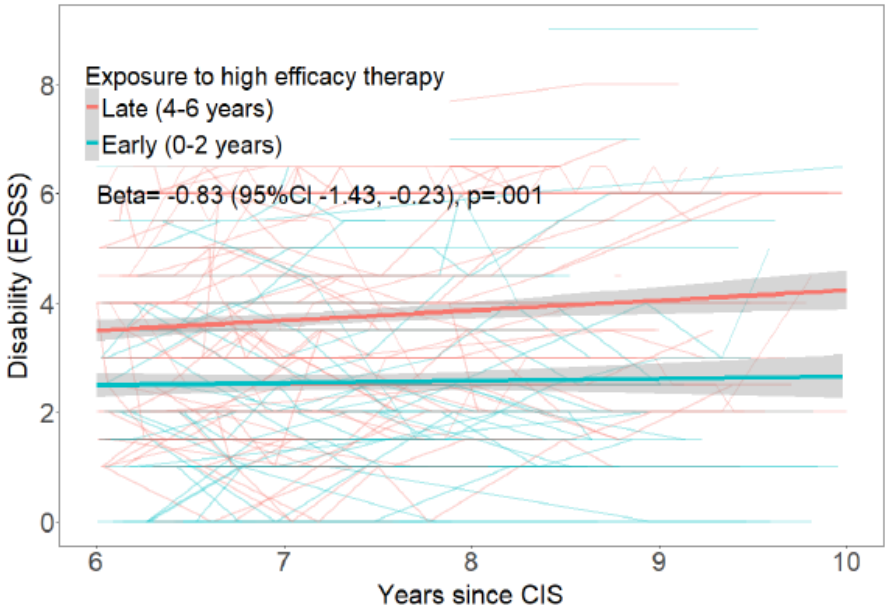
	active PPMS	inactive PPMS
Percentage of follow-up on disease modifying therapy (per 10%)	0.97 (0.940, 0.995)	1.02 (0.99, 1.05)

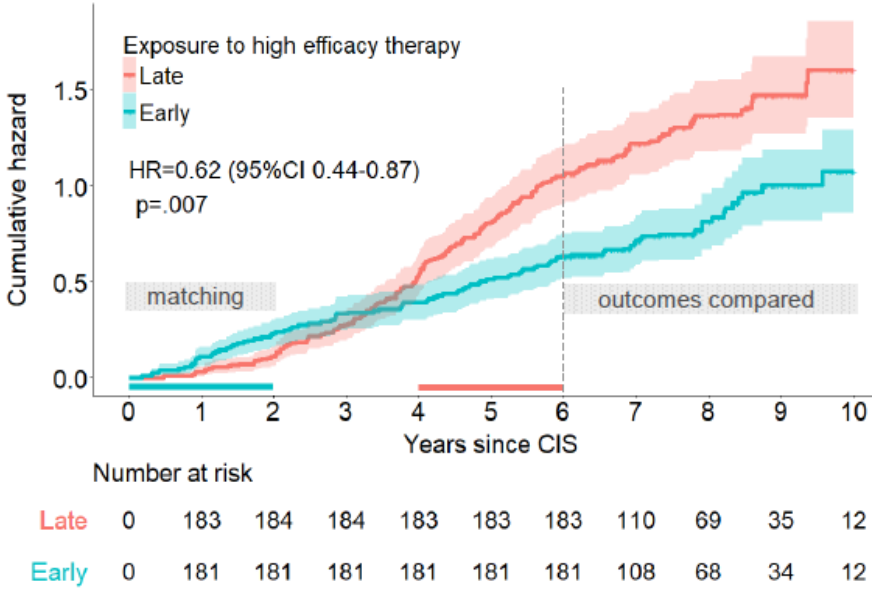
Lorscheider et al., Eur J Neurol *in press*

Hughes et al., JAMA Neurol *in press*

When to start high-efficacy therapy







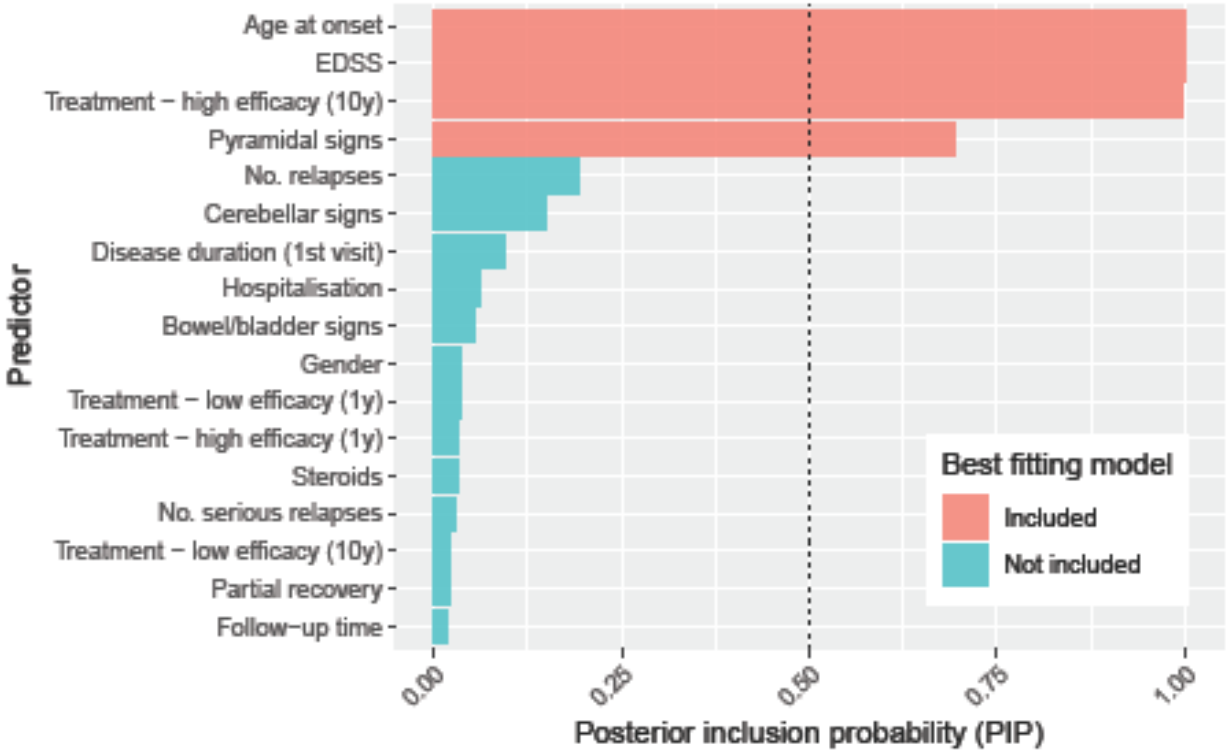
propensity score matching + pairwise censoring
ordinal regression
Andersen-Gill proportional hazards model

He et al., ECTRIMS 2018

Towards individualised MS therapy

…to identify aggressive MS early

Predictors: recorded during 1st years from MS onset
Outcome: 6-month confirmed EDSS ≥6 at 10 years from MS onset (prevalence 6%)



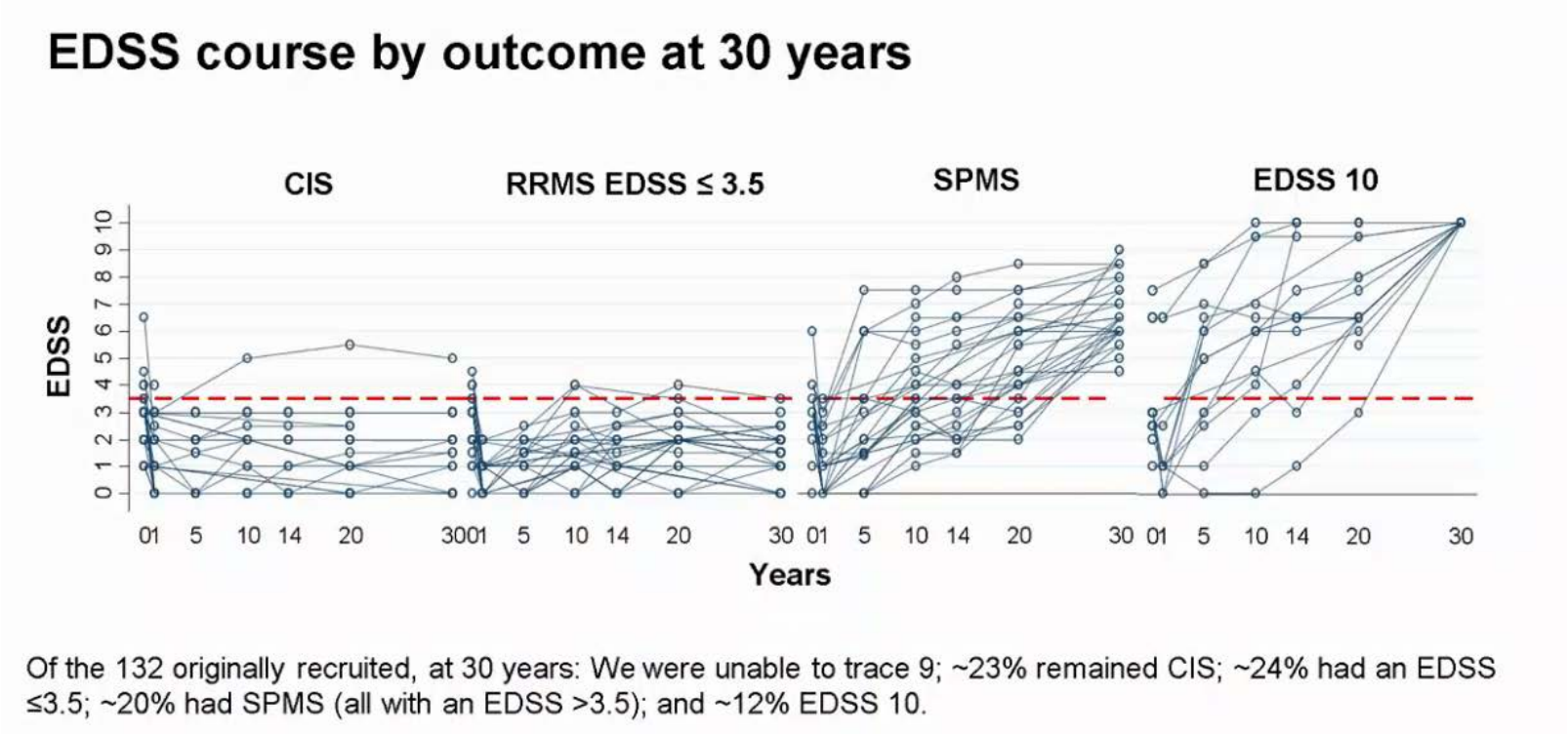
AUC: 0.81
sensitivity: 0.72
specificity: 0.78
negative predictive value: 0.98
positive predictive value: 0.17

validation: Swedish MS Registry

Bayesian model averaging (logistic model)

weighted posterior probability of the predictors across the whole model space

Disease course in initially benign MS

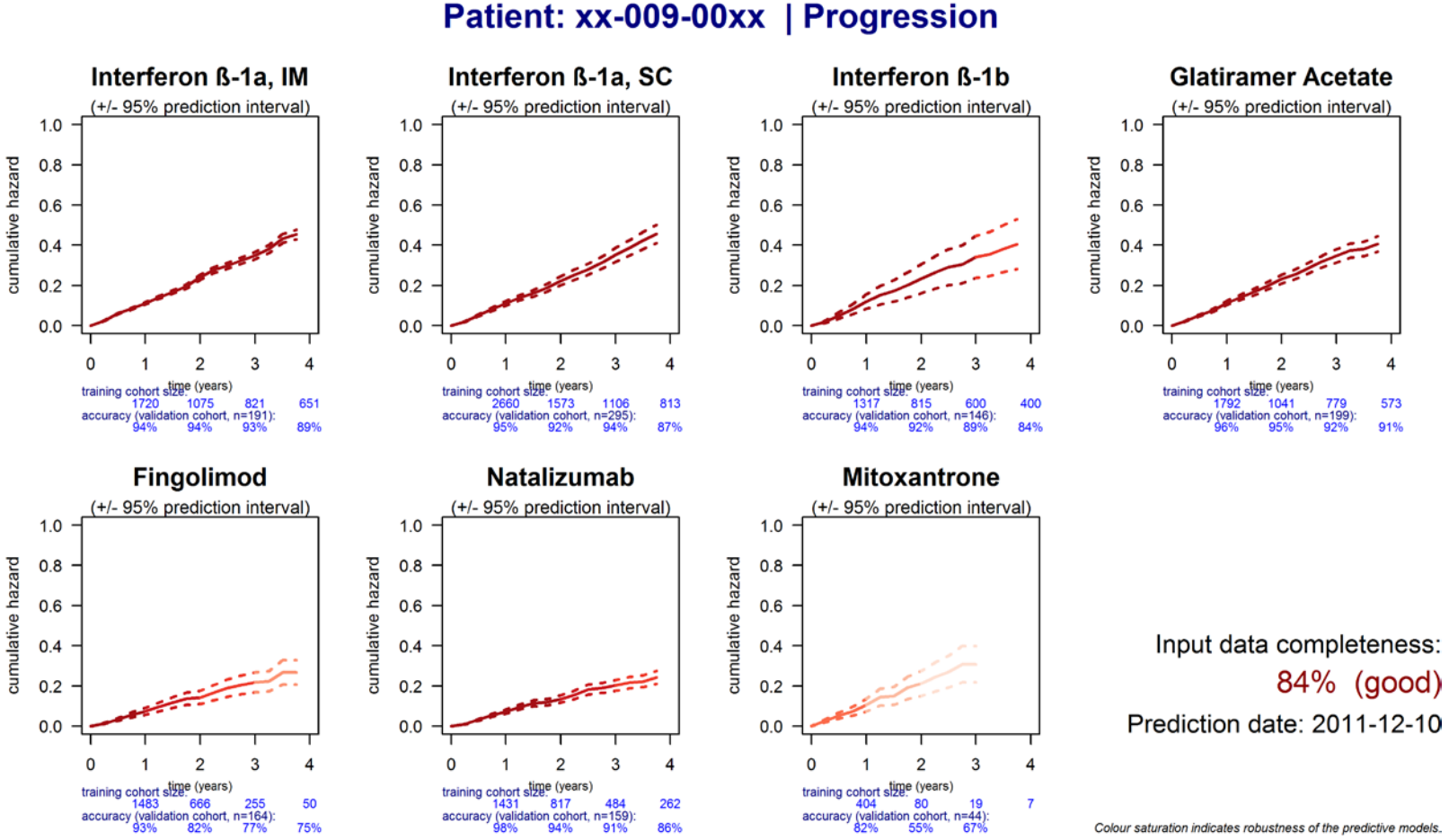


Of the 132 originally recruited, at 30 years: We were unable to trace 9; ~23% remained CIS; ~24% had an EDSS ≤3.5; ~20% had SPMS (all with an EDSS >3.5); and ~12% EDSS 10.

Chard et al., ECTRIMS 2017

Towards individualised MS therapy

Conditional response to therapy



multivariable Andersen-Gill cumulative hazards model
reduction of proportionality: PCA
external validation

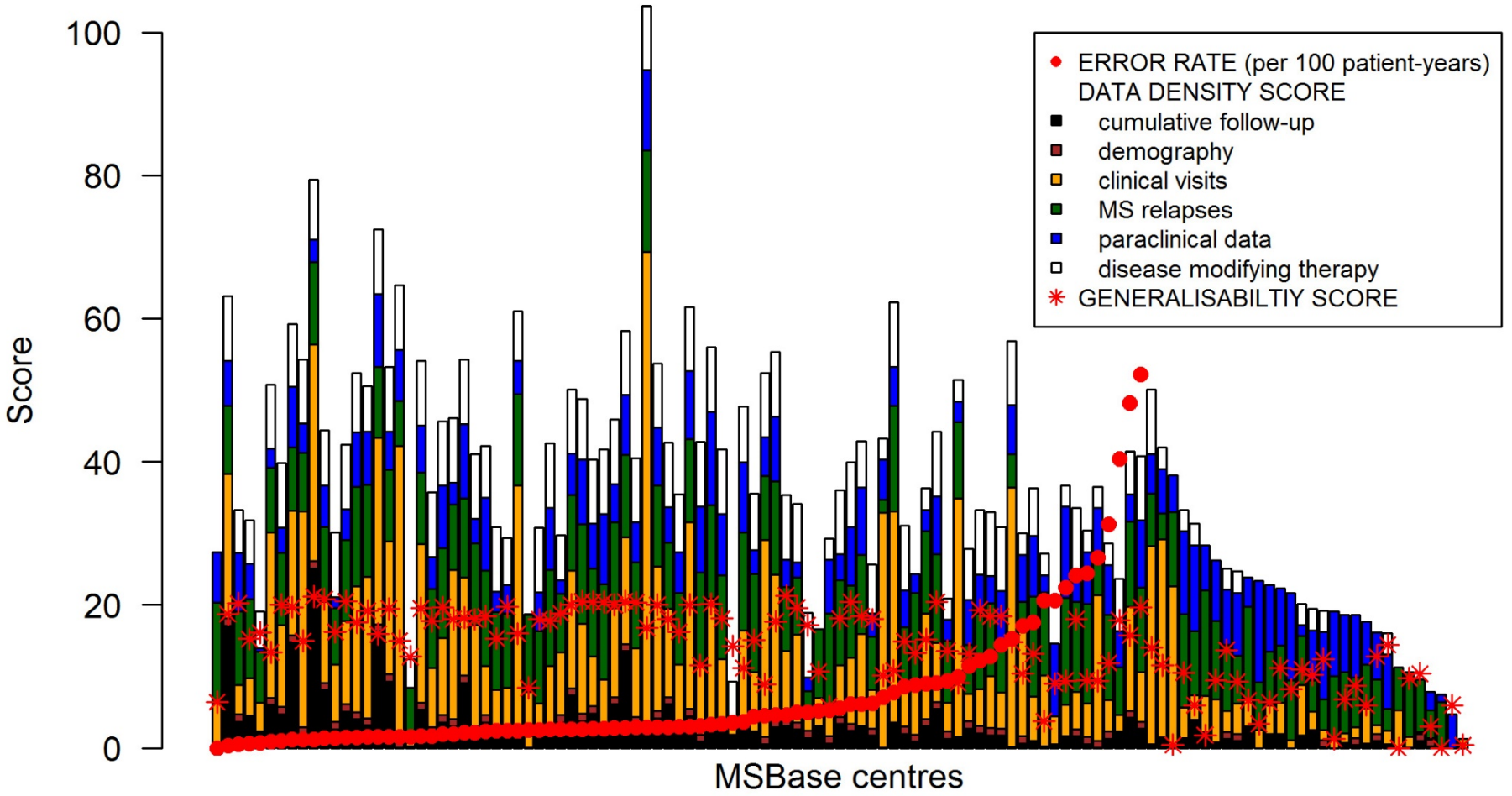
Kalincik et al., Brain 2017; 140:2426

CORe - MSBase standardised data quality process

- Duplicate patient records were removed.
- Centres with <10 patient records were excluded.
- Patients with missing date of birth were excluded.
- MS onset dates after the MSBase data extract date were removed.
- Patients with missing date of the first clinical presentation of MS were excluded.
- The dates of MS onset and the first recorded MS course were aligned.
- Patients with the age at onset outside the 0-100 range were excluded.
- A logical sequence of the MS courses (e.g. clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS) was assured.
- Entries with the initiation of progressive MS prior to its clinical onset of MS were excluded.
- Visits with missing visit date or the recorded date before the clinical MS onset or after the date of MSBase data extract were removed.
- EDSS scores outside the range of possible EDSS values were removed.
- Duplicate visits were merged.
- MS relapses with missing visit date or the recorded date after the date of MSBase data extract were removed.
- Duplicate MS relapses were merged.
- Relapses occurring within 30 days of each other were merged.
- Visits preceded by relapses were identified and time from the last relapse was calculated for each visit.
- Therapies were labelled as discontinued or continuing.
- Therapies with erroneous date entries were removed (e.g. commencement date > termination date, commencement after the MSBase data extract date, commencement of disease modifying therapy before the year 1980).
- MS disease modifying therapies were identified and labelled.
- Duplicate treatment entries were removed.
- Where multiple disease modifying therapies were recorded simultaneously, treatment end date of the previous therapy was imputed as the commencement date of the following therapy.
- Consecutive entries for certain disease modifying therapies were merged into a continuous treatment entry, given that the gap between the entries did not exceed 190 days for mitoxantrone, 365 days for cladribine, 90 days for other disease modifying therapies.
- The default duration of treatment effect was recorded as 190 days (mitoxantrone), 5 years (alemtuzumab) or 365 days (cladribine) from treatment commencement.

Kalincik et al., *Mult Scler* 2017;23:647

CORe - MSBase standardised data quality process



Kalincik et al., *Mult Scler* 2017;23:647

From information to evidence

Analyses of large data are changing the way we treat MS.

Observational data are enabling us to address detailed questions that inform clinical practice:

- diagnostic criteria
- deep phenotyping
- treatment effectiveness and safety
- prognostics
- individualised therapy
- maximise the impact of multimodal data
- generate hypotheses about pathophysiology of neurological diseases

Data is only half of the story. Analytics is the other half.

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http:\\core.melbourne

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