An Innovative Approach to Modelling the Optimal Treatment Sequence for Patients with Relapsing-Remitting Multiple Sclerosis: Implementation, Validation, and Impact of the Decision-Making Approach

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Supplemental Materials

Discrete Event Simulation

Calculation of ***disease trajectory***

The times to all events, with the exception of routine visits, in a patient's disease trajectory are derived from the annual probability of having the event and are calculated using the inverse transform method [1]. Routine physician visits take place once a year. The annual probability of a relapse at a point in time is the patient's simulated ARR given his/her disease duration. If the patient is treated with a DMT, this ARR is multiplied with the risk ratio (RR) of the DMT versus natural history to retrieve the ARR with treatment; it is assumed that the time to relapse follows an exponential probability distribution. The duration of a patient's next EDSS step given natural history is dependent on the patient's simulated disease severity. When the patient is treated with a DMT, the simulated severity is divided by the simulated treatment effect (a HR of disease progression) to obtain the estimated ttEDSS6 with treatment, which is divided by 6 to get the average duration of each EDSS step with treatment.

Natural history disease trajectory

Each simulated patient's disease trajectory starts at the diagnosis of RRMS. At this point, sex and age at onset are randomly drawn from independent statistical distributions in the patient population of interest (Supplemental Table 1).

Supplemental Table 1. Distribution of age at onset in modelled population [2]

Onset age (years)	Proportion of patients
<20	13%
20 to <30	40%
30 to <40	31%
40 to <50	13%
≥50	4%
Total	100%*

* Percentages do not sum to 100 due to rounding.

The time of the next EDSS step is based on the patient's severity (ttEDSS6), randomly drawn from a distribution of patient severities stratified by sex and age at onset (Supplemental Tables 2 and 3).

Supplemental Table 2. Survival rates until EDSS6 for males [2, 3]

	Proportion in group by age at onset (years)

Severity group (time to EDSS6)	<20	20 to <30	30 to <40	40 to <50	≥50
0 to <5 years	3.66%	4.27%	6.46%	7.56%	11.23%
5 to <10 years	5.95%	6.95%	10.47%	11.73%	16.66%
10 to <15 years	8.88%	10.69%	15.14%	16.73%	21.15%
15 to <20 years	10.97%	12.49%	16.17%	17.80%	20.29%
20 to <25 years	9.01%	10.33%	12.52%	13.61%	14.71%
25 to <30 years	9.84%	11.31%	12.66%	12.90%	10.46%
30 to <35 years	9.14%	9.46%	9.33%	9.30%	4.47%
35 to <40 years	5.86%	7.44%	6.56%	6.01%	0.98%
40 to <45 years	6.87%	6.86%	5.08%	3.11%	0.06%
45 to <50 years	13.69%	10.71%	4.49%	1.18%	0.00%
≥50 years	16.12%	9.48%	1.12%	0.06%	0.00%

EDSS6: Expanded Disability Status Scale (EDSS) state 6.

Supplemental Table 3. Survival rates until EDSS6 for females [2, 3]

Severity group (time to EDSS6)	Proportion in group by age at onset (years)				
	<20	20 to <30	30 to <40	40 to <50	≥50
0 to <5 years	1.94%	2.34%	3.86%	4.64%	7.39%
5 to <10 years	4.75%	5.88%	8.99%	10.27%	14.15%
10 to <15 years	5.81%	7.12%	10.46%	11.88%	15.91%
15 to <20 years	6.98%	8.41%	11.86%	13.39%	17.56%
20 to <25 years	8.83%	10.41%	13.72%	15.06%	18.45%
25 to <30 years	9.71%	11.17%	13.54%	14.62%	15.16%
30 to <35 years	8.22%	9.36%	10.51%	11.81%	8.63%
35 to <40 years	9.22%	10.18%	10.19%	10.20%	2.54%
40 to <45 years	11.60%	11.71%	9.42%	6.45%	0.22%
45 to <50 years	12.57%	11.49%	5.77%	1.60%	0.00%
≥50 years	20.37%	11.94%	1.68%	0.09%	0.00%

EDSS6: Expanded Disability Status Scale (EDSS) state 6.

The time of a relapse is based on a patient's individual ARR. The patient's ARR in the first five years after diagnosis is drawn from a distribution of ARRs given the patient's simulated severity (Supplemental Table 4) [4]. In addition, the ARR is assumed to decrease over the course of the disease based on the age at onset (Supplemental Table 5) [5].

Supplemental Table 4. ARR in the first five years by time to EDSS6 [4]

ARR	Severity group (time to EDSS6)			
	>0 to 10 years	>10 to 20 years	>20 to 30 years	>30 years
<0.2*	752	701	350	132
0.2 to <0.4	422	364	157	36
≥0.4**	702	533	153	18
Total	1872	1598	660	186

ARR: annualized relapse rate, EDSS6: Expanded Disability Status Scale (EDSS) state 6.

* The lower bound of this category was assumed to be 0.1.

** The upper bound of this category was assumed to be 0.6.

Supplemental Table 5. Decline in ARR per five years conditional on age at onset [5]

Age at onset (years)	Decline in ARR per 5 years of disease duration
<20	6.9%
20 to <30	16.9%
30 to <40	22.9%
≥40	30.5%

ARR: annualized relapse rate.

Application of treatment effect

For the purposes of the model validation only the treatments included in the model were those used in the Markov model used in the external validation. At the first visit following diagnosis, the initial DMT is assigned and times for the five potential events, given the assigned DMT, are calculated. A treatment effect, based on a NMA of cladribine tablets versus comparators, is applied to the natural history for relapses and EDSS progression (Supplemental Tables 6 and 7) [6]. The individual treatment effects used in the DES model were drawn from their respective distributions using random numbers. Furthermore, it is assumed that the treatment effects regarding disability worsening and relapses are independent within a patient (i.e., a patient may respond well to a treatment in terms of relapses but not in terms of disability worsening, and vice versa).

Supplemental Table 6. ARR relative to natural history (placebo) [6]

Treatment	Mean RR (95% CI)
Alemtuzumab	0.322 (0.259 - 0.391)
Cladribine	0.419 (0.318 - 0.538)
Dimethyl fumarate	0.535 (0.450 - 0.630)
Fingolimod	0.459 (0.398 - 0.525)
Glatiramer acetate	0.654 (0.590 - 0.721)
Interferon beta-1a (Rebif 44 μg)	0.662 (0.586 - 0.740)
Natalizumab	0.341 (0.281 - 0.406)
Ocrelizumab	0.367 (0.292 - 0.449)
Teriflunomide	0.671 (0.579 - 0.771)

ARR: annualized relapse rate, RR: risk ratio, CI: confidence interval.

Supplemental Table 7. Disability worsening relative to natural history (placebo) [6]

Treatment	Mean HR (95% CI)
Alemtuzumab	0.398 (0.207 - 0.726)
Cladribine	0.542 (0.294 - 0.986)
Dimethyl fumarate	0.639 (0.409 - 0.967)

Fingolimod	0.687 (0.451 - 1.049)
Glatiramer acetate	0.672 (0.418 - 1.071)
Interferon beta-1a (Rebif 44 μg)	0.712 (0.454 - 1.157)
Natalizumab	0.447 (0.252 - 0.797)
Ocrelizumab	0.431 (0.229 - 0.839)
Teriflunomide	0.819 (0.537 - 1.258)

HR: hazard ratio, CI: confidence interval.

The time of an SAE is based on incidence rates which were sourced from pivotal trials of the included DMTs (Supplemental Table 8). In addition, the patient's serological status with respect to JCV is drawn at baseline and is assumed not to change over time; PML risk is based on the duration of exposure to natalizumab and JCV index (Supplemental Table 9).

Supplemental Table 8. Annual probability of SAEs in the discrete event simulation

SAE	Annual probability (%)								
	ALE [7]	CLA [8]	DMF [9]	FIN [10]	GLA [11]	IFN [12]	NAT [13]	OCR [14, 15]	TER [16]
Infusion site reaction	1.61							1.25	
Injection site reaction						0.54			
Macular edema				0.10					
Hypersensitivity					0.38	0.27	1.30		
Gastrointestinal symptoms		0.30							0.27
Autoimmune thyroid-related event	1.19	0.03							
Severe infection	0.90	0.63	0.28	1.17	0.38	0.27	1.66	1.98	0.41
Influenza-like symptoms						0.54			
ITP	0.20								

SAE: serious adverse event, ALE: alemtuzumab, CLA: cladribine tablets, DMF: dimethyl fumarate, FIN: fingolimod, GLA: glatiramer acetate, IFN: interferon beta-1a, NAT: natalizumab, OCR: ocrelizumab, TER: teriflunomide, ITP: immune thrombo-cytopenia purpura. Empty cells indicate a probability of 0.

Supplemental Table 9. Risk of PML conditional on duration of natalizumab exposure and JCV index [17, 18]

Duration of natalizumab exposure (months)	Risk per 1000 patients			
	Negative antibody status	Antibody positive (JCV index ≤0.9)	Antibody positive (JCV index >0.9 to ≤1.5)	Antibody positive (JCV index >1.5)
1 to 12	0.1	0.1	0.1	0.2
13 to 24	0.1	0.1	0.3	0.9
25 to 36	0.1	0.2	0.8	3
37 to 48	0.1	0.4	2	7
49 to 60	0.1	0.5	2	8
>61	0.1	0.6	3	10

PML: progressive multifocal leukoencephalopathy, JCV: John Cunningham virus.

Treatment switching indicators

For effectiveness, the model switches a proportion of patients based on assumptions regarding relapses and/or EDSS worsening (Supplemental Table 10). For PML risk, the model compares the risk to an acceptable threshold: patients switch if they have an annualized PML risk that is higher than 3 per 1000 patients. Furthermore, the point at which the patient will terminate treatment is based on when a specific EDSS step is reached; the default distribution (58% of patients terminate when they reach EDSS7 and the remainder when they reach EDSS8) was derived from a Delphi study [19].

Supplemental Table 10. Treatment switching decision rule for reasons of effectiveness [20]

Relapses in preceding year	Disability worsening (preceding year and current EDSS)	Switching
0 relapses	No disability worsening or EDSS score <2	40%
	≥1 point disability worsening with and EDSS score of 2 to ≤4	50%
	≥1 point disability worsening with and EDSS score of >4	60%
1 non-severe relapse	No disability worsening or EDSS score <2	70%
	≥1 point disability worsening with and EDSS score of 2 to ≤4	80%
	≥1 point disability worsening with and EDSS score of >4	80%
1 severe relapse	-	90%
≥2 relapses	-	100%

EDSS: Expanded Disability Status Scale.

Markov Model

Disability worsening and relapses

When a decision is made to switch treatments, the Markov model is run to evaluate the costs and effects of all alternative treatment options. Patients start the Markov model in their current EDSS state and each cycle they may move to the next EDSS state or remain in their current state. The Markov model stops when a patient has reached EDSS10 or has died from other causes than MS, which can happen at any point in time. The monthly transition probability to move from one EDSS state to another is assumed to follow an exponential distribution (i.e., a constant rate). Given the Markov model calculates expected outcomes on the population level, it uses the mean HR of disability worsening and the mean RR of relapses to evaluate the expected outcomes with each treatment alternative.

Patients cannot skip states in clinical reality; the one-month cycle length is assumed to be short enough to allow a continuous path through each EDSS state. Backward transitions (i.e., EDSS improvements) are not modelled because these can be considered temporary

improvements. After EDSS6, it is assumed the average time in each health state is five years [21]. The average duration is equal for each severity group. After termination of all DMTs, no treatment effect is assumed, both for disability worsening and relapses.

The occurrence of relapses is modelled separately from disability worsening and independently of severity group (i.e., the probability of relapse is the same for each EDSS state for all severity groups) [22]. The modelling of relapses in the Markov model follows the same process as in the DES, except that population averages for the ARR in natural history are used rather than individual ARRs. The ARR diminishes with disease duration. The treatment effect, average RR of having a relapse, is multiplied with the ARR to obtain the expected ARR with treatment.

Markov model inputs

The Markov model makes use of cost and utility parameters which are also used in the DES. Since the Markov model uses monthly cycles, any annual values were converted to monthly values.

In the Markov model, the probability of experiencing AEs or tolerability issues is taken into account in the evaluation of possible subsequent treatment options, but in a different way than in the DES. All AEs, not only SAEs as in the DES, and tolerability issues are applied as one-off events assumed to occur during the first cycle of the evaluation (Supplemental Table 11). To this end, the treatment-specific (pooled) AE incidence rates from pivotal trials are multiplied with the associated costs and disutilities. The resulting treatment-specific cost and utility decrement is then applied for each treatment in the first month of the Markov model. The probabilities of the AEs were sourced from a cost-effectiveness model for cladribine tablets [23]. It should be noted, that while AEs associated with DMTs are encompassed in the approach taken here, not all serious, or rare events were included, due to uncertainty of available data for modelling purposes. It is not expected that these events would have a significant impact on the economic outcomes, yet these parameters may be an area for further research. In addition, marketing authorization and prescribing information for DMTs can vary by country and should also be considered if utilizing this approach. Relapse-associated costs were calculated as a weighted average of severe and non-severe relapses according to the proportions of severe and non-severe relapses in the population.

Supplemental Table 11. Probabilities of AEs applied in the Markov model [2]

AE	One-off (lifetime) probability of AE (%)									
	ALE	**CLA**	**DMF**	**FIN**	**GLA**	**IFN**	**NAT**	**OCR**	**TER**	**NH**
Infusion site reaction	90.1						23.6	34.3		
Injection site reaction					55.9	75.7				
Macular edema				0.4						
Hypersensitivity					11.7	1.2	4.0			
Gastrointestinal	22.8	24.5	35.2	30.4	18.6	21.0	22.8	22.8	39.4	22.8
Autoimmune thyroid-related event	11.3	5.1	1.2	1.2	1.2	2.6	1.2	1.2	1.2	1.2
Severe infection	2.3	2.8	2.1	2.2	1.6	0.7	1.9	1.9	2.0	1.9
Influenza-like symptoms	1.1	1.3	1.2	0.5	0.7	6.4	0.1	1.2	0.1	0.1
ITP	1.8									
PML							0.2			

AE: adverse event, ALE: alemtuzumab, CLA: cladribine tablets, DMF: dimethyl fumarate, FIN: fingolimod, GLA: glatiramer acetate, IFN: interferon beta-1a, NAT: natalizumab, OCR: ocrelizumab, TER: teriflunomide, NH: natural history, ITP: immune thrombo-cytopenia purpura, PML: progressive multifocal leukoencephalopathy. Empty cells indicate a probability of 0%.

Cost and Utility Inputs

Health-related quality of life inputs

Health-related quality of life values associated with disability status and utility decrements associated with relapses and AEs were included (Supplemental Tables 12 and 13). Each AE and relapse were associated with a temporary drop in quality of life modelled as a one-off QALY decrement at the occurrence of the event, calculated from the negative utility and the duration of the AE.

Supplemental Table 12. Utility values by EDSS state [24]

EDSS state	Utility value
EDSS0	0.846
EDSS1	0.762
EDSS2	0.711
EDSS3	0.608
EDSS4	0.609
EDSS5	0.531
EDSS6	0.496
EDSS7	0.392
EDSS8	0.025
EDSS9	-0.195

EDSS10 (death)	0

EDSS: Expanded Disability Status Scale.

Supplemental Table 13. Utility decrements associated with AEs and relapses [22, 25]

Outcome	Utility decrement	Duration (days)	QALY impact per event
Severe relapse	-0.071	90	-0.017
Non-severe relapse			
AE			
Infusion site reaction	-0.011	5	-0.0002
Injection site reaction	-0.011	1	-0.0002
Macular edema	-0.040	84	-0.0092
Hypersensitivity	-1.000	7	-0.0192
Gastrointestinal	-0.240	8	-0.0053
Autoimmune thyroid-related event	-0.110	365.25	-0.1100
Severe infection	-0.190	14	-0.0073
Influenza-like symptoms	-0.210	7	-0.0040
ITP	-0.090	28	-0.0069
PML	-0.200	93	-0.0510

AE: adverse event, QALY: quality-adjusted life-year, ITP: immune thrombo-cytopenia purpura, PML: progressive multifocal leukoencephalopathy.

Cost inputs

Costs are all reported in British Pounds Sterling for cost year 2019. Where necessary, costs were inflated to 2019 values using the Consumer Price Index section Health [26].

Disease management costs are the direct costs associated with each EDSS health state (Supplemental Table 14). These are applied as annual costs in the DES and multiplied with the number of years a patient spends in each EDSS health state [24]. An assumption is made that there are no costs associated with death. Furthermore, it was assumed that severe relapses correspond to a relapse with hospitalization and cost £3,733.64 each, whereas non-severe relapses equate to a relapse without hospitalization and cost £581.17 each [24]. Costs associated with AEs are applied as one-off costs at the occurrence of the event.

Supplemental Table 14. Disease management costs per EDSS state [24]

EDSS state	Annual cost (£)
EDSS0	1,164.62
EDSS1	1,039.02
EDSS2	817.52
EDSS3	762.71
EDSS4	1,144.07
EDSS5	1,148.63

EDSS6	1,488.88
EDSS7	1,502.59
EDSS8	3,790.72
EDSS9	3,790.72

EDSS: Expanded Disability Status Scale.

Annual treatment acquisition costs are calculated using the dose per year and the price per dose. Different drug costs associated with a different dosing schedule in year one compared to later years of treatment are taken into account for alemtuzumab. The costs and units per pack were sourced from the British National Formulary [27], while the annual number of doses was obtained from the respective Summaries of Product Characteristics (SmPCs) from the electronic Medicines Compendium (medicines.org.uk) [28]. The administration costs were sourced from the manufacturer submission of cladribine tablets [22]. See Supplemental Table 15.

Supplemental Table 15. Treatment and administration costs

Treatment	Cost/ pack (£) [27]	Units/ pack	Units/Year [28]	Annual drug cost (£)	Annual administration cost (£) [22][a]
Alemtuzumab 12 mg	7,045.00	1	5 (year 1) 3 (year 2+)	35,225.00 (year 1) 21,135.00 (year 2+)	2,901.48 (year 1) 1,749.31 (year 2+)
Cladribine tablets 10 mg	2,047.24	1	12.67[b]	25,952.86	-
Dimethyl fumarate 240 mg	1,373.00	56	723.5 (year 1) 730.5 (year 2+)	17,738.67 (year 1) 17,910.29 (year 2+)	-
Fingolimod 0.5 mg	1,470.00	28	365.25	19,175.63	576.08
Glatiramer acetate 20 mg	462.56	28	365.25	6,033.93	224.96
Interferon beta-1a 44 μg	813.21	12	156.54	10,608.03	224.96
Natalizumab 300 mg	1,130.00	1	13.04	14,740.45	7,489.08 (year 1) 7,489.08 (year 2+)
Ocrelizumab 300 mg	4,790.00	1	4	19,160.00	1,728.25 (year 1) 1,152.17 (year 2+)
Teriflunomide 14 mg	1,037.84	28	365.25	13,538.25	-

[a] Inflated to 2019 values.

The dose for cladribine tablets is based on weight. The weight categories and their respective dosing in year 1 and year 2 of treatment are in accordance with the SmPC of cladribine [29]; the proportion of patients in each weight category was assumed equal to the distribution at baseline in the CLARITY trial of cladribine tablets [30]. The average number of doses in each year is 12.67. Monitoring costs are applied each year of treatment in the model, where a distinction is made between the first year and later years of treatment, because the first year often requires a more intensive monitoring than later years of

treatment. The monitoring costs were sourced from a cost-effectiveness model of cladribine tablets and inflated to 2019 values [23]. For alemtuzumab, monitoring costs were applied until four years after the last infusion according to the SmPC [31].

Supplemental Table 16. Monitoring costs

Treatment	Year 1 cost (£)	Year 2+ cost (£)
Alemtuzumab	462.26	278.88
Cladribine	612.01	224.62
Dimethyl fumarate	744.40	182.30
Fingolimod	864.85	174.71
Glatiramer acetate	330.96	330.96
Interferon beta-1a 44 mcg	348.33	339.64
Natalizumab	563.18	570.78
Ocrelizumab	186.64	171.45
Teriflunomide	350.13	338.48

Alemtuzumab and cladribine tablets have a non-continuous treatment schedule. For alemtuzumab, all patients receive 2 courses of treatment at the start of year 1 and year 2 and a proportion of patients receive additional courses in later years [32]. For cladribine, no additional courses after year 2 were modelled in accordance with the pivotal trial [30], the SmPC [29] and NICE guidance [33]. The annual drug acquisition, administration, and monitoring costs for alemtuzumab and cladribine over the first 6 years were calculated.

AE costs (Supplemental Table 17) are multiplied with the number of AEs to obtain AE-related costs.

Supplemental Table 17. AE cost per event [34]

AE	Cost (£)
Infusion site reaction	0
Injection site reaction	7.37
Severe infection	3,567.49
Macular edema	266.36
Gastrointestinal	767.49
Hypersensitivity	170.02
Autoimmune thyroid-related event	589.91
Influenza-like symptoms	7.37
ITP	1,019.52
PML	1,376.06

AE: adverse event, PML: progressive multifocal leukoencephalopathy, ITP: immune thrombo-cytopenia purpura.

Updating the Prior of Severity

It was assumed that every patient's severity can be characterized by a single parameter α which can be interpreted as the expected duration spent in each EDSS step. The EDSS spectrum from EDSS0 (disease onset) to EDSS6 is divided into six steps (α); this means six EDSS steps must be made from disease onset to reach EDSS6. For a patient in severity group 2 (ttEDSS6 is >5 to 10 years), α will thus lie between 0.83 (5/6) and 1.67 (10/6) years. However, for a patient in severity group 5 (ttEDSS6 >20 to 25 years), α will lie between 3.33 (20/6) and 4.17 (25/6) years. The virtual physician has an expectation of the patient's α being between each of the limits of the severity groups, denoted as L_i for the lower limit and L_(i+1) for the upper limit. The result is a probability distribution for the patient residing in each of these severity groups, the prior of severity. These probabilities are mutually exclusive and collectively exhaustive, i.e. the patient must be in one, and only one, group – as such the probabilities sum to one.

At each visit, the virtual physician updates their expectation of the probability the patient belongs to each of the severity groups, i.e., P(L_i<α<L_(i+1)), using the following observations: 1) the patient's current EDSS (x), 2) the time since the patient made their last EDSS step, and 3) the time since the patient's disease onset. To this end, the limits of α, L_i and L_{i+1} are redefined at each visit. For example, a patient in EDSS0 at three years after onset would have to make 6 EDSS steps in 0 to 2 years to reach EDSS6 <5 years and have a severity of 0 to <5 years. This corresponds to making six steps in 0 to 2 years, i.e., 0/6<α<2/6. One year later, for this same patient 0/6<α<1/6 to have a severity of 0 to <5 years.

This can be generalized as follows: at each visit the virtual physician updates their expectation that the time from onset to EDSS6 will lie between lower limit T_l and upper limit T_u, where T_l is one of 0, 5, 10, …., 50 years and T_l is 5, 10, 15, …..55 years. To progress from the patient's current EDSS stage x to EDSS6, requires 6-x steps. The current point in time (T_{visit}) is defined as the time of the visit since onset. From T_{visit}, the 6-x steps need to occur over time period $(T_l - T_{visit})$ to $(T_u - T_{visit})$ for the patient to be in the severity group with limits T_l to T_u. The average duration of each EDSS step (α) is thus defined as:

$$\frac{T_l - T_{visit}}{6 - x} < \alpha < \frac{T_u - T_{visit}}{6 - x} \qquad (1)$$

From now on, L_i, the lower limit of α, will be defined as $\frac{T_l - T_{visit}}{6-x}$ and L_{i+1}, the upper limit, will be defined as $\frac{T_u - T_{visit}}{6-x}$.

The above applies to observations of EDSS steps given natural history. In case a patient is treated, the average α changes as well as the T_l and T_u and thus the limits L_i and L_{i+1}. When a patient is treated, T_l and T_u are adjusted by dividing these by the average HR of the treatment versus natural history.

Supplemental Figure 1. Illustration of the prior of disease severity changing over time

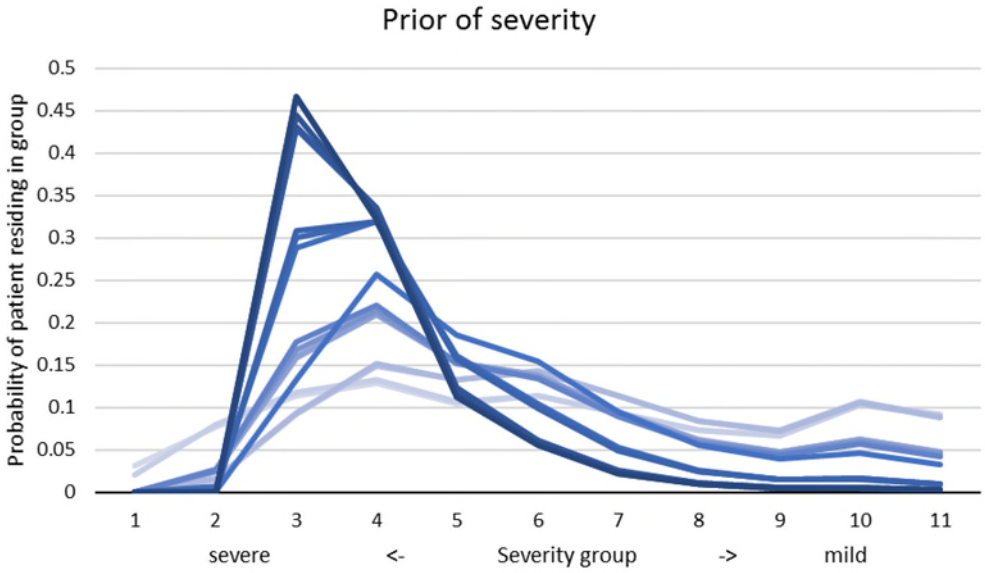


Figure legend. Prior of severity for a patient with a simulated severity of 10 years. The initial prior of severity is depicted in the lightest shade of blue, with darker shades representing priors at later points in time. The distribution of probabilities of patient severity narrows with increasing time, indicating that the physician gets more certain of the patient's severity.

Appendix

Figure 1. Proportion of patients in Expanded Disability Status Scale (EDSS) state <6 for a 25-year time horizon with model initiation in EDSS0

Figure legend. Black lines indicate the various severity groups; the red line indicates the weighted average of the Markov models; the green line indicates the reference model [23].

Figure 2. Average time spent in each health state over a 25-year time horizon for a cohort starting in Expanded Disability Status Scale (EDSS) state 0 (i) and state 3 (ii)

Figure legend. Palace et al. (2014) [21] refers to natural history.

Figure 1.

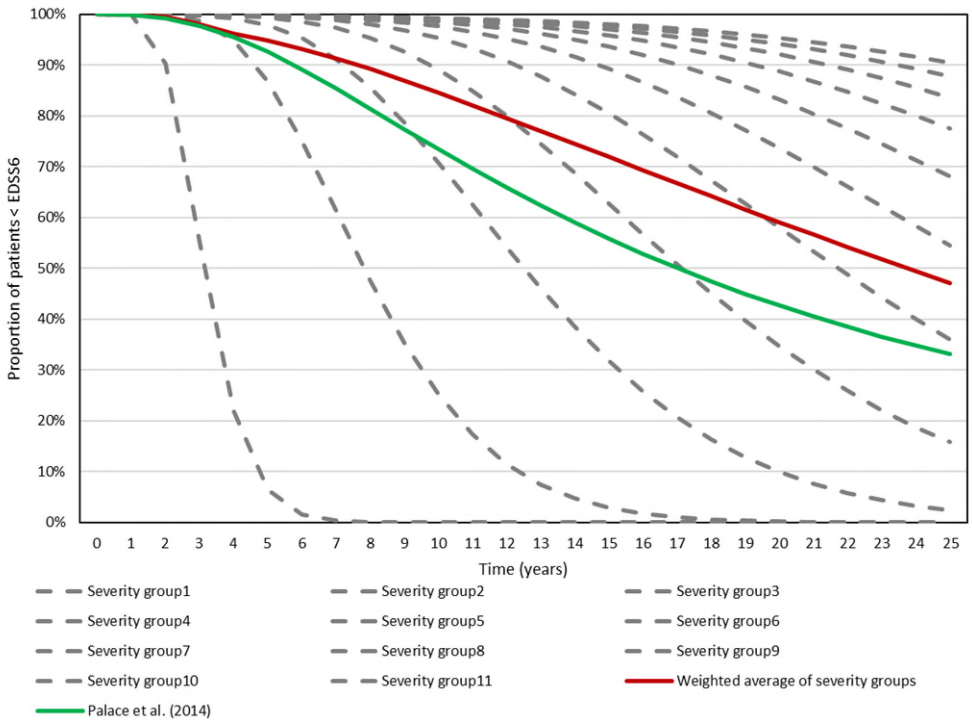
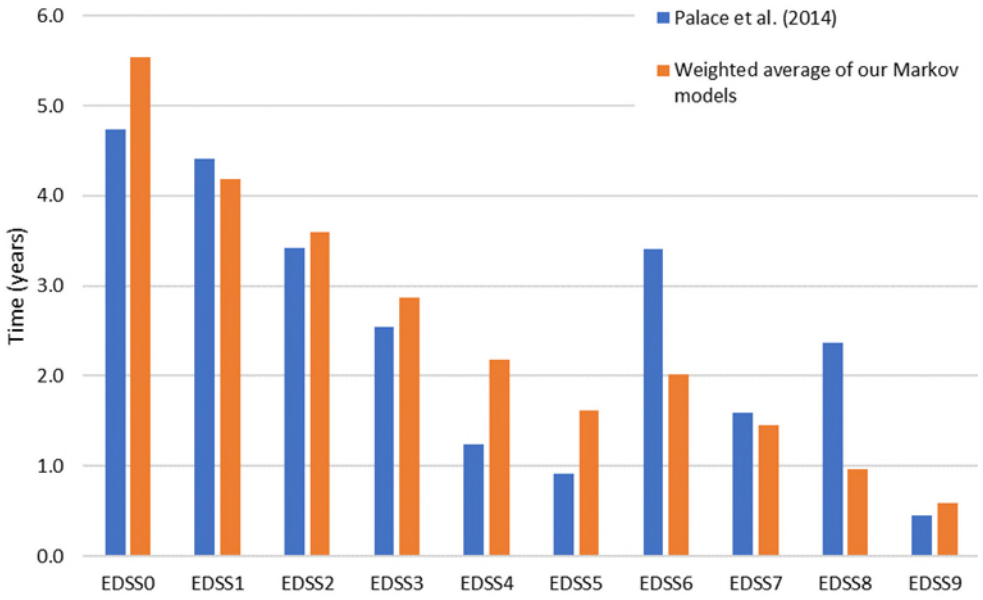
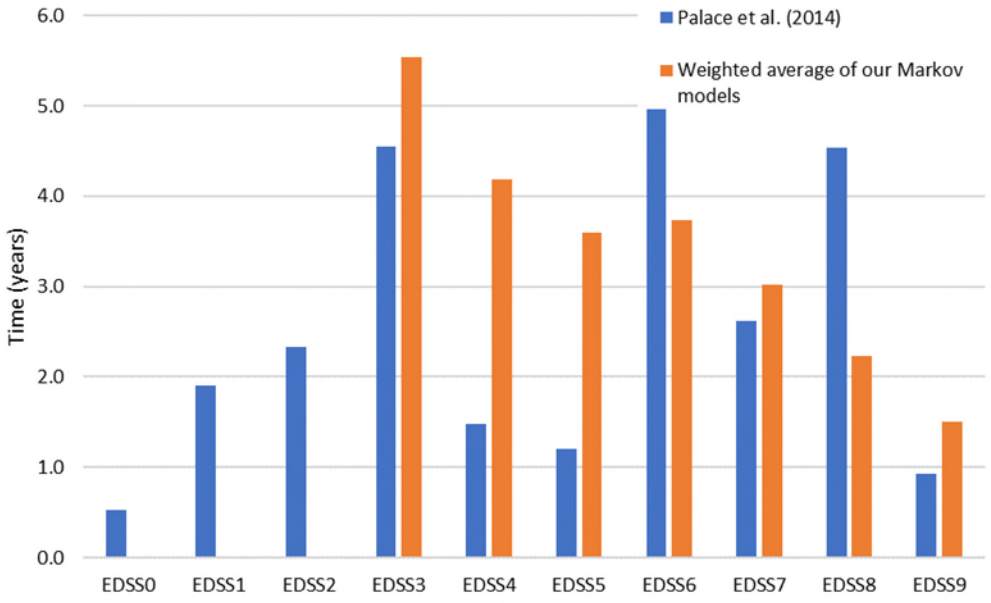


Figure 2.

(i)


6.0
5.0
4.0
3.0
2.0
1.0
0.0
Time (years)
Palace et al. (2014)
Weighted average of our Markov models
EDSS0
EDSS1
EDSS2
EDSS3
EDSS4
EDSS5
EDSS6
EDSS7
EDSS8
EDSS9

ii.


6.0
5.0
4.0
3.0
2.0
1.0
0.0
Time (years)
Palace et al. (2014)
Weighted average of our Markov models
EDSS0
EDSS1
EDSS2
EDSS3
EDSS4
EDSS5
EDSS6
EDSS7
EDSS8
EDSS9

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