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A two-stage prediction model for heterogeneous effects of many treatment options: application to drugs for Multiple Sclerosis

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Abstract

Treatment effects vary across different patients and estimation of this variability is important for clinical decisions. The aim is to develop a model to estimate the benefit of alternative treatment options for individual patients. Hence, we developed a two-stage prediction model for heterogeneous treatment effects, by combining prognosis research and network meta-analysis methods when individual patient data is available. In a first stage, we develop a prognostic model and we predict the baseline risk of the outcome. In the second stage, we use this baseline risk score from the first stage as a single prognostic factor and effect modifier in a network meta-regression model. We apply the approach to a network meta-analysis of three randomized clinical trials comparing the relapse rate in Natalizumab, Glatiramer Acetate and Dimethyl Fumarate including 3590 patients diagnosed with relapsing-remitting multiple sclerosis. We find that the baseline risk score modifies the relative and absolute treatment effects. Several patient characteristics such as age and disability status impact on the baseline risk of relapse, and this in turn moderates the benefit that may be expected for each of the treatments. For high-risk patients, the treatment that minimizes the risk to relapse in two years is Natalizumab, whereas for low-risk patients Dimethyl Fumarate might be a better option. Our approach can be easily extended to all outcomes of interest and has the potential to inform a personalised treatment approach.

1 Introduction

Personalized predictions are important for clinical decision-making. The question ‘Which treatment is best?’ can have two very different meanings: ‘Which treatment is best on average?’ or ‘Which treatment is best for a specific patient?’ Patients often experience different outcomes under the same treatment. One patient may benefit more by a treatment from which another patient may benefit less. Thus, it is essential to identify via risk modelling approach those patient characteristics that influence treatment effects in order to choose the best option for a given patient effects. Prediction models aim to identify and estimate the impact of patient, intervention and setting characteristics on future health outcomes. The baseline risk of patients is often a determinant of heterogeneous treatment effects (1).

The baseline risk expresses the probability of developing the studied outcome prior to any intervention. Models that link the baseline risk to patient characteristics have been referred to as *prognostic models or risk models*. A prognostic and a prediction model they can be combined in a *risk modelling approach* that uses the baseline risk of patients to predict heterogeneous treatment effects, typically within a randomised clinical trial (RCT) (1), (2), (3), (4). The first step is to develop a multivariable prognostic model that predicts the probability of developing the studied outcome blinded to the treatment - this can be done using observational or RCT data. We will term this *baseline risk* from now on, and a transformation of the risk will be termed *baseline risk score*. Several established methods exist for developing a prognostic model (5), (6), (7), (8). At a second step, relative treatment effects within RCTs can be estimated as a function of the baseline risk score using a prediction model (9). This methodology allows for heterogeneity in baseline risk, in the relative treatment effects and consequently in the absolute treatment effects too. The risk modelling approach has recently gained ground for personalized predictions under a treatment of choice (1), (3).

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system with several subtypes. The most common subtype is relapsing-remitting Multiple Sclerosis (RRMS)(10). Patients with RRMS present with intense symptoms (relapses) followed by periods without symptoms (remission) (11). Several treatments are available (12) with heterogeneous patient responses and each treatment has a very different safety profile.

The evidence about drugs for relapsing-remitting MS has been summarized using network meta-analysis (13), (14). These networks typically synthesize published aggregated data and therefore their ability to explore individual patient characteristics and to examine how treatment effects (relative or absolute) vary across different patients is limited. More efficient analyses use individual patient data (IPD), which are considered the gold standard in evidence synthesis and are necessary for estimating heterogeneous treatment effects and inform models that can make personalized predictions of expected outcomes (15), (16). Patient and setting characteristics can be included in network meta-regression models to make predictions for different treatments and subgroups of patients. However, this approach presents several computational and practical difficulties when many predictors are to be included in the model. Model selection techniques and shrinkage methods have not yet been

developed for IPD meta-regression models; with many predictors, issues of low power and optimism render the approach challenging.

2 *Methods*

In this paper, we aim to define a methodological framework that allows personalized predictions for the most likely outcome under several treatment options. To achieve this we adapt the risk modelling approach for the context of meta-analysis. We combine ideas from prognostic modelling to estimate the baseline risk score and include this score in an IPD network meta-regression (NMR). We apply this method in a set of trials comparing three drugs and placebo in patients with RRMS. We also examine how different prognostic models to estimate the baseline risk score influence the results of the predictive model and the estimated absolute and relative treatment effects (6), (17). We present results primarily for the absolute treatment effects, as these will vary across patient groups, even if heterogeneity is present only in the baseline risk but not in the relative treatment effects. We first describe the general framework, applicable to any type of data and network (section 2.1). In section 2.2, we detail the implementation of the framework in the context of drugs for RRMS.

2.1 *General description of the model*

We built a two-stage model where we first developed the baseline risk score and then estimated the probabilities of the post-treatment outcome as a function of the baseline risk score. The baseline risk score is determined using established methods (6), (17), (18). The second stage uses an IPD NMR model that includes the baseline risk score and its interaction with the treatment as predictors of the outcome. We describe the approach for a dichotomous outcome of interest, although continuous outcomes can also be modelled with minor modifications.

2.1.1 *Notation*

Let Y_{ij} denote the dichotomous outcome for individual i where $i=1, 2, \dots, n$ in the j study out of ns trials. PF_{ijk} is the k prognostic factor and np is the total number of prognostic factors. An individual can develop the outcome ($Y_{ij} = 1$) or not ($Y_{ij} = 0$) according to their risk at baseline, which is a function of the prognostic factors and we denote it with R_{ij} . Assume we have a set of treatments \mathcal{H} each denoted by $t \in \mathcal{H}$ where $t = 1, 2, \dots, T$. The

probability p_{ijt} is the probability of the outcome for the i individual in j study under treatment t and depends on treatment, baseline risk score and the interaction between the risk score and the treatment.

2.1.2 Stage 1: Developing a baseline risk score model

We developed a risk model using two different methods for a dichotomous outcome. Observational or RCT data may be used for this purpose; in the application of the model only placebo-controlled RCTs are available. According to previous recommendations, developing a baseline risk score using RCTs, should use not only the placebo arms, but the entire sample blinded to the treatment (2). The logistic regression model is

$$Y_{ij} \sim \text{Bernoulli}(R_{ij})$$

$$\text{logit}(R_{ij}) = b_{0j} + \sum_{k=1}^{np} b_{kj} \times PF_{ijk} \quad (1)$$

The regression coefficients and intercept can be independent, exchangeable ($b_{0j} \sim N(\beta_0, \sigma_{B_0}^2)$, $b_{kj} \sim N(\beta_k, \sigma_{B_k}^2)$) or common ($b_{0j} = \beta_0$, $b_{kj} = \beta_k$) across studies. For model selection, methods that include some form of penalization are preferred to stepwise selection (5), (6), (17). The latter include LASSO (Least Absolute Shrinkage and Selection Operator). However, including a set of predictors informed by prior knowledge (either in the form of expert opinion or previously identified variables in prognostic studies) has conceptual and computational advantages (17), (18), (19). The estimated effects of the selected covariates also needs some form of penalisation to avoid extreme predictions (6), (5). In the application, we discuss several possibilities (see section 2.2.2).

Validation is essential for evaluating the performance of a prognostic model (7). As external data were not available, we performed internal validation only. To evaluate the discriminative performance and the calibration ability we estimated the c-statistic and the calibration slope of the developed risk models. To account for optimism, which is particularly important when comparing various models, we used bootstrap (6). We produced 500 bootstraps samples and reran the model selection process and estimation in each sample. Then, we assessed the performance of each bootstrap-based model in the original sample (20), (21).

2.1.3 Stage 2: IPD Network meta-regression model

In the second stage we use the logit of the baseline risk as a covariate in an IPD NMR model (22). Each study j has an arbitrarily chosen baseline treatment $b_j \in \mathcal{H}$ and then each individual i is randomized to any treatment $t \in \mathcal{H}$. The meta-regression equation in study j with a baseline treatment b_j will be:

$$Y_{ij} \sim \text{Bernoulli}(p_{ijt})$$

$$\text{logit}(p_{ijt}) = \begin{cases} u_j + g_{0j} \times (\text{logit}(R_{ij}) - \overline{\text{logit}(R_{ij})}^j) & \text{if } t = b_j \\ u_j + d_{jb_{jt}} + g_{0j} \times (\text{logit}(R_{ij}) - \overline{\text{logit}(R_{ij})}^j) + g_{jb_{jt}} \times (\text{logit}(R_{ij}) - \overline{\text{logit}(R_{ij})}^j), & \text{if } t \neq b_j \end{cases} \quad (2)$$

where $\overline{\text{logit}(R_{ij})}^j$ is the average of logit-risk in all individuals in study j . The relative treatments effects are the log-odds ratios $d_{jb_{jt}}$ and can be random ($d_{jb_{jt}} \sim N(D_{b_{jt}}, \sigma_D^2)$) or fixed ($d_{jb_{jt}} = D_{b_{jt}}$) across studies. Then, assuming consistency we set the constraint $D_{b_{jt}} = \delta_t - \delta_{b_j}$ and $\delta_{ref} = 0$ where δ_t is the summary estimate for log-odds ratios for treatment t versus the overall reference treatment (*ref*). Parameter g_{0j} is the coefficient of the risk score (as a prognostic factor) and can be independent, exchangeable ($g_{0j} \sim N(\gamma_0, \sigma_{\gamma_0}^2)$), or fixed ($g_{0j} = \gamma_0$). Similarly, $g_{jb_{jt}}$ refers to the treatment effect modification of the risk score, for treatment t versus study's baseline treatment b_j , and can be random ($g_{jb_{jt}} \sim N(G_{b_{jt}}, \sigma_G^2)$) or fixed ($g_{jb_{jt}} = G_{b_{jt}}$), where $G_{b_{jt}} = \gamma_t - \gamma_{b_j}$ and $\gamma_{ref} = 0$. Finally, $\exp(\gamma_t)$ is the ratio of two ORs of treatment t versus the reference: the OR of a group of people with baseline score x over the OR in a group of people with baseline risk score $x - 1$.

Assume that there is an overall reference treatment (like placebo) for which predictions are less important. Then, consider a patient at the mean (logit) baseline population risk, \bar{R} who is also under this overall reference treatment. This logit-probability of the outcome is denoted with, say, α . To make predictions for a new patient with predicted risk $\widetilde{\text{logit}(R_i)}$ and in treatment t , we use the equation:

$$\text{logit}(p_i) = \alpha + \delta_t + \gamma_0 \times (\widetilde{\text{logit}(R_i)} - \overline{\text{logit}(R)}) + \gamma_t \times (\widetilde{\text{logit}(R_i)} - \overline{\text{logit}(R)}), \quad (3)$$

Estimation of a and $\overline{\text{logit}(R)}$ depends on the context within which we plan to make prediction. Registry data or observational studies can be used to extrapolate to a specific context, or the same RCT data as previously can be used. For example, $\overline{\text{logit}(R)}$ can be estimated as the mean of $\text{logit}(R_{ij})$ across all individuals and studies. Similarly, a can be estimated from the synthesis of all relevant arms (externally to the model) or by estimating the outcome in those patients in the overall reference treatment with baseline risk close to overall mean.

2.2 Application: predicting relapses in multiple sclerosis under different treatments

2.2.1 Data description

We analysed IPD from three phase III randomized clinical trials (23), (24), (25) on patients diagnosed with relapsing-remitting MS. Altogether, the trials included 3590 patients randomized to Placebo, Natalizumab, Dimethyl Fumarate, and Glatiramer Acetate. The outcome of interest was relapse or not relapse MS at two years. [Table 1](#) presents the aggregated-level data of the trial arms as well as some baseline characteristics. We also had access to IPD from 1083 patients with relapsing-remitting MS, randomized to placebo arms included in nine clinical trials. The latter data was provided by the Clinical Path Institute (<https://c-path.org/>) and is also described in [Table 1](#). We excluded variables with more than 50% missing values. Between variables that were correlated (correlation coefficient larger than 70%) we retain those that were biologically plausible to be associated with the outcome based on the literature, their distribution and the amount of missing values. Finally, we transformed some of the continuous variables to better approximate the normal distribution and merged categories with very low frequencies in categorical variables.

2.2.2 Stage 1: Developing a baseline risk model for relapse

We first examined if the available sample size was enough for the development of a prognostic model (26). We calculated the events per variable (EPV) accounting for categorical variables and non-linear continuous variables (27). We also used the method by Riley at al. to calculate the efficient sample size for the development of a logistic regression model (28). We set Nagelkerke's $R^2 = 0.15$ (Cox-Snell's adjusted $R^2 = 0.11$) and the desired shrinkage equal to 0.9.

We then fitted two main prognostic models. In the first model we included predictors with non-zero coefficients in the least absolute shrinkage and selection operator (LASSO) (29). We used the LASSO method both for the variable selection and for estimating the coefficients. We used 10 fold cross-validation to find the optimal penalty parameter that maximizes the area under the curve. The penalty parameter we chose is the one within one standard error of the minimum parameter, as previously recommended (6).

The second prognostic model was based on previously identified prognostic factors.

Pellegrini et al. analysed the annualized relapse rate MS in the DEFINE (training dataset) and CONFIRM (validation dataset) trials. They used different modelling approaches, including a fully additive model, ridge regression, LASSO, and elastic net regression. They selected the additive model including 14 prognostic factors based on its discrimination ability. We estimated the coefficients in each of these prognostic factors using penalized maximum likelihood estimation shrinkage method (30), (6). The optimal value of penalty was chosen as the one that maximizes a modified Akaike's Information Criterion (6). Both models use common effects for the intercept and the regression coefficients ($b_{0j} = \beta_0$, $b_{kj} = \beta_k$). This decision was taken because all three trials are designed by the same company in a very similar way and any differences in the included populations shall be captured by including the baseline risk in the network meta-regression model, as described in the following section.

2.2.3 Stage 2: IPD Network meta-regression model for comparing four treatments in relapsing-remitting multiple sclerosis

We assume that study-specific relative treatment effects do not have any residual heterogeneity beyond what is already captured by differences in baseline risk. Consequently, we employ a common effect IPD NMR model, both in the relative treatment effects d_{jb_jt} and for the treatment effect modification of the risk score. Note that the between studies variance could not be estimated with only three studies ($d_{jb_jt} = D_{b_jt} = \delta_t - \delta_{b_j}$, $\delta_{ref} = 0$, $g_{jb_jt} = G_{b_jt} = \gamma_t - \gamma_{b_j}$, $\gamma_{ref} = 0$). We also assumed common coefficients for the risk score ($g_{0j} = \gamma_0$), as all three studies very similar in terms of design characteristics.

To estimate the logit-probability (α) of the outcome of a patient at the mean baseline population risk score, $\overline{\logit(R)}$, under the overall reference treatment (i.e. Placebo), we used the external IPD Placebo-arm dataset. Then, we estimated the mean of $\logit(R_{ij})$ across all individuals and studies and we used this value as $\overline{\logit(R)}$.

2.2.4 Implementation and software

All our analyses were done in R (31). We made the analysis code available in a GitHub library: <https://github.com/htx-r/NMAPredictionsRiskModel>.

For the development of the baseline risk model (2.2.2), we used the `pmsampsize` command to estimate if the available sample size was enough for the developed model. The LASSO model was developed using `cv.glmnet`. We first fitted the pre-specified model using the `lrm` command and used the `pentrace` command for the penalized maximum likelihood estimation. For the bootstrap internal validation, we used self-programming R-routines.

The IPD Network meta-regression model (2.2.3) was fitted in a Bayesian framework and we used programming routines in the `R2Jags` package (32). We set a normal distribution ($N(0,1/1000)$) as prior distributions for all of the model parameters. We simulated two chains of 10,000 samples, we discarded the first 1,000 samples and we thinned for every 10 samples. This was appropriate based on the visualization of the chain convergence.

3 Results

3.1.1 Stage 1 Developing the baseline risk score

A total of 57 candidate prognostic factors were available. After exclusion of variables with missing data and highly correlated with other variables, we ended up with 31 candidate prognostic factors (Appendix figure 1, Appendix figure 2).

For the LASSO model, we used 2000 MS patients with complete data; 742 of whom relapsed in two years. The full model's degrees of freedom were 45 and the EPV was 16.5. The recommended sample size for a newly developed model is 3456 patients, which is above the available sample size. For the pre-specified model, which does not involve selection of variables, the small number of degrees of freedom (14) led to a large EPV of 53 and a recommended minimum sample size 1076; which is well below the available sample size.

Table 2 shows the two models, their coefficients and their performance with internal validation. Both models have almost the same discriminative ability, but the pre-specified model has a much better calibration slope.

Both models predict almost the same mean risk for patients in our data (about 37%) as shown in Figure . The variation of the estimated baseline risk score is much higher using pre-specified model. Figure 1 also indicates that the baseline risk could be a prognostic factor for relapsing-remitting MS in two years, as the baseline risk score is higher for patients that did relapse than for patients that did not relapse, using both models, although the overlap is large, as shown also by the c-statistics in Table 2.

3.1.2 Stage 2 Estimating heterogeneous treatment effects in an IPD network meta-regression model

Both models indicate the baseline risk as an important prognostic factor for relapsing MS in two years, as shown by the large values for γ_0 . The estimates of log ORs for each treatment versus Placebo (δ_t) are very similar with both models. However, they provide slightly different summary estimates for the coefficients of effect modification γ_0 . Overall, none of the coefficients γ_0 is large.

Figure 2 shows the estimated predicted probabilities to relapse within two years from the LASSO and Pellegrini risk models under the four available treatment options - appendix figure 3 presents the same results in OR scale. Both models give almost the same results for the treatment-effects estimation: Glatiramer Acetate seems to have the same performance as Dimethyl Fumarate in the observed range of baseline risk; Placebo results in the highest risk to relapse. Natalizumab is a drug initially considered less safe than the other two active options and associated with an increased mortality(33), (34), (33). Table 4 shows the estimated predicted probabilities and the ORs of relapsing under all three available active treatments, using both models separately, for all patients, for low-risk patients (baseline risk<30%) and for high-risk patients (baseline risk>50%). The benefit of all three treatments, depends on the risk group. For high-risk patients (baseline risk>50%) the absolute benefit of Natalizumab compared to Dimethyl Fumarate is 15% for pre-specified model and 10% for the LASSO model. These correspond into 7 and 10 patients respectively that need be treated with Natalizumab to prevent one relapse. For low risk patients (baseline risk<30%), absolute benefit of Dimethyl Fumarate compared to Natalizumab is 3% for pre-specified model and 2% for the LASSO model. The absolute differences between the treatments for all risk-groups are smaller using LASSO compared to the (penalized) pre-specified model. The predictions for the three drugs and Placebo for RRMS have been implemented in an interactive R-Shiny application available at <https://cinema.ispm.unibe.ch/shinies/koms/>.

4 Discussion

We developed a prediction model for heterogeneous treatment effects that combines risk modelling and network meta-analytical methods to make personalized predictions for an outcome of interest and to inform treatment decisions. We extended the idea of risk modelling approach (1) by combining network meta-analysis methods that allow comparing many treatment options via direct and indirect evidence (35). As the treatment options for each condition are numerous and most likely patient characteristics play an important role in the variability of treatment effects, this methodology could be an important tool for clinicians to make personalized decisions. Based on this model, we predicted the individualized probability to relapse within two years under each treatment. A crude network meta-analysis indicates that Natalizumab is the best treatment option on average. However, our model showed that not all patients will benefit from Natalizumab, but only those at high risk of relapse.

Given that a manageable number of characteristics is needed to establish the risk score, doctors and patients can enter these using our online tool (<https://cinema.ispm.unibe.ch/shinies/koms/>), estimate the risk to relapse in two years and see which of the three active treatments decreases the risk to relapse most. This tool shows the potential of the proposed approach, but may not yet be ready to be used in clinical practice. Decision-making tools need external validation with new patients, provide evidence about all available treatment options for many patient-relevant outcomes (e.g. long-term disability status), and also include issues of safety and cost. As few new trials might be available on existing drugs in the near future, observational data can be used to enhance the evidence.

We used two different prognostic models to develop the risk score, which resulted in quite different predictions for the absolute treatment effects. Our pre-specified model used variables previously identified as having an important prognostic ability. However, re-fitting the model to our data gave somewhat different results to those found by Pellegrini et al. This is because Pellegrini et al. examined a different outcome (annualized relapse rate MS), used a negative binomial distribution to model it, and used different methodology to develop their model. Additionally, variable selection approach via LASSO resulted into numerically

different results to the pre-specified model, but their clinical interpretation, both in stage one and stage two were similar. Based on our results, which are conditional on our dataset, we would recommend that the pre-specified model rather than LASSO is considered for further development and evaluation. The pre-specified model was expected to be more stable because it did not involve a selection process. Hence, the available sample size was sufficient. The discrimination ability of the models was small but sufficient for our aim: risk models with low predictive ability (0.6 – 0.65) are often adequate to detect risk-based heterogeneous treatment effects (3). Considering the results of the pre-specified model, Natalizumab is worth taking mainly when the baseline risk score is high (more than 50% risk of relapse). In these patients, the predicted risk to relapse in the next 2 years is about 15% lower on average compared to other treatments.

The applicability and usefulness of the application of our model in the relapsing-remitting MS example is limited by several factors. First, the probability to relapse is not the only outcome that patients will consider when choosing a treatment; long-term disability status would also determine their choice (36). Unfortunately, long-term outcomes are not available from RCTs. Consequently, the investigators who want to use this framework would need to establish the predictive ability of the short-term outcomes reported in RCTs to the long-term outcomes that matter to patients (typically available only in registries and observational programs). Unfortunately, we did not have access to such data, which would have also allowed us to validate externally the model. That can be a further line of future research. Finally, patients and doctors would most probably make decisions after considering several beneficial and harmful outcomes as well as treatment characteristics and include more alternative treatment options. We illustrated our model using the drugs tested in the RCTs that we had access to and consequently included only three active drugs out of a dozen possible choices. However, our framework is flexible enough and can be applied to as many outcomes and treatments as required. Then, the absolute effects of treatments could be synthesized across outcomes. In terms of further developments and to extend the application of the method, given that IPD from the entire network may not be always available, it would be valuable to extend the methods proposed here to situations where the evidence base is a mixture of IPD and AD.

Several limitations of the general approach need to be mentioned. First, our framework requires at least one IPD dataset for each included intervention to be able to estimate all

model parameters. Acquiring IPD data is not easy and several papers have documented the difficulties encountered in the process. When reducing all patient information into the risk score, we make the assumption that the set of selected variables captures adequately both prognosis and effect modification; in other words that all prognostic factors are also effect modifiers and vice versa. This is not necessarily the case as the variables that impact on prognosis might be different to those that modify the relative treatment effects. This assumption is difficult to evaluate, unless the outcome is well studied and many prognostic studies exist on the topic. Finally, in the present paper, the model to develop the risk score (the first stage) has been validated only internally while the predictive accuracy of our two-step framework has not been validated at all. In future work, its performance needs to be validated using not only the classical metrics such as discrimination and calibration, but also metrics related to the absolute benefit (33). To those limitations, one should add the standard challenges encountered in prognostic modelling. Some prognostic factors may not be available in one or more studies and multiple imputation methods, may be needed to address this problem (37). Finally, numerous candidate prognostic factors might render the available sample size insufficient and model selection challenging (6).

The approach offers many methodological advantages and opportunities for further development. Model selection approaches and methods to shrink coefficients to avoid extreme predictions are not available in the meta-analysis context. Our proposal to use the risk score as the only covariate in network meta-regression shifts the variable selection problem into the logistic regression model for which penalization methods are well established. Measuring treatment effects ideally relies on RCT evidence, and we had access to IPD data from 3 trials. Network meta-regression models can also include aggregated data from published studies, so our approach can be extended provided that mean values of important patients' characteristics are also reported in the published papers. That will considerably improve the power of the model. In this study, we used only RCTs, but observational data, from registers and cohorts can also be integrated in various stages: to develop the risk score, to calibrate or update the risk score model, to externally validate the model, to inform the baseline effects, or even the relative treatment effects and their interactions with the score using appropriate bias-adjusted modelling. Methods to include single arm trials in network meta-analysis are also available and could be incorporated to further extend the model. Finally, the flexibility of our model, fitted within a Bayesian framework, allows taking into account expert opinion about the importance of the included

variables or the credibility of the observational evidence. The major advantage of our approach is that, if applied to all health outcomes of interest, it has the potential to inform patients and their doctors, but also other stakeholders, including manufacturers and HTA agencies, about the treatment that is most appropriate for each one of patients and hence contribute to the major aim of the clinical society, this of personalized medicine.

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Conflicts of interest: KC, ES, ME and AM declare that they have no conflict of interest with respect to this paper. FP is an employee of and holds stocks in Biogen; GS was invited to participate in a meeting about real-world evidence organized by Biogen in 2018.

5 *References*

1. Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ*. 2018 Dec 10;363:k4245.
2. Burke JF, Hayward RA, Nelson JP, Kent DM. Using internally developed risk models to assess heterogeneity in treatment effects in clinical trials. *Circ Cardiovasc Qual Outcomes*. 2014 Jan;7(1):163–9.
3. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials*. 2010 Aug 12;11:85.
4. Kent DM, Nelson J, Dahabreh IJ, Rothwell PM, Altman DG, Hayward RA. Risk and treatment effect heterogeneity: re-analysis of individual participant data from 32 large clinical trials. *Int J Epidemiol*. 2016 Dec 1;45(6):2075–88.
5. Frank E. Harrell. *Regression Modelling Strategies*. 2006.
6. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. Springer Science & Business Media; 2008. 508 p.

7. Steyerberg EW, Moons KGM, Windt DA van der, Hayden JA, Perel P, Schroter S, et al. Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. *PLOS Med*. 2013;10(2):e1001381.
8. Moons KGM, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ*. 2009 Jun 4;338:b606.
9. Wynants L, van Smeden M, McLernon DJ, Timmerman D, Steyerberg EW, Van Calster B, et al. Three myths about risk thresholds for prediction models. *BMC Med*. 2019 Oct 25;17(1):192.
10. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. *Cell J Yakhteh*. 2017;19(1):1–10.
11. Goldenberg MM. Multiple Sclerosis Review. *Pharm Ther*. 2012 Mar;37(3):175–84.
12. Tramacere I DGC, Salanti G DR, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015 [Internet]. CD011381(9). Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011381.pub2/full>
13. McCool R, Wilson K, Arber M, Fleetwood K, Toupin S, Thom H, et al. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. *Mult Scler Relat Disord*. 2019 Apr;29:55–61.
14. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012 Jun;3(2):80–97.
15. Debray TP, Schuit E, Efthimiou O, Reitsma JB, Ioannidis JP, Salanti G, et al. An overview of methods for network meta-analysis using individual participant data: when do benefits arise? *Stat Methods Med Res*. 2016 Jan 1;962280216660741.
16. Belias M, Rovers MM, Reitsma JB, Debray TPA, Int'Hout J. Statistical approaches to identify subgroups in meta-analysis of individual participant data: a simulation study. *BMC Med Res Methodol* [Internet]. 2019 Sep 2 [cited 2019 Sep 23];19. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6720416/>
17. Steyerberg EW, Eijkemans MJC, Harrell FE, Habbema JDF. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med*. 2000;19(8):1059–79.
18. Multivariable Model - Building: A Pragmatic Approach to Regression Analysis based on Fractional Polynomials for Modelling Continuous Variables | Wiley [Internet]. Wiley.com. [cited 2019 Nov 14]. Available from: <https://www.wiley.com/en-us/Multivariable+Model+Building%3A+A+Pragmatic+Approach+to+Regression+Analysis+based+on+Fractional+Polynomials+for+Modelling+Continuous+Variables-p-9780470028421>

19. pubmeddev, al SE et. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. - PubMed - NCBI [Internet]. [cited 2019 Nov 14]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11206946>
20. Steyerberg EW, Harrell FE, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol*. 2001 Aug;54(8):774–81.
21. Steyerberg EW, Harrell FE. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol*. 2016 Jan;69:245–7.
22. Saramago P, Sutton AJ, Cooper NJ, Manca A. Mixed treatment comparisons using aggregate and individual participant level data. *StatMed*. 2012 Dec 10;31(1097-0258 (Electronic)):3516–36.
23. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006 Mar 2;354(9):899–910.
24. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012 Sep 20;367(12):1098–107.
25. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012 Sep 20;367(12):1087–97.
26. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement | The EQUATOR Network [Internet]. [cited 2020 Jan 20]. Available from: <https://www.equator-network.org/reporting-guidelines/tripod-statement/>
27. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015 Jan 6;162(1):W1-73.
28. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes - Riley - 2019 - Statistics in Medicine - Wiley Online Library [Internet]. [cited 2019 Nov 7]. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/sim.7992>
29. Kim SM, Kim Y, Jeong K, Jeong H, Kim J. Logistic LASSO regression for the diagnosis of breast cancer using clinical demographic data and the BI-RADS lexicon for ultrasonography. *Ultrasonography*. 2018 Jan;37(1):36–42.
30. Moons KGM, Donders ART, Steyerberg EW, Harrell FE. Penalized maximum likelihood estimation to directly adjust diagnostic and prognostic prediction models for overoptimism: a clinical example. *J Clin Epidemiol*. 2004 Dec 1;57(12):1262–70.
31. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>. 2019.

32. Yu-Sung Su, Masanao Yajima. R2jags: Using R to Run 'JAGS'. <https://CRAN.R-project.org/package=R2jags>. 2015.
33. Rafiee Zadeh A, Askari M, Azadani NN, Ataei A, Ghadimi K, Tavoosi N, et al. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 1. *Int J Physiol Pathophysiol Pharmacol*. 2019 Aug 15;11(4):95–104.
34. Hoepner R, Faissner S, Salmen A, Gold R, Chan A. Efficacy and Side Effects of Natalizumab Therapy in Patients with Multiple Sclerosis. *J Cent Nerv Syst Dis*. 2014 Apr 28;6:41–9.
35. Efthimiou O, Debray TPA, van Valkenhoef G, Trelle S, Panayidou K, Moons KGM, et al. GetReal in network meta-analysis: a review of the methodology. *Res Synth Methods*. 2016 Sep 1;7(3):236–63.
36. Lublin FD. Relapses do not matter in relation to long-term disability: no (they do). *Mult Scler Houndmills Basingstoke Engl*. 2011 Dec;17(12):1415–6.
37. Quartagno M, Carpenter JR. Multiple imputation for IPD meta-analysis: allowing for heterogeneity and studies with missing covariates. *Stat Med*. 2016 Jul 30;35(17):2938–54.

Table 1 Baseline characteristics of Multiple Sclerosis patients enrolled in the trials

Study	Treatment	Number of randomized patients	Number of patients with relapse of MS in two years	Age	Sex	Baseline EDSS	Number of relapses in previous year	
				Mean (sd)	Female N (%)	Male N (%)	Mean (SD)	Median (min, max)
AFFIRM		939	359 (38.2%)	36.0 (8.3)	657 (70.0)	282 (30.0)	2.3 (1.2)	1 (0, 12)
	Natalizumab	627	183 (29.2%)					
	Placebo	312	176 (56.4%)					
CONFIRM		1417	451 (31.8%)	37.3 (9.3)	993 (70.1)	424 (29.9)	2.6 (1.2)	1 (0, 8)
	Dimethyl Fumarate	703	185 (26.3%)					
	Glatiramer Acetate	351	117 (33.3%)					
	Placebo	363	149 (41.0%)					
DEFINE		1234	394 (31.9%)	38.5 (9.0)	908 (73.6)	326 (26.4)	2.4 (1.2)	1 (0, 6)
	Dimethyl Fumarate	826	212 (25.7%)					
	Placebo	408	182 (44.6%)					
Placebo arms dataset	Placebo	1083	801 (74.0%)	41.19 (10.3)	752 (69.4)	331 (30.6)	NA	NA

Table 2 Estimated LASSO shrunk coefficients and coefficients from the pre-specified model together with penalized maximum likelihood estimation. The discrimination (C-score) and the calibration slopes are also shown.

Variables	LASSO model Coefficients	Pre-specified model Coefficients (S.E.)
C-score	0.60	0.62
Calibration slope	1.54	1.05
Intercept	-0.4424	-0.8656 (0.866)
Age	-0.0013	-0.0181 (0.005)
Sex (male vs female)	-	-0.1379 (0.092)
Baseline weight	-0.0002	-
Baseline EDSS	0.0963	0.1683 (0.047)
Years Since Onset of Symptoms	-	0.0587 (0.063)
Ethnicity (white vs other)	-	-0.0142 (0.117)
No. of relapses 1 year prior to study	0.2971	0.5963 (0.170)
Months since pre-study relapse	-	-0.0126 (0.009)
Prior MS treatment group (yes vs no)	0.0241	0.1901 (0.085)
Region (India vs Eastern Europe)	0.0000	-
Region (North America vs Eastern Europe)	0.0000	-
Region (Rest of world vs Eastern Europe)	0.0000	-
Region (Western Europe vs Eastern Europe)	0.2374	-
Timed 25-Foot Walk	-	-0.1718 (0.158)
9-Hole Peg Test	-	0.3011 (0.208)
PASAT-3	-	0.0029 (0.004)
VFT 2.5%	-	-0.0010 (0.004)
Baseline Gadolinium volume	0.0001	-
Baseline SF-36 PCS	-0.0120	-0.0195 (0.005)
Baseline SF-36 MCS	-	0.036 (0.004)
Baseline Actual Distance Walked (>500 vs ≤500)	-0.0746	-

S.E: Standard Error; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SF-36 PCS: Short Form-36 Physical Component Summary;

Table 3 Estimated parameters from the network meta-regression model using the two different scores developed from the LASSO model and pre-specified model

Estimated parameters from IPD NMR model	LASSO model Mean (95% Cr. Interval)	Pre-specified model Mean (95% Cr. Interval)
γ_0	2.30 (1.78, 2.8)	1.26 (0.95, 1.58)
δ_{DF}	-0.92 (-1.20, -0.64)	-0.89 (-1.18, -0.60)
δ_{GA}	-0.72 (-1.15, -0.28)	-0.71 (-1.15, -0.26)
δ_N	-1.24 (-1.55, -0.93)	-1.22 (-1.53, -0.93)
γ_{DF}	0.90 (-0.20, 1.98)	0.25 (-0.35, 0.87)
γ_{GA}	0.64 (-1.02, 2.39)	0.23 (-0.71, 1.3)
γ_N	-0.02 (-1.16, 1.07)	-0.26 (-1.01, 0.43)

e^{γ_0} : OR of relapse in two years for one unit increase in logit-risk in untreated patients (placebo)

$e^{\delta_{DF}}$: OR of relapse under Dimethyl Fumarate versus Placebo at the study mean risk

$e^{\delta_{GA}}$: OR of relapse under Glatiramer Acetate versus Placebo at the study mean risk

e^{δ_N} : OR of relapse under Natalizumab versus Placebo at the study mean risk

$e^{\gamma_{DF}}$: OR of relapse under Dimethyl Fumarate versus placebo for one unit of increase in the logit risk

$e^{\gamma_{GA}}$: OR of relapse under Glatiramer Acetate versus placebo for one unit of increase in the logit risk

e^{γ_N} : OR of relapse under Natalizumab versus placebo for one unit of increase in the logit risk

DF: Dimethyl fumarate; GA: Glatiramer acetate; N: Natalizumab

Table 4 Predicted % probabilities and ORs (relative benefits) of relapse in two years, using baseline risk scores developed with the LASSO and pre-specified models. Results are shown for all patients, for low-

risk patients (baseline risk<30%) and for high-risk patients (baseline risk>50%) in the observed range of baseline risk

Benefits	Model	Treatment	All patients	Baseline Risk <30% Low-risk patients	Baseline Risk >50% High-risk patients
Absolute Benefits (%)	LASSO	Dimethyl Fumarate	62%	18%	93%
		Glatiramer Acetate	64%	23%	93%
		Natalizumab	54%	20%	82%
	Pre-specified	Dimethyl Fumarate	53%	20%	84%
		Glatiramer Acetate	56%	23%	86%
		Natalizumab	46%	23%	69%
Relative Benefits (OR)	LASSO	Dimethyl Fumarate vs Placebo	0.52	0.25	0.81
		Glatiramer Acetate vs Placebo	0.57	0.35	0.81
		Natalizumab vs Placebo	0.29	0.29	0.28
	Pre-specified	Dimethyl Fumarate vs Placebo	0.42	0.31	0.53
		Glatiramer Acetate vs Placebo	0.50	0.38	0.63
		Natalizumab vs Placebo	0.31	0.40	0.23

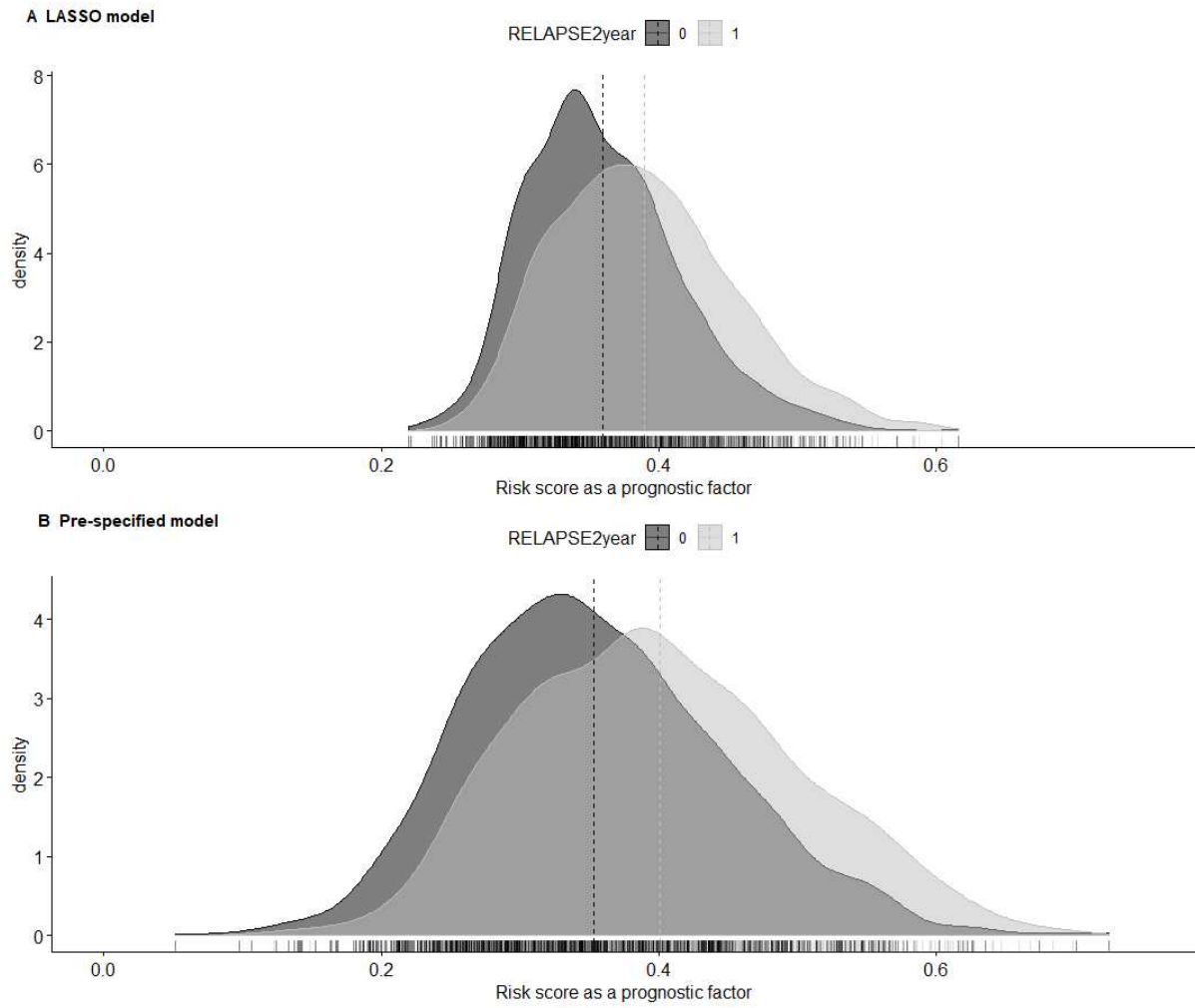


Figure 1 The distribution of baseline risk for LASSO model (A) and pre-specified model (B) for patients that did not relapse MS in two years (RELAPSE2year=0) and for patients that did relapse MS in two years (RELAPSE2year=1). The dotted lines indicate group means and the solid line the overall mean risk

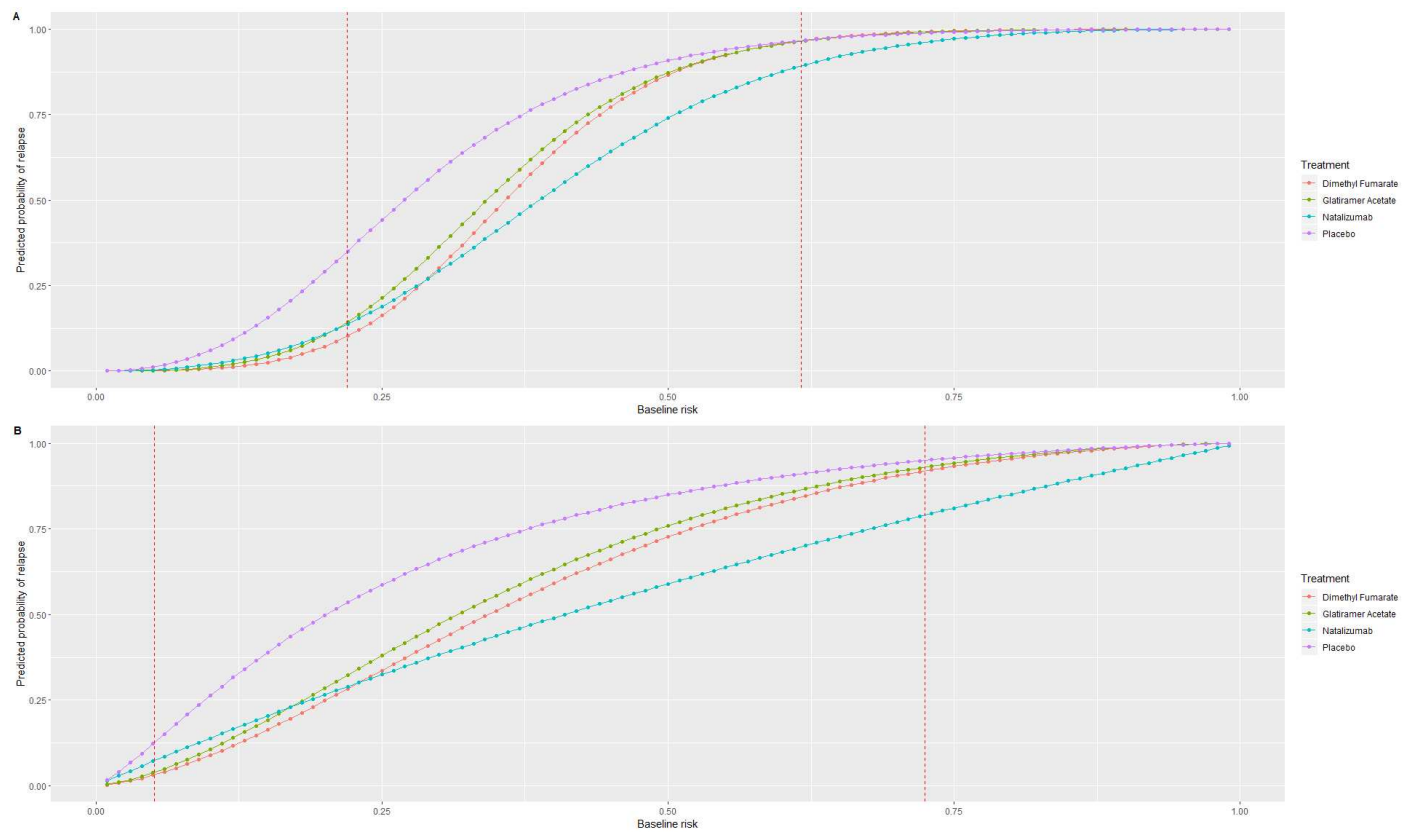
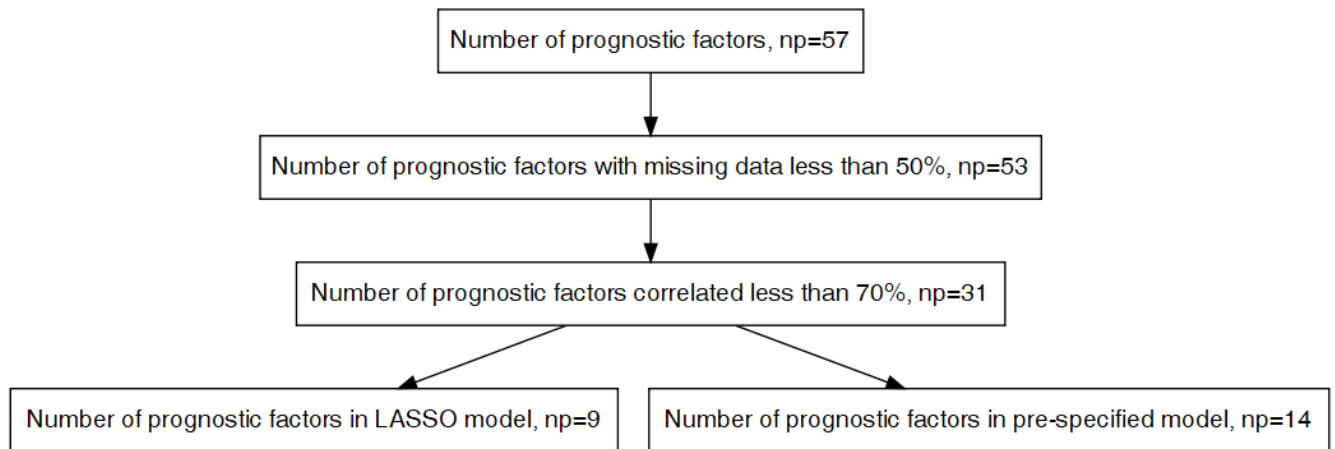
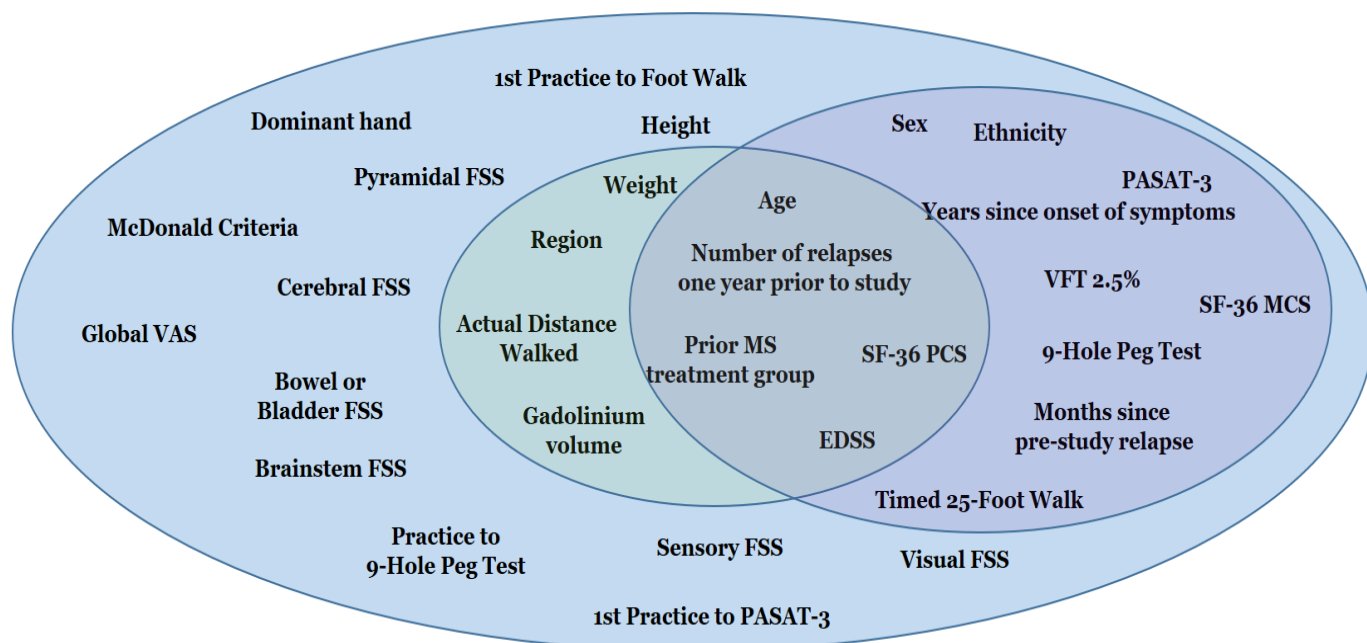


Figure 2 Predicted probability to relapse in two years as a function of the baseline risk estimated with LASSO (A) or pre-specified model (B). The x-axis shows the baseline risk score of relapsing in two years. Between the two dashed vertical lines are the baseline risk values observed in our data.

6 Appendix

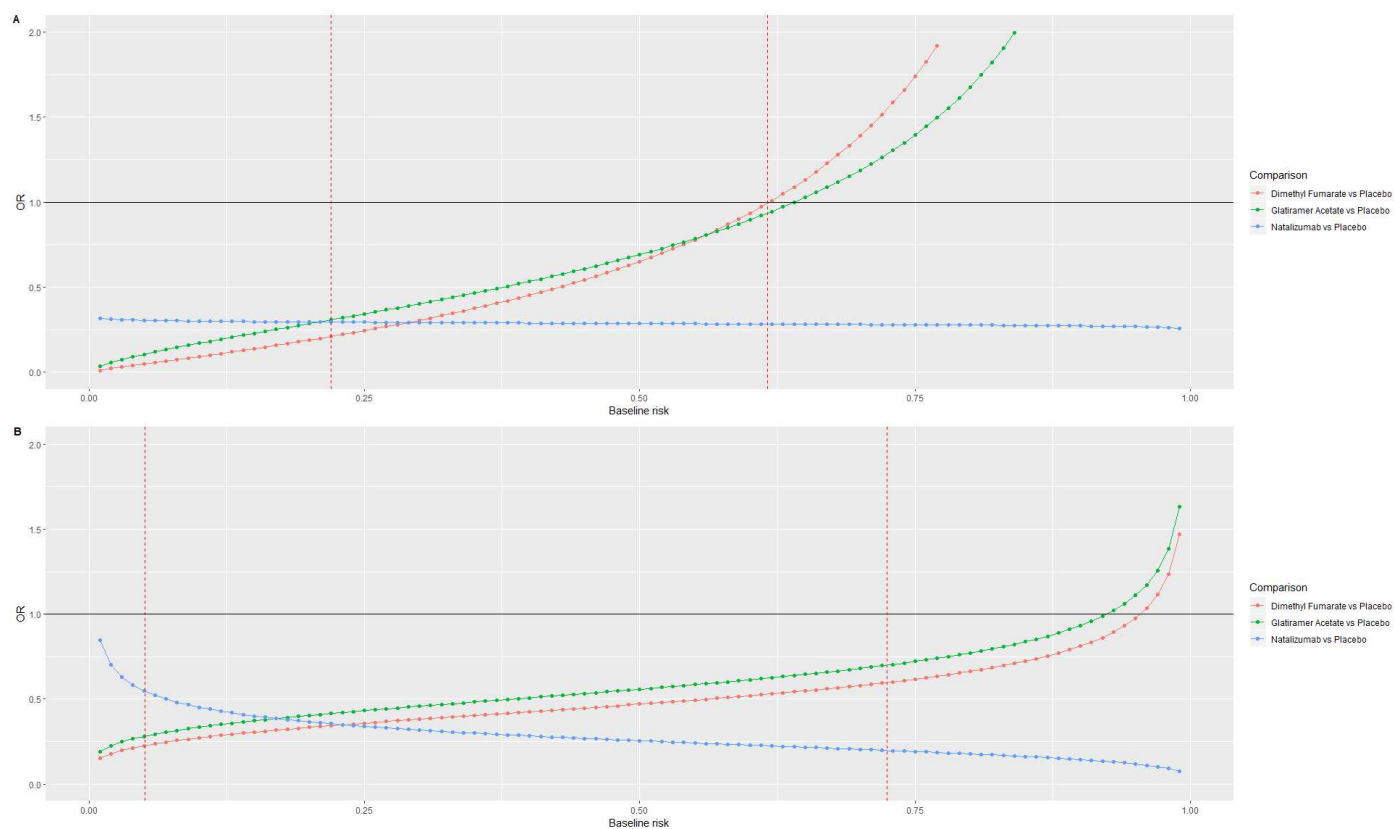


Appendix figure 1 Flow-chart for the number of candidate prognostic factors



FSS: Functional System Score; VAS: Visual Analog Scale; EDSS: Expanded Disability Status Scale; SF-36 PCS: Short Form-36 Physical Component Summary; SF-36 MCS: Short Form-36 Mental Component Summary; VFT: Visual Function Test.

Appendix figure 2 Venn diagram for candidate characteristics to include in the prognostic model (stage 1). Light blue indicates all 31 characteristics after deleting the correlated variables and those with a big amount of missing values (>50%). Light green indicates the variables selected by LASSO and purple indicates the variables included in pre-specified model



Appendix figure 3 ORs of relapse in two years as a function of the baseline risk estimated with LASSO (A) or pre-specified model (B). The x-axis shows the baseline risk score of relapsing in two years. Between the two dashed vertical lines are the baseline risk values observed in our data