A two-stage prediction model for heterogeneous effects for many treatment options

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Background

A question of public health interest: **"Which treatment is best for a specific patient based on a specific outcome?"**

Different patients often have different health outcomes under the same treatment. It is essential to understand how different treatments vary across different patients, thus estimating **Heterogeneous Treatment Effects (HTE)**

1. Individuals' characteristics influence the variation of HTE and their **baseline risk score prior to treatment** seems to be a determent predictor for HTE [1]
2. Numerous treatments options available for each disease ➡ **Network meta-analysis (NMA)** is a key-tool for comparing many different treatment options [2]

AIM

To develop a ***two-stage*** evidence synthesis ***personalized prediction model*** to predict the most likely outcome under several possible treatment options while accounting for patients' characteristics using ***individual participant data network meta-regression*** with ***risk scores,*** by combining **observational studies** and **randomized clinical trials**

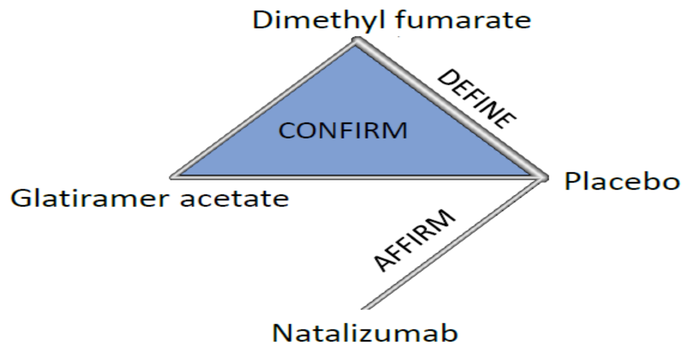
Data

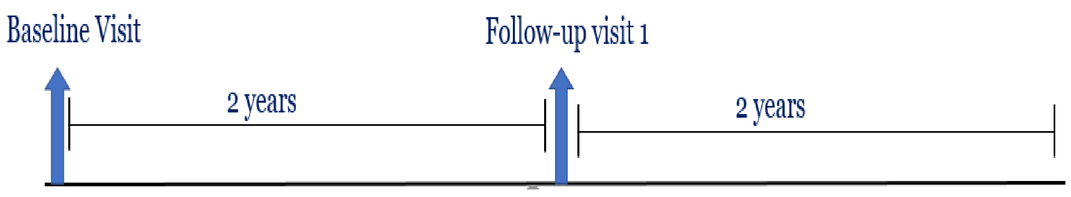
RCTs

- 3 randomized clinical trials (phase III), 2990 observations in total
- Disease: Relapsing-remitting Multiple Sclerosis (MS)
- Outcome: Relapse MS in 2 years

Observational study – Swiss Multiple Sclerosis Cohort (SMSC)

- Disease: Relapsing-remitting Multiple Sclerosis (MS)
- Outcome: Relapse MS in 2 years
- 935 patients, 1752 follow-up cycles – 1,2, or 3 for each patient (i.e. repeated measures)





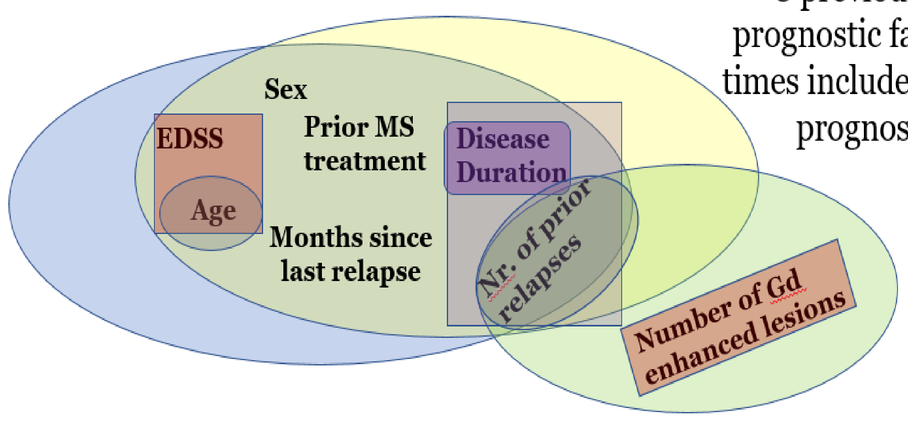
Methods - Results

Stage 1 – Development of risk score blinded to treatment – SMSC study

Prognostic factors – Pre-existing prognostic models, **Model** - Bayesian, generalized linear mixed-effects model, **Shrinkage** – Laplace prior distributions to regression coefficients, **Missing data** – Multilevel joint modelling multiple imputations, **Update** – Recalibration

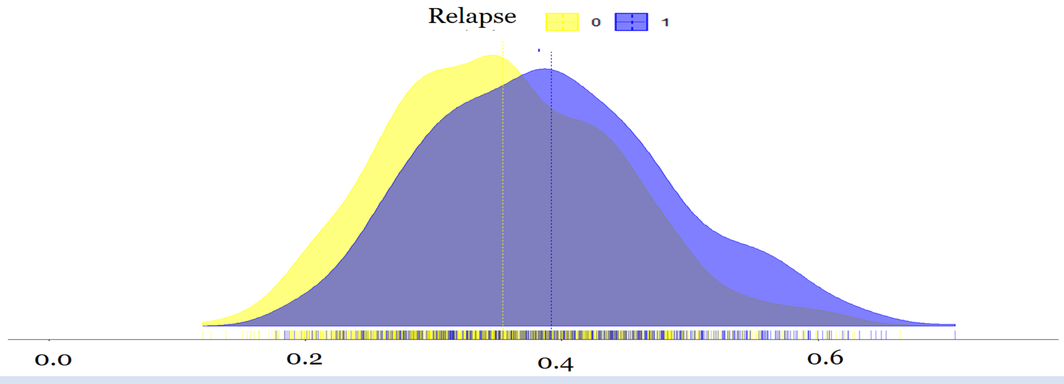
Model's output: The probability of Relapse MS in two years "blinded" to treatment, taking into account several prognostic factors

Selection of prognostic factors



8 previously identified prognostic factors (at least 2 times included in pre-existing prognostic models)

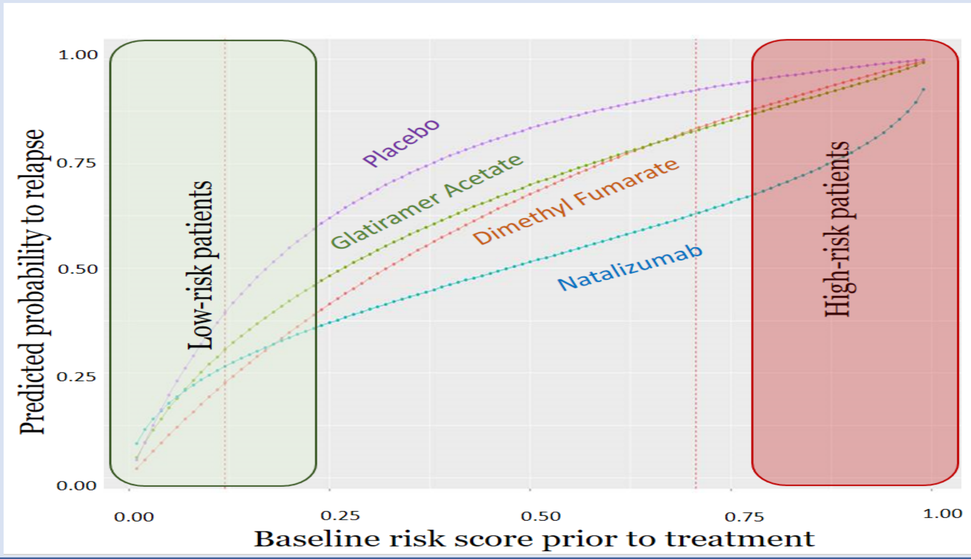
Risk of relapse in two years in RCTs



Stage 2 – Development of Treatment-effects prediction model– RCTs

Prediction model with ***IPD Network meta-regression*** using the ***baseline risk score*** as the only predictor

Natalizumab seems to be the best treatment option **on average.** However this is not the case if we divide patients based on their baseline risks prior to treatment. **Dimethyl fumarate** is the best treatment option for **low-risk patients** (<25%), whereas **Natalizumab** is the best option for **high-risk patients** (>75%) **.**



Treatment	Mean	Less than 25% Risk	More than 75%
Natalizumab	51%	26%	76%
Glatiramer Acetate	65%	30%	92%
Dimethyl Fumarate	62%	23%	93%

Best treatment **Dimethyl fumarate - 3% Absolute benefit** compared to Natalizumab

Best treatment **Natalizumab- 17% Absolute benefit** compared to Dimethyl Fumarate

Conclusions

- The baseline risk score of patients moderates the absolute benefit of treatments
- This is the first personalized prediction model that combines IPD from both observational data and RCTs, and uses risk score from a nested prognostic model within a IPD Network meta-regression

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Funding: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825162.

References: [1] Kent DM, Steyerberg E, van Klaveren D., "Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects", BMJ. 2018

[2] 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