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

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Background

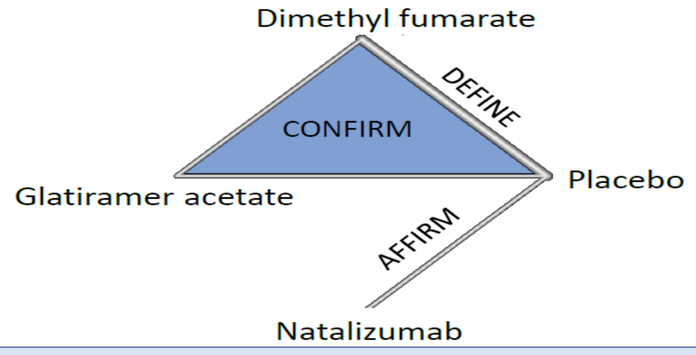
A question of public health interest: **"Which treatment is best for a specific patient?"**.
Different patients often have different health outcomes under the same treatment. It is essential to understand how different treatments vary across different patients, thus estimating **Heterogeneous Treatment 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 ***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***

Data

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



Methods

Stage 1 – Development of risk score prior to treatment

We fit five prognostic models with three shrinkage approaches and we select the one with the best discrimination and calibration
Model's output: The probability of Relapse MS in two years "blinded" to treatment, taking into account several prognostic factors

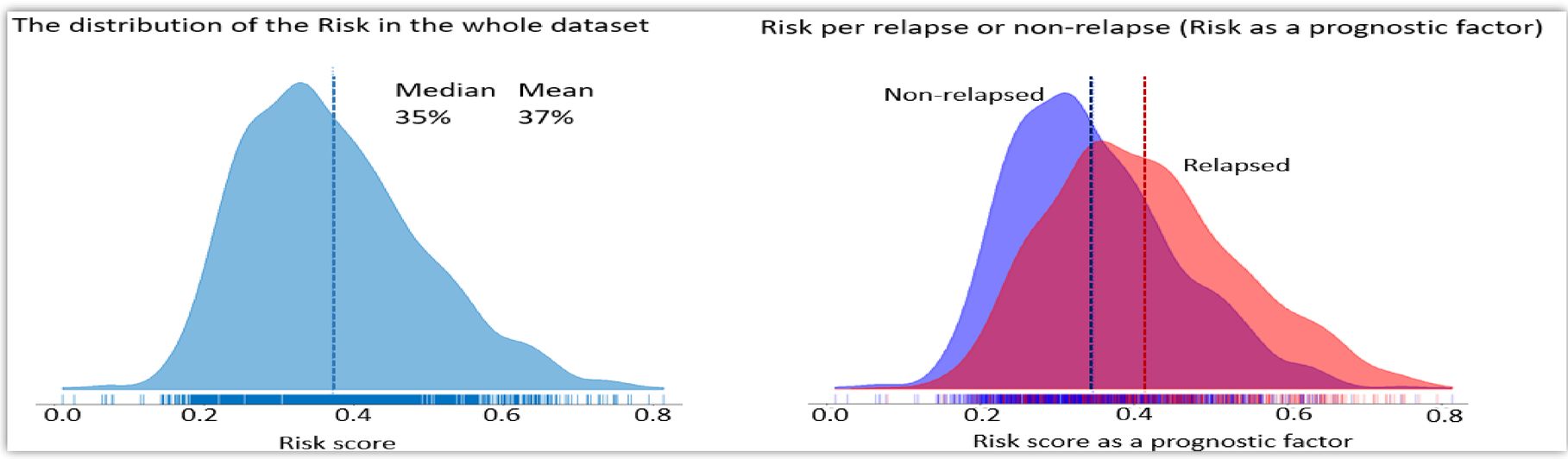
Stage 2 – Development of Treatment-effects prediction model

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

Results

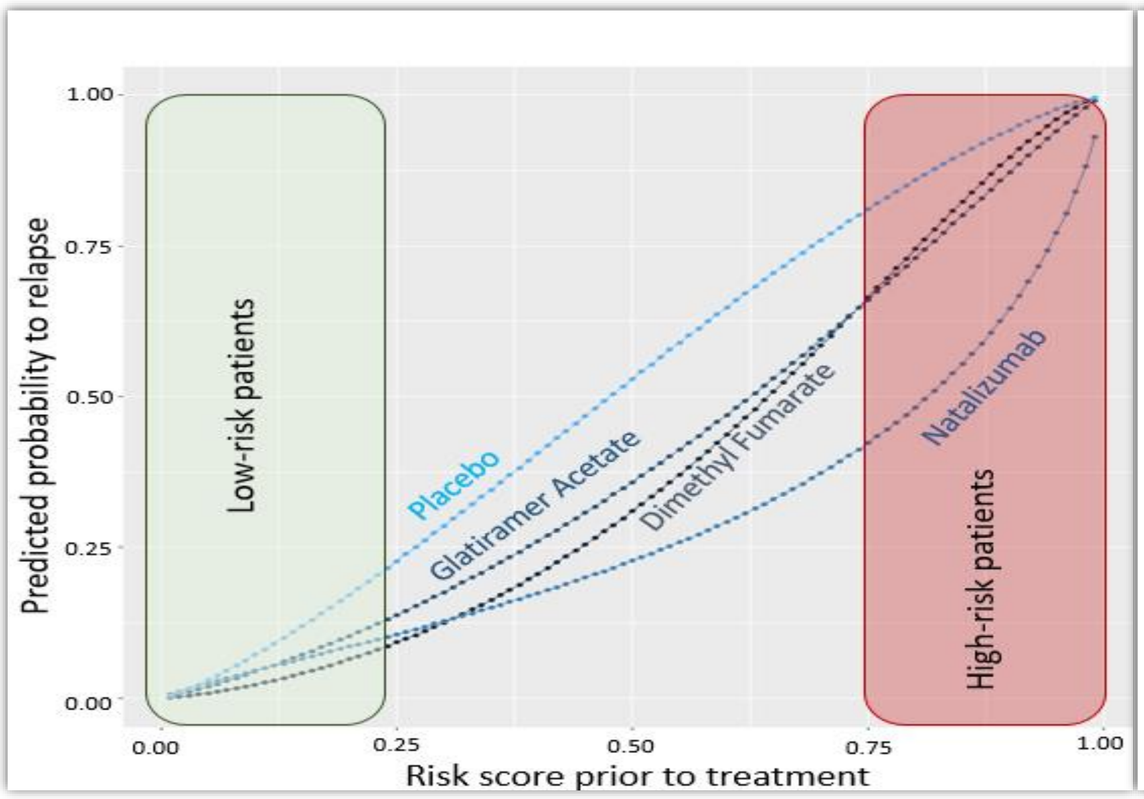
Stage 1 – Development of risk score prior to treatment

The best model (c-index=0.65, calibration-slope=1.03) is a model with 12 prognostic factors selected via **lasso method** and using **penalized maximum likelihood estimation** shrinkage approach.



Stage 2 – Development of Treatment-effects prediction model

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** (<30%), whereas **Natalizumab** is the best option for **high-risk patients.**



Treatment	Mean	Less than 25% Risk	More than 75%
Natalizumab	29%	12%	48%
Glatiramer Acetate	41%	10%	60%
Dimethyl Fumarate	39%	9%	62%

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

Best treatment **Natalizumab- 14% Absolute benefit** compared to Dimethyl Fumarate

Conclusions

- ❑ The baseline risk score of patients moderates the absolute benefit of treatments
- ❑ This is the first prediction model that uses risk score from a nested prognostic model within a IPD Network meta-regression

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

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