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]

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

AIM

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

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

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

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%).