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

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Motivation: Effectiveness of drugs in Relapsing-Remitting Multiple Sclerosis (MS)

- Several drugs, compared in Network Meta-Analyses (NMA) #not personalized predictions
- We focus on Dimethyl Fumarate, Glatiramer Acetate, and Natalizumab
- Outcome: Relapse MS in 2 years (Yes/No) for patients diagnosed with relapsing-remitting MS
- We want to find the drug that minimizes the risk of relapse, subject to patient characteristics
  - Previous evidence suggests that patients at different age groups and at different stages of the disease might respond differently to the same treatment ➔ Heterogeneous Treatment Effects
Question: Which treatment is the best for a specific patient?

1. Individual characteristics influence the variation of HTE
   ➢ **Baseline risk score prior to treatment** of patients seems to be a determinant predictor for HTE, **Prognosis research** is a key-tool for estimating risk scores

2. Numerous treatment 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
Treatments

Dimethyl Fumarate → Predicted Outcome A

Glatiramer acetate → Predicted Outcome B

Natalizumab → Predicted Outcome C

Placebo → Predicted Outcome D

Prognostic model

\[ h(y_i) = \beta_0 + \sum_{j=1}^{n} \beta_j \times PF_{ij} \]

Risk score

Prediction model using IPD Network meta-regression with PF and EM

Prediction model with IPD Network meta-regression using only the risk score
**Risk score**

**Prediction model using IPD Network meta-regression using only the risk score**

\[ h(y_i) = \beta_0 + \sum_{j=1}^{n} \beta_j \times PF_{ij} \]

### #STAGE1

**Prognostic model**

**#STAGE2**

**Prediction model using IPD Network meta-regression using only the risk score**

- **Dimethyl Fumarate** → Predicted Outcome A
- **Glatiramer acetate** → Predicted Outcome B
- **Natalizumab** → Predicted Outcome C
- **Placebo** → Predicted Outcome D

**Treatments**
Treatments

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

Predicted Outcome

A
B
C
D

Risk score

Prognostic model

\[ h(y_i) = \beta_0 + \sum_{j=1}^{n} \beta_j \times PF_{ij} \]

Prediction model using IPD Network meta-regression using only the risk score

#STAGE1
Development of prognostic models

Two different prognostic models for comparable reasons

LASSO model
1. **Prognostic factors:**
   Selected via LASSO method
2. **Shrinkage of coefficients:**
   LASSO shrinkage of coefficients

Pre-specified model
1. **Prognostic factors:**
   14 prognostic factors identified by Pellegrini et al. for annualized relapse rate of MS.
   These variables included in this model
2. **Shrinkage of coefficients:**
   penalized maximum estimation likelihood
Included variables

Prognostic factors included in LASSO model

Prognostic factors included in pre-specified model

All 31 prognostic factors

- 1st Practice to Foot Walk
- Dominant hand
- Pyramidal FSS
- McDonald Criteria
- Cerebral FSS
- Global VAS
- Bowel or Bladder FSS
- Brainstem FSS
- Practice to 9-Hole Peg Test
- Actual Distance Walked
- 1st Practice to PASAT-3
- Sensory FSS
- Visual FSS
- Timed 25-Foot Walk
- SF-36 PCS
- EDSS
- Prior MS treatment group
- Number of relapses one year prior to study
- PASAT-3
- Years since onset of symptoms
- VFT 2.5%
- SF-36 MCS
- Months since pre-study relapse
- 9-Hole Peg Test
- Sex
- Ethnicity
- Age

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Baseline risk score

LASSO model

Pre-specified model
Prediction model using IPD Network meta-regression using only the risk score

\[ h(y_i) = \beta_0 + \sum_{j=1}^{n} \beta_j \times PF_{ij} \]
**IPD Network meta-regression**

**Notation**

- $i$: Individuals
- $j$: study
- $k$: treatment
- $b_j$: baseline treatment in study $j$

**Likelihood**

$Y_{ijk} \sim Bernoulli(p_{ijk})$

$B$: Individual level covariate regression term for Risk / the impact of Risk as prognostic factor

$D_{bjk}$: the treatment effect of treatment $k$ versus placebo / **fixed effect**

$G_{bjk}$: The interaction of treatment and risk. Different for each treatment vs study’s control / the impact of Risk as effect modifier

\[
\text{logit}(p_{ijk}) = \begin{cases} 
    u_j + B \times (\text{logit}R_{ij} - \text{logit}R_j) & \text{if } k = b_j \\
    u_j + D_{bjk} + B \times (\text{logit}R_{ij} - \text{logit}R_j) + G_{bjk} \times (\text{logit}R_{ij} - \text{logit}R_j), & \text{if } k \neq b_j 
\end{cases}
\]

Saramago et al., 2012
IPD Network meta-regression

Results: Estimation of model parameters

OR for relapse for one unit increase in logit-risk in untreated patients (placebo) - \( \exp(B) \) = 3.32

| Drug                | OR for relapse versus placebo at the study mean risk \( \exp(D) \) | OR versus placebo for one unit of increase in the logit risk \( \exp(G) \) |
|---------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Natalizumab         | 0.18                                                          | 0.67                                                          |
| Glatiramer Acetate  | 0.41                                                          | 0.87                                                          |
| Dimethyl Fumarate   | 0.43                                                          | 1.06                                                          |

\[
\text{logit}(p_{ijk}) = \begin{cases} 
    u_j + B \times (\logit R_{ij} - \logit R_j) & \text{if } k = b_j \\
    u_j + D_{bk} + B \times (\logit R_{ij} - \logit R_j) + G_{bk} \times (\logit R_{ij} - \logit R_j), & \text{if } k \neq b_j 
\end{cases}
\]
Predicted relapse rate by baseline risk score

| 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
Further research

Treatments

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

Predicted Outcome

- A
- B
- C
- D

New External Dataset
IPD from Swiss MS Cohort

Risk score

$\mathbf{h}(\mathbf{y}_i) = \beta_0 + \sum_{j=1}^{n} \beta_j \times \mathbf{PF}_{ij}$

Prognostic model

#STAGE1

Combination of AD and IPD

26 studies - Published reports (Tramacere, 2018)

#STAGE2

Validation methods

Prediction model using IPD Network meta-regression using only the risk score
R-Shiny app

https://cinema.ispm.unibe.ch/shinies/koms/