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
- Glatiramer acetate
- Natalizumab
- Placebo

Predicted Outcome

A

B

C

D

Predicted Factors

Effect modifiers

Risk score

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

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

**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**
Risk score

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

Prognostic model

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

#STAGE1

Treatments

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

Predicted Outcome

- A
- B
- C
- D
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

All 31 prognostic factors

Prognostic factors included in LASSO model

Prognostic factors included in pre-specified model

- 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 Foot Walk
- Height
- Weight
- Region
- Number of relapses one year prior to study
- Prior MS treatment group
- Gadolinium volume
- EDSS
- Sensory FSS
- Visual FSS
- 1st Practice to PASAT-3
- Sex
- Ethnicity
- PASAT-3
- Years since onset of symptoms
- VFT 2.5%
- SF-36 PCS
- 9-Hole Peg Test
- Months since pre-study relapse
- Timed 25-Foot Walk

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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**

\[
Y_{ijk} \sim \text{Bernoulli}(p_{ijk})
\]

**Variables**

- \( B \): 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

**Logit Model**

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

Saramago et al., 2012
IPD Network meta-regression

Results: Estimation of model parameters

OR for relapse versus placebo at the study mean risk \( \exp(D) \)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OR for relapse versus placebo at the study mean risk ( \exp(D) )</th>
<th>OR versus placebo for one unit of increase in the logit risk ( \exp(G) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>0.18</td>
<td>0.67</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>0.41</td>
<td>0.87</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>0.43</td>
<td>1.06</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>Less than 25% Risk</th>
<th>More than 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>29%</td>
<td>12%</td>
<td>48%</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>41%</td>
<td>10%</td>
<td>60%</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>39%</td>
<td>9%</td>
<td>62%</td>
</tr>
</tbody>
</table>

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**
  - Predicted Outcome A

- **Glatiramer acetate**
  - Predicted Outcome B

- **Natalizumab**
  - Predicted Outcome C

- **Placebo**
  - Predicted Outcome D

**New External Dataset**
IPD from Swiss MS Cohort

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

- Risk score

**Combination of AD and IPD**

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

**Validation methods**

- **#STAGE1**
  - Further research
  - Validation methods

- **#STAGE2**
  - 26 studies - Published reports (Tramacere, 2018)

**Treatments**

- **Dimethyl Fumarate**
- **Glatiramer acetate**
- **Natalizumab**
- **Placebo**
R-Shiny app

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