Conflicts of Interest

Konstantina Chalkou declares that she has no conflict of interest with respect to this work
A prediction model of heterogeneous treatment effects using randomized and observational data

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Data from:
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Suvitha Subramaniam, Benkert Pascal - University of Basel
Network meta-analysis is often used in HTA to estimate relative effects between competing treatments. Synthesis of a network of 5 studies (3910 patients)

Compare Dimethyl Fumarate, Glatiramer Acetate, and Natalizumab in patients with relapsing-remitting MS

Outcome: Relapse at 2 years (binary)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimate [Lower CI, Upper CI]</th>
<th>Relative Risk</th>
<th>Lower CI [Lower CI, Upper CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl fumarate</td>
<td>1.24 [0.84, 1.83]</td>
<td>-</td>
<td>0.71 [0.54, 0.94]</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>1.17 [0.84, 1.66]</td>
<td>-</td>
<td>0.63 [0.45, 0.89]</td>
</tr>
<tr>
<td>2.3 [1.4, 3.7]</td>
<td>1.95 [1.16, 3.28]</td>
<td>Natalizumab</td>
<td>0.31 [0.20, 0.46]</td>
</tr>
<tr>
<td>0.71 [0.54, 0.93]</td>
<td>0.60 [0.44, 0.83]</td>
<td>Placebo</td>
<td>0.31 [0.20, 0.47]</td>
</tr>
</tbody>
</table>
One size does not fit all

Treatment choice is (or should be) personalised
Not all patients have the same response to the same treatment

**Heterogeneous Treatment Effects**
Effect modification operates in many treatments and setting
So, the optimal treatment depends on patients characteristics
Patient A

Predicted probabilities to relapse in two years

Dimethyl Fumarate - 25% / Glatiramer Acetate - 28% / Natalizumab - 27% / Placebo - 50%

Ranking of predicted probabilities to relapse in two years

1. The lowest probability to relapse is under treatment:
   Dimethyl Fumarate with 24.8% probability to relapse.

2. Second best choice based on the probability to relapse:
   Natalizumab with 26.6% probability to relapse.
Patient B

Predicted probabilities to relapse in two years
Dimethyl Fumarate - 71 % / Glatiramer Acetate - 75 % / Natalizumab - 58 % / Placebo - 84 %

Ranking of predicted probabilities to relapse in two years
1. The lowest probability to relapse is under treatment:
   Natalizumab with 58 % probability to relapse.
2. Second best choice based on the probability to relapse:
   Dimethyl Fumarate with 71.4 % probability to relapse.
One size does not fit all

Treatment choice is (or should be) personalised
Not all patients have the same response to the same treatment
**Heterogeneous Treatment Effects**
Effect modification operates in many treatments and setting
So, the optimal treatment depends on patients characteristics

At the population level, **recommendations should be specific to subgroups** and **cost-effectiveness will depend on the distribution of effect modifiers within each country**
Treatments

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

Predicted Outcome A
Predicted Outcome B
Predicted Outcome C
Predicted Outcome D

Relative treatment effects

Patient characteristics

Risk score
the probability of the outcome at baseline

IPD from RCTs

Network meta-regression methods

IPD from Observational studies or registries

Prognostic modelling methods
Data

RCTs

3 randomized phase III clinical trials 2990 observations in total
Observational data
Swiss MS Cohort (SMSC)

Patients with confirmed RRMS and at least two-year follow-up period from the baseline visit date

935 patients, each one with 1, 2, or 3 treatment cycles (i.e. repeated measures)

1752 follow-up cycles
Treatments

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

**IPD from Observational Data SMSC**

**#STAGE1**

Prognostic model

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

**Risk score**

**#STAGE2**

Re-calibration and re-estimation of the developed risk model and calculation of the new risk score in the RCTs dataset

**#STAGE3**

Prediction model with IPD Network meta-regression using only the risk score
Predicted Outcome A
Dimethyl Fumarate

Predicted Outcome B
Glatiramer acetate

Predicted Outcome C
Natalizumab

Predicted Outcome D
Placebo

IPD from Observational Data
SMSC

IPD from RCTs

HTE

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

Re-calibration and re-estimation of the developed risk model and calculation of the new risk score in the RCTs dataset

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

Treatments

Risk score

#STAGE1

#STAGE2

#STAGE3
Stage 1: Development of the prognostic model

Step 1 - Selection of prognostic factors

8 previously identified prognostic factors (at least 2 times included in pre-existing prognostic models)
Stage 1: Development of the prognostic model

Step 2 – Development of the model

Logistic mixed effects model in a Bayesian framework

\[ Y_{ij} \sim \text{Bernoulli}(R_{ij}) \]

\[ \logit(R_{ij}) = \beta_0 + u_{0i} + \sum_{k=1}^{P} (\beta_k + u_{ki}) \times PF_{k,j} \]

**Notation**

i: individuals, where \( i = 1, 2, \ldots, N \)

j: time point, where \( j = 1, 2, 3 \)

PF\(_{kj}\): kth prognostic factor at jth time point, where \( k = 1, 2, \ldots, P \)

\( \beta_0 \): fixed effect intercept

\( u_{0i} \): random effect intercept

\( \beta_k \): fixed effect slopes of kth prognostic factor

\( u_{ki} \): the individual-level random slopes of kth prognostic factor
Stage 1: Development of the prognostic model

Step 3 – Sample size efficiency

EPV = 13.7

Recommended more than 10

Our sample size **efficient** for
• agreement between apparent and adjusted model performance

• precise estimation of risk

- Riley RD. et al., 2018

Our sample size **not efficient** for
• avoiding optimism

Addressed via the **shrinkage** in the next step
Stage 1: Development of the prognostic model

Step 4 – Shrinkage of coefficients
Bayesian shrinkage methods use a prior on the regression coefficients to address the problem of overfitting in prognostic models. We used Laplace prior distribution on the regression coefficients to shrink the coefficients.

Step 5 – Handling of Missing data
We used Multilevel Joint Modelling Multiple Imputation approach. We imputed 10 datasets.
### Stage 1: Development of the prognostic model

#### Step 6 - Estimated ORs

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Estimations (ORs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.15</td>
</tr>
<tr>
<td>Age</td>
<td>0.97</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>1.38</td>
</tr>
<tr>
<td>Edss</td>
<td>1.12</td>
</tr>
<tr>
<td>Gd enhanced lesions</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of previous Relapses (1 vs 0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Number of previous Relapses (more than 2 vs 0)</td>
<td>1.12</td>
</tr>
<tr>
<td>Months Since Relapse</td>
<td>0.61</td>
</tr>
<tr>
<td>Treatment Naive</td>
<td>1.15</td>
</tr>
<tr>
<td>Gender</td>
<td>0.28</td>
</tr>
<tr>
<td>Treatment During Cycle (Yes vs No)</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Stage 1: Development of the prognostic model

Step 7 – Internal validation

We used bootstrap internal validation approach to correct for optimism in discrimination and calibration ability of the developed model.

Optimism-corrected AUC = 0.67
Optimism corrected calibration-slope = 1.00
Stage 1: Development of the prognostic model

Step 8 – R-shiny app

Prevention of relapses in patients with Relapsing-Remitting Multiple Sclerosis

Risk score the probability of the outcome at baseline

© The HTx Consortium 2019-2023. This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement Nº 825162.
IPD from Observational Data SMSC

Predicted Outcome A
Dimethyl Fumarate

Predicted Outcome B
Glatiramer acetate

Predicted Outcome C
Natalizumab

Predicted Outcome D
Placebo

Risk score

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

Re-calibration and re-estimation of the developed risk model and calculation of the new risk score in the RCTs dataset

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

Treatments

#STAGE1

#STAGE2

#STAGE3
### Stage 2: Re-calibration and re-estimation of the risk model to RCTs

We update the model to improve predictions for new patients from the new setting (i.e. RCTs)

<table>
<thead>
<tr>
<th>Methods</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Update</td>
<td>0.57</td>
</tr>
<tr>
<td>Update only the intercept (Re-calibration)</td>
<td>0.57</td>
</tr>
<tr>
<td>Update intercept and coefficients (Re-calibration)</td>
<td>0.57</td>
</tr>
<tr>
<td>Model revision (Re-calibration &amp; selective re-estimation)</td>
<td>0.61</td>
</tr>
</tbody>
</table>
Risk of relapse in two years in RCTs

Risk score blinded to treatment

AUC=0.61
**Treatments**

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

**Predicted Outcome**

- A
- B
- C
- D

**IPD from Observational Data SMSC**

**HTE**

**Risk score**

**Prognostic model**

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

**#STAGE1**

**#STAGE2**

Re-calibration and re-estimation of the developed risk model and calculation of the new risk score in the RCTs dataset

**#STAGE3**

Prediction model with IPD Network meta-regression using only the risk score
Stage 3: IPD Network Meta-regression

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

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

**Notation**

- **i**: Individuals
- **j**: study
- **k**: treatment
- **bj**: baseline treatment in study j
- **B**: Individual level covariate regression term for Risk / the impact of Risk as prognostic factor
- **D_{bk}**: the treatment effect of treatment k versus placebo / **fixed effect**
- **G_{bk}**: The interaction of treatment and risk. Different for each treatment vs study’s control / the impact of Risk as effect modifier

Saramago et al., 2012
### Stage 3: IPD Network Meta-regression

**Results: Estimation of model parameters**

OR for relapse for one unit increase in logit-risk in untreated patients (placebo) - \( \text{(exp}(B)) = 2.7 \) (2.1, 3.9)

<table>
<thead>
<tr>
<th></th>
<th>OR for relapse versus placebo at the study mean risk ( \text{(exp}(D)) ) &amp; 95% Cr. Intervals</th>
<th>OR versus placebo for one unit of increase in the logit risk ( \text{(exp}(G)) ) &amp; 95% Cr. Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Natalizumab</strong></td>
<td>0.28 (0.21, 0.37)</td>
<td>0.60 (0.31, 1.15)</td>
</tr>
<tr>
<td><strong>Glatiramer Acetate</strong></td>
<td>0.53 (0.34, 0.78)</td>
<td>0.73 (0.32, 2.10)</td>
</tr>
<tr>
<td><strong>Dimethyl Fumarate</strong></td>
<td>0.43 (0.3, 0.57)</td>
<td>0.89 (0.50, 1.87)</td>
</tr>
</tbody>
</table>
Stage 3: IPD Network Meta-regression

Results: Estimation of model parameters

<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>46%</td>
<td>33%</td>
<td>57%</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td>61%</td>
<td>43%</td>
<td>75%</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>57%</td>
<td>34%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Best treatment **Natalizumab**

1% Absolute benefit compared to Dimethyl Fumarate

Best treatment **Natalizumab**

28% Absolute benefit compared to Dimethyl Fumarate
R-shiny apps

https://cinema.ispm.unibe.ch/shinies/koms/
We developed a new framework to combine observational data and RCTs via prognostic research and network meta-regression. This model allows personalized predictions under several treatment options. Modern estimation and selection methods such as shrinkage are not available in network meta-regression. Our multi-stage model enables their use. The models needs IPD data from (some) RCTs.

**Extensions**
We will use measures relevant to clinical usefulness to validate the model. We will include RCTs that have only aggregated data. We will include cost-effectiveness analysis.