IPD Network meta-regression to make predictions for heterogeneous treatment effects

Work done as part of the PhD research by **Konstantina Chalkou**
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A patient with RRMS

Age (years)

18 — 42 — 60

18 23 28 33 38 43 48 53 58 60

☐ Male

☐ White

☐ Prior treatment

Baseline EDSS

0 — 0.5 — 6

0 1 2 3 4 5 6

Years since onset of symptoms

1 — 45

0 5 10 15 20 25 30 35 40 45

Number of relapses the last 1 year

0 — 20

0 2 4 6 8 10 12 14 16 18 20

Months since last relapse

0

Baseline Timed 25-Foot Walk

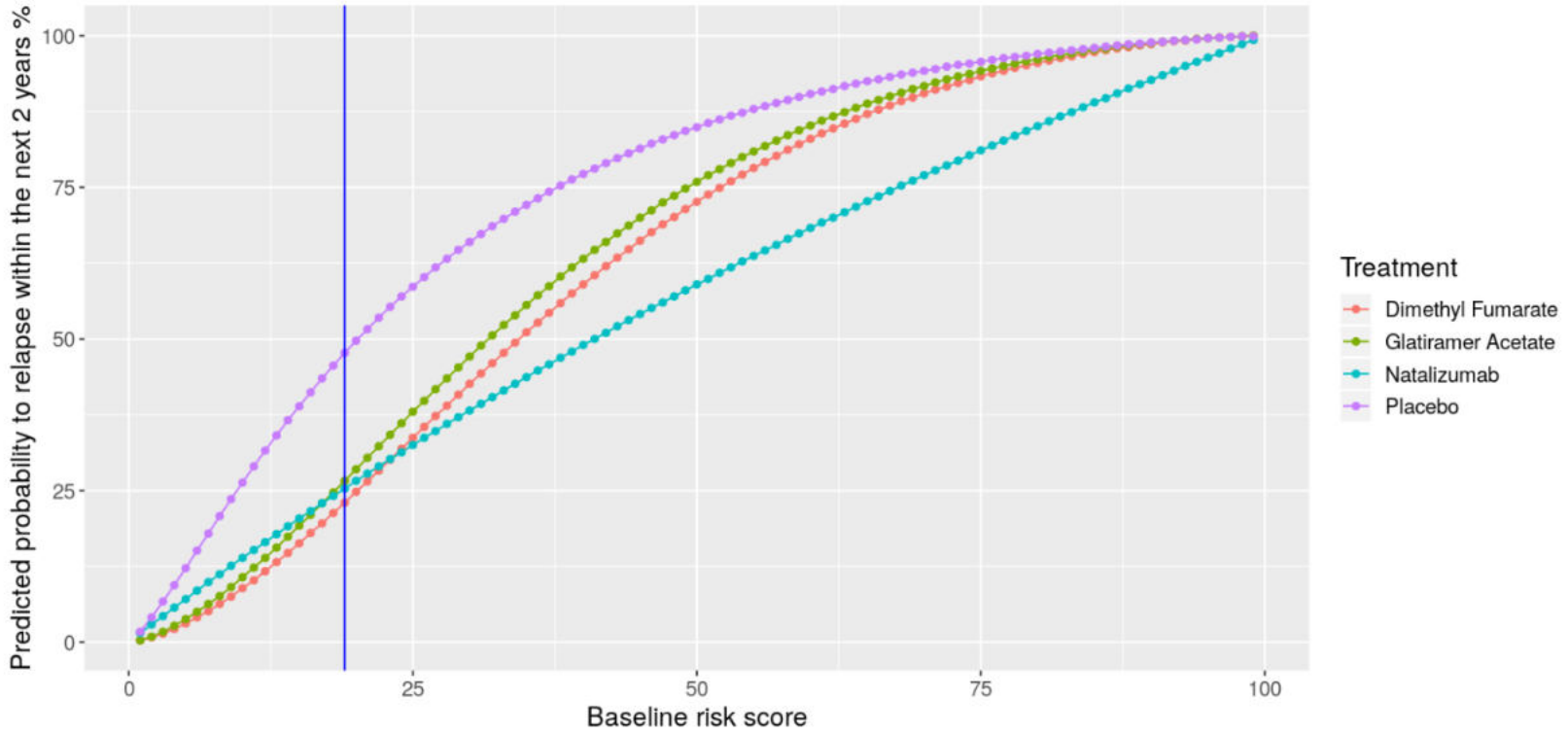
1

Baseline PASAT 3

0 — 15 — 80

0 8 16 24 32 40 48 56 64 72 80

Plot of predicted probabilities



A two-stage prediction model for heterogeneous effects of treatments. Stat Med. 2021

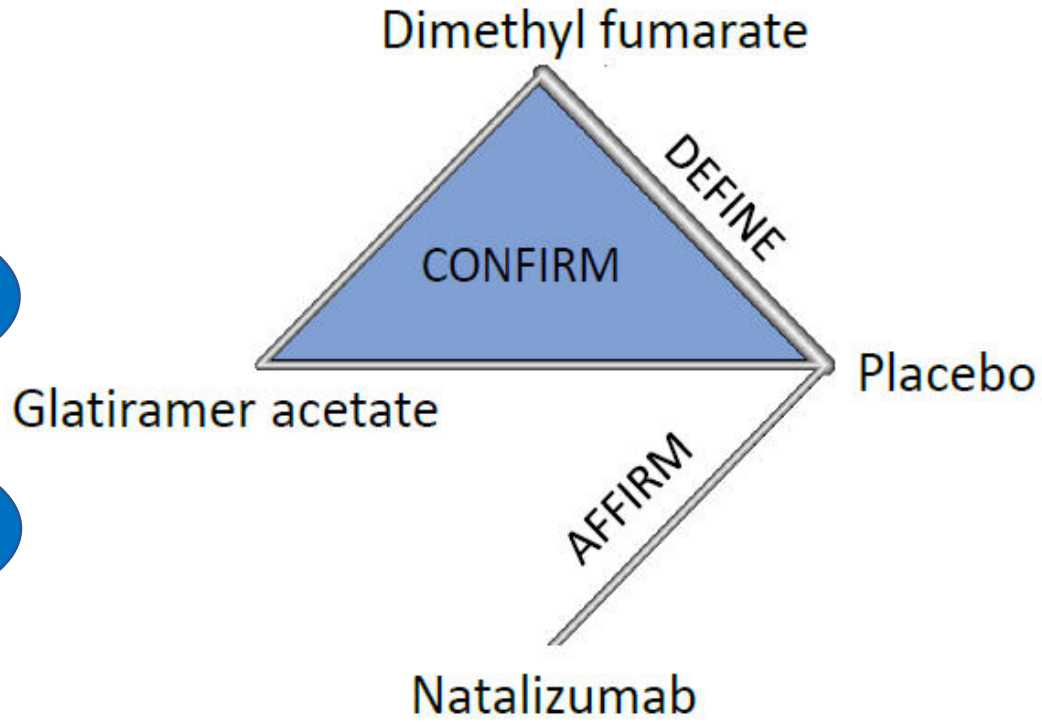
Predicted probabilities

Dimethyl Fumarate - 23 % / Glatiramer Acetate - 27 % / Natalizumab - 25 % / Placebo - 48 %

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

Treatments

- Dimethyl Fumarate
- Glatiramer acetate
- Natalizumab
- Placebo

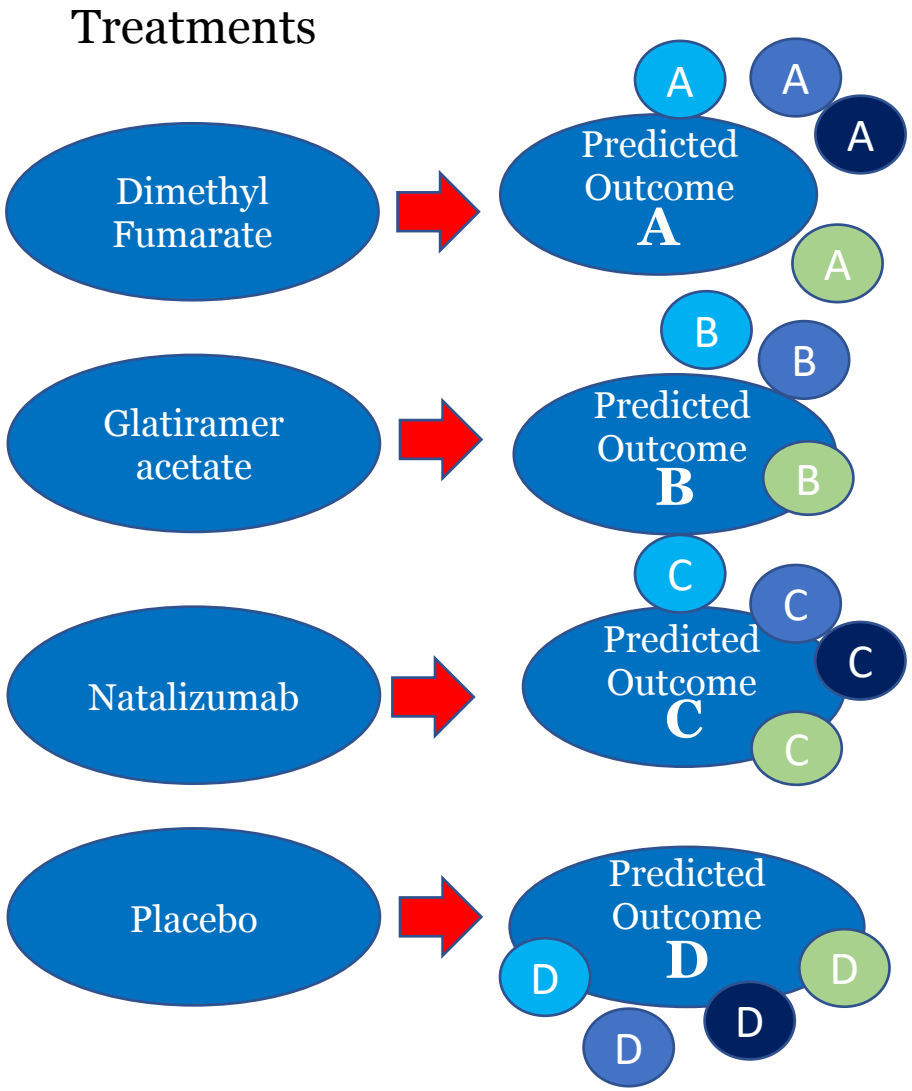


3 randomized RCTs with IPD
2990 observations

Direct estimates

Dimethyl fumarate	1.24 [0.84, 1.83]	-	0.71 [0.54, 0.94]
1.17 [0.84, 1.66]	Glatiramer acetate	-	0.63 [0.45, 0.89]
2.3 [1.4, 3.7]	1.95 [1.16, 3.28]	Natalizumab	0.31 [0.20, 0.46]
0.71 [0.54, 0.93]	0.60 [0.44, 0.83]	0.31 [0.20, 0.47]	Placebo

NMA estimates



~~Prognostic Factors~~
~~Effect modifiers~~

HTE

Risk score

Prognostic model

$$h(y_i) = \beta_o + \sum_{j=1}^{n} \beta_j \times PF_{ij}$$

The probability of relapsing independent of the treatment

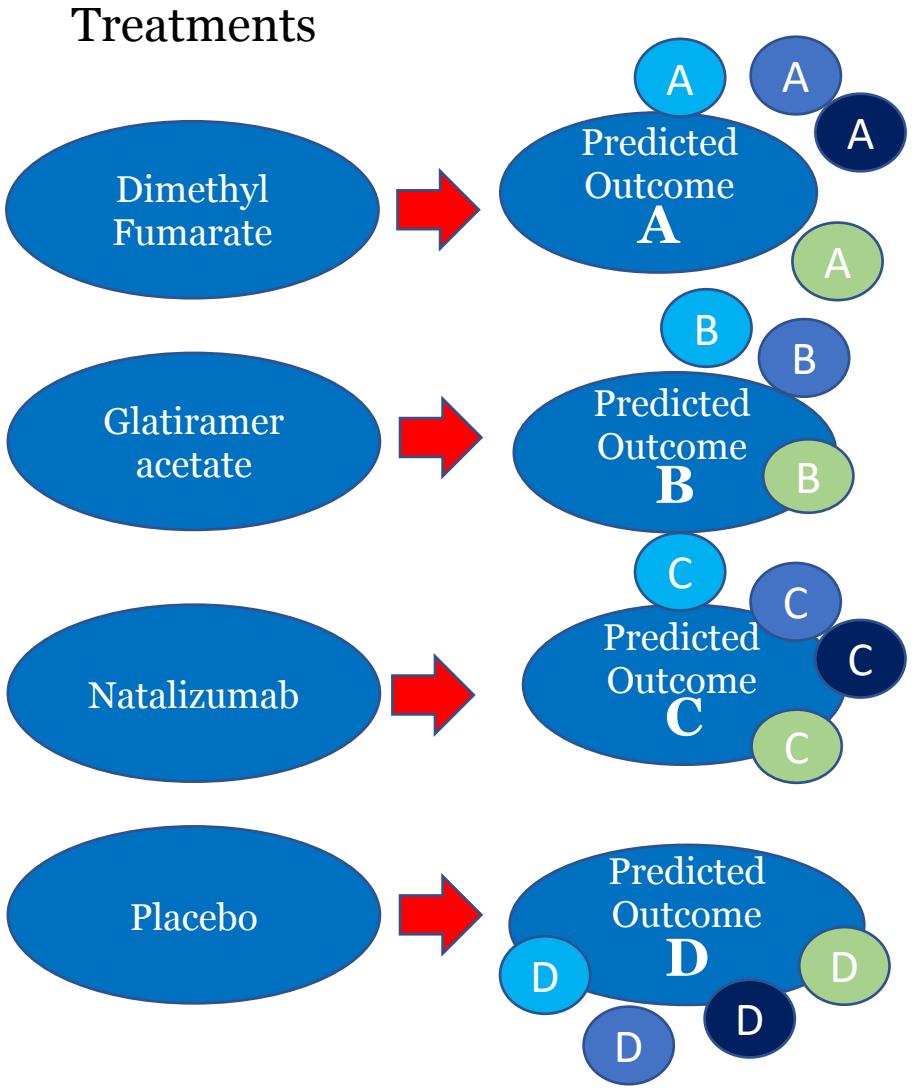
Prediction model using IPD network meta-regression with many covariates

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

Risk modelling for predictions

- **Risk modelling:** treatment effect variability is modelled as a function of outcome risk – and outcome risk is a function of the covariates
- **Reduces the risk of overfitting**
  - Second stage: treatment effect heterogeneity is modelled with a single covariate (the risk score)
  - First stage: We take advantage of the existing penalisation methods
  - **Assumptions:** the heterogeneous treatment effects are proportional to the main effects of the covariates vector

A tutorial on individualized treatment effect prediction from randomized trials with a binary endpoint, Hoogland et al. Stat Med 2021



Prognostic model

$$h(y_i) = \beta_o + \sum_{j=1}^{n} \beta_j \times PF_{ij}$$

#STAGE1

Risk score

HTE

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

#STAGE2

Development of prognostic risk scores (Stage 1)

Two prognostic models using all data, not just placebo arms

Burke et al. Circ Cardiovasc Qual Outcomes 2014
PATH statement by Kent et al AIM 2020

LASSO model

Prognostic factors: 9/28 selected via LASSO
Shrinkage of coefficients: LASSO shrinkage of coefficients

Pre-specified model

Prognostic factors: 14 prognostic factors identified by Pellegrini et al. for annualized relapse rate
Shrinkage of coefficients: penalized maximum estimation likelihood (ridge regression)

The resulting risk score has low discrimination (C=62%) but we don't mind!
The aim of this stage is to reduce dimensionality, not to provide predictions!

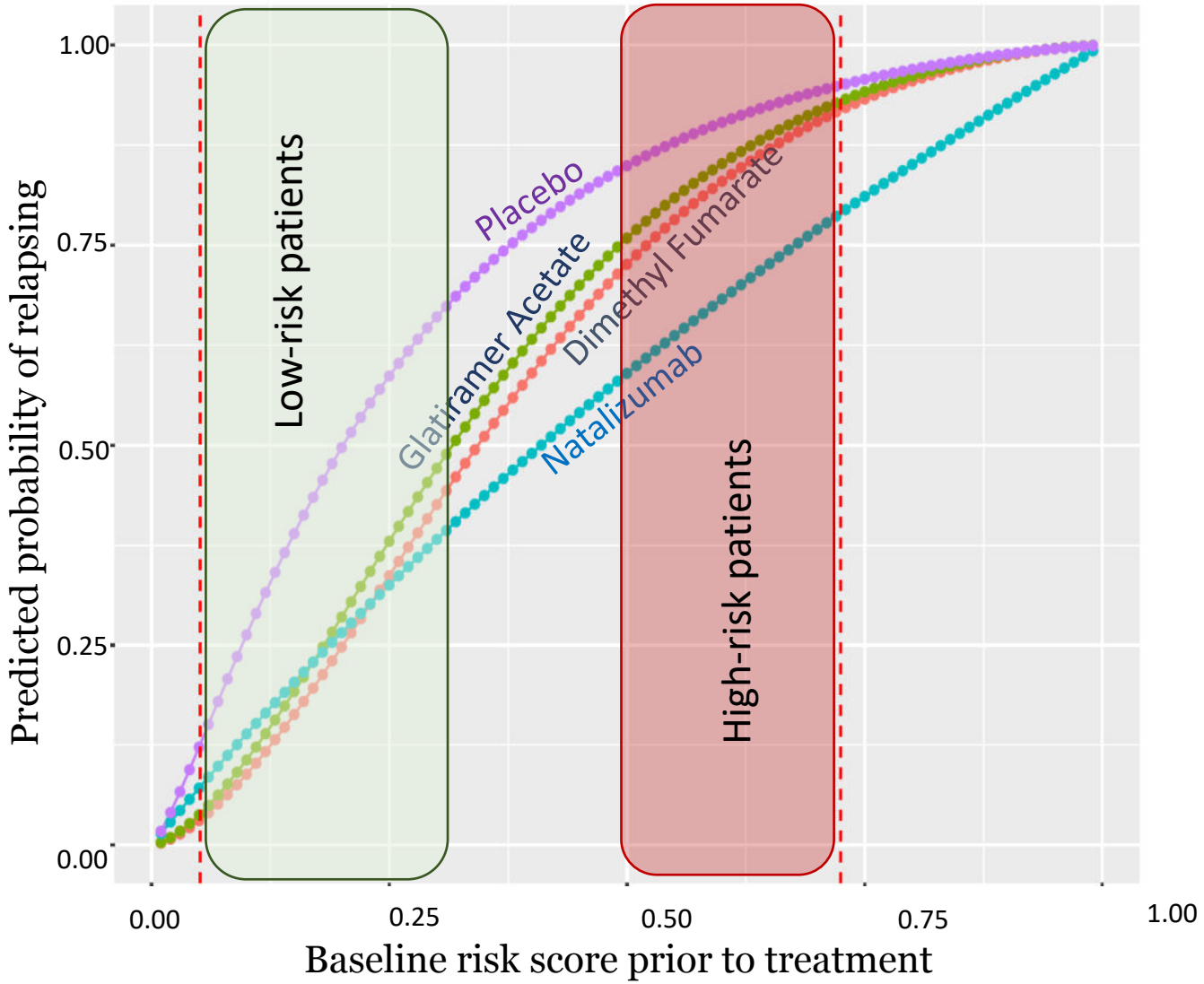
IPD network meta-regression (stage 2)

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

$$logit(p_{ijk}) = \begin{cases} u_j + B \times logitR_{ij} & if \ \ k = b_j \\ u_j + D_{b_j k} + B \times logitR_{ij} + G_{b_j k} \times logitR_{ij}, & if \ k \neq b_j \end{cases}$$

	OR drug vs placebo at the study mean logit-risk **exp(D)**	OR drug vs placebo for one unit increase in the logit-risk **exp(G)**
Natalizumab	0.18	0.67
Glatiramer Acetate	0.41	0.87
Dimethyl Fumarate	0.43	1.06

Predicted relapse rate by baseline risk score



Treatment	Mean	Less than 30% risk	More than 50% risk
Natalizumab	46%	23%	69%
Glatiramer Acetate	56%	23%	86%
Dimethyl Fumarate	53%	20%	84%

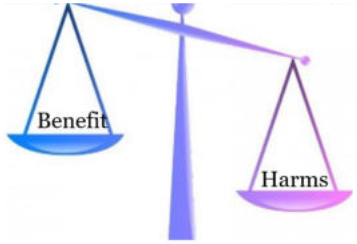
Low risk: Best treatment **Dimethyl Fumarate**
no added benefit of Natalizumab

High risk: Best treatment **Natalizumab**
15% absolute benefit compared to Dimethyl Fumarate

Clinical relevance of a prediction model

- Implementation of a prediction model **does not necessarily lead to better decisions**
- Compare the strategy "*Choose the treatment according to model*" vs "*Treat everyone with Natalizumab*" vs "*Treat everyone with Dimethyl Fumarate*" vs "*Treat no one*"
- We compare the strategies in terms of **Net Benefit** within a **decision curve analysis;** a technique that investigates whether making clinical decisions based on a model would do more good than harm. *Vickers et al. Med Decis Making.2006*
- Previously applied for a single intervention vs reference and primarily within an RCTs

Generalized Net Benefit for many alternative treatment strategies



Reduction in a harmful event rate

$$NB_s = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j$$

proportion of people who will take the treatment (and its side effects)

× the treatment threshold ("exchange rate")

ε_0 the event rate under no treatment

ε_s the event rate under strategy s

$\pi_{s,j}$ the proportion of patients treated with treatment j under strategy s

Treatment threshold T_j is the anticipated benefit that will lead to choosing treatment j, after considering its safety and tolerability.

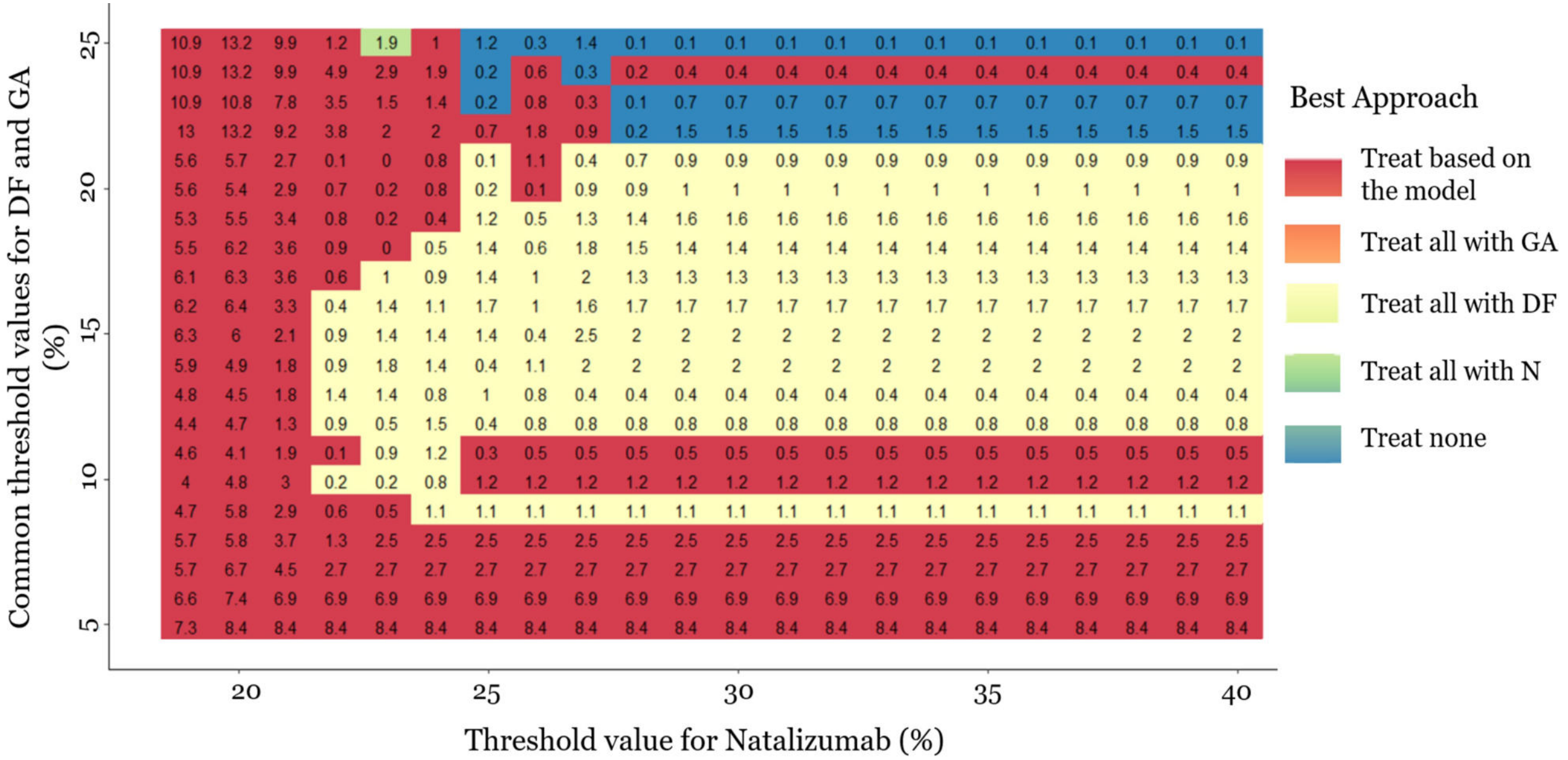
Natalizumab has issues with safety

$T_N = 3\%$

$T_N = 35\%$

Generalised Net Benefit

number of fewer patients with relapse per 100 participants



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RESEARCH ARTICLE

Statistics in Medicine WILEY

A two-stage prediction model for heterogeneous effects of treatments

Konstantina Chalkou[1] | Ewout Steyerberg[2] | Matthias Egger[1,3] | Andrea Manca[4] | Fabio Pellegrini[5] | Georgia Salanti[1]

Medical Decision Making
Volume 43, Issue 3, April 2023, Pages 337-349

https://doi.org/10.1177/0272989X221143058

SAGE journals

Original Research Article

Decision Curve Analysis for Personalized Treatment Choice between Multiple Options

Konstantina Chalkou, MSc [1,2], Andrew J. Vickers, PhD [3], Fabio Pellegrini, PhD[4], Andrea Manca, PhD[5], and Georgia Salanti, PhD[6]

Conclusions & limitations

- We extended the risk modelling approach for network meta-regression
  - The model is time-consuming
  - We haven't evaluated the perfomance of the second stage – see *Efthimiou et al. Stat Med 2023*
  - Needs IPD from each drug
  - The work ended being methodological as it does not reflect the real need of RRMS patients (in terms of outcomes and treatments)
- We extended the DCA methodology into multidimensional setting
  - We have some estimation problems in DCA: small congruent datasets, missing drugs
  - Patient surveys are needed to identify the range of threshold values in which patients are interested in
  - Results depend on which range of thresholds one considers realistic

Thank you!
Questions?

Adjustment for baseline covariates

from https://www.fharrell.com/post/covadj/

- There may be 3 compelling arguments in favor of conditioning on baseline covariates when we consider binary outcomes.
- **Interpretation and statistical power**
  - *Hauck et al, 1998* recommend that the primary analyses adjust for important prognostic covariates in order to come as close as possible to the clinically most relevant subject-specific measure of treatment effect. Additional benefits would be an increase in efficiency of tests for no treatment effect and improved external validity.
  - *Robinson & Jewell 1991* the estimated treatment effect after adjustment is more precise (for non-liner models like logistic)
- **Correction for baseline imbalance**
  - *Steyerberg et al*

Generalized Net Benefit for many alternative treatment strategies

Estimation

$$NB_s = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j$$

$\pi_{s,j}$ the proportion of patients treated with treatment j under strategy s

Estimated from the **congruent dataset** for strategy s, $Data_s$

Congruent dataset the subset of the original $Data$ including those patients where recommended treatment = actual given treatment

Using $Data_s$, we estimate each $\pi_{s,j}$ as the pooled proportion of people under each treatment j

Generalized Net Benefit for many alternative treatment strategies

Estimation

$$NB_s = \varepsilon_0 - \varepsilon_s - \sum_j \pi_{s,j} \times T_j$$

ε_s the event rate under strategy s

Estimate pooled placebo event rate $\hat{\varepsilon}_{s,0}$

Estimate NMA risk ratio of each treatment versus the control from the congruent dataset $RR_j^{Data_s}$

Estimate the treatment-specific event rates as $\hat{\varepsilon}_{s,j} = \hat{\varepsilon}_{s,0} \times RR_j^{Data_s}$