Decision curve analysis for personalized treatment choice between multiple options

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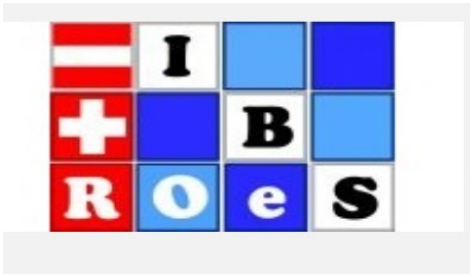


Background

Several strategies to decide upon treatments

Default-average strategies:

Treat all patients with Treatment 1

Treat all patients with Treatment 2

Treat nobody

Individualized treatment choices:

Treat patients according to an individualized prediction model

Several prediction models available

Background

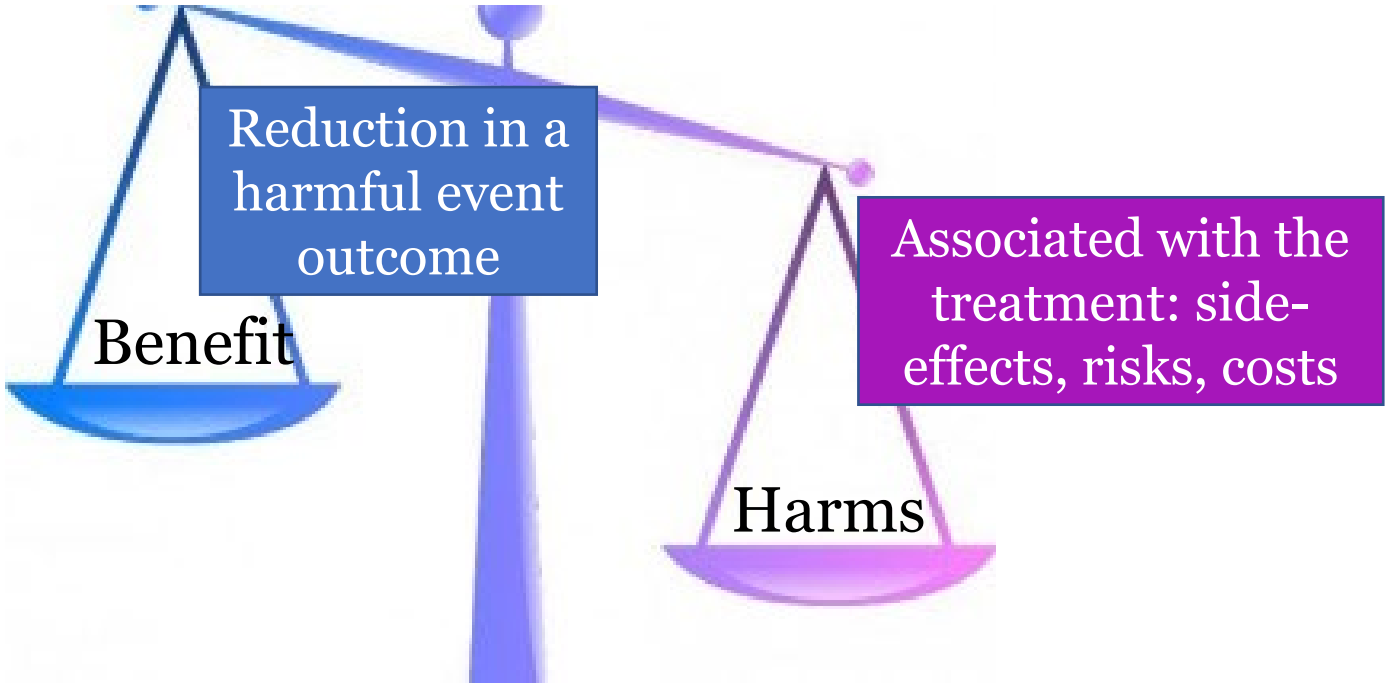
Decision curve analysis methods (DCA)

- The main methodological vehicle **to evaluate the clinical relevance** of each strategy

- Evaluate **which strategy** leads to better clinical decisions

Measure of performance in DCA – Net Benefit

Net benefit (NB)



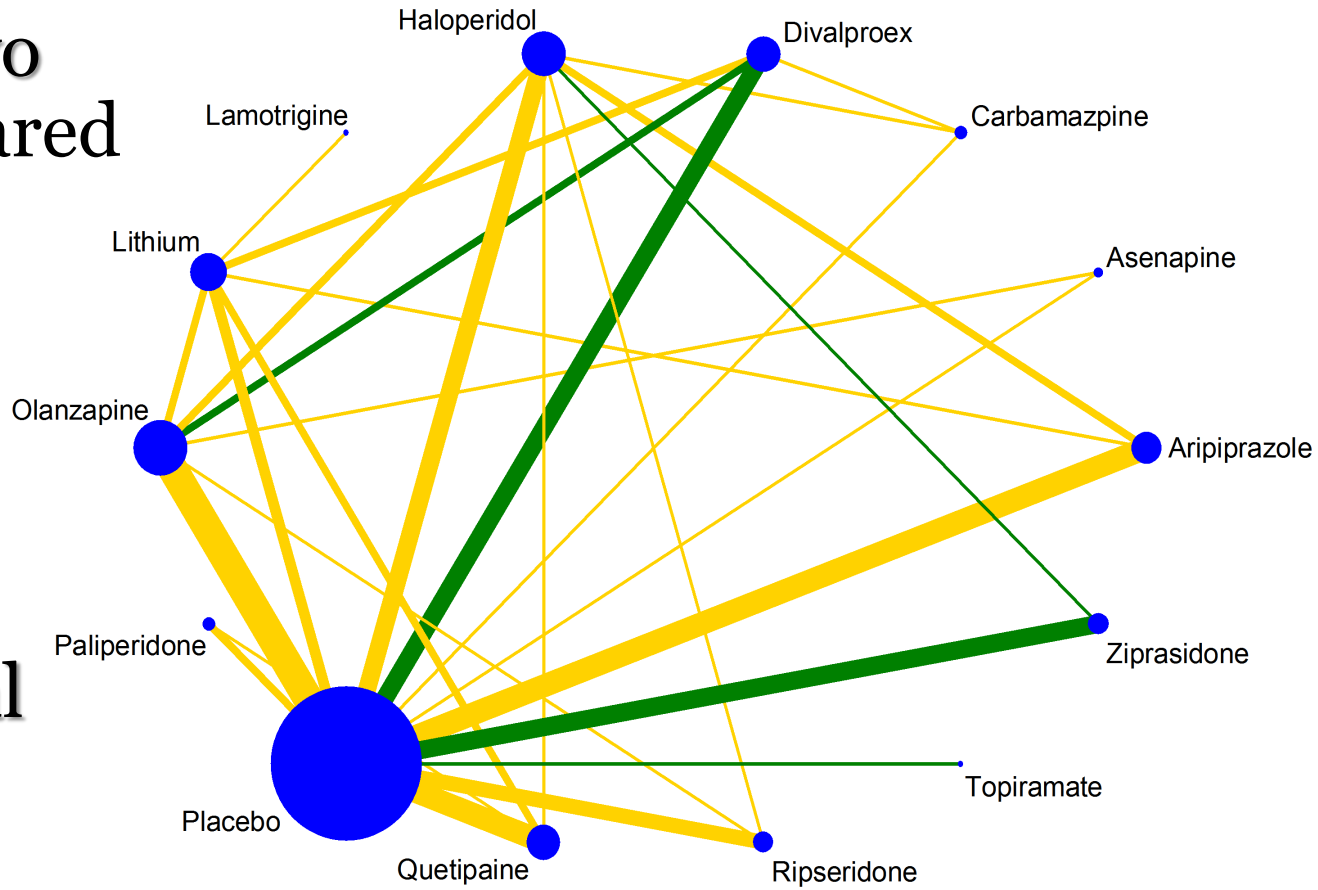
The NB can be estimated for each strategy s: $\boldsymbol{NB_s}$

The strategy with the highest NB leads to better clinical decisions

Background

DCA methods well established into an RCT framework where two treatment options are compared

Nowadays, several treatment options exist for the same condition, evaluated in several RCTs for the same outcome

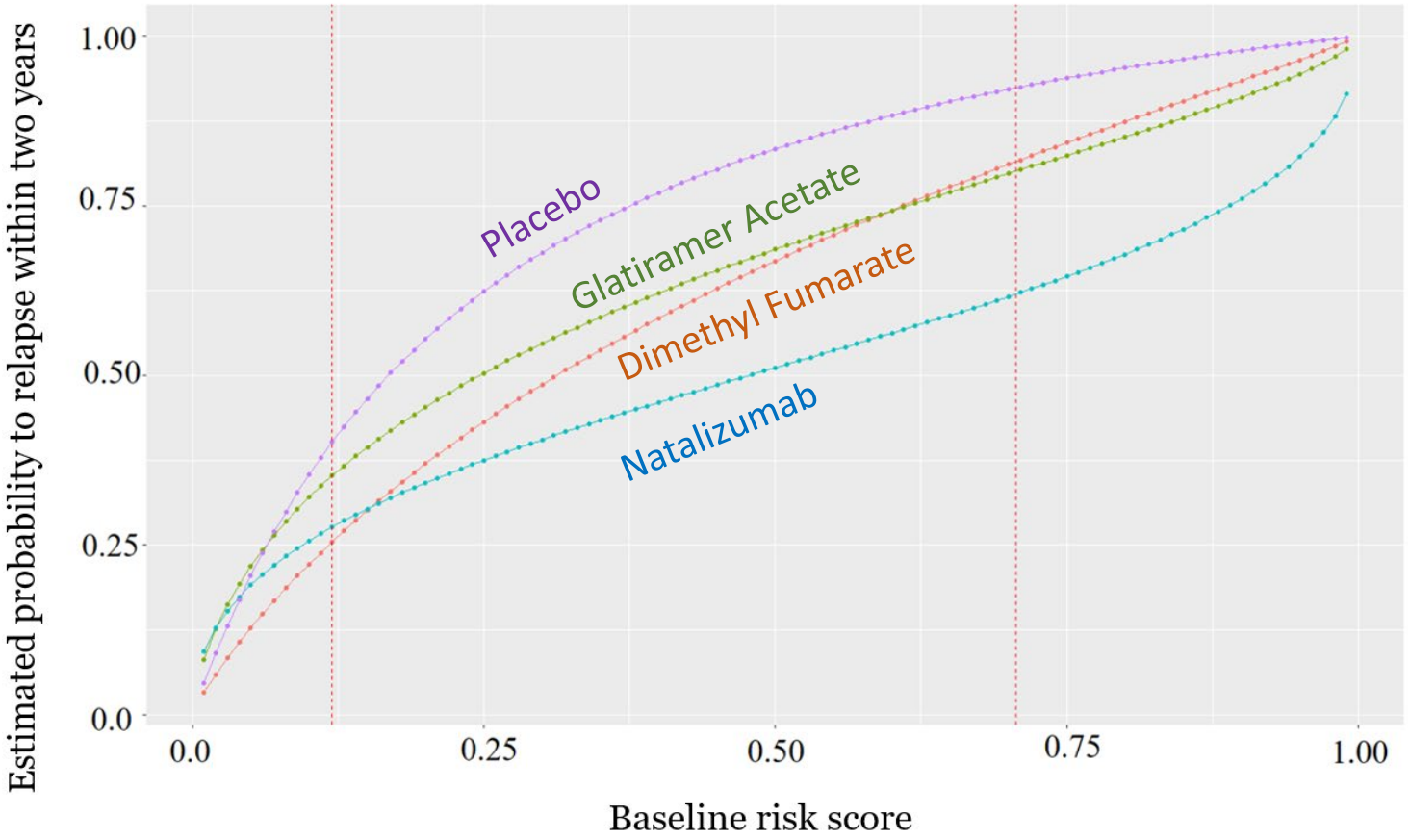


Objectives

We aim to extend the DCA methodology, into a **network meta-analysis framework (NMA)**, where several treatment options are compared coming from several studies, to compare default average strategies with individualized strategies

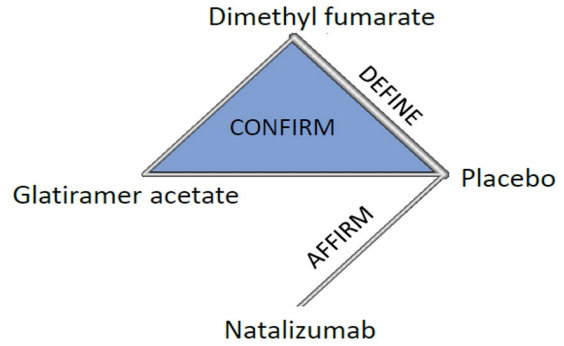
Case study

Individualized treatment recommendation for patients with relapsing-remitting multiple sclerosis (RRMS)



Stage 1 – Baseline risk score SMSC study

Stage 2 – IPD Network Meta-regression
3 RCTs
https://cinema.ispm.unibe.ch/shinies/koms/



Reaching treatment recommendations when we have multiple options via a model

Threshold value T_j

Even if a treatment *j* is efficient treatment's side-effects, inconvenience and risks need to be taken under consideration

$RD_{i,N} = 3\%$ 

$RD_{i,N} = 35\%$ 

"Which is the minimum risk difference compared to control that renders treatment j worthwhile taking?"

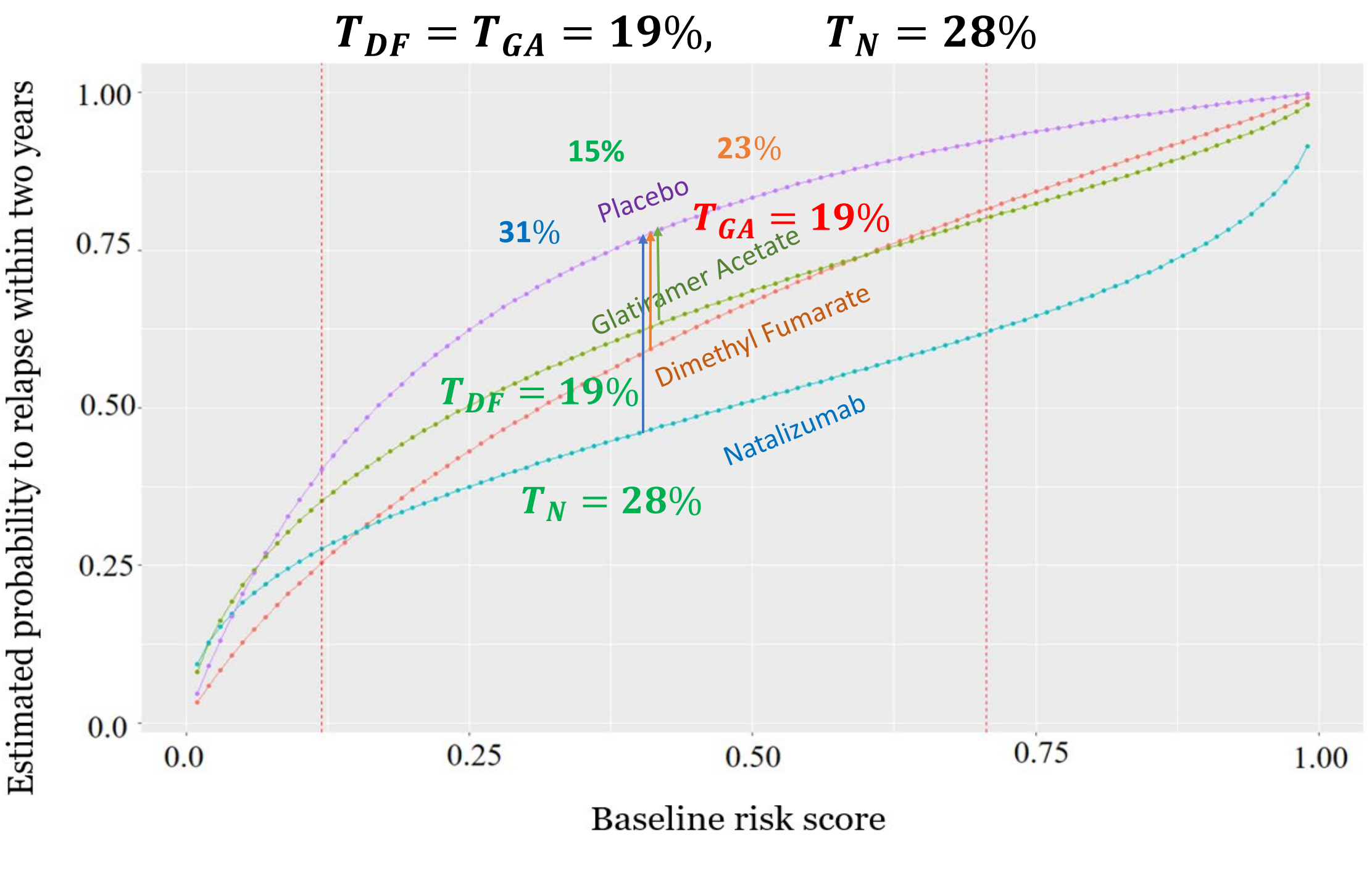
For instance, a T_j of 20% means that we would be willing to treat no more than 5 patients to prevent one relapse

Reaching treatment recommendations when we have multiple options via a model

Let us assume: $\boldsymbol{T_{DF} = T_{GA} = 19\%, \quad T_N = 28\%}$

Decision rule

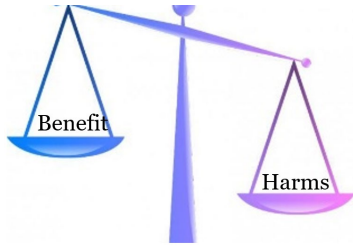
For a patient i, the recommended treatment j under the prediction model is the one that satisfies $max\left\{RD_{i,j} - T_j\right\}$, between those treatments with $RD_{i,j} \geq T_j$. When all active treatments lead to $RD_{i,j} < T_j$, then the control treatment is recommended for patient i


$T_{DF} = T_{GA} = 19\%,$
$T_N = 28\%$
Estimated probability to relapse within two years
1.00
0.75
0.50
0.25
0.0
0.0
0.25
0.50
0.75
1.00
Baseline risk score
15%
23%
31%
Placebo
$T_{GA} = 19\%$
Glatiramer Acetate
Dimethyl Fumarate
$T_{DF} = 19\%$
Natalizumab
$T_N = 28\%$

Reaching treatment recommendations when we have multiple options via a model

Treatment	Placebo	Glatiramer Acetate	Dimethyl Fumarate	Natalizumab
Predicted risk to relapse within two years ($R_{i,j}$)	75%	60%	52%	43%
Predicted risk difference vs placebo ($RD_{i,j}$)	-	15%	23%	31%
Threshold value for treatment j (T_j)		19%	19%	28%
$RD_{i,j} - T_j$		-4%	**4%**	3%
Recommended treatment via the prediction model		**Dimethyl Fumarate**		

Measure of performance in DCA – Net Benefit



Reduction in a harmful event outcome

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

Associated with the treatment: side-effects, risks, costs

ε_0 denotes the event rate under no treatment,

ε_s the event rate under strategy s, and

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

T_j the thrsehold values chosen for treatment j

Measure of performance in DCA – Net Benefit

Estimation of ε_0, depends on the framework

A) One RCT available

Observed proportion of events in the placebo arm,
$\widehat{\varepsilon_0} = e_0^{Data}$, where $Data$ the available dataset

B) Several RCTs

Pooled event rate estimation, via a meta-analysis of all placebo events, in the dataset of all available RCTs $Data$

Patients randomized within trials but not across them

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

Measure of performance in DCA – Net Benefit

Estimation of $\pi_{s,j}$

We need the **congruent dataset** for strategy s, $Data_s$ – the subset of $Data$ including those patients where:
recommended treatment = actual given treatment

Using $Data_s$, we estimate all $\pi_{s,j}$ as the observed proportion of people under each treatment j, $\hat{\pi}_{s,j} = p_{s,j}^{Data_s}$

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

Measure of performance in DCA – Net Benefit

Estimation of ε_s

The weighted average event rate under strategy s:

$$\hat{\varepsilon}_s = \sum_{j=0}^{J} p_{s,j}^{Data_s} \times \hat{\varepsilon}_{s,j}$$

$p_{s,j}^{Data_s}$ is the observed proportion of patients treated with treatment j in the congruent dataset, $Data_s$

$\hat{\varepsilon}_{s,j}$, is the event rate under treatment j using strategy s

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

Measure of performance in DCA – Net Benefit

Estimation of ε_s, depends on the framework

1. One RCT

$\hat{\varepsilon}_{s,j} = e_j^{Data_s}$ i.e., $\varepsilon_{s,j}$ the observed proportion of events under arm j in $Data_s$

2. Several RCTs

Step 1: Pooled placebo event rate $\hat{\varepsilon}_{s,0}$

Step 2: Risk ratio of each treatment versus the control $RR_j^{Data_s}$

Step 3: The treatment-specific event rates are $\hat{\varepsilon}_{s,j} = \hat{\varepsilon}_{s,0} \times RR_j^{Data_s}$

$$\hat{\varepsilon}_s = \sum_{j=0}^{J} p_{s,j}^{Data_s} \times \hat{\boldsymbol{\varepsilon}}_{\boldsymbol{s,j}}$$

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

Measure of performance in DCA – Net Benefit

Estimation of ε_s, depends on the strategy

1. Treat all patients with treatment j=x

Estimated from the entire dataset $Data$ as $\hat{\varepsilon}_{s,x} = \hat{\varepsilon}_x = \widehat{\varepsilon_0} \times RR_x^{Data}$

The observed proportion $p_{s,x}^{Data_s}$ is equal to 1, whereas the observed proportion $p_{s,j\neq x}^{Data_s}$ is equal to 0.

2. Treat nobody

NB=0 as $\hat{\varepsilon}_{s,0} = \widehat{\varepsilon_0}$, and the $\hat{\pi}_{s,j} = p_{s,j}^{Data_s}$ is 0 for all the available treatments j

$$\hat{\varepsilon}_s = \sum_{j=0}^{J} p_{s,j}^{Data_s} \times \hat{\boldsymbol{\varepsilon}}_{\boldsymbol{s,j}}$$

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

Exemplifying the methodology deciding for treatment in patients with RRMS

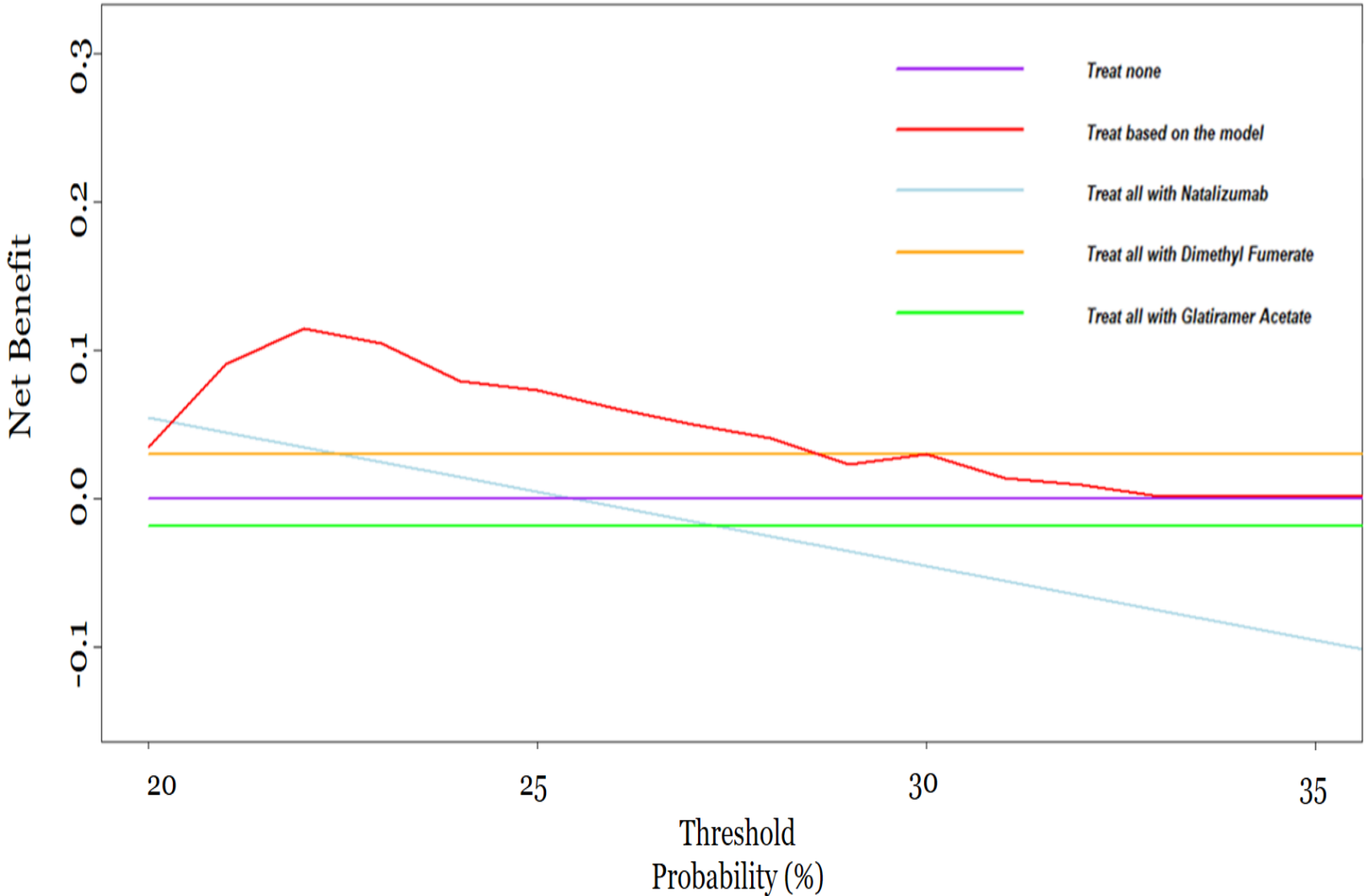
Approach	$T_{DF} = T_{GA} = 19\%, \quad T_N = 28\%$	Net Benefit
Treat nobody		0.000
Treat all patients with Natalizumab		0.025
Treat all patients with Dimethyl Fumarate		0.030
Treat all patients with Glatiramer Acetate		0.019
Treat patients according to the prediction model		0.050

The strategy “treat patients according to the prediction model” leads to 5 fewer patients that will relapse per 100 participants compared to “treat nobody” strategy, and 2 fewer patients compared to strategy “treat all patients with Dimethyl Fumarate”

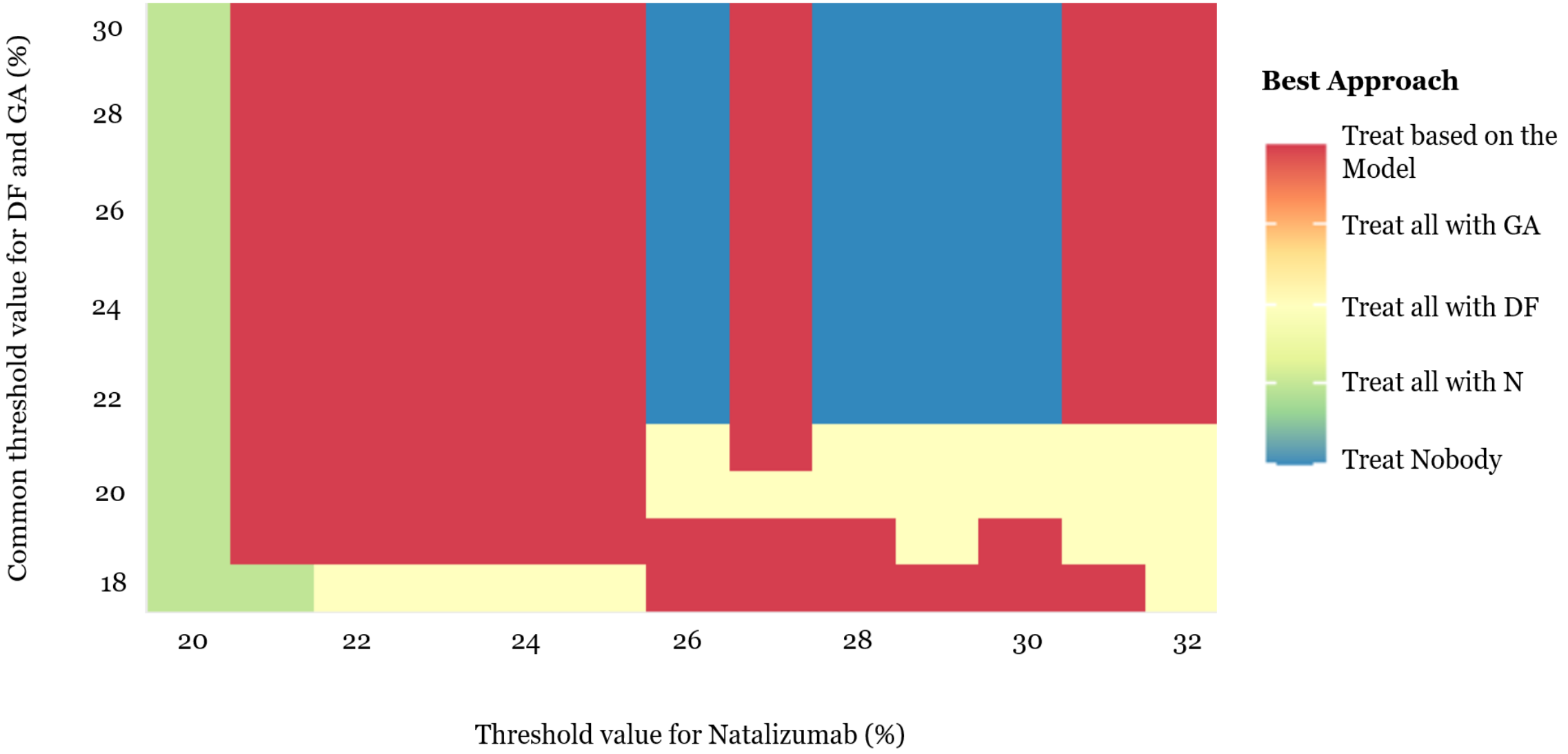
Exemplifying the methodology deciding for treatment in patients with RRMS

Different patients might weight differently the risk to relapse and the risks associated with each treatment

$$\boldsymbol{T_{DF} = T_{GA} = 19\%,}$$
$$\boldsymbol{T_N = 20 - 35\%}$$



Exemplifying the methodology deciding for treatment in patients with RRMS



Conclusions

- We extended the DCA methodology, a vehicle for evaluating which strategy leads to better clinical treatment decisions *into a NMA framework*
- The methodology can be applied to compare any *group-level strategy* with *individualized-level strategies*, when IPD RCTs are available
- The methodology can be applied to compare the clinical relevance *of several personalized prediction models* to identify which one leads to better clinical treatment decisions
- The *individualized prediction model* for deciding upon treatments for patients with relapsing-remitting multiple sclerosis seems to *lead to better clinical treatment decisions* into *a wide range of threshold values* compare to default strategies

References

- Vickers AJ, Elkin EB. Decision Curve Analysis: A Novel Method for Evaluating Prediction Models. *Med Decis Making*. 2006;26(6):565-574. doi:10.1177/0272989X06295361
- Chalkou K, Steyerberg E, Egger M, Manca A, Pellegrini F, Salanti G. A two-stage prediction model for heterogeneous effects of many treatment options: application to drugs for Multiple Sclerosis. *Stat Med* 2021 Sep 10;40(20):4362-4375.
- Chalkou K, Steyerberg E, Bossuyt P, Subramanian S, Benkert P, Kuhle J, Disanto G, Kappos L, Egger M. Development, validation and clinical usefulness of a prognostic model for relapse in relapsing-remitting multiple sclerosis. arXiv:2105.06941v1 [stat.AP]. https://arxiv.org/abs/2105.06941

Thank you for your attention!