A prediction model of heterogeneous treatment effects using randomized and observational data

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Data from:

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One size to fit all

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)

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

One size does not fit all

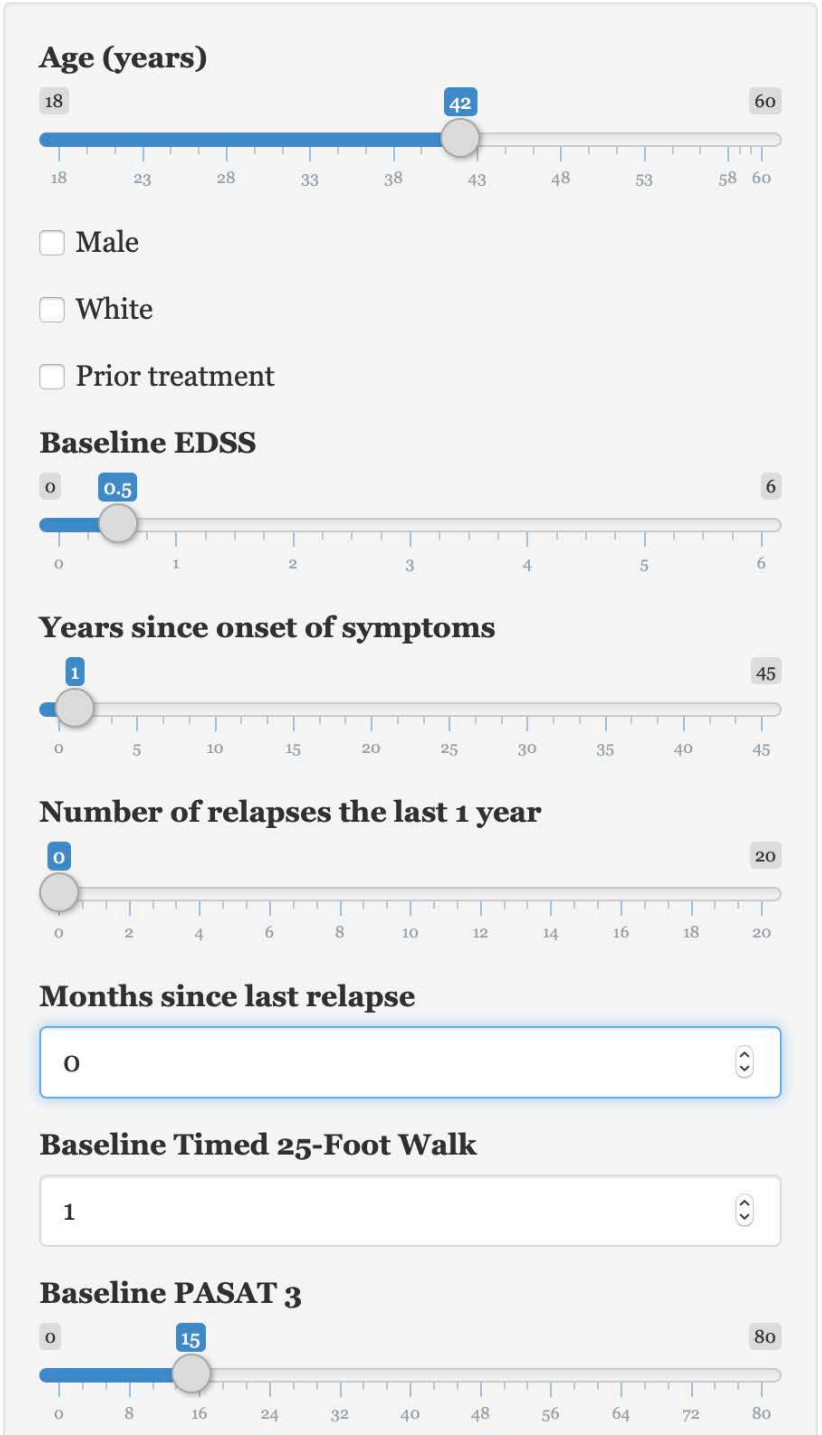
Treatment choice is (or should be) personalised

Not all patients have the same response to the same treatment

Heterogeneous **T**reatment **E**ffects

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 %

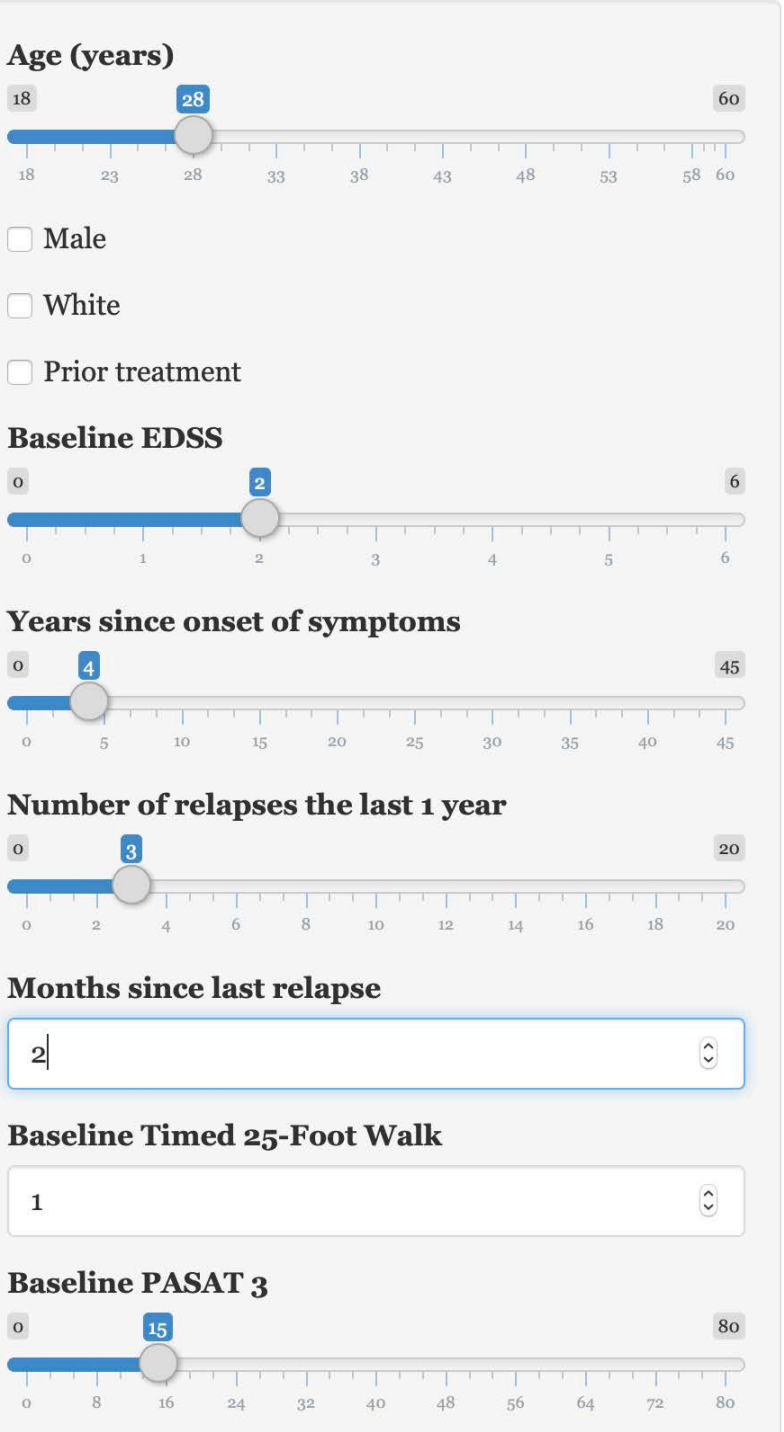
Ranking of predicted probabilities to relapse in two years

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

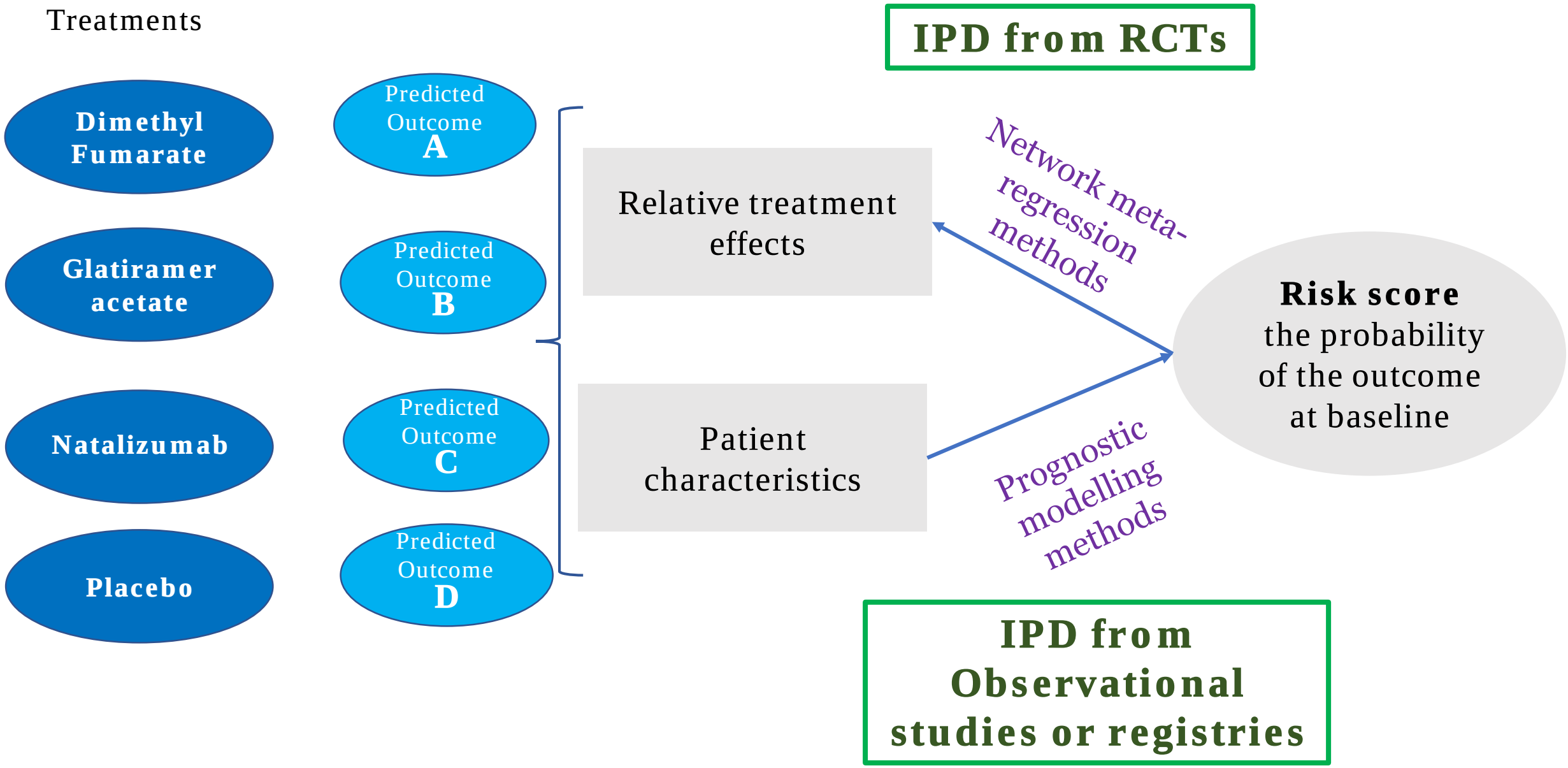
Not all patients have the same response to the same treatment

Heterogeneous **T**reatment **E**ffects

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
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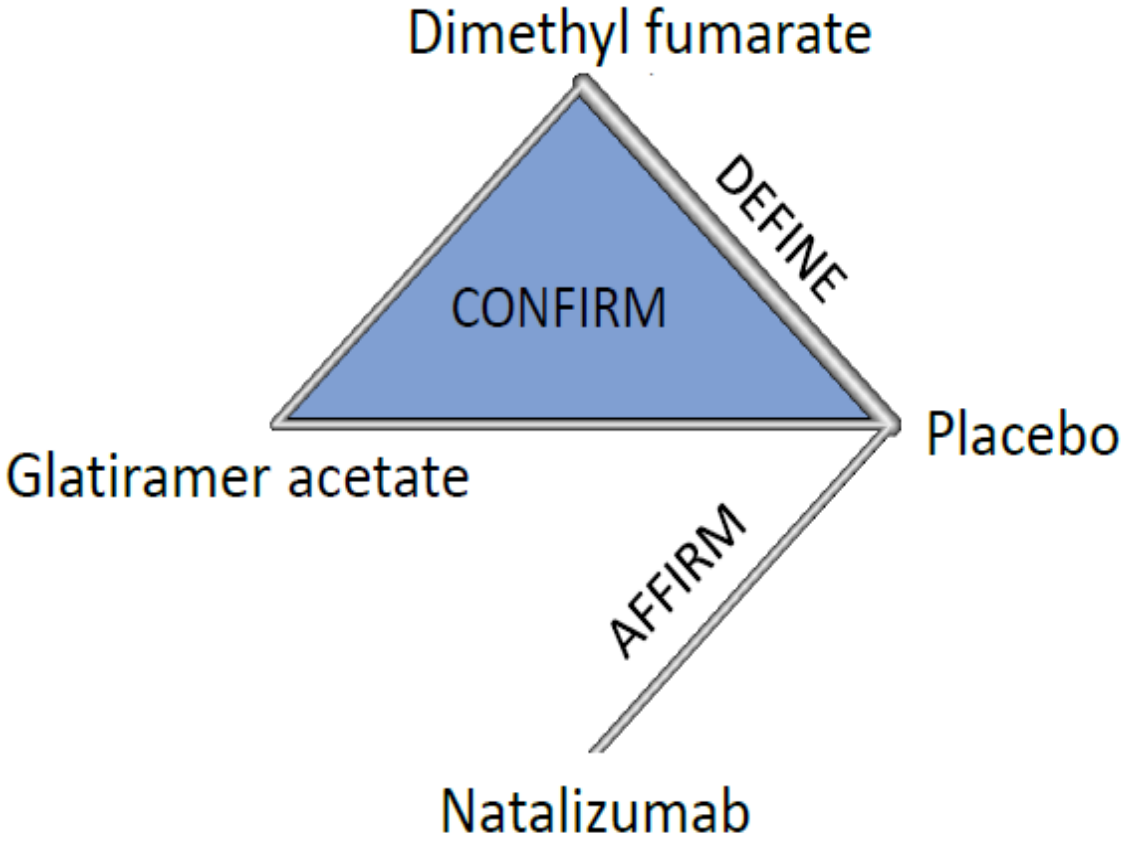
Placebo
Predicted Outcome A
Predicted Outcome B
Predicted Outcome C
Predicted Outcome D
Relative treatment effects
Patient characteristics
IPD from RCTs
Network meta-regression methods
Prognostic modelling methods
Risk score
the probability of the outcome at baseline
IPD from Observational studies or registries

RCTs

3 randomized phase III clinical trials 2990 observations in total

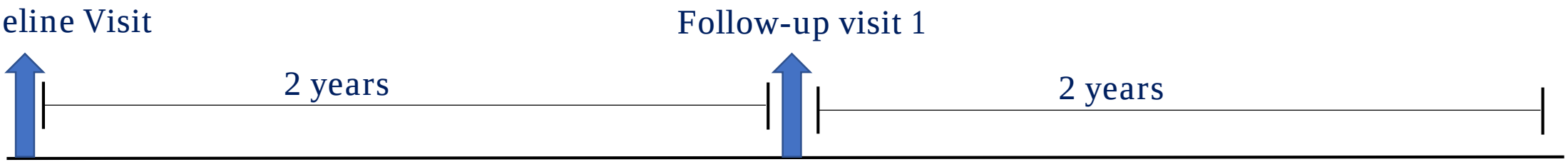


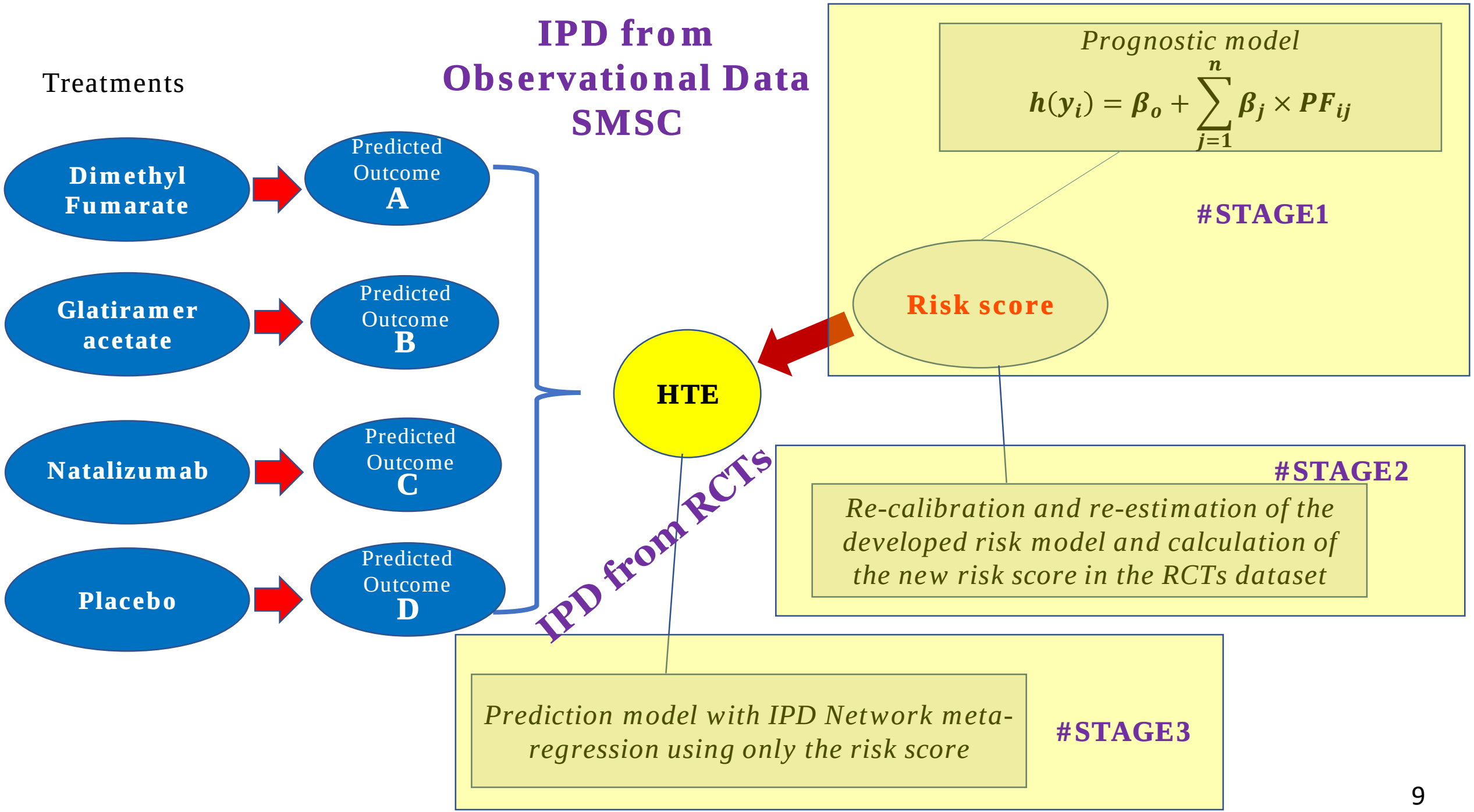
Observational data
Swiss MS Cohort (SMSC)

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




IPD from Observational Data SMSC
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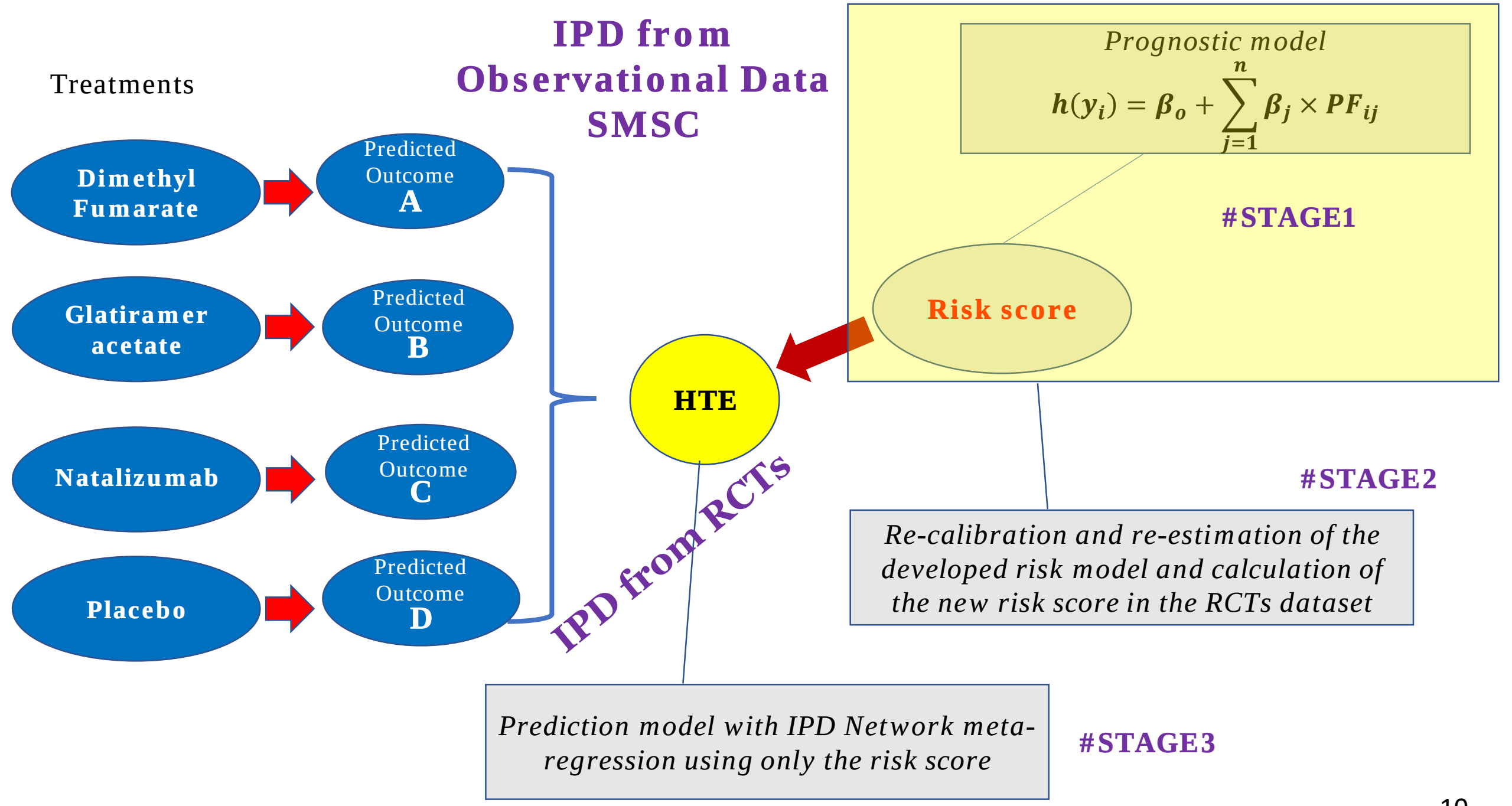
HTE
IPD from RCTs
Prognostic model
$h(y_i) = \beta_o + \sum_{j=1}^{n} \beta_j \times PF_{ij}$
#STAGE1
Risk score
#STAGE2
Re-calibration and re-estimation of the developed risk model and calculation of the new risk score in the RCTs dataset
Prediction model with IPD Network meta-regression using only the risk score
#STAGE3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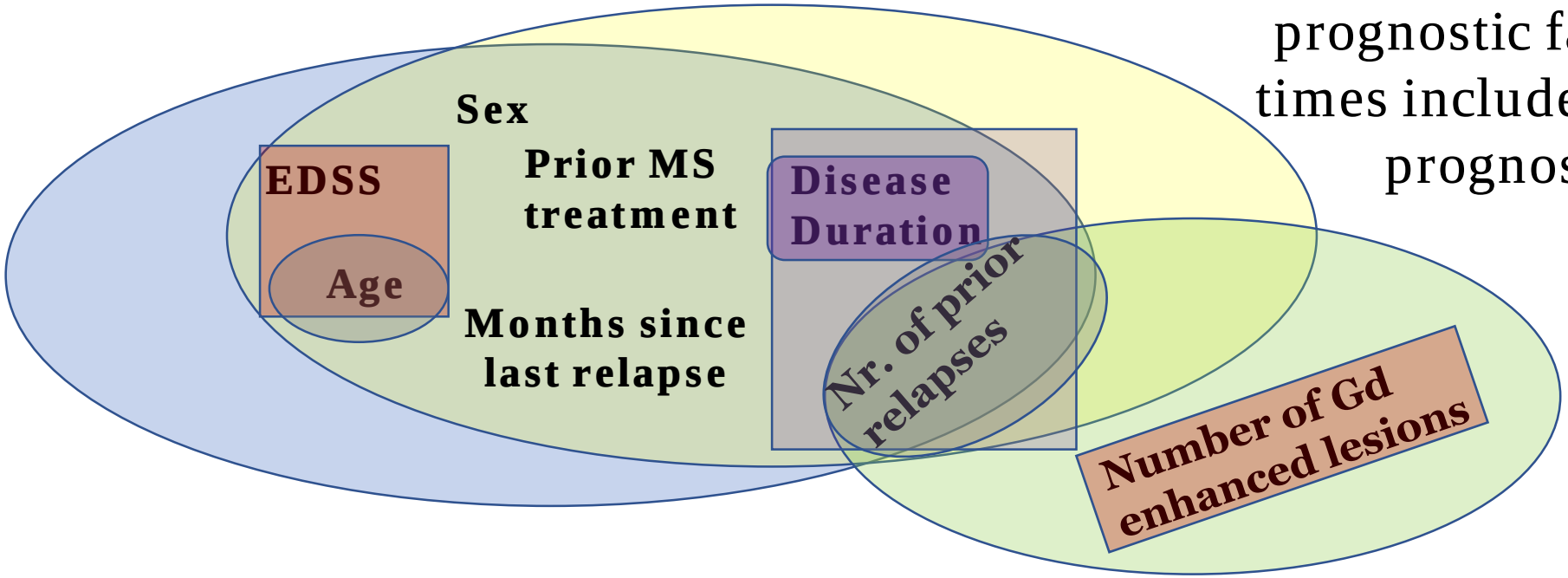
Stage 1: Development of the prognostic model

Step 1 - Selection of prognostic factors

8 previously identified prognostic factors (at least 2 times included in pre-existing prognostic models)



Pellegrini | Stühler | Cree | Held | Sormani | Signori | Kalincik

European Union's Horizon 2020 research and innovation programme under grant agreement № 825162.

Stage 1: Development of the prognostic model

Step 2 – Development of the model

Logistic mixed effects model in a Bayesian framework

$$Y_{ij} \sim \text{Bernoulli}(R_{ij})$$

$$\text{logit}(R_{ij}) = \beta_0 + u_{oi} + \sum_{k=1}^{P} (\beta_k + u_{ki}) \times PF_{k,j}$$

Notation

i: individuals, where $i = 1, 2, \ldots, N$

j: time point, where $j = 1, 2, 3$

$PF_{k,j}$: kth prognostic factor at j^{th} time point,

where $k = 1, 2, \ldots, P$

β_0: fixed effect intercept

u_{0i}: random effect intercept

β_k: fixed effect slopes of k^{th} prognostic factor

u_{ki}: the individual-level random slopes of k^{th} 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

Prognostic factors	Estimations (ORs)
Intercept	0.15
Age	0.97
Disease Duration	1.38
Edss	1.12
Gd enhanced lesions	1.00
Number of previous Relapses (1 vs 0)	0.92
Number of previous Relapses (more than 2 vs 0)	1.12
Months Since Relapse	0.61
Treatment Naive	1.15
Gender	0.28
Treatment During Cycle (Yes vs No)	0.79

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

Age (years)
17 23 80
17 24 31 38 45 52 59 66 73 80

Disease Duration (years)
5

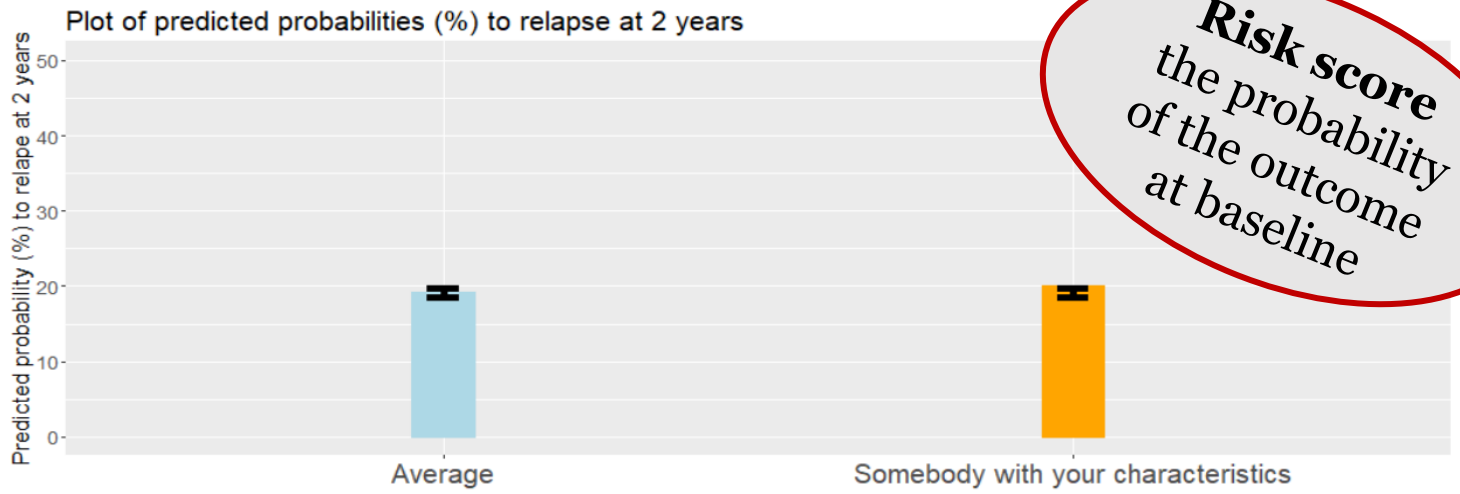
EDSS
0 6 7
0 1 2 3 4 5 6 7

- [x] Number of Gadolinium enhanced lesions > 0
- [ ] 1 prior relapse
- [x] 2 or more prior relapses

Months since last relapse
1

- [x] Treatment Naive
- [x] Female

Your risk to relapse at 2 years is 20 %



Risk score the probability of the outcome at baseline

Numerical Results:

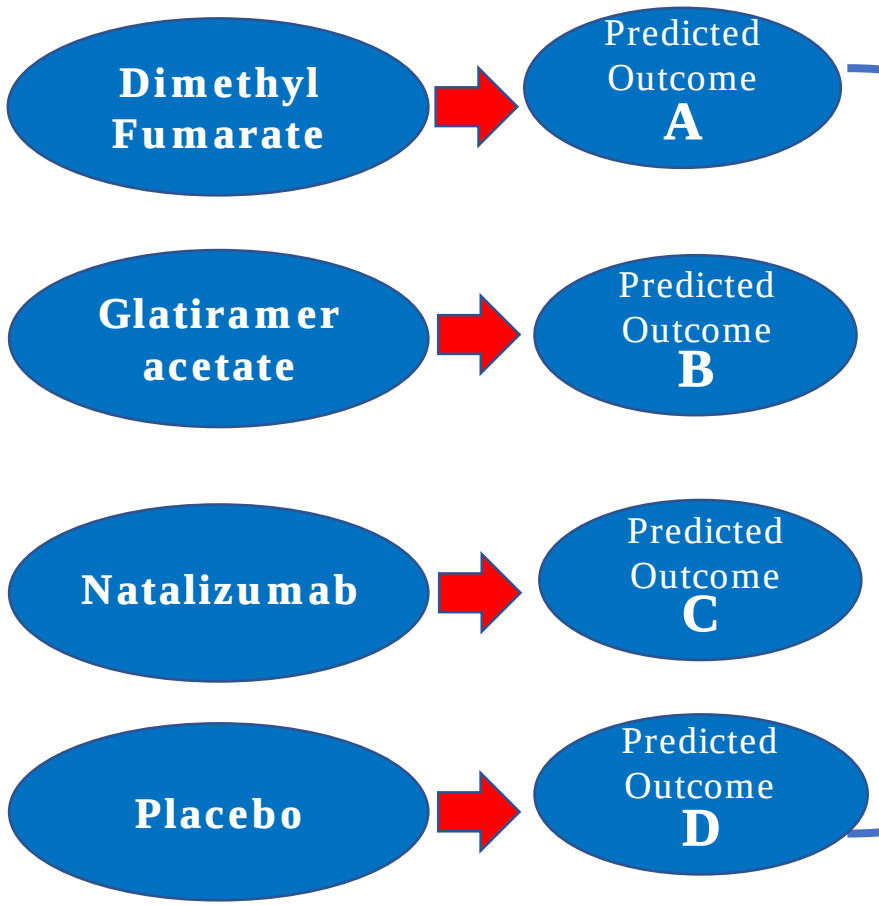
The average predicted probability (%) to relapse at 2 years is 19.2 with 95% C.I. (18.6, 19.7)

Somebody with your characteristics has 20 % predicted probability (%) to relapse at 2 years

Your predicted probability (%) to relapse at 2 years is 0.800000000000001 % higher than the average

IPD from Observational Data SMSC

Treatments



Prognostic model

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

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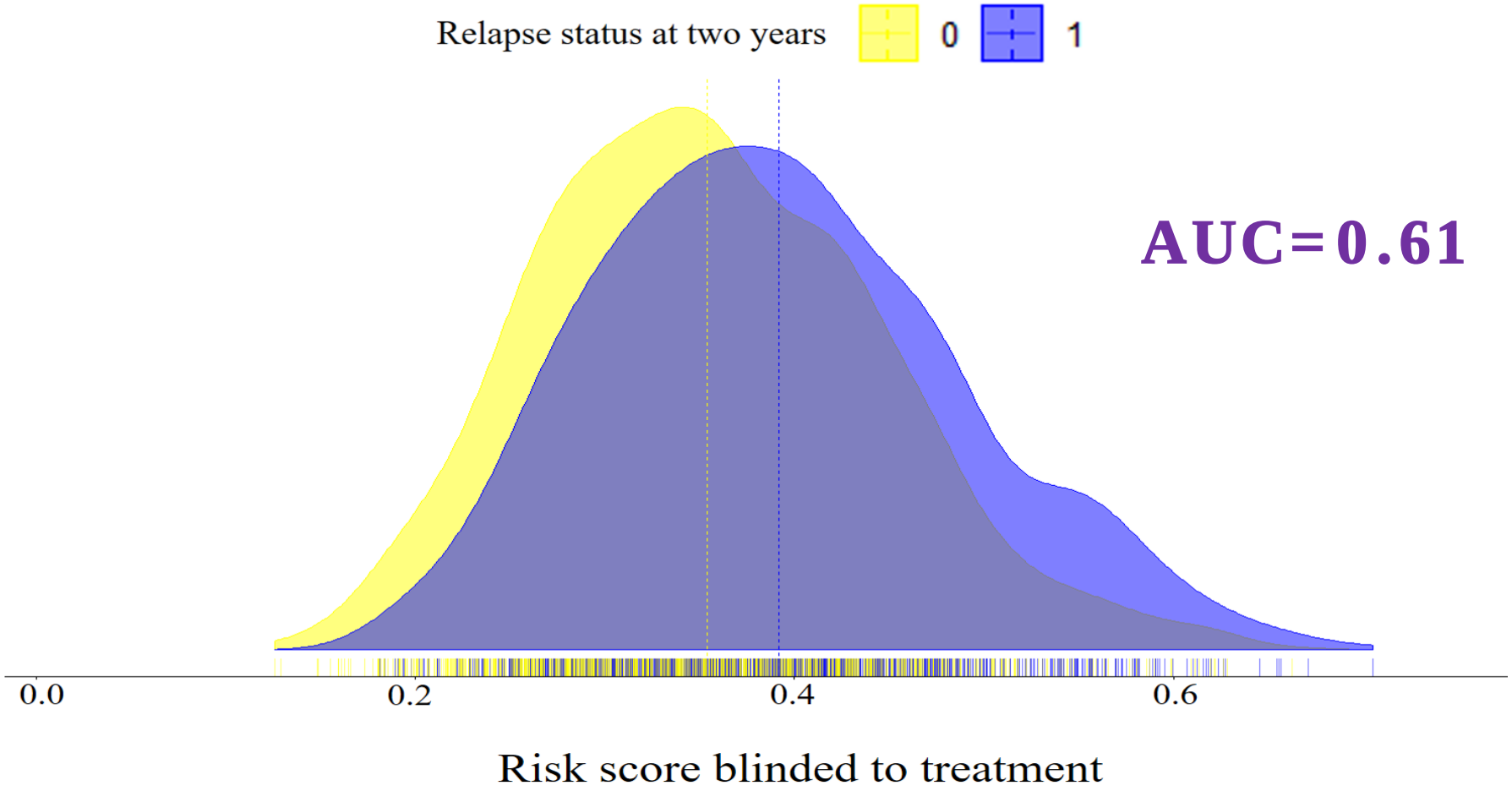
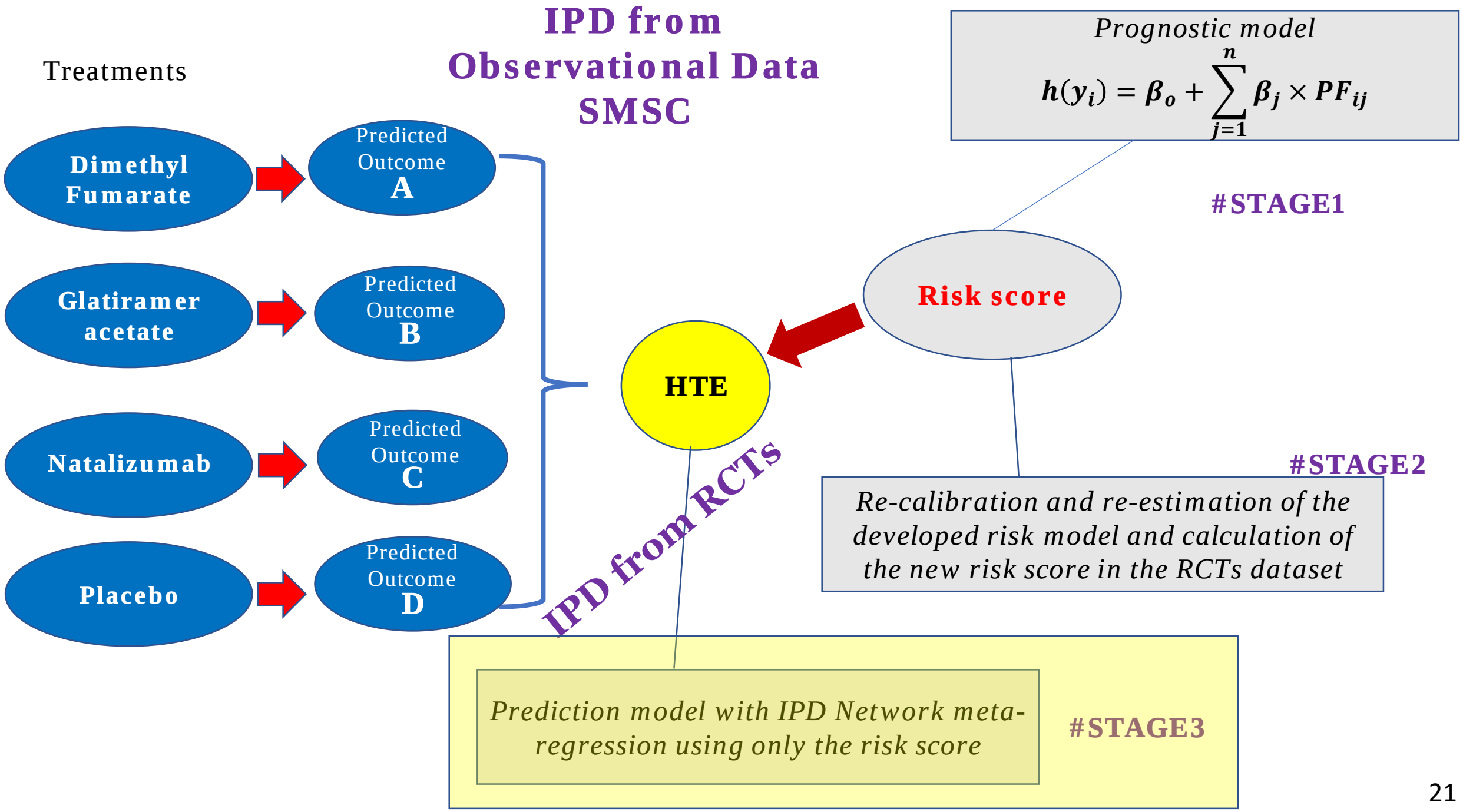
Stage 2: Re-calibration and re-estimation of the risk model to RCTs

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

Methods	AUC
No Update	0.57
Update only the intercept (Re-calibration)	0.57
Update intercept and coefficients (Re-calibration)	0.57
Model revision (Re-calibration & selective re-estimation)	0.61

Risk of relapse in two years in RCTs

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Stage 3: IPD Network Meta-regression

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

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

Notation

i: Individuals

j: study

k: treatment

b_j: baseline treatment in study j

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

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

$G_{b_j k}$: 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

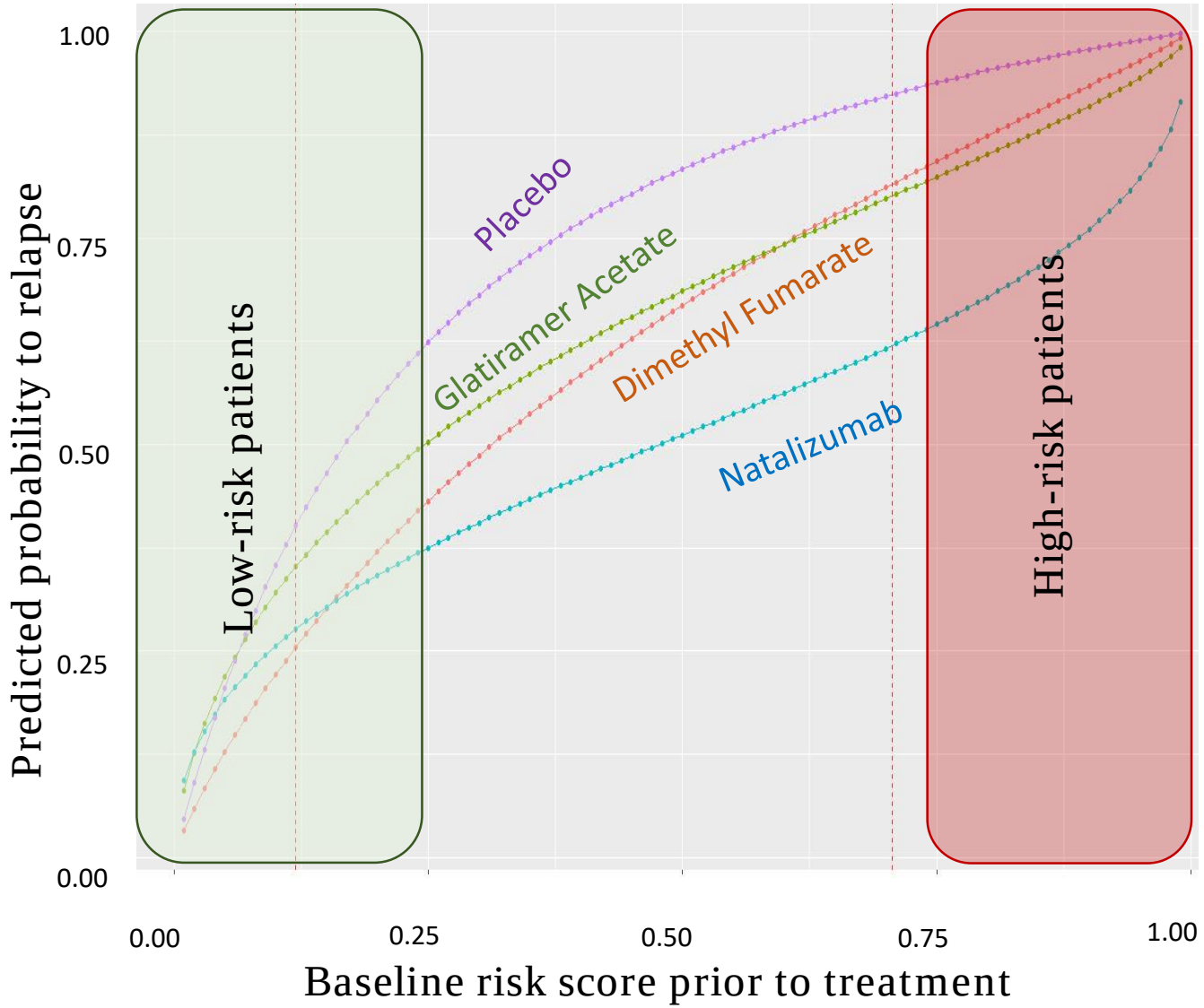
Results: Estimation of model parameters

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

	OR for relapse versus placebo at the study mean risk **(exp(D))** & 95% Cr. Intervals	OR versus placebo for one unit of increase in the logit risk **(exp(G))** & 95% Cr. Intervals
Natalizumab	0.28 (0.21, 0.37)	0.60 (0.31, 1.15)
Glatiramer Acetate	0.53 (0.34, 0.78)	0.73 (0.32, 2.10)
Dimethyl Fumarate	0.43 (0.3, 0.57)	0.89 (0.50, 1.87)

Stage 3: IPD Network Meta-regression

Results: Estimation of model parameters



Treatment	Mean	Less than 25% Risk	More than 75%
Natalizumab	46%	33%	57%
Glatiramer Acetate	61%	43%	75%
Dimethyl Fumarate	57%	34%	75%

Best treatment **Natalizumab 1% Absolute benefit** compared to Dimethyl Fumerate

Best treatment **Natalizumab-28% Absolute benefit** compared to Dimethyl Fumarate

R-shiny apps

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

Summary

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**