HTx - 2nd General Assembly

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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 ➞**H**eterogeneous **T**reatment **E**ffects

Question:
Which treatment is the best for a specific patient?

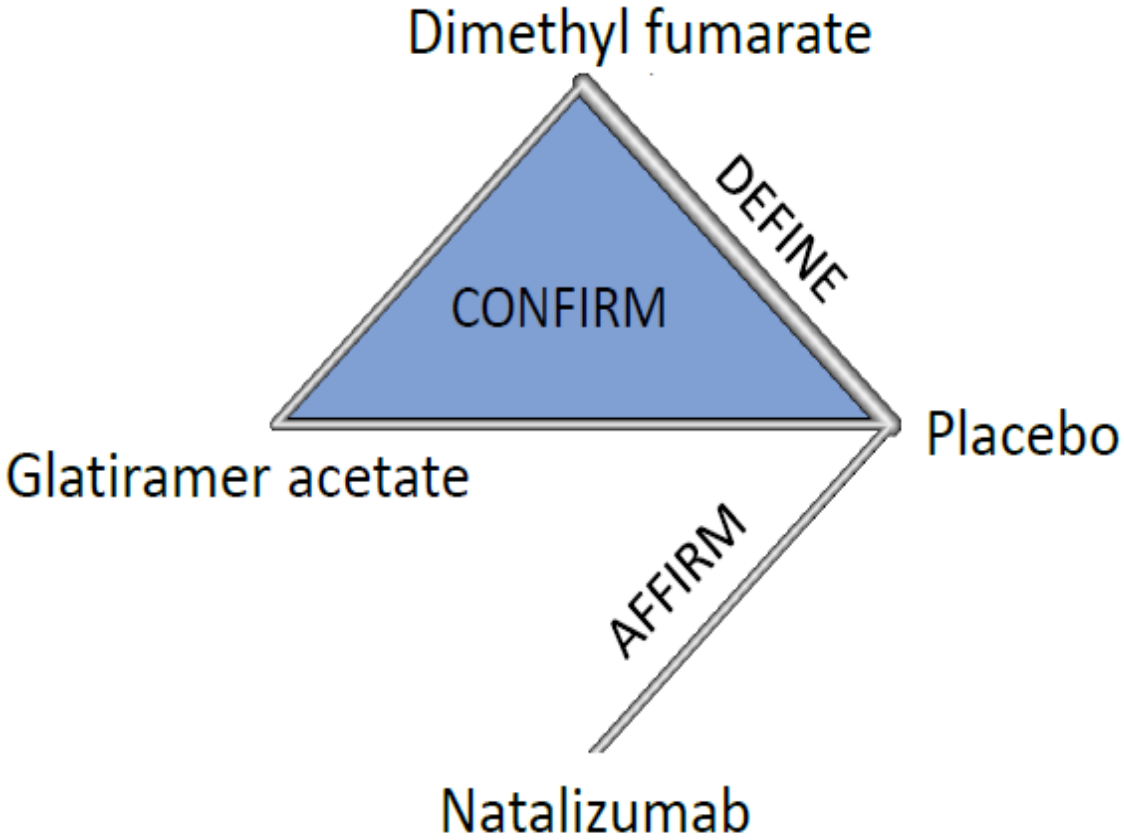
1. Individual characteristics influence the variation of HTE
   - **Baseline risk score prior to treatment** of patients seems to be a determinant predictor for HTE, **Prognosis research** is a key-tool for estimating risk scores
2. Numerous treatment options available for each disease
   Network meta-analysis (NMA) is a key-tool for comparing many different treatment options [2]

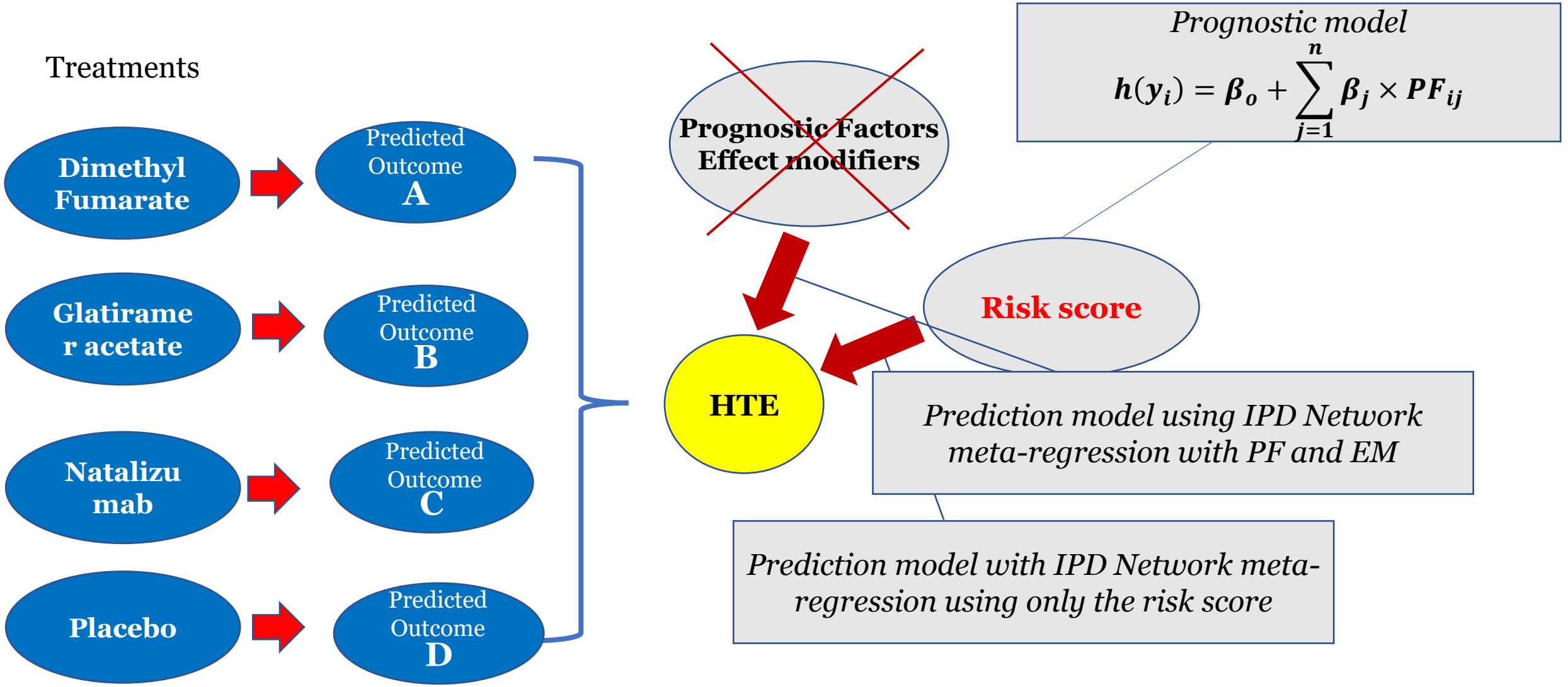
Aim

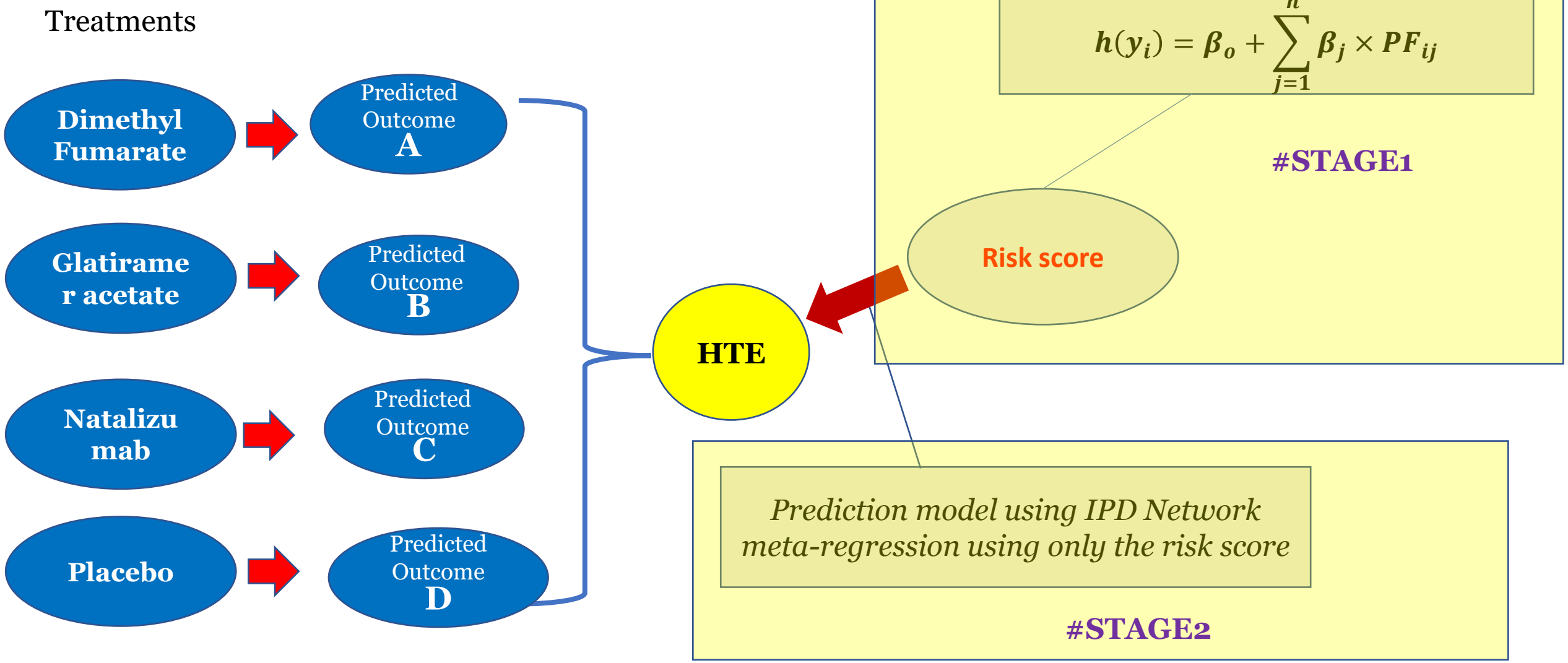
To develop a ***two-stage*** evidence synthesis ***prediction model*** to predict the most likely outcome under several possible treatment options while accounting for patients' characteristics using ***individual participant data network meta-regression*** with ***risk scores***

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
Predicted Outcome B
Predicted Outcome C
Predicted Outcome D
Prognostic Factors
Effect modifiers
HTE
Prognostic model
$h(y_i) = \beta_o + \sum_{j=1}^{n} \beta_j \times PF_{ij}$
Risk score
Prediction model using IPD Network meta-regression with PF and EM
Prediction model with IPD Network meta-regression using only the risk score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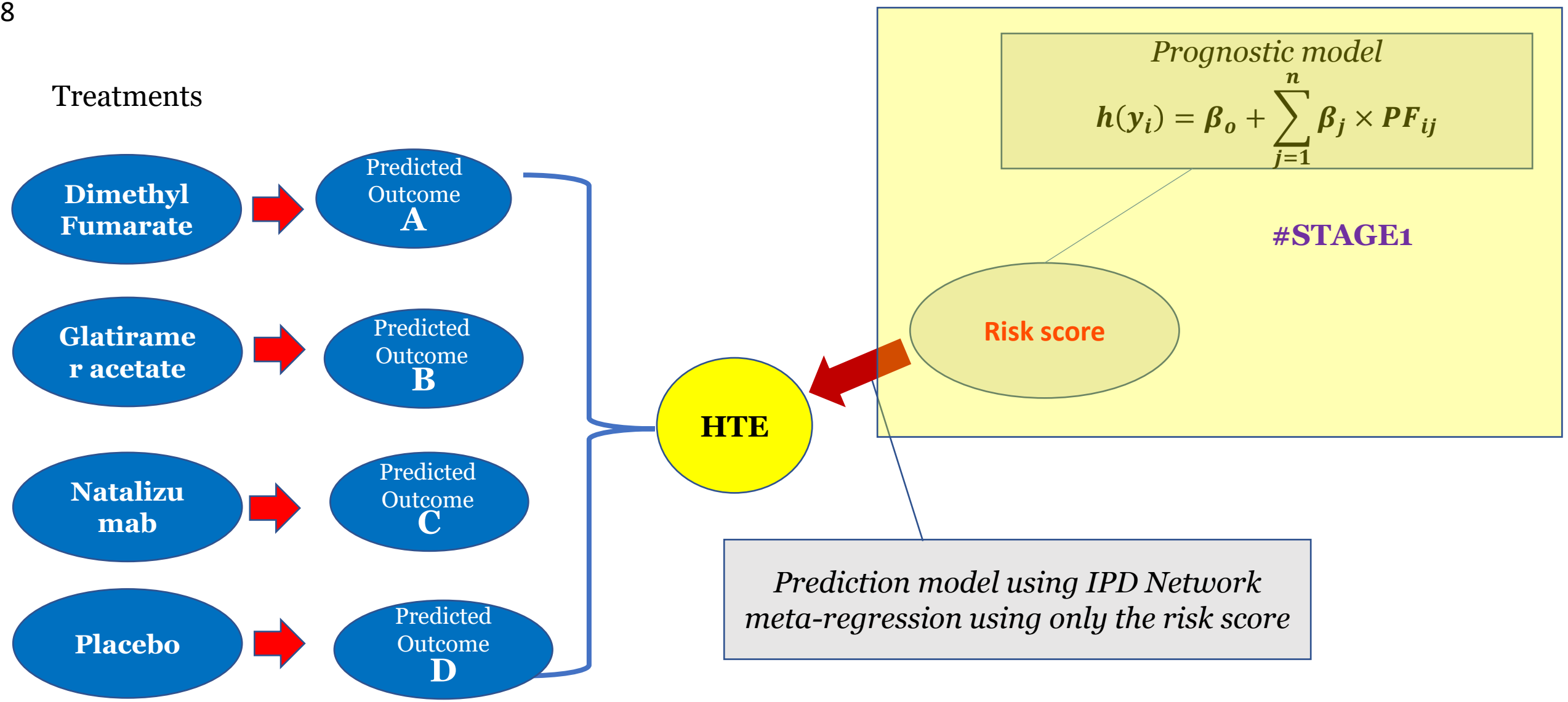
#STAGE1
Risk score
Prediction model using IPD Network meta-regression using only the risk score
#STAGE2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Prediction model using IPD Network meta-regression using only the risk score

Development of prognostic models

Two different prognostic models for comparable reasons

LASSO model

1. Prognostic factors:
Selected via LASSO method

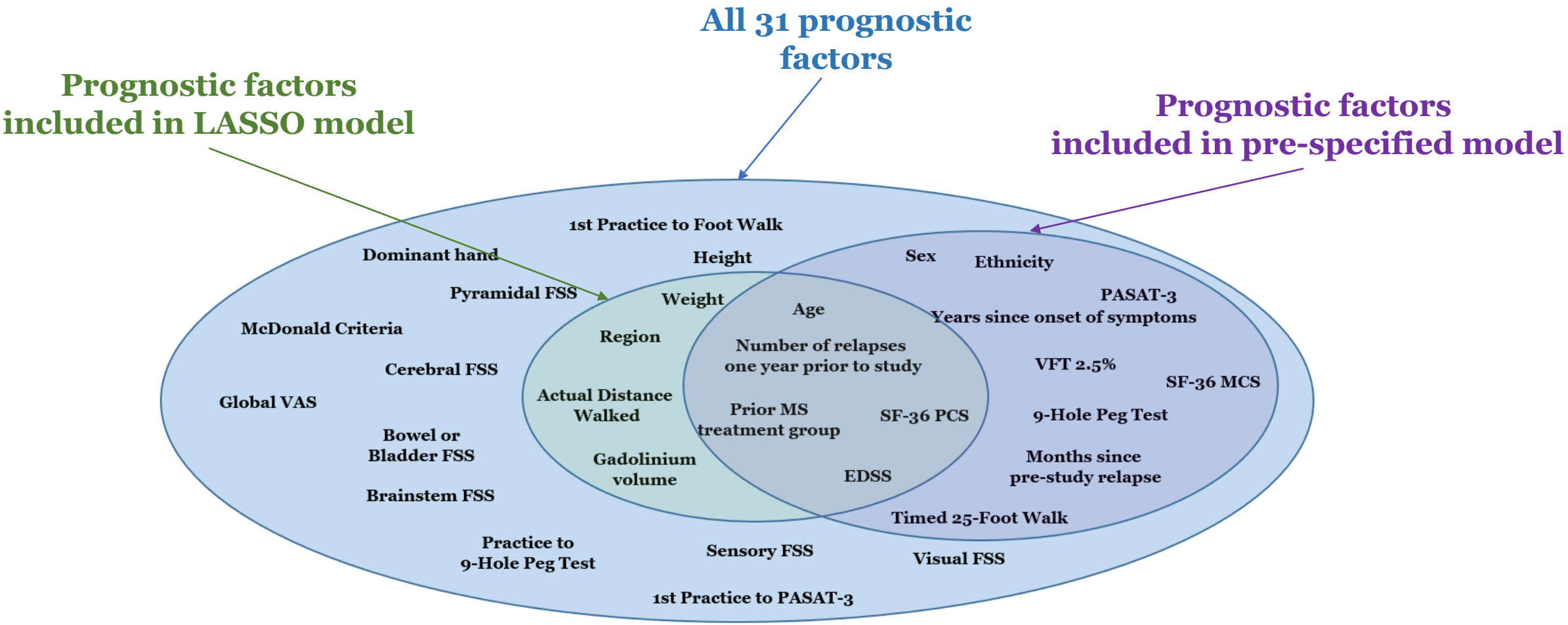
2. Shrinkage of coefficients:
LASSO shrinkage of coefficients

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

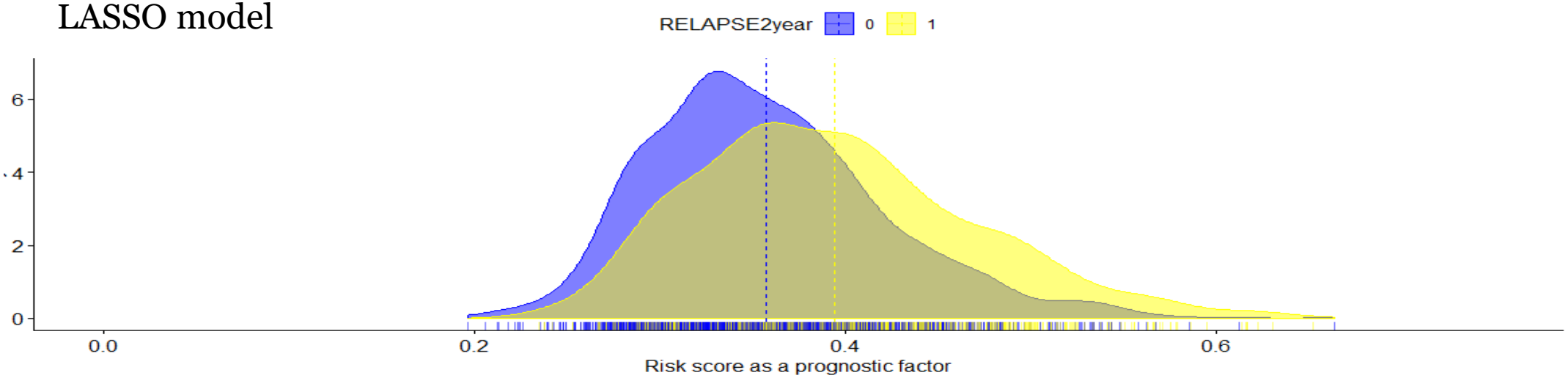
2. Shrinkage of coefficients:
penalized maximum estimation likelihood

Included variables

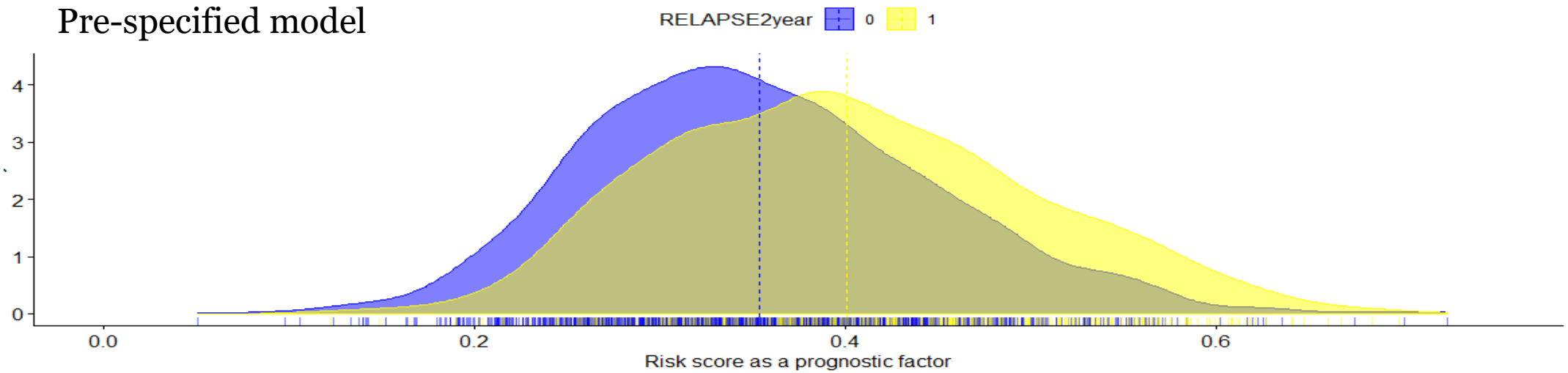


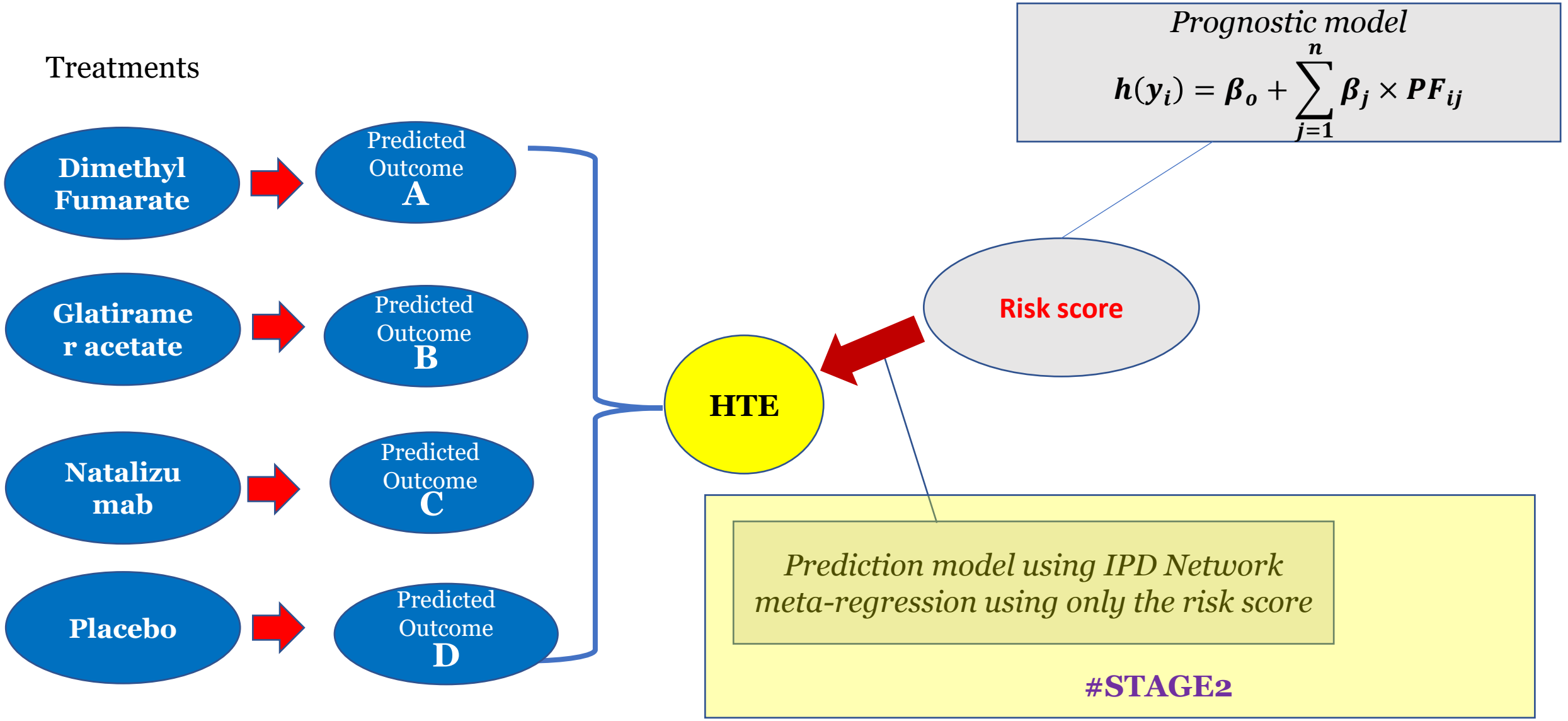
Baseline risk score

LASSO model



Pre-specified model

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#STAGE2

IPD Network meta-regression

Notation

i: Individuals

j: study

k: treatment

b_j: baseline treatment in study j

Likelihood

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

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

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

Saramago et al., 2012

IPD Network meta-regression

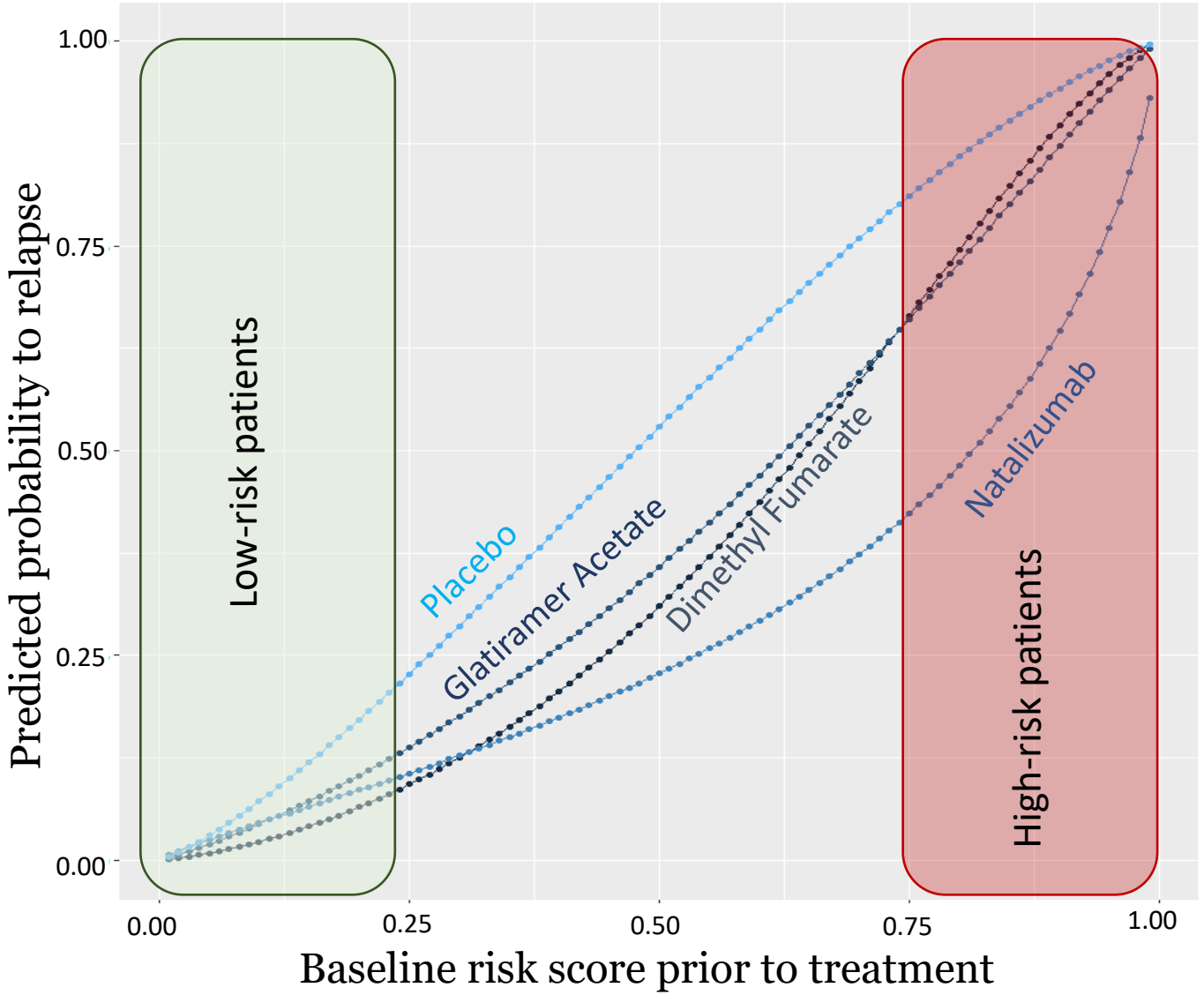
Results: Estimation of model parameters

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

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

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

Predicted relapse rate by baseline risk score



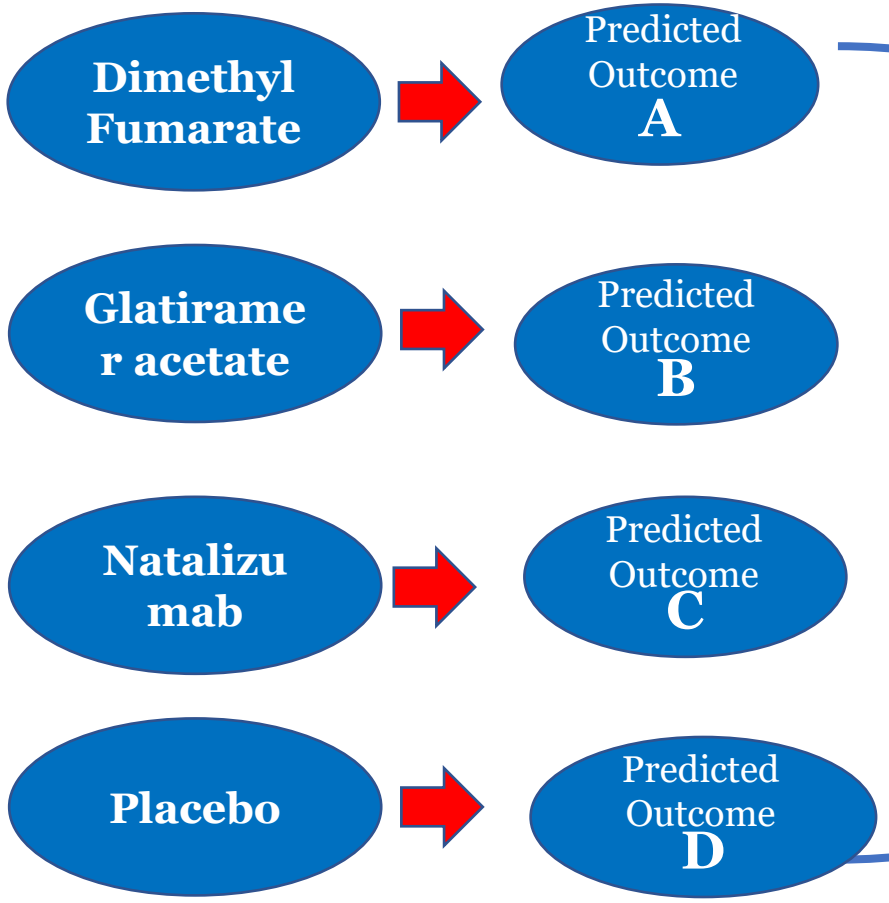
Treatment	Mean	Less than 25% Risk	More than 75%
Natalizumab	29%	12%	48%
Glatiramer Acetate	41%	10%	60%
Dimethyl Fumarate	39%	9%	62%

Best treatment **Dimethyl fumarate - 3% Absolute benefit** compared to Natalizumab

Best treatment **Natalizumab- 14% Absolute benefit** compared to Dimethyl Fumarate

Further research

Treatments



New External Dataset
IPD from Swiss MS Cohort

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

Combination of AD and IPD

Validation methods

26 studies - Published reports (Tramacere, 2018)

R-Shiny app

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