HTx – 4th General Assembly

Budapest, 20-21 April

CS3 Showcase

1

CASE 3
Optimal treatment for relapsing-remitting Multiple Sclerosis (MS)

Setting: *Many treatments with heterogeneous effects, many sources of data*

Georgia Salanti UNIBE

2

One size to fit all

Network meta-analysis is often used to estimate relative effects between *several competing treatments*

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

Outcome: Relapse within the next 2 years (binary) Synthesis of a network of 5 studies (3910 patients)

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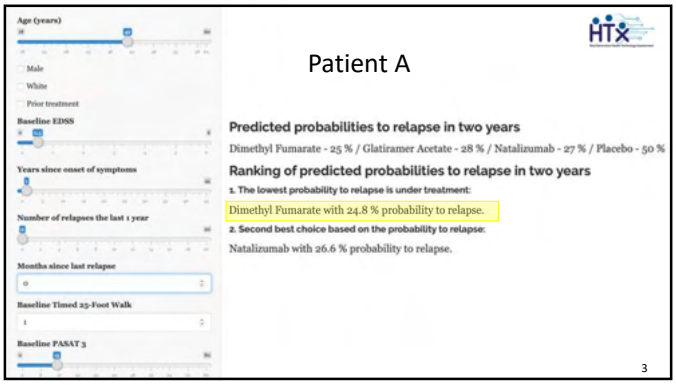

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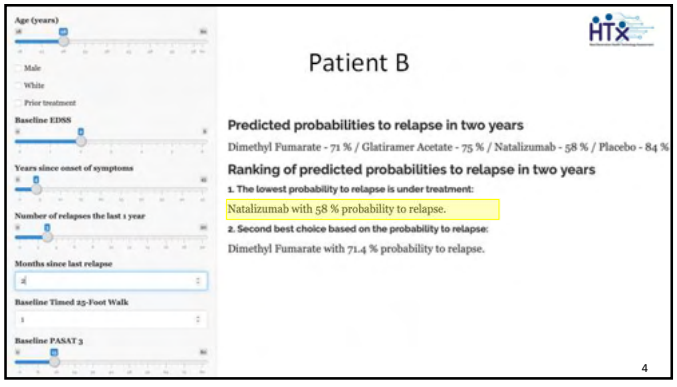

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One size does not fit all

Treatment choice is (or should be) personalised
Not all patients have the same response to the same treatment
Heterogeneous **T**reatment **E**ffects
So, the optimal treatment depends on patients characteristics

2

6

Aim

To develop an evidence synthesis ***prediction model*** to predict the most likely outcome under several possible treatment options while accounting for patients' characteristics in real-world population

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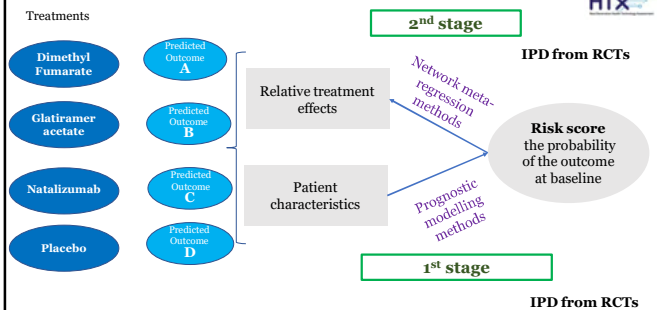
3

7

Predictions for RCTs population



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8

Predictions for RCTs population

R-Shiny app

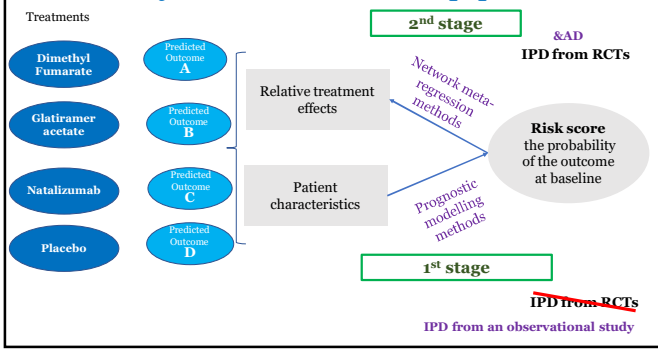
https://cinema.ispm.unibe.ch/shinies/koms/

Published

A two-stage prediction model for heterogeneous effects of treatments

9

Predictions for RCTs and real-world populations



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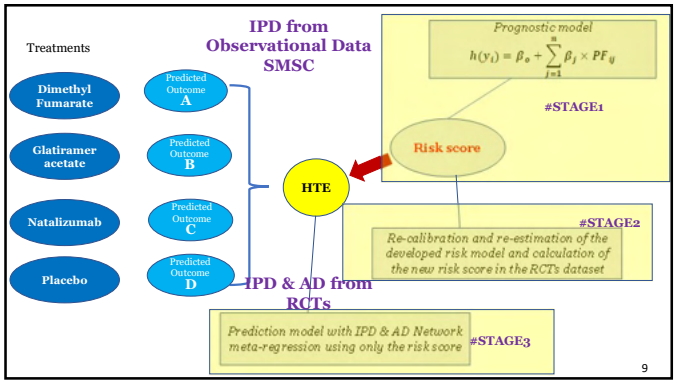
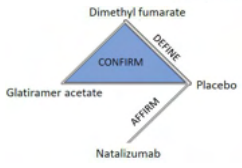


11

Data

Randomized clinical trials (RCTs)

- 3 phase III RCTs - 2990 participants
- Placebo-arms from 9 phase III RCTs 1083 participants
- AD of 2 phase III RCTs
  Glatiramer Acetate vs Placebo



Observational data – Swiss MS Cohort (SMSC)

https://dkf.unibas.ch/en/competencies/registries-cohorts/swiss-ms-cohort/

Started in June 2012, 8 centres in Switzerland
- 1554 patients
- 10'651 visits (median follow-up 5.7 years)

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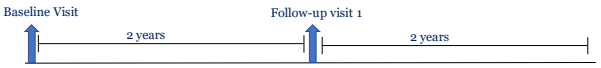
12

Data

Observational data – Swiss MS Cohort (SMSC)

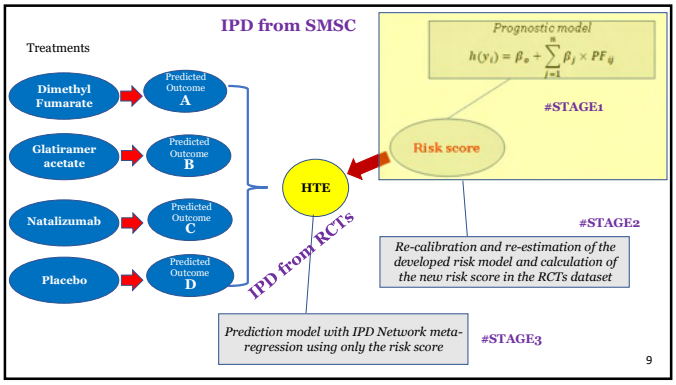
We included only patients with RRMS with at least 2 years of follow-up



Number of follow-up cycles	Number of patients
1	324
2	405
3	206

935 participants were included with 1752 two-year cycles

13



14

Stage 1: Development of the prognostic model

Steps

Step 1	Selection of clinically relevant predictors	Via the literature: 8 previously identified prognostic factors (at least 2 times included in pre-existing prognostic models)
Step 2	Development of the statistical model to estimate the regression coefficients	Logistic mixed-effects model, to account for the repeated measures
Step 3	Sample size efficiency needs to be examined	EPV=13.7 Riley's method: recommended 2084 (we have 1752)
Step 4	Shrinkage of the coefficients needs to be applied to avoid overfitted models	Laplace prior in the Bayesian model to shrink the coefficients
Step 5	In case of missing data, multiple imputations need to be performed to avoid potential bias induced	Multiple Imputations (10 imputed datasets)
Step 6	Internal validation to avoid the risk of misspecification, with methods correcting for optimism	Bootstrap internal validation

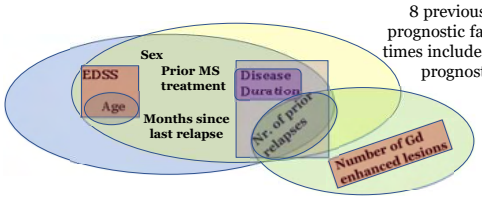
11

15

Stage 1: Development of the prognostic model

Selection of prognostic factors

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



10

16

Stage 1: Development of the prognostic model

Generalized linear mixed effects model – 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

11

17

Stage 1: Development of the prognostic model

Shrinkage

Bayesian shrinkage methods use a prior on the regression coefficients

- O'Hara et al., 2009

Laplace prior distributions for regression coefficients

$$\pi(\beta) = \prod_{k=1}^{p} \frac{\lambda}{2} e^{-\lambda|\beta_k|}, \quad p: number\ of\ regression\ coefficients$$

- Genkin et al., 2007

Small coefficients → **towards zero faster**

Large coefficients → **smaller shrinkage**

12

18

Stage 1: Development of the prognostic model

Missing data - Multilevel Joint Modelling Multiple Imputations

4 prognostic factors with missing data

Steps

1. Check for **auxiliary variables** – **1 variable was identified and used as auxiliary**
2. Creation of 10 imputed datasets – Use of the same model (i.e. the substantive one) to impute the datasets – `mitml` R-package
3. Application of the Bayesian model to all 10 imputed datasets
4. Pooled estimates via Rubin's rules for m imputed datasets

13

19

Stage 1: Development of the prognostic model

Estimated coefficients

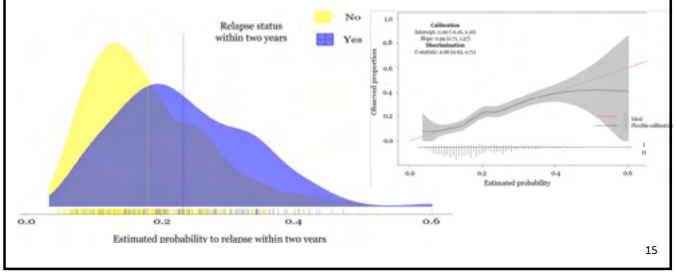
Parameters	β_k	OR	95% CrI
Age	-0.035	0.97	(0.95, 0.98)
Disease duration	0.337	1.40	(0.90, 2.18)
EDSS	0.122	1.13	(1.02, 1.25)
Number of gadolinium enhanced lesions (>0 vs 0)	-0.034	0.97	(0.69, 1.36)
Number of previous relapses (1 vs 0)	-0.070	0.93	(0.69, 1.26)
Number of previous relapses (2 or more vs 0)	0.133	1.14	(0.81, 1.61)
Months since last relapse	-0.478	0.62	(0.49, 0.78)
Treatment naïve (Yes vs No)	0.086	1.09	(0.80, 1.49)
Gender (Female vs Male)	0.254	1.29	(0.97, 1.72)
On treatment (Yes vs No)	-0.221	0.80	(0.50, 1.27)

15

20

Stage 1: Development of the prognostic model

Internally validated with bootstrap method
AUC=0.65



15

21

Stage 1: Development of the prognostic model

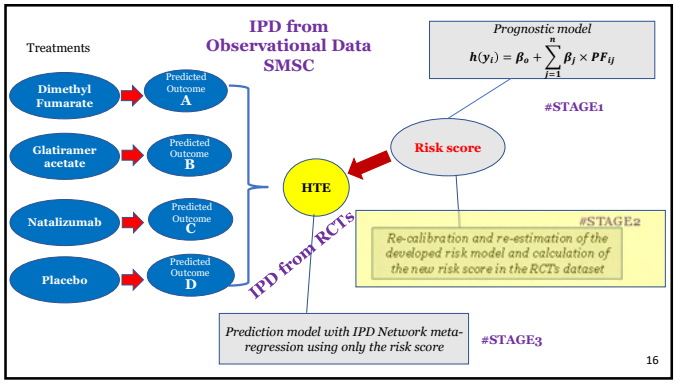
R-Shiny app

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

Published

Development, validation and clinical usefulness of a prognostic model for relapse in relapsing-remitting multiple sclerosis

22



16

23

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

Aim

To 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)	0.50
Update intercept and coefficients (Re-calibration)	0.57
Model revision (Re-calibration & selective re-estimation)	0.61

17

24

Stage 1: Development of the prognostic model
Update

Re-calibration & selective re-estimation

$$lp_{new} = a_{new} + \beta_{overal} \times lp_{previous} + \gamma_{p,pvalue\leq 0.05} \times X_{p,pvalue\leq 0.05}$$

lp_{new}: new linear predictor

a_{new}: re-calibrated intercept

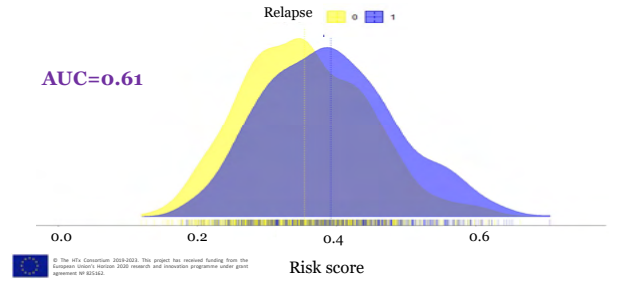
β_{overal}: updated calibration slope

$lp_{previous}$: previous linear predictor

$\gamma_i = \beta_i - \beta_{overal} \times lp_{previous}$, for i = 1, 2, .., p factors

25

Risk of relapse in two years in RCTs



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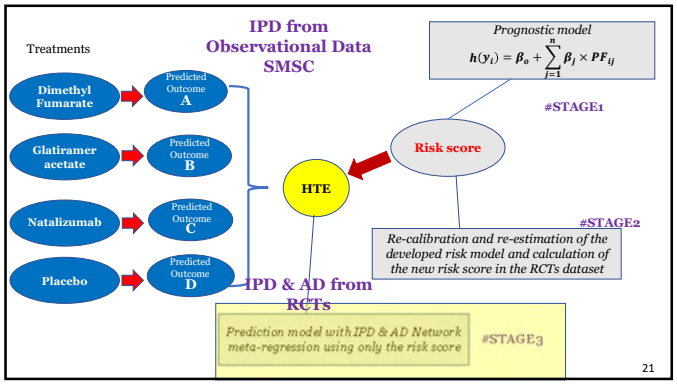
26



21

27

Stage 3: IPD & AD Network Meta-regression

i: Individuals

j: study

t: treatment

h_j: baseline treatment in study j

Part 1 – IPD only

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

$$logit(p_{ijt}) = \begin{cases} u_j + g_0 \times \left(logit(R_{ij})\right) \; if \; t = h_j \\ u_j + d_{jh_jt} + (g_0 + g^W{}_{jh_jt}) \times \left(logit(R_{ij})\right) + (g^B{}_{jh_jt} - g^W{}_{jh_jt}) \times \left(\overline{logit(R_{ij})}^j\right), if \; t \neq h_j \end{cases}$$

Part 2 – AD only

$$r_{jt} \sim Binomial(p_{jt}, n_{jt})$$

$$logit\left(p_{jt}\right) = \begin{cases} u_j \\ u_j + d_{jh_jt} + g^B{}_{jh_jt} \times \left(\overline{logit(R_j)}^j\right), if \; t \neq h_j \end{cases}, if \; t = h_j$$

g_0 : Individual level covariate regression term for Risk / the impact of Risk as prognostic factor

d_{jh_jt}: the treatment effect of treatment t versus placebo / ***fixed effect***

$g^W{}_{jh_jt}, g^B{}_{jh_jt}$: The within and the between study effect modifiers. Different for each treatment vs study's control / the impact of Risk as effect modifier

Saramago et al., 2012 22

28

Stage 3: IPD & AD Network Meta-regression
Missing study-level covariates

If the mean (here continues) covariate values are reported in all studies with AD, the risk score of study j:

$$\overline{logit(R_{.j})} = \beta_0 + \beta_1 \times \overline{x_{1j}}^j + \beta_2 \times \overline{x_{2j}}^j + \cdots + \beta_{np} \times \overline{x_{npj}}^j$$

Many times, published studies do not report the required study-level covariates

Estimation of $\overline{R_{.j}}$ difficult.

29

Stage 3: IPD & AD Network Meta-regression

Estimated parameters from network meta-regression model	Mean (95% CrI)
OR of relapsing for one unit increase in logit-risk (e^{γ^0})	2.73 (2.02, 3.72)
OR of relapsing under DF vs placebo ($e^{\delta_{DF}}$)	0.43 (0.32, 0.56)
OR of relapsing under GA vs placebo ($e^{\delta_{GA}}$)	0.51 (0.34, 0.80)
OR of relapsing under N vs placebo (e^{δ_N})	0.28 (0.21, 0.38)
OR of relapsing under DF vs placebo for one unit increase in logit-risk ($e^{\gamma^W_{DF}}$)	0.88 (0.46, 1.67)
OR of relapsing under GA vs placebo for one unit increase in logit-risk ($e^{\gamma^W_{GA}}$)	0.72 (0.28, 1.85)
OR of relapsing under N vs placebo for one unit increase in logit-risk ($e^{\gamma^W_N}$)	0.60 (0.30, 1.19)

30

Stage 3: IPD & AD Network Meta-regression
Predictions

We can predict the probability to experience the outcome, $logit(p_{i_{new}})$, in treatment arm t, for any new patient i_{new}:

$$logit(p_{i_{new}}) = a + \delta_t + (\gamma_0 + \gamma_t^W) \times logit(R_{i_{new}}) + (\gamma_t^B - \gamma_t^W) \times (\overline{logit(R)})$$

The values for δ_t, γ_t^W, and γ_t^B, are those estimated in the third stage of the network meta-regression prognostic model and $logit(R_{i_{new}})$ can be estimated using the observed covariate values of patient i_{new} and the estimated regression coefficients in stage 2.

31

Stage 3: IPD & AD Network Meta-regression
Predictions

$$logit(p_{i_{new}}) = a + \delta_t + (\gamma_0 + \gamma_t^W) \times logit(R_{i_{new}}) + (\gamma_t^B - \gamma_t^W) \times (\overline{logit(R)})$$

What data to use to obtain values for a, the logit-probability of the outcome under the reference treatment (placebo, in our example), $\overline{logit(R)}$, the mean of logit baseline risk across all individuals, and γ_0, the coefficient of the baseline risk, depend on the context within which we plan to make predictions.

For example, if we want to make predictions for the ***Swiss real-world population*** we could estimate a and γ_0 by using placebo patients from the SMSC and $\overline{logit(R)}$ as the mean of $logit(R_i)$ across all individuals in the SMSC.

If we want to make predictions for the ***RCTs population***, we can estimate a and γ_0 by synthesizing data from RCT placebo arms and $\overline{logit(R)}$ as the mean of $logit(R_i)$ across all individuals in IPD RCTs.

32

Real-world and RCTs population predictions

R-Shiny app

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

Ongoing work

Combining randomised and non-randomized data to predict heterogeneous effects of multiple treatments

33

Stage 3: IPD & AD Network Meta-regression
Results: Predictions for RCTs population

Treatment effects	Treatment	All patients	Baseline Risk <25% Low-risk patients	Baseline Risk >50% High-risk patients
Absolute benefit of active drug vs placebo (%) (95% CrI)	Dimethyl fumarate	45 (33, 58)	21 (10, 40)	65 (49, 78)
	Glatiramer acetate	50 (38, 62)	24 (12, 46)	70 (58, 78)
	Natalizumab	33 (20, 48)	21 (10, 42)	42 (24, 61)
OR of active drug vs placebo (95% CrI)	Dimethyl fumarate	0.43 (0.31, 0.61)	0.43 (0.27, 0.69)	0.43 (0.27, 0.68)
	Glatiramer acetate	0.52 (0.39, 0.72)	0.52 (0.35, 0.87)	0.53 (0.39, 0.68)
	Natalizumab	0.28 (0.19, 0.42)	0.46 (0.28, 0.76)	0.17 (0.09, 0.30)

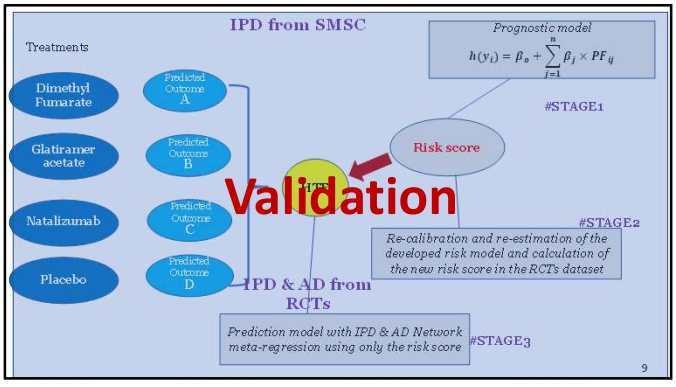
24

34

Baseline characteristics of participants

Study	Treatment	Number of patients	Number of patients experiencing relapse at two years (%)	Mean age (sd)	Number of females (%)	Mean baseline EDSS score (sd)	Mean Baseline risk (prior to treatment) (95%CrI)
SMSC	Total	935	[illegible]	40.8 (11.2)	631 (67.5)	2.3 (1.4)	20.1 (2.8, 37.5)
AFFIRM	Total	939	[illegible]	36.0 (8.3)	657 (70.0)	2.3 (1.2)	36.5 (18.8, 54.1)
	Natalizumab	627	[illegible]	35.6 (8.5)	449 (71.6)	2.3 (1.16)	
	Placebo	312	[illegible]	36.7 (7.8)	208 (66.7)	2.3 (1.19)	
CONFIRM	Total	1417	[illegible]	37.3 (9.3)	993 (70.1)	2.6 (1.2)	37.2 (18.6, 55.7)
	Dimethyl fumarate	703	[illegible]	37.8 (9.4)	495 (70.4)	2.5 (1.2)	
	Glatiramer acetate	351	[illegible]	36.7 (9.1)	247 (70.3)	2.6 (1.2)	
	Placebo	363	[illegible]	36.9 (9.2)	251 (69.1)	2.6 (1.2)	
DEFINE	Total	1234	[illegible]	38.5 (9.0)	908 (73.6)	2.4 (1.2)	36.9 (17.7, 56.0)
	Dimethyl fumarate	826	[illegible]	38.5 (9.0)	602 (72.9)	2.4 (1.2)	
	Placebo	408	[illegible]	38.5 (9.1)	306 (75)	2.5 (1.2)	
Placebo arms dataset	Placebo	1083	[illegible]	41.2 (10.3)	752 (69.4)	NA	NA

35



36

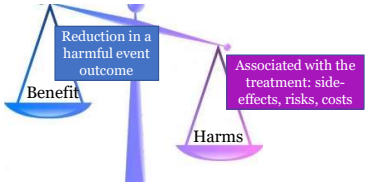
Aim

Extension of decision curve analysis methods into a network meta-analysis framework

37

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

38

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

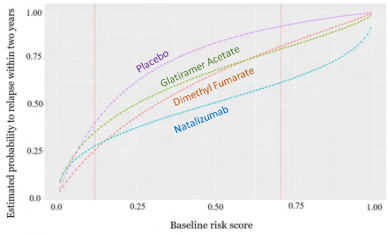
$\pi_{s,j}$ the proportion of patients treated with treatment j under strategy s

T_j the thrsehold values chosen for treatment j

39

Case study

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



40

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

41

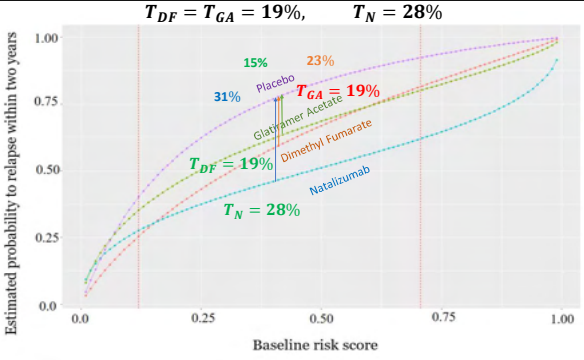
Reaching treatment recommendations when we have multiple options via a model

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

Decision rule

For a patient i, the recommended treatment j under the prediction model is the one that satisfies $max\{RD_{i,j} - T_j\}$, 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

42



43

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**	

44

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

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

45

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, $\hat{\pi}_{s,j} = p_{s,j}^{Data_s}$

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

46

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

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

47

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 $\hat{\varepsilon}_{s,j} = \hat{\varepsilon}_{s,0} \times RR_j^{Data_s}$

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

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

48

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

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

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

49

$T_{DF} = T_{GA} = 19\%, \quad T_N = 28\%$

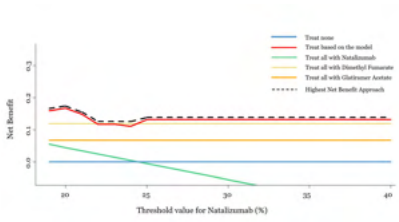
Approach	Net Benefit
Treat nobody	0.000
Treat all patients with Natalizumab	0.025
Treat all patients with Dimethyl Fumarate	0.030
Treat all patients with Glatiramer Acetate	0.019
Treat patients according to the prediction model	0.050

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"

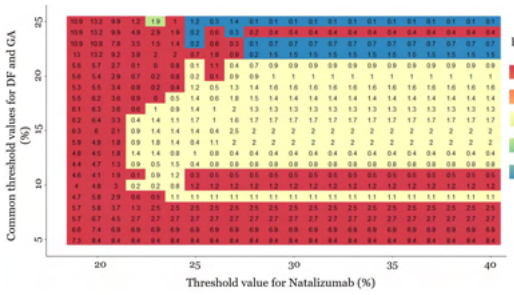
50

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

$T_{DF} = T_{GA} = 20\%$,
$T_N = 20\%$ *to* 40%



51



52

DCA in network meta-analysis prediction models

53

Additional work in CS3

Submitted *In Research Synthesis Methods journal*
Available in Arxiv

The package was submitted

The package was submitted to R-CRAN (now ti is available in GitHub)

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54

Discussion

- Our framework can inform the clinical practice and the decision making as allows individualized treatment recommendations
- It can combine all the relevant information via several data sources and can be applied to any health-condition and include as many treatments as required
- The application on RRMS is not ready for use:
  - ➢More IPD RCTs are needed to include all treatment options available
  - ➢The model needs to be externally validated
  - ➢The patient relevant threshold values T need to be defined (e.g., through a survey)

55

Ongoing work in CS3

- Cost-effectiveness analysis

Thank you!

56