Model (PHREND®) for personalized prediction of treatment response in relapsing remitting multiple sclerosis (RRMS)

E. Stihler, F. Lionetto, Y. Heer, Tozzi V., P. Kassraian-Fard, E. Jules, P. van Hövell – PwC, Digital Services, Data and Analytics, Switzerland
S. Braune, A. Bergmann – NeuroTransData (NTD) GmbH, Germany

Project goals

- In multiple sclerosis (MS), treatment decision is currently based on intuition from physicians.
- "Trial and error" takes up time, is cost intensive and accelerates the disease progression.
- Patients have a desire to get a second opinion on which treatment could work best for them based on the experience from similar patients.
- "Intuitive" decision by physicians.
- Based on non-personalized study results.

Variables of interest

- ESS
- V1, V2, V3, V4
- Today
- 2-4 years from today
- Indicators of treatment response
  1. Which treatment can reduce the number of on-therapy relapses?
  2. Which treatment can reduce the probability of an on-therapy confirmed disease progression (CDP) based on the ESS value?

Real-world evidence (RWE) data

- Since 2008 a Germany-wide network of physicians has maintained a database that currently documents more than 20,000 MS patients.
- The number of patients represents approx. 15% of the total market of MS patients in Germany (cf. Vfa 2014).
- The database contains demographic data, such as patient’s age and gender, as well as clinical data, such as patient’s quality of life, diagnosis, treatments, side effects, rationale for a change of treatment, and several others – over 10,000 variables in total.
- On average: >3 visits V1 per patient per year and 5 years observation period per patient.
- The database is active and with every half a year 5000 entries are newly added.
- In total, more than 20,000 therapy cycles.

Business application

- Input from physician: currently 12 easy-to-enter variables summarising the patient’s profile.
- Options: desired prediction period.
- Number crunching: predictive model used to provide two indicators of treatment response for all disease modifying MS-treatments (if sufficient RWE data is available).
- Output: probability of being relapse-/CDP-free + confidence interval for all available treatments.
- User friendliness: model embedded in an enhanced tool to better guide the patient/physician communication and decision.

Calculation

- How well do predictions compare to observations?
- Generalisability: can the model be successfully applied to new data?
- Leave-one-out cross-validation;
- Validation on test set
- Comparison to benchmark models of decreasing complexity: is the knowledge of the patient’s profile improving the predictions?
- Empirical test of the predicted treatment benefit: do patients profit from adhering to the recommendation?
- Robustness: is the model sensitive to different choices of the priors, to the characteristics of the patient population and to the sample size?
- Quality of predictions assessed using the following statistical measures: mean squared error (MSE), log-likelihood, and Harrell’s concordance statistic (C-Index).

Results and future prospects

Further developments

- Model refinement and extension (new variables and indicators of treatment response)
- Collection of new data
- Analysis of collected data on therapy decision

Status

- Currently in beta testing phase
- Roll out to German doctors’ offices in 2018
- Results to be published in a scientific journal (in progress)
- Web-based App CE certified as medical device

Key success factors

- From doctors for doctors
- Use of RWE data
- Impact size
- Independence
- Living model
- Scalability to other diseases

Model performance assessment

- Calibration: how well do predictions compare to observations?
- Generalisability: can the model be successfully applied to new data?
- Leave-one-out cross-validation;
- Validation on test set
- Comparison to benchmark models of decreasing complexity: is the knowledge of the patient’s profile improving the predictions?
- Empirical test of the predicted treatment benefit: do patients profit from adhering to the recommendation?
- Robustness: is the model sensitive to different choices of the priors, to the characteristics of the patient population and to the sample size?
- Quality of predictions assessed using the following statistical measures: mean squared error (MSE), log-likelihood, and Harrell’s concordance statistic (C-Index).

Modelling approach

- Predictive models based on the assumption that:
  1. the number of on-therapy relapses follows a negative binomial distribution;
  2. the CDP follows a binomial distribution.
- Hierarchical generalized linear models (GLM) are employed for both indicators of treatment response, with model parameters depending on patient’s profile and treatment.
- The correlation between measurements coming from the same clinical site is incorporated through random effects.
- The duration of the therapy cycles is included as an offset term.
- Bayesian inference preferred due to the possibility of specifying (weakly informative) priors and preventing overfitting.

Calibration

- How well do predictions compare to observations?