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

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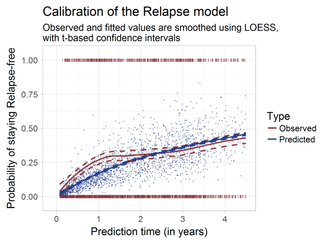
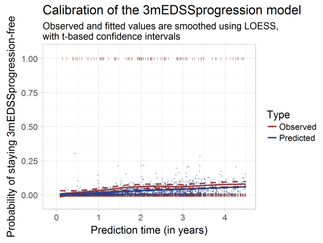
Background: Therapeutic decisions in RRMS have become a complex task as many disease modifying therapies (DMTs) with different benefit/risk ratios are available. Clinical study data do not match individual patient characteristics and can not cover all possible efficacy comparisons. Advanced statistical models were developed to utilize real-world evidence data for personalized prediction of treatment outcome in different DMTs for individual RRMS patients.

Aim: Development of a tool based on statistical models to support therapy decisions by providing individualized probabilities for freedom of relapse and freedom of 3-months-confirmed-EDSS-progression (3mCEP)*. These predictions are provided for each DMT based on individual clinical RRMS history and other characteristics of single RRMS patients.

Methods: **PHREND® (Predictive Healthcare with Real-world-Evidence in Neurological Disorders)** is based on:
Data base: NeuroTransData MS registry from 2009 onwards, data extracted from overall 18947 adult RRMS patients with an initial EDSS <6.5 and with therapies initiated later than 6 months after diagnosis of RRMS, identifying 2354 DMT therapy cycles.
Parameters employed in the models: age, gender, duration of RRMS, previous therapy and its duration, indicator if one of the two previous therapies was second line, EDSS total score, number of relapses within last 12 months, time since last relapse.
Outcome parameters: probability of freedom of relapse activity and of 3-month-confirmed-EDSS-progression (3mCEP)*
Predictive mathematical models are based on the assumption, that EDSS progressions follow a binomial and the number of relapses a negative binominal distribution. Generalized linear models are employed for both efficacy responses using Bayesian inference, integrating cluster effects for the multiple doctor centers and variable duration of therapies in the database. Models were evaluated with 10-fold cross-validation. 10% of available data were used only for data validation. Mean square error of the forecast (Brier score) and Harrell's concordance-index mark quality of prediction. Comparative prognostic models based on relapse rate and EDSS progression were implemented for benchmarking.
* Definition 3mCEP: lasting EDSS increase associated with a relapse. Confirmed progression is assumed if EDSS increase is reproduced at least 3 months later. EDSS increase is defined as at least 1 point if EDSS ≤ 5.5, as at least 0.5 point if EDSS >5.5

Calibration of prediction: (Brier score)

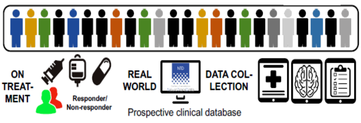




Validity of prediction

Harrell's concordance-index (**C-Index**) (0.0 = no discrimination, 1.0 = perfect discrimination)
Brier Score **(BS)** (0.0 = perfect prediction, 1.0 = no prediction)

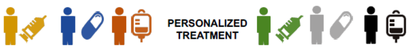
	Training set		Cross-Validation set		10% test data	
Prediction	C-Index	BS	C-Index	BS	C-Index	BS
relapse-free	0.67±0.00	0.18±0.01	0.61±0.04	0.19±0.01	0.61±0.04	0.19±0.02
3mCEP-free	0.73±0.01	0.04±0.01	0,56±0.11	0.04±0.01	0.41±0.11	0.04±0.01

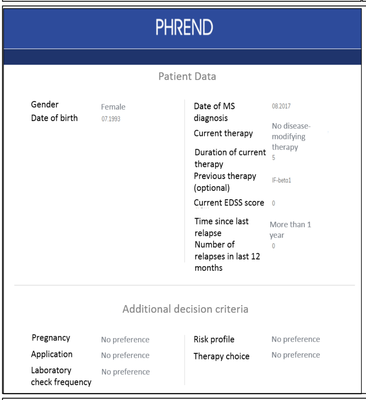


From qualified, living RWE-registry data .....

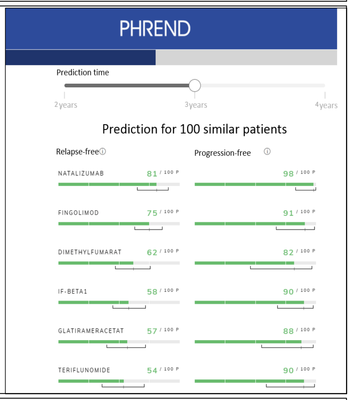
..... by advanced statistical methods and machine learning

..... to personalized optimal treatment efficacy





Results:
Based on individual patient history, PHREND® calculates a prediction for each available DMT regarding probability of freedom of relapse activity and of 3mCEP for selectable yearly periods between 2 and 4 years. Results are presented in a hierarchical manner.
Range of results is communicated by underlying bars indicating 95% credible intervals of each predictive calculation.
Graphical presentation supports the comparison of available DMT options to support the shared decision process between treating physician and patient. The joint decision is selected and documented for electronic storage or printout.



Summary: Qualified real-world-evidence data of the NTD MS registry and advanced statistical methods enable robust validated prediction of the probability of being relapse- or 3mCEP-free over a prospective period up to 4 years for available DMTs in RRMS based on patient's individual RRMS history. **PHREND® (Predictive Healthcare with Real-world Evidence for Neurological Disorders)** supports transparently the shared decision process between treating physician and patient to find the individually best-performing/ most effective DMT to continue after failure of the current therapy. PHREND® shall improve control of disease activity, allocation of resources and cost efficacy of medical care. Additional studies are in progress that address further internal and external validation of these results.

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