Individualized treatment effect was predicted best by modeling baseline risk in interaction with treatment assignment

# Abstract

Our objective was to compare different risk-based methods for optimal prediction of individualized treatment effects from RCTs.

We simulated RCT data using diverse assumptions for the average treatment effect, a baseline prognostic index of risk (PI), the shape of its interaction with treatment (none, linear, quadratic or non-monotonic) and the magnitude of treatment-related harms (none or constant independent of the PI). The combination of these settings resulted in the definition of 648 simulation scenarios. In each sample we predicted absolute benefit using: models with a constant relative treatment effect; stratification in quarters of the PI; models including a linear interaction of treatment with the PI; models including an interaction of treatment with a restricted cubic spline (RCS) transformation of the PI; an adaptive approach using Akaike’s Information Criterion. We evaluated predictive performance using root mean squared error and measures of discrimination and calibration for benefit.

The linear-interaction model and the RCS-interaction model outperformed the constant treatment effect model in many simulation scenarios. The RCS-model was optimal when quadratic or non-monotonic deviations from a constant treatment effect were stronger, and when sample size was larger. Larger sample size also supported the adaptive approach. All the simulation results can be explored at <https://arekkas.shinyapps.io/simulation_viewer/>. We also illustrated the appliaction of the considered methods in the GUSTO-I trial, which confirmed our simulations’ findings.

In conclusion, an interaction between baseline risk and treatment assignment should be considered to improve treatment effect predictions. Non-linear interactions should be considered only in larger sample sizes.