

ORAL PRESENTATION

Open Access

Prediction of treatment benefit in high-dimensional cox models via gene signatures in randomized clinical trials

Nils Ternès^{1,2*}, Federico Rotolo^{1,2}, Georg Heinze³, Stefan Michiels^{1,2}

From 3rd International Clinical Trials Methodology Conference
Glasgow, UK. 16-17 November 2015

Background

Stratified medicine seeks to identify gene signatures predicting whether a patient will benefit from a treatment. We evaluated several approaches to identify such signatures using high-dimensional Cox models in randomized clinical trials (RCT).

Methods

We investigated four approaches: penalize biomarker main effects and biomarker-by-treatment interactions using a lasso penalty (*full-lasso*); control of main effects by principal components or ridge penalty, and lasso on interactions (*sPCA+lasso* or *ridge+lasso*); and '*modified covariates*' in a penalized regression model (Tian et al. 2014). We performed simulations under null and alternative scenarios by varying the sample size n , number of biomarkers H , number of true main effects or treatment-modifiers, effect sizes and correlations. We proposed two novel measures of treatment effect prediction for gene signatures: a difference in C-indices and a Wald-based interaction statistic. We used gene expression data from a RCT of adjuvant chemotherapy in non-small cell lung cancer ($n=133$) for illustration.

Results

When $n=500$ and $H=20$ or 100, methods performed similarly in null scenarios apart from the *full-lasso* that gives poor results in presence of main effects only. In alternative scenarios: the *ridge+lasso* and the *full-lasso* predicted well the treatment benefit for future patients; the *modified covariates* approach performed poorly when also main effects were present. More extensive simulation results will be presented. In the lung cancer

trial, the *full-lasso* and the *ridge+lasso* selected a gene signature with four and seven treatment-modifiers.

Conclusion

Preliminary results suggest that *ridge+lasso* and *full-lasso* are promising approaches in high-dimensional Cox models to predict the treatment benefit.

Authors' details

¹CESP, INSERM U1018, Paris-Sud Univ., Villejuif, France. ²Gustave Roussy, Service de biostatistique et d'épidémiologie, Villejuif, France. ³Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Vienna, Austria.

Published: 16 November 2015

doi:10.1186/1745-6215-16-S2-O86

Cite this article as: Ternès et al.: Prediction of treatment benefit in high-dimensional cox models via gene signatures in randomized clinical trials. *Trials* 2015 16(Suppl 2):O86.

Submit your next manuscript to BioMed Central
and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit



¹CESP, INSERM U1018, Paris-Sud Univ., Villejuif, France

Full list of author information is available at the end of the article