ESR Researcher Project: Non-technical Summary

"Development of a biomarker score to identify a subgroup of treatment responders"

Team: Nicolas Ballarini, Martin Posch

An important objective in the development of personalized medicines is the identification of patient subgroups which are more likely to benefit from an experimental treatment. If such subgroups can be identified at an early stage of development, this will lead to a more efficient drug development overall. If the heterogeneity of the treatment effect is ignored this could result in stopping the development of a useful treatment due to a dilution of the treatment effect in the full population.

Recent developments in subgroup analysis consider subgroups that are defined in terms of a score, also called the predicted individual treatment effect, which in turn may depend on multiple biomarkers. This measure indicates the difference on outcome for each subject should she receive the experimental treatment instead of the control one. In our work, we study the properties of different modelling strategies to estimate the predicted individual treatment effect. These strategies take into account that there may be a large number of potential markers to define subpopulations, but only few biomarkers may be useful. Using state-of-the-art inferential techniques, we were able to derive both point estimates and confidence intervals for the predicted individual treatment effect, which is challenging when biomarkers are selected to define the final statistical model. We evaluated the performance of using the predicted individual treatment effect and its confidence intervals to identify subgroups where a novel treatment leads to better outcomes compared to a control treatment.

Part of our work centered in the communication of results of subgroup analyses in general. Graphical approaches play a key role in subgroup analyses to visualize effect sizes of subgroups, aid identification of groups that respond differentially, and communicate the results to a wider audience. However, many existing approaches do not capture the core information and/or are prone to lead to misinterpretation of subgroup effects. Therefore we also performed an extensive review in which we critically appraised existing visualization techniques. We proposed useful extensions to current approaches to increase their utility and attempted to develop an effective visualization approach. Our work can help to make effective graphics in the subgroup analysis setting.

Finally, we also explored techniques to optimize clinical trials that are conducted in multiple stages and consider a pre-specified subgroup for investigation, in addition to the overall population. This type of techniques are encapsulated in the confirmatory subgroup analysis framework. Our work may help statisticians to define how many patients should be enrolled

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.

in the study, what is the best sample allocation, and to choose the optimal testing strategy when analysing the data in such situations.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.