Nicolás Ballarini

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PhD Thesis:	Development of a biomarker score to identify a subgroup of treatment responders
Project title:	IDEAS: Improving Design, Evaluation and Analysis of early drug development Studies

Project description:

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. A major statistical challenge is the vast number of potential subgroups that can be built by biomarkers and their combination, e.g. next generation sequencing offers a prohibitively large number of potential markers to define subpopulations. The development of a biomarker score will be structured in subgroup identification and subgroup confirmation steps that will be integrated in a comprehensive framework. For the subgroup identification step we will use large scale multiple testing procedures controlling the false discovery rate, model selection tools as the Lasso combined with unsupervised statistical learning algorithms to define biomarker scores. To make efficient use of clinical trial data information from multiple endpoints (clinical and surrogate endpoints) will be used to measure the treatment effect in different subgroups. We will consider both, dichotomous and continuous endpoints and biomarkers and address the optimal choice of thresholds on the biomarkers to define subgroups. More generally, the sensitivity to identify treatment responders correctly will be taken into account.

To integrate subgroup identification and confirmation in a unified framework, special focus will be given to enrichment designs, with an adaptive interim analysis that allows restricting recruitment in the second stage to subpopulations identified in the first stage data. In settings where a large number of hypothesis are tested, such designs have shown to be superior to fixed sample designs and we expect that similar gains in efficiency can be obtained in the determination of subgroups. To address the risk to restrict the population too early such that not all patients benefiting from a drug are correctly identified, we will apply a Bayesian decision-theoretic approach to evaluate how much evidence is needed to drop a subgroup or to decide to carry it forward to the next development phase.