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Università Commerciale Luigi Bocconi

**Department of Decision Sciences**

Statistics Seminar

# Towards stratified medicine - instead of dichotomization, estimate a treatment effect function for a continuous covariate

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## Abstract

Given the enormous amount of resources spent on conducting large clinical trials, it is surprising that greater efforts are not made to try to extract more information from the resulting data (1). Investigations are hampered by well-known problems of multiplicity, resulting in inflated type I error probabilities and biased estimates resulting from data-dependent model building. The restrictive role of regulators may make matters worse. However, to improve treatment research, exploratory analyses using sophisticated statistical analysis methods are definitely required.
In RCTs, potential interactions between treatment and prognostic factors are important essential ingredients of stratified medicine, rather than assuming that 'one size fits all'. When a covariate is continuous (such as age or hormone receptor level), such interactions are often sought by crude and inadequate statistical methods, typically involving dichotomizing the continuous covariate (2). Sometimes, treatment effects are compared in derived subgroups; the results often depend on the cut-point chosen (3). Methods that keep all the information in the covariate are considerably more powerful than dichotomization. The Subpopulation Treatment Effect Pattern Plot (STEPP) and MFPI, an extension of the multivariable fractional polynomial (MFP) approach, are two strategies recently proposed (3,4,5,6). The latter tests for an interaction between treatment and a continuous covariate and estimates a continuous treatment effect function. It also allows adjustment for other covariates.
Following a non-technical introduction to MFPI and STEPP, we use these methods as exploratory tools to investigate possible treatment-covariate interactions in several RCTs comparing treatments in patients with cancer. For MFPI we propose checks to reduce the problem of type I error. This approach can also be used to improve investigation of pre-specified treatment covariate interactions if the covariate is measured on a continuous scale. MFPI has more power than the usual approach based on dichotomization or categorization.

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