

## Please join the Biometric Colloquium

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## **USING PERMUTATION-BASED TESTS TO EVALUATE AN ADAPTIVE MOLECULAR TREATMENT ALGORITHM IN RANDOMIZED PRECISION ONCOLOGY TRIALS**

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Seminarraum Center for Medical Data Science

Spitalgasse 23, Room 88.03.512

Medical University of Vienna, 1090 Wien

Host: Martin Posch and Franz König

### **Abstract:**

In precision oncology, molecular treatment algorithms that match targeted therapies to patients' tumor profiles often need to be modified during the course of randomized trials. Two types of adaptive modifications were investigated here: excluding one of the targeted treatments from the algorithm due to an unplanned external event, or dropping the least effective targeted treatment following a pre-planned interim futility analysis. We proposed permutation-based tests (permutation and randomization tests) to control type I error rate of such adaptive changes. We compared them with classical tests in terms of rejection probabilities in two simulation studies with normally distributed outcomes and in two actual clinical trials conducted in France with time-to-event endpoints. We first conducted two simulation studies—addressing each type of modification. In both scenarios, participants were either excluded or oriented to an alternative targeted treatment after adaptation. Simulation settings varied by biomarker prognostic effects, treatment effects, and shifts induced by patients' orientation. In the case of interim analysis, different futility thresholds were considered, and permutations were conditioned on the interim decision. The proposed methods were then applied to two clinical trial datasets and compared with standard inference methods. Simulation results show that permutation tests control type I error rate under both unplanned and data-driven modifications to the molecular treatment algorithm. Proper specification of the test statistic is fundamental for preserving power, and, when applicable, permutations must be properly conditioned on interim decisions. The results of the clinical trial applications further confirm the feasibility of using randomization tests in both scenarios.