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Title:  
A multi-step classifier identifies cohort heterogeneity in cancers leading to improved accuracy of prognostic biomarkers

Abstract:  
Ongoing research in cancers continues to highlight the extensive genetic diversity both within and between tumours. This intrinsic heterogeneity poses one of the central challenges in predicting patient clinical outcome as well as the personalisation of treatments. Efforts to classify patients according to disease trajectory have been vast and varied, and, despite advances in classification methods, moderate error rates in the accuracy of patient classification persist.

That is to say there are subsets of patients who remain outside the sensitivity of the models proposed to date. Recent work, examining the prognostic ability of biomarkers to classify individual patients, provides a way of identifying the presence of distinct prognostic signals in a cohort. We demonstrate in three independent cancer cohorts (melanoma, breast, and colorectal) that clinico-pathologic variables can predict patients that are correctly classified by a biomarker; using this information in a multi-step classification procedure not only improves classification performance but also points to specific clinical attributes which can explain the heterogeneity in each cohort. This paves the way for a new generation of interpretable prognostic biomarkers for complex disease.

This is joint work with Ellis Patrick and Jean Yee Hwa Yang.