Dan Schlauch
Harvard TH Chan School of Public Health
677 Huntington Ave
Boston, MA 02115
(617) 838-3904
dschlauch@fas.harvard.edu

Editor
American Journal of Human Genetics

August 19, 2016

Dear Editor,

We are pleased to submit our manuscript entitled “On the detection of genetic heterogeneity in whole-genome sequencing studies: A statistical test for the identification of “genetic outliers” due to population sub-structure or cryptic relationships” by Dan Schlauch, Heide Fier, and Christoph Lange for consideration for publication in *The American Journal of Human Genetics*.

In this manuscript we present a formal statistical measure of similarity in the context of genetic studies which has far reaching utility. We demonstrate that our approach effectively detects such features as population structure and cryptic relatedness in a statistically rigorous manner. Furthermore, our work exploits the increased relative value of low MAF variants to provide more sensitive measurement of fine-scale population structure compared to standard methods such as PCA (EIGENSTRAT). These claims are tested using data from all 26 populations in the 1000 Genomes Project, which revealed previously undocumented levels of genetic heterogeneity and cryptic relatedness across the groups.

Our method is made available in an R package and can be easily implemented. We hope it will be used as a standard quality control step in any into existing and future pipelines analyzing genome data.

Because of the wide applicability of our method to genetic studies, it will be of great interest to the readers of *The American Journal of Human Genetics*. Researchers doing any kind of genetic study will be able to use our work to formally test their data or subsets of their for assumptions of homogeneity and absence of cryptic relatedness.

This work is not published or submitted for publication at any other journal and we do not declare any conflicts of interest. If you determine our manuscript to be appropriate for *AJHG*, we suggest the following field experts:
1.) Hongyu Zhao, Yale
2.) Chris Amos, Dartmouth
3.) Ingo Ruczinski, Johns Hopkins
4.) Daniel Schaid, Mayo Clinic

Thank you for your consideration,

Dan Schlauch
Department of Biostatistics,
Harvard T.H. Chan School of Public Health