**Manuel A. Rivas**

Department of Biomedical Data Science

*Assistant Professor*

rivaslab.stanford.edu

**Mailing address**

1265 Welch Road

Room X3C67

Stanford, CA 94305-5464

*Faculty Fellow Center for Population Health Sciences.* Office: (650) 724-6077

Stanford University Email: mrivas@stanford.edu

*Research Affiliate*

Broad Institute of MIT and Harvard

March 10, 2018

Dear Editors,

We’re pleased to submit the attached manuscript entitled “Bayesian model comparison for rare variant association studies of multiple phenotypes” for consideration as a Research Article in PLOS Genetics. In this manuscript, we present a statistical method for rare variant association analysis across multiple phenotypes from exome and genome sequencing studies using individual and summary level data. Furthermore, we present results from its application to two diseases, asthma and glaucoma, in the UK Biobank study. The manuscript contains several major components that contribute substantially to the current body of knowledge available for both statistical genetics methods and genetic analysis in population biobanks.

1. We first present a Bayesian model comparison method for summary and individual level data. analytical derivations for computing a Bayes Factor using summary level data as input from common and rare variant association studies. We present approximations that allows users to compute p-values from Bayes Factors.
2. We then seek to compare the method to commonly used frequentist statistical tests including the Sequence Kernel Association Test and Burden test.
3. Second, we apply a model to prioritize protective modifiers of disease risk and jointly analyze multiple phenotypes and variants using the UK Biobank data identifying promising gene associations.
   1. We find strong evidence of association between asthma, eosinophil counts, and forced vital capacity and forced expiratory volume in 1-second (FEV1) with rare variants in *IL33* previously reported by Smith et al. PLOS Genetics 2017, and moderate evidence of association with rare coding variants in *CCR3*.
   2. We find strong evidence of association between glaucoma, intra-ocular pressure and corneal resistance factor with rare variants in *ANGPTL7*. The effects are consistent with protection to glaucoma, illustrating the power of the approach at prioritizing potential targets.

Given the strong interest in the field of human genetics to identify rare variant associations, and the emergence of population-scale datasets from UK Biobank and Million Veterans Program we think this method and manuscript are timely.

Sincerely,

Dr. Manuel A. Rivas