



May 20, 2021

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Dear Dr. Sofer,

The Jackson Heart Study (JHS) Publications and Presentations Subcommittee (PPS) thank you for your manuscript titled "Gradient Boosted Trees Capture Non-Linear Genetics Effects and Allele Interactions in Complex Phenotypes: Supplementary Materials". The sequential number M1509 has been assigned to your manuscript, so please reference this number should you have to inquire about this manuscript. The PPS decision regarding your manuscript was to "**accept with comments**". Evaluator's comments are attached for your review. Please review the guidelines below regarding the publication of your manuscript.

Manuscripts with National Institutes of Health (NIH) author/co-authors must be reviewed by the National Heart, Lung, and Blood Institute (NHLBI). In this case, the lead author must send the manuscript and a copy of the PPS letter of approval via email to NHLBI at [nhlbi\\_ebpdocs@nhlbi.nih.gov](mailto:nhlbi_ebpdocs@nhlbi.nih.gov) and copy the Project Officer, Sharon Smith at [smithsh1@mail.nih.gov](mailto:smithsh1@mail.nih.gov) before submission to a journal for publication.

The following **acknowledgement** and **disclaimer** must be included in your submitted manuscript:

**JHS acknowledgement-** The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS.

**JHS disclaimer-** The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

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We look forward to your final product.

Sincerely,

Mario Sims, PhD, MS, FAHA  
Chair, Publications and Presentations Subcommittee

### **Evaluator's Comments:**

1. This is a very nice study examining the incremental utility of a gradient boosted tree ML model for developing polygenic risk scores and consequently explaining variance in complex phenotypes from SNPs data. I am almost certain that non-linearity and interactions in the associations between SNPs and phenotypes account for the improved explanatory capability of the ML model. Curiously the multiethnic model outperformed the race/ethnicity specific model for African Americans likely due to the large multiethnic training dataset.
2. The paper is beautifully written and presented. The underlying work and methodology are very nice. The discussion of the limitations is appropriate.
3. It is not clear to me a JHS investigator participated. One author is not referenced as to affiliation (#9, Yan Guo)? I am wondering if this is an error and it is actually Yan Gao at UMMC & JHS. We also have a Yan Guo at UMMC in the informatics department, but I would not have expected her to be involved in this project. Should Yan Gao be listed as the JHS co-author/co-investigator??