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December 28, 2017

Dear Steering Committee members,

We are submitting a revised version of our manuscript entitled “Passenger mutations in > 2500 cancer genomes: Overall molecular functional impact and consequences”. Briefly, in the revision we have updated our main text to fix issue related to terminologies, built new covariate-corrected background model for the additive variance analysis and discussed potential drawback of the current background models. We also provide a detailed response document [[where?]], which addresses each issue/suggestion raised by reviewers in systematic manner. Finally, we also highlight corresponding texts in the manuscript to reflect relevant points.

We are thankful to all reviewers for carefully going through our manuscript and providing suggestions to improve our work. It took us little bit longer to submit the revised manuscript than we anticipated, as we wanted to ensure that the updated manuscript is in line with the overall message of PCAWG. For this, we closely worked with Gaddy over last 3 months to implement all his additional suggestions.

The current updates are in extension of 3 earlier revisions, which we have made over a year to the manuscript while accommodating all suggestions made by the steering committee members [[timeline?]]. In the last version of the manuscript, steering committee showed interest in our additive variance analysis. However, there were lot of concerns raised for the PCAWG-wide background model, which was used. We were also asked to design better background model taking into account of various covariate. As you will note in our updated text and detailed response document, we have addressed this issue in depth. In contrast, the steering committee found our analysis related to functional impact to be satisfactory and no objections were raised. Thus, even after addressing all issues related to background model, we volunteered to remove the additive variance analysis from the manuscript to expedite the submission of our manuscript. However, Gaddy suggested to keep the additive variance part and gear it more toward addressing issue of missing drivers in PCAWG as this will complement similar efforts addressed in other PCAWG papers.

We strongly believe that inclusion of reviewer suggestions makes our manuscript much stronger and we hope that steering committee approves the manuscript for submission in the revised form.

Yours sincerely,

Mark Gerstein

Albert L. Williams Professor

of Biomedical Informatics