**Response to Panel and Reviewers’ Comments of Previous Submission**

We are pleased that the panel has characterized the investigatory team and environment as “*excellent”*, “*highly experienced and qualified*”, and our proposal as “*well thought out..* *as regards the recruitment of the AA patients*”, with “*novel concepts, hypotheses* and *bioinformatics*”. We would also like to thank the reviewers for the very thoughtful and constructive suggestions and criticisms, which we address below:

**Stratification and pre-selection of Genomes.** One of the panel’s major concern was the need for further stratification. R#1 asked “*how the variants will be segregated or ruled out of analysis, which are not due to race but influenced by other factors..* ”. R#2 noted that the absence of a planned enrollment report made it “*difficult to ascertain the actual ethnic distribution*”, while R#3 pointed that our proposal *“failed to stratify patients into men, women and children, since mechanisms may vary”*. (A) We have included an updated version of LARVA (NIMBus) that identifies mutational burden, while regressing on multiple factors that might influence the mutation rate across individual genomes. (B) We have added two genotyping analyses, in order to genetically confirm the ethnicity, as well as improve the comparison between our tested groups in Aims I and IV. Finally (C), we have now added in Aim II C-2-c-5, an extra data stratification plan for the identification of burdened germline regions.

**Biological and Clinical implications.[[STL to edit]]** The panel discussed the absence of extended discussion concerning the ccRCC and pRCC mechanisms. R#1 noted that “*there is a gap between .. mutations and clinical features*”. R#3 added that “*the current knowledge of genetic mechanisms and biological factors .. should have been provided*”. In this direction: (A) We have provided a more detailed listing of gene regions and pathways associated with kidney cancer. [[where?]] (B) We have particularly focused on the study of mutations that disturb metabolic and genetic pathways. (C) We have now included two more analyses including the study of loss of function mutations, as well as examining the prevalence of deleterious mutations. Finally (D), to strengthen our proposal’s relevance, we provide preliminary results from 14 genes associated with Kidney cancer with a heavier mutational burden in the germline of African-Americans..

**Improving Deliveries for Specific Aims.** One reviewer expressed his concern for the degree of independence between the aims and the significance of the respective deliveries. Specifically, R#3 noted that “*The success of Aim 3 is dependent on Aim 2, and Aim 4 is dependent on Aim 3*”. [[reword: inter-dependent but separate deliverables]] Even though our aims might appear inter-dependent, they also provide separate deliverables. Moreover we have now increased the significance of our intermediate deliverables by including a) a loss of function analysis, b) the study of mutational signatures, c) the study of regulatory networks burdened by somatic and germilne mutations, but more importantly, we d) plan to compare the mutational burden between different ethnic groups with respect to the EXAC database.

**Providing Additional Preliminary Results.** Some concerns were also raised concerning the lack of preliminary results that support our hypothesis. Apart from previous studies that suggest a higher risk of pRCC cancer for African Americans, we have now included an additional figure of preliminary results showing that gene regions previously suggested as important for the development and progression of Kidney cancer are more heavily burdened with deleterious mutations in specific ethnic groups compared to others. Moreover SIGNATURES Shantao to add here [[more specifics]]

**Providing additional Controls.** Concern was raised by the panel for the lack of extra control datasets for the validation of the identified somatic and germline mutation. R#3 suggested that “*the experimental design lacked controls; it is not enough to use TCGA controls...*. We have now included in Aim IV the validation of additional regions to act as a third level of control in addition to the regions obtained by the different ethnic groups.

**Other additions and changes:**