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Dear Editor of *Plos Genetics*, (or address them directly? Dr. Creighton and Dr. Kwiatkowski?)

We would like to submit our revised manuscript titled “Whole-genome analysis of papillary kidney cancer finds significant non-coding alterations”. First, we want to thank you and your colleagues for considering our manuscript. Our work helps to better characterize the second most common type of kidney cancer, papillary renal cell carcinoma (pRCC) in genomic aspect. It is the first detailed whole genome analysis of this cancer.

We appreciate and value the comments from the reviewers. During the revision, we addressed all the concerns raised by the reviewers. Some of our major work includes: 1) we conducted a refined structure variant (SV) discovery and analysis using whole genome sequence data. By carefully remapping more than 100 billion reads, we were able to generate a high-confident SV callset. Along with other impactful SVs, we found recurrent deletion of *SDHB*. Moreover, in comparison with CNVs from the TCGA publication, our SVs predict *CDKN2B* expression better. 2) We generated individual evolutionary trees for all 35 samples. This is, to our best knowledge, the first evolutionary tree construction in pRCC using both coding and non-coding SNVs. Trees reflect the level of tumor heterogeneity and show various topologies, allowing us to better understand the development and heterogeneity of pRCC. We observed the samples have different evolutionary profile. 3) We further explored the role of *NEAT1* and discovered high *NEAT1* expression level links with significant worse outcome in ccRCC. Additionally, *NEAT1* tightly co-expresses with *MALAT1*, which is a known cancer gene linked with pediatric RCCs. These results further support the significance of the noncoding mutation hotspot we identified in *NEAT1*.

By exploring potential noncoding drivers and tackling tumor heterogeneity through scrutinizing mutation patterns, landscape and evolutionary profiles, we are able to better characterize pRCC. As the first comprehensive whole genome study of pRCC,our finding help complete the portrait of the tumor.

This research is original, has not been submitted previously, and none of the authors have any conflict of interest.

Yours sincerely,
Mark Gerstein
Albert L. Williams Professor
of Biomedical Informatics