Reviewer's report

Title: Plasma metabolites and lipids associate with kidney function and kidney volume in hypertensive ADPKD patients early in the disease course

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Reviewer: Kenneth Raymond Hallows

Reviewer's report:

This study by Kim et al. examines HALT-PKD Study A participants' baseline plasma samples for the potential predictive role of metabolites and lipids in a non-targeted platform to predict the measured eGFR and ht-TKV with the hope that certain identified species will correlate with these parameters and potentially inform on disease progression and prognosis. They find that a limited set of 12 metabolites significantly correlated with eGFR and 2 triglycerides significantly correlated with baseline ht-TKV at FDR q-values <0.05. As ht-TKV has been reported to correlate with disease severity and potential for disease progression, the authors propose that metabolites or lipids that correlate with ht-TKV and eGFR may be predictive of progression, although this is not tested in this study. Another limitation is that only Caucasian patients are used, which may limit the generalizability of the study to all patients and should be mentioned in the Discussion. Nevertheless, the study provides a useful foundation or baseline for potential future work. I have a number of additional specific comments and queries for the authors to address to strengthen the study.

1. In addition to plasma metabolic changes, urinary biomarkers may also be useful and potentially more specific to study, and this point should be mentioned by the authors in the Discussion.

2. It would be useful for the authors to make the point that the identification of new blood or urine biomarkers would be potentially less costly and more convenient than ht-TKV.

3. p. 7, line 31: Should say "data".

4. p. 7, line 60: It says that the concentration of each internal standard is found in Table S1, but that information does not appear to be there.

5. p. 8, lines 49-53: The authors mentioned that there was one sample that was markedly dispersed from the rest of the samples and removed. More detail about the criteria used to judge and remove outlier(s) would be beneficial to include.

6. Table 1: For urine creatinine, potassium and sodium levels, the units given are in mEq/L/day, but it should likely be mEq/L if it is based on a spot collection or mEq/day if it is a 24-h collection. Please address.
7. p. 12, lines 44-47: Would revise to say "association was generally reversed by sex...". As the authors note later in the paragraph, creatinine exhibited negative associations for both males and females (Fig. 3 and Table S1).

8. All figure labels (writing) need to be made larger and more legible. The Figure 2 heat map is particularly difficult to read, thereby limiting its usefulness.

9. p. 14, line 13: The authors should refer to Supplemental Table S3 rather than "data not shown", as the data are present in Table S3.

10. Much of the data shown is not significant when corrected by Storey's false discovery rate (FDR). The authors should consider mainly or only focusing on those with significant q values. Discussing the data with "significant" p values but insignificant q values may be misleading because there is really no reason to believe that these values have any significance.

11. Re. the unknown metabolite (191801), given the very highly significant p and q values, the authors should work it up further (as they probably plan to). One issue with these studies is that the data are biased toward the most abundant metabolites, which may not have the best significance. Identifying lower abundance metabolites that are highly discriminative would be impactful and potentially very useful clinically.

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