Peer Review File

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Reviewer A

Comment 1: 1. On page 3, line 83, "SVM-RFE" appears first without any explanation of abbreviation.
Reply 1: Thank you so much for your kindly and professional advice. The support vector machine recursive feature elimination, the abbreviation of "SVM-RFE" was added as advised (See Page 3, line 83).
Changes in the text: See page 4, line 74.

Comment 2: On page 4, line 117, Figure 2 differs from the description in the manuscript.
Reply 2: Thanks for your careful review and thoughtful comments. The revised sentence on page 5, line 109 reads: The process of our study was illustrated in **Figure 2**.
Changes in the text: See page 5, line 109.

Comment 3: On page 5, line 230, The sentence "Research into the ……. described above" should not be in the Result section but in the Discussion section.
Reply 3: Thank you for your careful review and kindly reminds. The sentence "Research into the ……. described above" was deleted because the sentence "the mechanism needed to be supported by solid evidence from other researches" in the Discussion section (see page 12, line 256) was similar to this sentence.
Changes in the text: See page 12, line 256.

Comment 4: Figure 3A, 5G, 5H and 5I were not explained in the manuscript.
Reply 4: Thank you so much for your evaluation of our manuscript. We really appreciate this advice and added the words "**(Figure 3A)**" on page 11, line 222. The words "**(Figure 5)**" was revised with "**(Figure 5E-I)**" on page 11, line 229.
Changes in the text: See page 11, line 222 and page 11, line 229.

Reviewer B

Comment: I have suggested the authors add/comment on the feasibility, costs, and timeline of testing.
Reply: Thanks for your careful review and valuable suggestions. We added a paragraph "Finally, we discussed potential clinical applications of noninvasive biomarkers, such as the period of time for results of testing and costs. The time to library preparation and sequence a sample on specific gene sets takes upwards of a week 34. To our knowledge, the cost comparison between gene expression biomarkers and conventional means (biopsies) is controversial and needed solid evidence to demonstrate. Costs for these techniques (including microarrays and next-generation sequencing technologies) have

dropped dramatically over the last decade and are now comparable to other methods utilized routinely in commercial diagnostic laboratories based on improved workflows and analytical tools 35. Puttarajappa et al. raised interesting points that protocol biopsies are more cost-effective methods than noninvasive biomarkers 36. However, there are several concerns about the study by Abhijit S et al. indicate that analysis by Puttarajappa et al does not provide sufficient evidence to support their conclusion 37. Moreover, the gene expression signature for monitoring kidney recipients with stable renal function caused $6509 savings per year gross versus using surveillance biopsies 37. Furthermore, the development of commercial kits for a stable noninvasive biomarker can strengthen the feasibility of testing, shorten the time for library preparation and reduce costs." to clearly answer this question (see page 15, lines 325-341).

Changes in the text: See pages 15, lines 325-341.