We thank both referees for their positive comments and useful suggestions for improving our manuscript. We have provided a point-by-point response in the referee feedback form. All the modified text was highlighted in red. Some notable changes include:

1. The overall workflow of our data analysis was rather complicated. We have prepared a new flowchart illustrating which data sets were used for each part of the analysis (new Supp. Figure 11).
2. We took Reviewer #2’s advice, and split MHBs based on CpG density for enrichment analysis, which revealed an interesting difference for MHBs that have low CpG density (new Supp. Figure 1).
3. We have applied the analysis that we did on Figure 1C to two sets of recently published kidney cancer data, and observed consistent results (new Supp. Figure 2)
4. Both reviewers asked questions related to the clinical information of primary tumor and cancer plasma. We have included the information in Supplementary Table S12a.
5. We have prepared three additional figures to specifically address reviewers’ comments: Only-for-Reviewer-Figure 1/2/3