We thank the editors for the suggestion on the revision.

1. We now require a Data Availability Statement (DAS) with all published papers. Please see the attached PDF for details. All data sources should be mentioned in the DAS, even if the data are available in the manuscript or associated supplementary files.

Done

2. The remaining concerns of referee #2 need to be resolved. We agree with the points in your previous email stating that the analyses should remain in the paper. However, we ask that you explicitly state the potential implications of batch effects on the results, as suggested by the referee, within the results section.

3. Please also address the final comment of referee #2 asking you to avoid overstating any claims. We will also carefully check and edit as needed before accepting the final version.

4. Please address all other remaining comments of the referees. These are minor and/or aesthetic.   
General formatting:

5. Article/Technical Report: Our standard word limit is 4,000 words for the Introduction, Results and Discussion. Your current manuscript is 4,431 words, and you will need to cut 431 words. Please contact me if you have any difficulty with this.

Now, we need remove more words since we added a new section: ‘Joint analysis of tumor and normal tissue for non-invasive cancer detection in plasma”.

6. Online Methods do not have a strict limit, but we suggest 3,000 words as a target. You currently have both an Online Methods section in the main manuscript file and a separate Online Methods in a different file. Please consolidate these and include up to 3,000 words of Online Methods in the main manuscript file. Equation-heavy portions, discussion, or other details that extend significantly beyond 3,000 words should be included in the Supplementary Note.

Done, move most important sections of online method (2,255 words) to main manuscript and save the remaining as Supplementary Note (2,326 words)

7. Your abstract must be fewer than 150 words and should not include citations.

8. The title should provide a clear and compelling summary of the main findings in fewer than 18 words. We suggest the following title: “**Identification of methylation haplotype blocks aids in deconvolution of heterogeneous tissue samples and tissue-of-origin mapping from plasma DNA**.” Please let me know if you have any concerns.

9. Genes must be clearly distinguished from gene products (e.g., “gene Abc encodes a protein kinase,” not “gene Abc is a protein kinase”). For genes, provide database-approved official symbols (for human genes throughout the paper use <http://varnomen.hgvs.org/>). For the relevant species, use NCBI Gene: <http://www.ncbi.nlm.nih.gov/gene.> Italicize gene symbols and functionally defined locus symbols; do not use italics for proteins, noncoding gene products and spelled-out gene names.

Done

10. For descriptions of variants, use HGVS notation according to the guidelines at [http://varnomen.hgvs.org/.](http://varnomen.hgvs.org/) Include the accession code for the corresponding reference sequence at first mention of a variant.

Done

Figures and Tables:  
  
11. All figures and tables, including Supplementary items, must be cited in the text in numerical order. Please correct the following: Supplementary Table 12 cited out of order (Currently cited after supp table 1 and before supp table 2).

Done

12. Figure legends should be concise. Begin with a brief title and then describe what is presented in the figure and detail all relevant statistical information (as described and declared in the supplied checklist), avoiding inappropriate methodological detail.

Done

13. Shadings or symbols in graphs must be defined in some fashion. We prefer that you use a key within the image; do not include colored symbols in the legend. Please remove the yellow background shading in Figure 4.

Done

14. Please remove the top/right borders from the plots in Figures 4 and 5.

Done

15. The pie charts in Figure 5b are not necessary. Please remove them, and place sample size numbers in parentheses next to the appropriate tissue type label on the heatmaps.

Removed and Done

16. All relevant figures must have a definition for any error bars.

Done

17. Red/green color contrasts can confuse our colorblind readers; please recolor red/green images in figures 1 and 5.

Done (include Figure 1c, 5b)

18. All bar graphs should be converted to a dot-plot format or to a box-and-whisker format to show data distribution. All box-plot elements (center line, limits, whiskers, points) should be defined. Please convert the bar graphs in Figure 4.

Done (Figure 4) ，box-and-whisker format was provided.

Statistics and Reproducibility:  
  
19. The Methods must include a statistics section where you describe the statistical tests used. The supplied checklist provides details of which statistics need to be in the Figure legends, and which assumptions and analytical procedures need to be supplied in the Methods. For all statistics (including error bars), provide the EXACT numbers used to calculate the statistics (reporting individual values rather than a range if n varied among experiments) AND define type of replicates (e.g., cell cultures, technical replicates). Please avoid use of the ambiguous term “biological replicates”; instead state what constituted the replicates (e.g., cell cultures, independent experiments, etc.). For all representative results, indicate number of times experiments were repeated, number of images collected, etc. Indicate statistical tests used, whether the test was one- or two-tailed, exact values (NOT for example: <0.05) for both significant and non-significant P values where relevant,  
F values and degrees of freedom for all ANOVAs, and t-values and degrees of freedom for t-tests.

Done

20. The reproducibility checklist must be complete, accurate and up to date.

Supplementary Information:  
  
21. Please rename the supplementary tables to match journal style. For example, “Supplementary Table 1” instead of “Table S1”.

Done

22. Please use the attached ISI supplementary figures template to prepare your supplementary figures. All other supplementary items (except for Excel files or the Supplementary Data Set [Perl and R codes]) should be included in a single merged PDF file.

Done

23. Any references cited only in the supplementary information should be placed directly within the relevant supplementary files, rather than in the main reference list. For Supplementary Figures, cite any references within the legend text.

In addition to addressing these points, please refer to the attached policy and rights checklist, which contains information on how to comply with our legal guidelines for publication and describes the files that you will need to upload prior to final acceptance. You must initial the relevant portions of this checklist, sign it and return it with your final files. I have also attached a formatting tipsheet for you to consult as you prepare the revised manuscript. Careful attention to this guide will ensure that the production process for your paper is more efficient.