We thank both referees for their positive comments and useful suggestions for improving our manuscript. We were pleased to see that the referees found no major issue with our manuscript. Additionally, they raised important questions and suggested a reasonable number of analyses to address those questions.

In particular, both referees wrote positively about our cancer detection methodology via cfDNA and asked that more clinical information for the 59 cancer patient samples be provided. We agree with the referees that this information would be helpful to understanding how our method could be applied in a clinical setting. However, this work was a proof of concept and we had very limited access to samples and clinical information about each sample. Ideally, the variabilities among the patient samples that we observed could be better understood through stratification of the patient samples, and in a larger study with many more samples. Nonetheless, this work demonstrated that it is feasible to utilize cfDNA to detect cancer in patients with good specificity and sensitivity. Furthermore, we’ve identified potential areas where technical improvements toward creating higher complexity sequencing libraries from cfDNA samples will help bring us closer to clinical usage.

With regard to inter-sample differences, particularly between progenitors, adult tissues, and primary tumor tissues, the referees were correct to point out potential technical factors such as sample size, sample preparation, sequencing, and data processing. The WGBS data used for Figure 1B and Figure S3 were produced by 5 different groups, as follows: the progenitor cells were all from Xie et al. 2013, the adult tissues were from Schultz et al. 2015, Heyn et al. 2013, and we produced 10 adult tissue WGBS, and the primary tumor tissues were from Ziller et al. 2013 and Heyn et al. 2016. We have processed all the datasets using the same analysis pipeline to reduce technical factors. All of the samples were sequenced using the Illumina platforms and we have performed adaptor and quality trimming to remove low quality base pairs from the reads. Figure S3 is a demonstration of how technical factors did not obscure biological differences, besides the progenitors, the adult tissues data were produced by two different groups, and the primary tumor tissues were also from two groups. For Figure 1B, the primary tumor tissues were comprised of 3 colon cancers and 3 lung cancers together and therefore, we do not know if the reduction of perfectly coupled CpGs could be extended to other types of primary cancers. To check for whether additional primary tumor samples will follow a similar trend, we added two kidney cancer samples generated by another group (Chen et al. 2016) to the analysis and found even further reduction of coupled CpG pairs (Supplementary Fig 2).

In the revision, we have made all of the corrections in the references, figures, and figure legends and generated 6 additional supplementary figures and 1 additional supplementary table.