In the present manuscript, Dr. Maggi and colleagues provided a comprehensive pipeline for genome-wide cfDNA methylation sequencing technique in which long DNA fragment could be removed and then only the most interesting 100-200bp DNA fragments was kept and be sequencing. It is a quite interesting study design since none of such study design was conducted before, especially in mouse circulating DNA samples. However, what a pity, the further biological or clinical analysis were suspended caused by limited sample size and coverage/depth. I only have several suggestions.

1, the authors find a quite interesting result that the WT mice had significantly higher cfDNA levels per ml of plasma than control human samples. However, none of further discussion or explanation were conducted.

2, The method to estimate the proportion of the DNA origin applied in line 205 of page 8 should be given more details.

3, Between line 175 and line 177, It seems the authors suppose the short cfDNA fragment were derived from cancer samples while long fragments were from normal cells. Is there any evidence to support this hypothesis? Why long fragments cannot be derived from cancer cells? Can we suppose that the small fragments can also be derived from WBC with certain limited proportion and can we estimate the corresponding proportion?

4, On the section of “Sequencing results and biological findings”, more details could be covered such as How many CpG islands were covered? How many previous reported cancer hypermethylated regions could be repeated by the current method? The distribution of the depth to the different genomic regions, such as promoter, enhancer, CpGI et.c and Is there any significant enriched or it is stochastic distribution for these elements? What’s more, is there any possibility to share the raw data to GEO so that the further analysis could be conducted by the readers who are interesting in it.

**Minor Essential Revisions**

1, the title can be made a little change with more specific to show the advantage in technique part since when I read the title in the first eye, I thought it is a study with large and deep methylation sequencing to cancer cfDNA samples. However, when I finish the reading, I found it is a quite interesting technique paper with great innovation in sequencing method.