Response to Reviewers document:

(1)Finish first draft of the response to the reviewers addressing all the clarifications and corrections. Majority of questions were answered with ideas for new figures and tables. **DONE!**

(2)Ref #1: 5 & Ref #2: 8: Get TNM information from Sharmeela. **Done！**

(3) Ref #1: 10, rebuttal with reasons why these questions should be answered in a separate study. *11/21.*

(4) Ref #2: 3, rebuttal with examples of typical coverage for MHB & boundary regions. *11/21.*

(5) Ref #2: 4, rebuttal with % CpGs with no reads coverage after merging all BAM files, % reads with < 2 CpGs. *11/21.*

(6) Ref #2: 7, rebuttal with reasons why Fantom enhancers & super enhancers are significantly overlapped with MHBs but tissue specific H3K4me1 histone is not enriched. *11/21.*

(7)Proofread responses. Make citation to published works consistent. *11/22*

Manuscript:

**Add new 2016 Plasma data to GEO!!!**

(1)References in Table S12d needs to be corrected. **DONE!**

(2)Add references in main text. **DONE!** *(Remember to add the Chen et al 2016 if we ended up using the kidney cancer WGBS)*

(3)Replace CI’s in lines 240-254 with IQR’s since variabilities among patients/samples may not be normally distributed. **DONE!**

(4)Provide description of cross validation methodology in the Methods section. *11/22.*

(5)Provide ranges for “caHMH”: In the matched primary tumors and plasma methylation haplotype analysis, the range of the cancer associated haplotype is from **15 to 97**. And in the extended analysis with all the samples, the range of the cancer associated haplotype is from **10 to 327**. *11/22.*

Figure legends needs to be revised. *11/22.*

Re-number figures and tables. *11/22.*

New/Updated figures and tables

(1)~~Figure 4: redo with new analysis by Shicheng.~~ *~~11/21.~~*

(2)Move Fig. S5 to Figure 4d ? *Both Referees thought Fig. S5 and Fig. S6b has important message & should be brought to main figure. CHECK WORD limits.*

*New items are numbered X# and Y# for now, will need to re-number figures and tables later.*

(3) Supplementary Figure X1 – a) histogram of MHB sizes, b) histogram of MHBs by CpG density (CpG/bp), c) distribution of overlapping MHBs in each feature by CpG density. **DONE!**

(4) Supplementary Figure X2 - bisulfite conversion rate bar plots **DONE!**

(5)Supplementary Figure X3 – figure like Figure 1C for primary tumor tissues with 2 kidney cancers, showing reduction of perfectly coupled pairs.

(~~6)Supplementary Figure X4 – figure like Figure 1E for non-CGI MHBs enrichment in different features.~~

~~(6)Supplementary Figure X5 – figure like Figure S2 for Super-enhancers and Fantom-enhancers (maybe just a few tissues?).~~ *~~11/21~~*

(7)Supplementary Figure X4 – figure to show coverage within WGBS high coverage boundaries and coverage of MHB boundaries. *11/22*

(8)Supplementary Figure X5 – flowchart 11/22

Tables

(7)Supplementary Table Y1 – GREAT analysis of CpGs with loss of coupling in primary tumor tissues. 11/22

(8) Supplementary Table Y2 – WGBS technical factors – conversion rate, genome coverage, average mapped read lengths 11/22

(9) ~~Supplemtary Table Y3 - To understand the improvement in distinguishing plasma from cancer patients from normal plasma samples, a Figure like Supp. Fig. 5 should be added (also for later comparisons with Supp. Fig. 6).~~