*Science Advances* 28 March 2019

Dear Editor,

I am submitting the Letter entitled “Long-Region Hypo-methylation in HBV Integration Regions Enhance HCC Non-invasive Surveillance by Low-pass Whole Genome-wide Bisulfite Sequencing” on behalf of all authors for consideration of publication in Nature Genetics.

Genome-wide DNA hypo-methylation has been demonstrated to be the hallmark phenotypes of human cancer genome. Meanwhile, circulating cell-free DNA methylation is the best medium for non-invasive cancer diagnosis. However, the amount of cell-free DNA is too limited for conventional high-depth/coverage genome-wide bisulfite sequencing (WGBS). In this original manuscript, we proposed a novel strategy to apply low-pass WGBS for cancer early diagnosis. We developed a novel measurement of Long-Region Un-methylation Index (LRUI) to be the biomarker for cancer surveillance ranging from hepatitis, cirrhosis, early stage HCC and advanced HCC. We find low-pass based WGBS could provide stable and powerful diagnosis for early stage HCC. Furthermore, the method provided a stable approach for surgery quality evaluation. We also found over-represented differential methylation CpGs based on low-pass WGBS data enriched in HBV integration regions which is the most important risk factors of liver cancer, indicating our method is suitable for HCC diagnosis and clinical decision-making with low-cost characteristic. Since the novel strategy and interesting findings, we believe the readers of *Science Advances* will find this manuscript highly interesting.

This manuscript has not been submitted elsewhere. Thank you for your consideration.

Sincerely,

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