*Science Advances*

11 June 2019

Dear Editor,

I am submitting the Letter entitled “Circulating cell-free DNA based low-pass genome-wide bisulfite sequencing aids non-invasive surveillance to Hepatocellular carcinoma” on behalf of all authors for consideration of publication in Science Advance.

Circulating cell-free DNA has been demonstrated to provide a promising opportunity for non-invasive cancer diagnosis, especially DNA methylation in circulating cell-free DNA which have been demonstrated in cancer diagnosis and tissue-of-origin mapping. We know that genome-wide DNA hypo-methylation is the hallmark phenotypes of human cancer genome and therefore can be applied in cell-free based 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 to monitor DNA methylation levels in cell-free DNA fragments. We developed a novel measurement of Long-region hypo-methylation 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 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. HBV integration based DNA methylation regions showed better prediction performance (AUC=0.93). 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,