Editorial Office,

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February 1, 2019

Dear Editor,

We would like to submit our manuscript, “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 XXXX.

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.

All authors have read and approved the final version of the manuscript. This article has not been published and is not under consideration for publication elsewhere. The authors declare that there are no competing financial interests. The following is a list of potential reviewers who are experts in this field and are well qualified to evaluate the merits of this manuscript.

Sincerely,

1. XXX

Your consideration for this manuscript is highly appreciated.

We look forward to hearing from you soon.

Steven J. Schrodi, Ph.D.

Principal Investigator

Laboratory of Immunopathology Genomics and Theoretical Genetics

Center for Human Genetics

Faculty, Computation and Informatics in Biology and Medicine

University of Wisconsin-Madison

Email: [schrodi@wisc.edu](mailto:schrodi@wisc.edu)

Tel: (715) 221-6443

Email: [schrodi.steven@mcrf.mfldclin.edu](mailto:schrodi.steven@mcrf.mfldclin.edu)