ANSWERING REVIEWERS

January 7, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5938-Edited.doc).

Title: Genetic variations in colorectal cancer risk and clinical outcome

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5938

Thanks for the insightful comments from you and your reviewers. We believe the manuscript has been significantly improved according to these suggestions. Specifically, we made the following revisions to the manuscript:

1. Format has been updated according to Journal's revision policy for Topic Highlight.

2. Revision has been made according to the suggestions of the reviewers. All changes reported below are highlighted in yellow color in the manuscript:

(1) Key words: Four keywords were added – Signaling transduction pathway, Cell cycle control; Gene desert; Genome instability
(2) Abstract (line 3): "diseases" *revised to* "disease".
(3) Abstract: Added four lines to meet the requirement on the number of words in abstract – "The findings from these studies suggest that there is a lack of understanding of the mechanism of many SNPs that are associated with CRC. In addition, the utility of SNPs as prognostic markers of CRC in clinical settings remains to be further assessed. Finally, the currently validated SNPs explain only a small fraction of total heritability in complex-trait diseases like CRC. Thus, the "missing heritability" still needs to be explored further."
(4) Core tip was added: "This review covers the recent advances in Genome-wide association studies (GWASs) that have identified genetic variants associated with an altered risk of colorectal cancer (CRC). In this review, we summarize single nucleotide polymorphisms (SNPs) located in or near genes that play crucial roles in signal transduction pathways, genome stability, cell cycle control, and gene expression and regulation. SNPs that are found in gene desert regions are also discussed. The relationship between genetic variations and clinical outcomes in CRC is presented from epidemiological studies that have identified SNPs with methods other than GWASs."
(5) Introduction (First paragraph, lines 4-9): "It is estimated that cumulatively… at an age cutoff that is a function of family history" *revised to* "It is estimated that cumulatively, these and other well-characterized genetic syndromes with Mendelian mode of inheritance account for up to 10% of all CRC cases. In an estimated further 25% of cases, family history contributes to CRC risk in the absence of one of these identifiable genetic syndromes. The important role of family history in CRC risk is reflected in the guidelines published by the American College of Gastroenterology and the American Cancer Society, which recommend starting screening colonoscopies at an age cutoff that is a function of family history [3]."
(6) Introduction (Second paragraph, line 1): "The overall effect of these well-known genetic

components" *revised to* "The combined effect of genetic syndromes and family history may …"

(7) Figure 1 was added at the end of manuscript.

(8) "Genetic variants and clinical outcome" section (First paragraph, lines 3-5): "However, the majority of reported outcome-related SNPs are generated from candidate gene or pathway-based studies whereas, as yet, no GWAS has been reported to interrogate genetic variations and CRC clinical outcome" *revised to* "However, the majority of reported outcome-related SNPs are generated from candidate gene or pathway-based studies. As of yet, no GWAS has been reported to examine a direct relationship between genetic variations and CRC clinical outcome."

(9) "Genetic variants and clinical outcome" section (Second paragraph, lines 5-7): "Dai et al. evaluated 26 CRC risk variants derived from 10 GWAS-identified chromosome loci using a Caucasian population of 285 stage II or III CRC patients receiving fluorouracil-based chemotherapy" *revised to* "Dai et al. used a Caucasian population of 285 stage II or III CRC patients receiving fluorouracil-based chemotherapy to evaluate 26 CRC risk variants derived from 10 GWAS-identified chromosome loci."

(10) "Genetic variants and clinical outcome" section (Third paragraph, lines 3-7): "This is mainly due to the fact that, compared to case-control studies to identify etiology loci, clinical outcome studies … the confounding effects from heterogeneous patients and treatments" *revised to* "All of these studies are based on candidate gene or pathway-based approaches instead of GWAS. This is largely because compared to case-control studies, clinical outcome studies are generally based on cancer patients with highly heterogeneous characteristics and treatments that confound the very modest effect of genetic variants on patient outcomes. This issue could be partly resolved by the use of clinical trial patients that have more homogeneous characteristics and treatments, or consortium studies with much larger number of patients."

(11) Reference section: Four references were added for Figure 1.

(12) Legend for Figure 1 was added after References.

3. References and typesetting were corrected, and the PubMed citation numbers offered.

4. The manuscript was revised by an English language expert. Any additions or significant changes in sentence structure are reported above. Grammatical corrections and simple word substitutions are not detailed above.

Again, we greatly appreciate the comments provided by you and your reviewers that have helped us significantly improve the manuscript. We hope that the revised manuscript is now acceptable in the *World Journal of Gastroenterology*. If there is any question, please feel free to contact me: phone, 215-503-6521, fax, 215-503-9506, or email hushan.yang@jefferson.edu.

Sincerely yours,

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