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Date: March 28, 2019

Dear Professor Ghosh, dear Professor Tarnawski,

We would like to thank the editorial board for the opportunity to resubmit our manuscript entitled "*Predicting (side)effects for patients with Inflammatory Bowel Disease: the promise of pharmacogenetics*" for publication as an opinion review in *World Journal of Gastroenterology.*

We would also like to extend our appreciation to the editors and reviewers for taking the time and effort necessary to review our manuscript. We believe that the reviewers' comments identified points that required improvement, and the manuscript has benefitted from the changes suggested by the reviewers. In the letter that follows, we provide a point-by-point response to the reviewers' comments. New or revised text in the manuscript has been denoted in red.

This manuscript is not being submitted simultaneously elsewhere. All authors have participated in revision of the manuscript and approved the final version.

We look forward to hearing from you.

Also on behalf of prof. R.K. Weersma,

yours sincerely,

Eleonora A.M. Festen MD, PhD

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Reviewer 1:
A mini-review summarizing genetic variations that can affect individual responses to drugs for the treatment of inflammatory bowel diseases. There are very little data on the topic discussed except thiopurine S-methyltransferase.

Author's response:
First of all, we would like to thank this reviewer for carefully reading our manuscript. We have only discussed pharmacogenetic associations identified at genome-wide significance levels, that have been replicated in independent cohorts. Some small hypothesis-driven pharmacogenetic studies have reported conflicting conclusions which have failed replication. This raises concern among clinicians and will slow down the uptake of pharmacogenetic testing in IBD clinical practice.

Next to the *TPMT* gene, *NUDT15* and two *HLA* haplotypes have been identified as genetic determinants of response to IBD drugs. We have discussed all of these (novel) drug-gene interactions in our manuscript. We believe that therapeutic recommendations based on *TPMT* and *NUDT15* genotypes should be incorporated into clinical IBD management guidelines. Therapeutic recommendations based on these *HLA* genetic variants should be further investigated prior to implementation into clinical guidelines.

Reviewer 2:
In this paper, the authors discussed several clinically useful genetic determinants of both treatment responses and side effects. It's an interesting review, that sounds well. My major observation is that the authors should be more critical and clearly state which of these genetic tests they believe should be mandatorily included in the clinical practice guidelines.

Author's response:
We would also like to thank this reviewer carefully reading our manuscript and pointing to this lack of clarity. We believe that pharmacogenetic-guided thiopurine dosing, based on *TPMT* and *NUDT15* genotypes, should be incorporated into clinical practice guidelines. We have adjusted the conclusion section of our manuscript accordingly.

Reviewer 2:
Minor point: - language should be revised for minor mistakes. Only as an example on page 4 the sentence "avoiding the prescription of (expensive) drugs that are either ineffective in or harmful to a particular group of patients" should be reformulated.

Author's response:
We thank the reviewer for this suggestion. We have reformulated this sentence and have revised the manuscript for mistakes throughout.

Author's response to Editor:
We have addressed all issues raised by the Editor in our revised manuscript. However, we have still denoted *TPMT* and *NUDT15* star (*) alleles with the * symbol. There is a consensus to the numbering of known genetic variation in these genes, which we have applied throughout our manuscript. We believe that we should adhere to this consensus. We apologize for any inconveniences this may cause.