

Response to the reviewers

Reviewer #1

Comments To Authors: It is an interesting editorial and well written

Reviewer #2

Comments To Authors: This is a thorough editorial. I have several comments and suggestions.

- 1) Page 5- **“fecal samples were collected from 8 UC patients and their healthy partners”- Would specify how many samples and at what time points they were collected as this is a weakness of the study.**

Good point. A sentence highlighting this issue has been added in the critique to the paper (page 6)

- 2) Page 5- **“Microbiota dysbiosis and altered microbial metabolism were detected in both UC patients and their healthy partners, with the most relevant genera in the latter group being Akkermansiam, Bacteroides, Escherichia, Lactobacillales, Klebsiella, and Parabacteroides. “ You point out the differences they noted among the two groups but you don’t highlight enough what the similarities between the two groups was and this is the thrust of their argument- that the two groups were similar. If you don’t think the authors of the study highlighted the similarities enough this has to be mentioned.**

I agree – however the paper does not give details on this issue. The authors only say (page 10) that by 3 different metrics the microbiota of UC patients and their spouses were not different. We have added a sentence on page 5 to reflect this.

- 3) **I think the reader would also want to know how they determined that the healthy control had a “dysbiosis” when they did not use a control population of healthy**

neighbors or others in the same community- also a limitation of the study as you point out.

I agree. But this was already highlighted in the the original Editorial on page 7.

4) Conclusions- if you are happy that the authors determined that the healthy partners had a “dysbiosis” and did not have IBD, maybe you could comment that further studies are needed but dysbiosis alone is likely not enough to result in IBD which is why the partners are not thought to develop IBD.

I agree again. However this was also highlighted in the original version of the Editorial. We have added an additional sentence on page 7 stating that “...dysbiosis in and by itself is likely insufficient to cause disease...” as you have suggested.

Reviewer #3

Comments To Authors: The Editorial is well written and does offer a critical appraisal of the topic covered in the original manuscript (which I did not see, so I base this statement on what I read). Limitations and the need to cautious interpretation are well discussed. However, a few additional points require consideration: General Comments:

1. The original study focuses on UC. I would restrict most comments to UC and not IBD overall.

In principle I agree. However many of the data on IBD and microbiome do not really distinguish among the two diseases UC and CD. For this reason in the introduction we chose to discuss IBD in general. Wherever appropriate we have specified what relates specifically to UC.

2. Core tip, page 3: the major finding of the original study appears to be that there is some microbial sharing between spouses and that this alone is likely insufficient to

induce disease, as well stated in the Editorial. This would suggest that in relation to the cause vs. effect question, posed at the top of the 'core tip', this study offers more support for effect than cause, although one cannot directly conclude this from this study. It might be a good idea to reflect this point in the 'core tip', obviously with need for caution in interpreting results.

I have incorporated the suggested changes in the new version of the "core tip". Due to its length now exceeding the maximum allowed we had to make few additional edits to this section.

3. The main additional criticism on the original study that I would add (assuming this was not done in the original study – I did not receive access to the manuscript the Editorial relates to) is that spousal effect was not controlled for. Beyond the inclusion of local healthy controls, as discussed on the top of page 7, I would have liked to see if spouses of UC patients are more or less similar to their partners than in couples without GI disease.

The microbiome can be transferred from healthy individuals to healthy individuals within the same family. This was briefly discussed in the final sentence of the original Editorial.

4. Another important point to consider is whether one partner having UC could impact the spouse's microbiome indirectly, through diet for example. It is possible that when one family member has a chronic intestinal disease the diet of the entire household changes.

I agree with the suggestion. We have added (page 6): "The study does not clarify whether the transfer of the microbiome might occur by direct contact or by other means."

Specific Comments:

1. **Abstract, Page 2: suggest changing 'If this finding impacts..' to 'Whether this finding impacts...'**

Done

2. **Editorial, bottom of page 3: the statement that 'this symbiotic microbial cell population (or microbiome) outnumbered that of the human host by 10:1' should be modified in light of the following paper: Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans. Sender et al., Cell. 2016 Jan 28;164(3):337-40. doi: 10.1016/j.cell.2016.01.013. 3.**

Thank you. I have modified the sentence and added that paper to the list of references.

3. **When abbreviated after first use Genus names should be followed by a ' '. For example, E. coli, not E coli.**

Thank you. I have corrected this.

4. **Top of page 6 – the first sentence should be rewritten. I think you are trying to say that including a follow up could have clarified whether spousal microbes impact disease course, but the way this is written now the message is not clear.**

I have added "...and bear any clinical meaning. " I did state later in the paper that cohabiting with UC spouses is not known to increase the risk of the disease in healthy partners.

5. **There are several extra spaces throughout the Editorial that should be removed.**

Thank you. I have checked the paper again and hopefully fixed the problem – but I will leave it to the publisher to check the final format, spaces etc.