Response to Reviewer 1 Comments

At first we would like to express our gratitude to both reviewers for their critical revision of our manuscript and for the commentaries and suggestions. As we found them highly valuable we incorporated the required changes into our revised manuscript. Changes in the manuscript were made through the Track Changes option. Our specific replies to each critique of Reviewer 1 are included directly in the manuscript (through Comments) and are also provided below:

Point 1: Keywords should be limited to 10 words.
  - Response 1: We reduced the number of keywords.

Point 2: Line 52-56, to emphasize significance of NGS technologies in introduction is not appropriate. It should be moved to a different section
  - Response 2: We do agree with the reviewer. We decided, however, not to move the mentioned part into a different section, rather to delete it entirely. Following re-reading we realized that it is not really relevant for this manuscript.

Point 3: Lines 69-70: please consider revising the sentence.
  - Response 3: We revised the sentence – revisions are highlighted directly in the text.

Point 4: Line 75: “Outbreak of cfNAs analyses....” Please use different term (outbreak)
  - Response 4: We changed “outbreak” to “spread”.

Point 5: Lines 117-121, revise the paragraph or give an appropriate title to Figure 1, which shows “Origin and organization of cf-NAs.”
  - Response 5: We revised both the paragraph as well as the entire Figure 1.

Point 6: Line 126: “4. Exosomes in IBD” This section describe exosomes and proteins associated with it. This section should focus on biological significance of nucleic acids that are associated with exosomes. Does nucleic acids associated with exosome considered cfNA? Needs a discussion.
  - Response 6: We added two citations and two sentences at the end of the paragraph (lines 225-228 according to the updated line numbering). As stated in previous sections, nucleic acids associated with exosomes are considered cfNA. However, the exact role of exosome-bound NAs is not well known.
Point 7: Line 186-187: “These traps are then able to capture the bacteria and neutralize them.” The term neutralization should be explained or the changed.

- Response 7: We changed the word to “kill”. Hope this is a more accurate expression.

Point 8: Line 183: “Neutrophil extracellular traps in IBD” In previous paragraphs author state that cfDNAs are highly fragmented molecules to the size of approximately 160 bp, while mt DNA is fragmented to 30 to 80 bp. miRNAs are even shorter. Based on these data a short discussion is needed to explain how neutrophil extracellular trap complexes considered cfDNA.

- Response 8: We modified the relevant text in page 3, where we described the length ranges of cfDNAs in more details. We also included a short sentence about the contribution of NETs to the total pool of cfDNAs here into the “Neutrophil extracellular traps in IBD” paragraph (the insertion is highlighted).

Point 9: Line 244: “…including TLR9, Sting and AIM2 [55]. CfDNAs are able to bind toll-like receptor 9 (TLR9). Please spell out TLR9 first. Same for Sting and AIM2.

- Response 9: We corrected this mistake – the corrections are highlighted directly in the manuscript.

Point 10: Lines 345-347; “DNase can directly cleave the circulating cfDNA, but can also break the structure of NETs, thereby reducing their proinflammatory properties.” Please site paper or explain.

- Response 10: We added two citations.

Point 11: Line 409: Please be consistent microRNA or miRNA

- Response 11: We corrected this mistake.

Point 12: Line 368: “Cell-free miRNA in IBD” A short paragraph is needed on how miRNAs regulate gene expression.

- Response 12: We added a paragraph on the role of miRNAs in gene expression (lines 428-434 according to the updated line numbering).

Point 13: Line 403: delete “but”

- Response 13: We deleted it.
Point 14: Line 420 “Cell-free IncRNA in IBD” A short paragraph is needed to describe roles of long non-coding RNAs in gene regulation

- Response 14: We added a short paragraph on the role of IncRNA in gene expression (lines 481-486 according to the updated line numbering).

Point 15: Conclusion: please summarize present understanding on role of cfNAs in IBD and UC instead of what is missing from the literature. “….. therefore a significant tool of liquid medicine which is reaching the clinical care …. “ “…… with regard to the role in IBD only a limited number of publications are available” “….. these represent a significant basis for the future research…..”

- Response 15: We briefly summarized the most relevant roles of cfNAs in IBD (lines 530-545 according to the updated line numbering).