Author responses to reviewer comments number 2677979

1. INTRODUCTION: NEED BETTER EXPLANATION ON WHAT COMPRISES IBD.

Added: Although the disease pathogenesis is not fully understood, IBD is characterized by chronic inflammation of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors.

2. IBD AND RISK OF CANCER: NOT CLEAR MEANING OF FIRST SENTENCE.

Corrected: In patients with IBD, chronic intestinal inflammation is the primary risk factor for the development of gastrointestinal malignancy.

3. NEED TO SHOW A TABLE SHOWING DIFFERENCES BETWEEN INFLAMMATORY CONDITIONS AND FACTORS THAT CHARACTERIZE THEM. (ALSO INCLUDE REFERENCE FOR EACH ONE)

Added: Tables showing specific cancer types secondary to intestinal inflammation with standardized incidence ratios, and secondary to immunosuppression with references.

4. EXPLAIN MORE ON THE POTENTIAL FUNCTIONAL ROLE OF MICROBIOTA AN IBD AND CRC.

We agree with the reviewer that the role of the gastrointestinal microbiome in CRC and IBD is critically important in our growing understanding of these disease states. As this is a clinical/translational highlight, there is not substantial relevant evidence on this topic. Given this, the authors added a sentence stating “Although we are just beginning to understand the association between specific gastrointestinal microbes and cancer, much remains unknown regarding the causes and effects of these relationships and how manipulating the microbiome may have therapeutic potential.”

5. PAGE 5: FIRST SENTENCE..." OTHER THAN CRC... " NEED A SMOOTH TRANSITION.

Corrected to “ In addition to …”

6. PAGE 6: ON SKIN CANCER PARAGRAPH: THERE IS NOT CLEAR TAKE TO HOME MESSAGE TO READERS.

Added as last sentence: "As such, thiopurines increase the risk of NMSC whereas TNF-α antagonists increase the risk of melanoma."

7. LAST PARAGRAPH PAGE 6: .... THE CESAME... (INCLUDE NUMBER OF PATIENTS)

Added and corrected to: "In 17,047 patients in the CESAME prospective observational cohort, exposure to immunosuppression was independently associated with the development of cancer with an adjusted HR of 1.9 (95% CI 1.2 to 3.0) [30]."

8. PGE 7 SECOND PARAGRAPH: ... IN ADDITION.... (INCLUDE AGE AND OTHER DEMOGRAPHICS)

Other demographic data were not included in the analysis for this study.

9. PAGE 8: IBD RISK FACTORS NEED TO DISCUSSED THOROUGHLY.

The authors are not clear about which risk factors the reviewer is referring to. Risk of cancer and cancer recurrence secondary to immunosuppression of varying types is discussed at length. Other risk factors for cancer in IBD are discussed in the introduction.

10. PAGE 9:DATA FROM CLINICAL TRIALS FOR IBD AND CRC NEED TO BE DESCRIBED

The authors agree with the reviewer that clinical trials on IBD and CRC are important. However, to date, there are no clinical trials regarding this specific patient population.

11. IN GENERAL CONCLUSIONS ARE WEAK

Corrected to: "Patients with IBD are at an increased risk of cancer secondary to long-standing intestinal inflammation and secondary to immunosuppressive therapies. As the population of patients with IBD ages, there is an increasing risk of cancer development. Many of these patients will require cancer treatment and many will require further treatment for their IBD.

Much research is being devoted to exploring the role of chronic intestinal inflammation from IBD in carcinogenesis, and the role of immunosuppressive medications used to treat IBD in the promotion and prevention of cancer. Despite these efforts, much remains unknown regarding the interaction

between IBD, medications for IBD, and cancer treatment, and the risk of cancer recurrence in patients with IBD and a history of cancer.

Understanding the effects of chemotherapy, hormonal therapies, radiation, and surgery for cancer on IBD may help identify patients at the highest risk for disease exacerbation during and after specific cancer treatments, especially in those who may require re-initiation of immunosuppressive therapies for IBD. In addition, while retrospective data has demonstrated some evidence for the safety of immunosuppression in patients with IBD and a history of cancer, prospective data are needed to validate these findings. Furthermore, data is lacking regarding specific cancers, treatments, and risk of recurrence under varying immunosuppressive medications for IBD. More data will permit the development of evidence-based, quantitative risk-benefit models including cancer and IBD-related variables to assist clinicians in managing this complex patient population. “