Dear Reviewers,

We have edited our minireview to reflect the suggested revisions. Please see below for the detailed breakdown of the revisions.

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Page 3: "TNF inhibitors available to patients for treatment of active IBD" perhaps change with the phrase "TNF INHIBITORS AVAILABLE FOR TREATING ACTIVE IBD". The sentence next to this is also hard to understand "Studies have confirmed that there is a correlation between clinical response and serum (laboratory studies??) trough levels of anti-TNF agents."

Author response to Reviewer #1: This paragraph was re-written as reflected below:

TNF inhibitors available for treating active IBD include infliximab, adalimumab, certolizumab, and golimumab. Studies have confirmed that there is a correlation between clinical response and drug concentrations of anti-TNF agents measured via serologic work-up.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: it is an interesting review, however since it is about monitoring the ways available for monitoring should be highlighted in each therapeutic agent (ie drug traffic levels, total antibodies etc) and which is the clinical utility of those approaches in therapy prediction
Author Response to Reviewer #2:

A paragraph labeled "Immunoassay methods for the detection of antibodies" was added to the review article in order to discuss the varying assays we have for detection of antibodies and their application to the varying biologics. See below for the paragraph. References 61-63 were added to reflect the additional papers that were reviewed.

Immunoassay methods for the detection of antibodies

Although it is well known that patients with inflammatory bowel disease are at risk of

developing antibodies to biologics, more attention should be paid toward the optimal

methodology used to detect these antibodies. The various immunoassay methods for detection of drug antibodies are suspected to yield varying results when assessing immunogenicity of biologics due to the presence of drug and the potential underestimation of ADA[61]. Drug interference limits the detection of ADA due to the formation of ADA-drug complexes in the assay. Drug tolerant assays were developed that can detect free ADA and ADA bound in a complex. This assay can dissociate the ADA from the drug to estimate the quantity of ADA more accurately in a sample. Drug-sensitive antibody detection methods such as the antibody binding test (ABT) and bridging enzyme-linked immunosorbent assay (ELISA) preceded the drug-tolerant assays [62].

A study by Ruwaard et al. compared the efficacy of three different immunoassays to detect ADA, including ABT, ELISA, and drug-tolerant assays in 86 patients on adalimumab. There was a significant difference in the ability to detect ADA between the assays, with drug-tolerant assays detecting ADA in 69% of patients, compared to 30% in the ABT, and 2% using the ELISA. This suggests that drug-tolerant assays should be the standard when detecting ADA in patients on adalimumab[61]. A study by Wang et al. compared ELISA to a drug tolerant assay, the homogenous mobility shift assay (HMSA), in patients treated with infliximab. This study illustrated that the HMSA was significantly more sensitive in detecting ADA, especially in the presence of high serum drug concentrations. HMSA can overcome artifacts encountered using drug-sensitive assays, as it can dissociate the ADA from the drug [62]. These studies suggest

that future studies should consider using drug-tolerant assays as their method of detecting ADA to standardize the methodology and prevent inconsistent results between different studies.

It is still well-known that ADA formation leads to lower drug concentrations and worse outcomes in patients with IBD on biologics. The data suggest that drug-tolerant assays are ideal for detection of ADA in patients on adalimumab and infliximab. Standardization in detection of ADA would improve the variability amongst studies, thus improving clinicians' ability to use and perform therapeutic drug monitoring. Unfortunately, the available data focus on TNF inhibitors, and the applicability to non-TNF inhibitor biologics is limited. Further studies with inclusion of all biologics could help lead to implementation of international standards and improve our understanding on the impact of ADA on clinical outcomes[63].

Thank you for your time.

Sincerely,

Shanti Rao MD and Nilesh Lodhia MD