A retrospective chart review was done of patients attending the IBD centres at Cedars-Sinai IBD Centre from 2005 to 2016. This study was done to describe the type and frequency of adverse events associated with anti-TNF-α therapy in patients diagnosed with Inflammatory Bowel Disease (IBD) in a large cohort and to evaluate for any serological and genetic associations. This study was warranted because there are few studies documented that investigates the adverse effects of anti-TNF-α therapy. The research group were able to cover their objectives and addressed the adverse events associated with therapy. A relatively large study population was used compared with study populations used in similar studies in the past. The findings from this study would go towards helping to reduce the adverse effects of therapy and would give more patients a better chance of improve compliance and tolerance to anti-TNF-α therapy. Major Issues 1. The researches indicated that the overwhelming majority of the patient population studied was of European ancestry. No mention was made of what percentage of patients was of European ancestry. IBD is known to affect all racial groups, so the population studied did not fully represent the patient population of IBD as minority groups were definitely underrepresented in this study. The paper did not mention the reason for this variation in the study group. This is most likely due to the Cedars-Sinai Medical Centre being located in the predominantly Caucasian neighbourhood of Beverly Grove, Los Angeles, California. The ethnic demographics are not typical of the multicultural Los Angeles. Correlation of results with a study done in a more multi-ethnic medical centre would have been valuable. In conclusion, this paper was informative and the authors described clearly the methodology used and results which were obtained. Limitations in the study, as well as, recommendations such as the need for further research were addressed.

We thank the reviewer for the comment. Our study population was predominantly of European ancestry. While IBD is rising in non-Europeans, the highest percentage is still of European ancestry. For this reason, and the location of Cedars-Sinai Medical Center in west Los Angeles, the majority of our patients are of European ancestry. Previous work have shown ethnic differences in genetic associations with adverse events (**Yang SK**,

Hong M, Baek J, et al. A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. Nat Genet 2014;**46(9)**:1017-20. [PMID: 25108385 DOI: 10.1038/ng.3060]), and a study similar to this one will need to be performed for other ethnic groups.

The study includes 1,258 patients (954 CD, 260 UC, 44 IBDU) and 21% were found to have adverse events to anti-TNF-alpha therapy. In CD IgA ASCA was identified as potential biomarker. Comments 1. A subgroup analysis is necessary. Is there any evidence that CD includes an anti-TNF-alpha sensitive group with an increased rate of adverse events? Can you characterize this subgroup by clinical or molecular parameters? 2. The IBDU patients should be analyzed in more detail. The frequency of events should be correlated with CD as well as UC patients. Is there any re-classification possible?

We thank the reviewer for the comment, and we agree that subgroup analysis can be helpful, which is why we looked at serologies. Our data suggests IgA ASCA with CD, have a decreased risk of adverse events, and IgG ASCA and total ASCA also showed a decreased risk of adverse events, but did not reach significance.

We also agree that it would be interesting to see how the adverse events in IBDU patients correlate with both CD and UC. However, our study, which showed an overall prevalence of 21% with adverse events, and a total of only 44 IBDU patients, does not have enough adequate power to answer this. We think that this would be a very interesting question for a multicenter cohort in the future.

Congratulations on this interesting study. My only suggestions is to shorten the introduction and discussion and highlight the genetic results in the conclusions.

We thank the reviewer for the comment. I have shortened the introduction and discussion, and included more information on the genetic results. Please see the revised manuscript for a complete detail of the revision.

Thank you for the interesting and well done study. The paper is well written, but an issue needs further development. As your result show that IgA ASCA is associated with lower risk of any adverse event to anti TNF, I would like you to include in discussion section a proposed mechanism for this interaction. The same regarding Anti I2 in UC patients, where anti I2 were associated with infusion reactions.

The association with ASCA and I2 are interesting. Perhaps these markers identify patients with a predilection towards small bowel involvement. Patients with colonic disease tend to respond less to anti-TNFs or require higher doses (**Yoon SM**, Haritunians T, Chhina S, et al. Colonic Phenotypes Are Associated with Poorer Response to Anti-TNF Therapies in Patients with IBD. *Inflamm Bowel Dis* 2017; **8**: 1382-1393. [PMID: 28590340 DOI: 10.1097/MIB.0000000000001150]; **Cohen RD**, Lewis JR, Turner H, Harrell LE, Hanauer SB, Rubin DT. Predictors of adalimumab dose escalation in patients with Crohn's disease at a tertiary referral center. Inflamm Bowel Dis 2012;**18(1)**:10-6 [PMID: 21456032 DOI: 10.1002/ibd.21707]). Therefore, perhaps these patients are more likely to develop antibodies or reactions to anti-TNFs.