**Fig 3G, the microbiome sequencing and what exactly is being displayed here, is not explained well in the legend, text, or methods. What is the z score? What is this subset of ASVs (I assume they are ASVs because the methods mentions ASVs) shown? It is unconventional to not show a more global view as well (PCA or stacked bar charts).**

**The main text cites this panel and says the knockout mice have a depletion of Lachnospiraceae: this isn’t clear. Is the z score implying a single lachnospiraceae ASV was detected in 2/6 mice in WT and 0/6 in knockout mice? That seems to be not great evidence. Methods state the use of ANCOM and Lefse which are statistical models for differential abundance: but the results of those are nowhere to be found.**

To the reviewer

The Z-score corresponds to the ANCOM computed z-score of the centered-log ratio of the ASV in any individual mouse. It does not refer to the comparison of Lachno present in 2/6 versus 0/6, but rather the significantly higher abundance of a given Lachno ASV in a given mouse relative to the other taxa present in that same mouse. LEfSe is not used in any of these results and has been deleted from methods (Supp page 11, reference 87). The new heatmap is updated to resolve this ambiguity, and the figure legend (lines 1029-1030) have been updated accordingly.

Alpha and beta diversity (PCoA) plots are added to provide a more global view; the WT has a significantly higher Shannon Entropy than the Igah-/- (p=0.015), however there are not significantly different compositions in beta diversity (unweighted UniFrac, p=0.32).

To Cerutti et al.

-The original heatmap has the 10 most abundant and 10 least abundant ASVs; not sure why the least abundant 10 were used (I didn’t see any discussion in the text for Clostridia) so I used only the most abundant 10 for the new heatmap.

- I generated an alpha barplot (Shannon Entropy, p=0.015 via Kruskal-Wallis) and beta PCoA (Unweighted Unifrac, p=0.32 via PERMANOVA) in response to the more global view. The taxa barplot doesn’t seem to show any major differences in the two populations either so showing alpha, beta, and ANCOM I think offers the best and most concise summary.

-**Please** **change figure legends (see below):** Please update figure legends with the text below (to add in line 1029) and also add the alpha and beta diversity plots before the heatmap which was originally old figure G. Subsequent figure legends and labels will need to be incremented accordingly.

-**Please change supplemental methods:** Page 11 of supplemental methods to say ‘Differential abundance analysis was performed using ANCOM (88)’ instead of “LEfSe (87) and ANCOM (88)” – will need to change reference order as well. No change to main manuscript methods.

(**G**) Alpha diversity (as measured by Shannon Entropy) comparing colonic microbiome of the WT and Igha-/- strains (p=0.015). (**H**) Beta diversity (unweighted UniFrac) comparing the colonic microbiome between the WT and Igah-/- strains (PERMANOVA p=0.32). (**I**). Heatmap showing the ANCOM Z-score of the abundance of a given ASV (rows) in each sample (columns).

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