Lines 28-29: H pylori-negative gastritis can be detected by endoscopy, such as in autoimmune atrophic gastritis...what exactly do the authors mean by “endoscopic gastritis?” This term is never clearly defined in the text, but I presume it means some or one or all of the endoscopic findings they describe. Additionally, the line that only H pylori-induced endoscopic gastritis requires gastric cancer surveillance is dubious. Gastric cancer surveillance in this setting sounds like regular endoscopic procedures, but what happens when the H pylori is eradicated from the patient? I don’t think endoscopic gastric cancer surveillance is still performed after eradication. It is unclear what the authors mean with this line. Additionally, gastric cancer surveillance occurs in many non H pylori related conditions, and this line may inadvertently confuse the reader.

Supplementary Figure 1: I do not have access to this. I see the legend at the end of the document, but the supplementary document only contains the supplementary tables.

Line 163: Means and standard deviations can just be calculated from the data, whereas the t-test tests if these data sets are different. Please clarify this statistic description.

Line 213: “The combined inflammation score was correlated...” should be “A combined inflammation score ≥2 was correlated with H pylori in H pylori-infected patients, and with Variovorax paradoxus and Porphyromonas gingivalis in H pylori-negative patients.” It would be clearer to state “an increased combined inflammatory score” or a “combined inflammatory score ≥2” elsewhere in the text as well (for example line 276). But if the species in question actually increases with each combined score value, then leave the correlation as is.

Line 215: After listing the species positively correlated with inflammation in the duodenum, “Table 2” should be inserted in order to direct the reader to the table that lists this information.

Table 2: The top category headings Microbiota and Combined inflammation score, but I don’t think these headings are necessary, the next subheadings state Site, Level, Positive Correlation, Negative Correlation, which state all the information. Then in the table legend, it should state that these are correlation between the relative abundance of microbiota and “a combined inflammation score ≥2.” Also, in line 238, “each microbiota” does not sound right. Microbiota is a community of microorganisms, so it isn’t really each community of organisms but rather “each genus or species” of the microbiota. This occurs elsewhere (lines 25, 26, 43, 54 microbiota other than..., etc). The use of microbiota sounds correct when the authors use it in lines 46 or 49, for example. Consider changing microbiota to bacteria (assuming all are bacteria) when possible, including results subheadings.

Figure 3: I didn’t think about this before, but how were the p-values here calculated and was a correction for multiple comparisons made? It seems the authors checked at least 8 endoscopic findings and 2 different stomach sites, not to mention the 500+ species tested. Can you please explain how the statistics were done? It seems complicated, similar to microarray analysis. If an alpha of 0.05 is set, that means that there is a 1/20 chance that two similar populations will show a difference. Thus 1-(0.95)^500 becomes a certainty that one will find a difference in at least one species. Additionally, as I mentioned before, I think separating H pylori-infected patients from non-infected patients is necessary, especially when comparing relative abundances. For example, in Figure 3, hemorrhagic spots, the relative abundance of P acnes is 1% in the body when hemorrhagic spots are present in the fundus, and 8.2% when this finding is absent, with a p value of 0.007. However, this may be misleading precisely because this is a relative abundance value, and H pylori is dominant (90.8%) when this finding is present, and very little (0.6%) when this finding is absent. Thus examining H pylori-infected vs uninfected is important. Additionally, as I mentioned before,
perhaps examining the relative abundance of non-H pylori species would be interesting. In that same example, if one only examines the relative abundance of P acnes as compared to all other species other than H pylori, does value change when hemorrhagic spots are present vs absent? I think that data would be interesting. Overall, I think this figure needs to be re-done, and is almost meaningless as H pylori completely alters the data, and its very presence would be expected to decrease the relative abundances of all other species (as was observed). Notice how when H pylori species is present, it is never the case that a different species is higher when an endoscopic finding is present vs absent. The authors should consider how this might affect other data (such as table 2 or table 3).

Supplementary table 2: Same criticism for this table as for figure 3. I don’t think the comparison is valid in this manner.

Lines 260-263: This data is not shown, and does not necessarily need to be shown in a table, but were these significant correlations or just stronger correlations? Additionally, the results in Table 3 are not presented in the results section, perhaps some highlights can be presented.

Table 3: There is a subsection with correlations found in 61 H pylori negative subjects...does that mean the first part consisted of all patients or just H pylori positive subjects?

Section 3.6: I personally would like the H pylori negative subject data presented in order along with the figures rather than separately, but that is just my preference. Perhaps the discussion can synthesize all the data for H pylori negative subjects instead of the results.

Section 3.7: Were all these patients technically H pylori negative? The relative abundance for H pylori (0.62%) seems low enough for that to be the case, but the H pylori status should be stated. Again, I think separating H pylori positive from negative patients is necessary.

Lines 328-331: Atrophy is an independent risk factor for gastric cancer, but I don’t think these studies say that hypertrophic rugae, diffuse redness, and nodularity increase the risk of diffuse-type gastric cancer, but rather these findings are associated with diffuse type gastric cancer. However, I have not exhaustively perused these references, but please consider the wording of risk vs association.

Lines 343-347: The discussion of the ENS comes out of nowhere, but I know the other reviewer wanted it in there. However, I think the authors could be more speculative rather than suggestive. They state “our findings further suggest that the duodenal microbiota...and gastric microbiota...may negatively affect ENS modulation via neurogenic inflammatory process.” Nowhere in the data presented is this suggested. The data does not even touch neurogenic inflammatory processes. Rather, the authors could speculate something like “Perhaps the finding of a stronger correlation between symptomatic gastritis of certain species in the duodenum than in the stomach may be explained by differing interaction with the ENS...” Or perhaps H pylori modulates the ENS to depress the ENS? But certainly no data is stated to support this, and the line 347 “This increases our understanding.” is unwarranted in this context.

Line beginning 367: I think symptomatic gastritis should be evaluated and managed differently because it is less likely to show H pylori, not because it is more strongly correlated with certain duodenal species. This can be separated and one could speculate that perhaps these species in the duodenum may cause symptomatic gastritis. But more work would need to be done to conclusively say that. Anyway, I think the line is awkward, but it should emphasize that lack of correlation between symptomatic gastritis and the H pylori.