**Author’s response to reviews**

**Title:** Serological Biomarker Testing Helps Avoiding Unnecessary Endoscopies in Obese Patients Before Bariatric Surgery

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Response to reviewers

Reviewer reports:

Kjell Grankvist (Reviewer 1): This is an interesting and novel paper describing the usability of a biomarker panel to exclude endoscopies before bariartic surgery in obese patients.

A drawback with the paper is that the authors does not systematically compare the biopanel test with the two golden standards EGDS and biopsies respectively.

It should be clearly stated that the biomarker panel (software-aided) classification of patients into healthy stomach (HS) and non-healthy stomach is tested against the two golden standards and that the paper (results, discussion) as well as the abstract structured accordingly (panel vs EGDS, panel vs biopsy results) followed by a symptoms results and discussion.

Response

The validity of GastroPanel to diagnose and delineate healthy stomach and H. pylori gastritis with or without atrophy is strong and validation has already been done in many independent clinical investigations against the golden standard (endoscopy with endoscopic histology). There are, in addition, at least two systematic reviews on this issue (Syrjänen K., 2016. A Panel of
Serum Biomarkers (GastroPanel®) in Non-invasive Diagnosis of Atrophic Gastritis. Systematic Review and Meta-analysis; Zagari RM et al., 2017. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-Helicobacter pylori antibodies serum assays for the diagnosis of atrophic gastritis. Aliment Pharmacol Ther 2017;1-11, doi: 10.1111/apt.14248). Therefore, to do validation within this study would be more or less an exaggeration. In addition, the present number of patients (65) and especially the cases with substantial pathology (mucosal atrophy) is too low to do reliable and true validation.

Gastro Panel can be compared to histological findings, but in the case of comparing GP vs endoscopic findings alone, only esophagitis has been proposed to be potentially detectable by means of using biomarkers, although the published results have been controversial (as mentioned also in discussion).

(We restructured partly our manuscript, taking into account also your suggestions, separating more clearly the sections comparing GP vs histology and GP vs endoscopy).

A short summary of the biomarker panel software classification should be included in the methods section.

Response

Short summary added in the methods section, lines 117-124, page 6.

Specific:

Abstract - Rewrite and structure as suggested above. It is no meaning in doublewriting that the biomarker panel HS and NHS groups were classified according to biomarker profile as this is obvious and also not surprising that the groups profiles therefore were significantly different.

Response

Changes to abstract made

Methods - Add more on how the biopanel classification was performed by the software. Heading - add Histologi to EGDS heading Result text - Structure comparisons of biomarker systematically a) panel results with EGDS and then b) panel with histology results with tables accordingly. Comment on the biomarker panel misclassification of panatrophy vs histology superficial gastritis (table 2).

Results - tables - Table 1 - move "n(%) from column to to table characteristics were relevant - e.g. females, concomitand disease et cetera. Table 3 - consider to present as supplementary table as software classification considers several biomarkers?? Change to "." instead of "," in p-value table.

Response
Table 1 corrected, Table 3 also corrected.

Table 4 - Partially overlapping results with present table 2? Can all histology results be presented in table 2. Separate table on EDGS (as one of the golden standards) and biomarker panel as suggested above.

Response

Table 4 was changed, histology was removed from Table 4 and focus was placed on the endoscopic finding vs gastropanel.

Gil Faria (Reviewer 2): This is a very interesting clinical question and the methods are adequate to study it.

However, there are some minor issues I would like the authors to address.

1 - The authors state that the serological panel is cheaper than EGDS. Please provide more information about it and include a cost-effectiveness analysis. From the data presented by the authors, for the serological panel to be cost-effective, the panel would need to cost about 1/3 of the EGDS. What would be the number of EGDS avoided for the panel to be cost-effective?

Response

Cost-effectiveness is, of course, also country specific, as the prices for EGDS + pathohistological evaluation can differ to a large degree. For example, the cost per patient for GP in Finland is 125 EUR versus about 600 (average) EUR for EGDS with pathohistological evaluation. In Estonia GP is not routinely available on the market and its cost-effectiveness is difficult to evaluate.

We agree that for the population cluster studied, the GP price should be about 1/3 of EGDS complex.

Information about the GP price was added to the introduction, lines 78-80, page 4.

2 - The serological panel detects gastritis and HP infection. But what about other lesions like GIST or NET? In the sample, there were no patients with either pathology, but some reports state that GIST prevalence might be as high as 20%. Would the panel detect those lesions?

Response

The GP was primarily developed for detecting patients with atrophic gastritis. The study population did not reveal GIST or NET patients. According to some data GP may not be capable of detecting these pathologies. On the other hand, it is advocated not to perform EGDS in bariatric patients without complaints at all. From this point of view, we suggest to reduce routine EGDS, but still testing also patients without complaints, using GP, to select particular patients...
for EGDS also from this group. As mentioned in Discussion, populations (also HP prevalence etc) are different in different countries and regions, and therefore also corresponding guidelines could be potentially different.

3 - Very few patients had severe gastritis in the sample. Would the results be different for patients with severe gastritis?

Response

Indeed, as mentioned, GP was developed for atrophic gastritis screening mainly in elderly (over 50 years) people. The bariatric population of the study group is much younger (and the number of expected serious findings from the gastric mucosa is also lower). As bariatric surgery is suggested today to be feasible also in older persons (over 60 years), the importance and value of GP in detecting severe gastritis could potentially be much higher in such subgroups, as proposed also in our Discussion.

4 - Most importantly 10% (2/20) of the patients that would be recommended to avoid EGDS had erosive esophagitis. The authors discuss the selection of gastric sleeve vs gastric bypass, but if these (asymptomatic) patients were offered a gastric sleeve, chances are they would worsen their esophagitis. So... how much is too much? If we select the "wrong" surgery in 1/20 patients, does that worth the cost of not performing EGDS?

Response

Esophagitis and potential gastric sleeve operation have been discussed increasingly more intensively in recent years. The substantial part of esophagitis patients can be without typical complaints. There is no total consensus on this issue. By following most guidelines and not to perform EGDS in complaintless patients would also miss these cases. Unfortunately, GP was not able to detect them in our study group, although some studies (not in overweight patients) have suggested that GP can potentially detect also esophageal lesions. Of course, here we could discuss whether for patients in whom gastric sleeve is intended EGDS could be still mandatory?