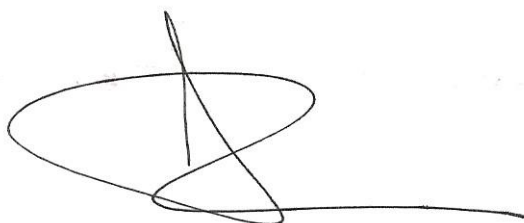Ourense, 15h July 2021

Dear Editor

We appreciate the opportunity to provide a revised version of the manuscript entitled "Impact of a CRC screening programme implantation on delays and prognosis of non-screening detected CRC" (World Journal of Gastroenterology Manuscript NO: 66666).

The revised manuscript has been modified to reflect the very helpful comments provided by the reviewers. Our responses are outlined in this cover letter (blue) and incorporated in the revised manuscript (red).

Best wishes,

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Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: This is a retrospective intervention study with a pre-post design to confirm the hypothesis that implementation of a CRC screening program may increase the awareness of primary care physicians, and reduce the diagnostic delays in CRC detected outside the screening program and improve prognosis. The author identified the pre-implantation and post-implantation cohort consisted of 322 and 285 patients, respectively. Baseline differences weren't be detected between both

cohorts. The results of their study confirmed that the implementation of the CRC screening program reduced the diagnostic delays due to an increase in the direct referrals to colonoscopy from primary healthcare. However, their study demonstrated that such reduction in the delay had no effect on the stage at diagnosis or in the two year survival according to the multivariable Cox regression analysis. As the author mentioned, the study firstly evaluate the effect of the CRC screening programme on the diagnostic delays of CRC detected in symptomatic patients. This topic is of potential interest to the Journal's readership. However, the study still have some weakness. Principally, there are some problems in the use of statistical methods. Cox multivariate regression analysis was used to determine which variables were independently related to survival after diagnosis. Prior to this, univariate regression analysis was not performed to screen variables. Due to the correlation between the included variable, this approach may produce much confounding bias. Furthermore, the conclusion that reducing in referral delay had no effect on CRC staging at diagnosis seems to be controversial. Through the analysis of this study, the conclusion seems to be lack of evidence, because it did not confirm the impact of referral delay on CRC staging. In summary, I agree to publish this manuscript after modification.

Answer to the reviewer 1:

1. I agree with the reviewer with respect to the Cox multivariable analysis. However, the main aim of the Cox analysis was to control confounding variables in order to confirm the initial results in the Kaplan-Meier analysis. In this analysis, we did not find differences in survival between both cohorts. On account of the comments included by the reviewer we have changed the methods and the results section:

Methods

"Finally, to control confounding variables we performed a Cox multivariate regression analysis and we determined which variables were independently associated with survival after diagnosis"

Results

"These results were confirmed in the Cox multivariate regression analysis and there were no differences in the survival between both cohorts (post-implantation cohort HR 1.12, 95% CI 0.83-1.51)".

2. Although the reviewer comments that the relation between referral delay, CRC stage and prognosis seems controversial, our results are consistent with the available evidence as we discuss in the fourth paragraph of the discussion. The results are supported by the available meta-analysis.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is an interesting and well written analysis that yields results that a first glance seem to be counter-intuitive, but, the results are what they are and the Discussion explains the situation reasonably. The statistical analysis is sound.

Answer to the reviewer 1:

Thanks for the comments.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The Authors present their analysis on two cohorts of patients diagnosed with CRC in a Spanish region before and after the implementation of an institutionalised screening programme. Their goal is to demonstrate whether the screening could "reduce health system delays and improve CRC staging at diagnosis and long term survival". The Authors do not report any survival data, and the follow up is way too short to analyse the long term survival. They also fail to demonstrated any significant benefit or impact on the CRC population. The CRC screening programmes have been implemented in many countries across the World, and nowadays 30+ European countries offer their citizens a screening programme. It is unlikely that this scenario will be reverted, because of the numerous benefits of the screening and the

good general acceptance by the populations. It is therefore anecdotal to evaluate any further benefit in terms of diagnostic and referral timings, that are probably anyway not comparable since the 2 population of this study are from different time periods, when protocols, pathways, referral processes and diagnostic/therapeutic capacity could have been modified and improved over time.

Answer to the reviewer 3:

1. I agree that we have not been able to demonstrate an effect on CRC stage or survival. However, we have analyzed survival (The incidence of metastatic CRC remained stable (20.1%) in both cohorts and overall survival after one and two years was 71.3% and 70.3% without differences in the log-rank test (*P*=0.9) as we show in Figure 4.) and we have included a figure showing survival.

2. I do not completely agree with the comment of the reviewer that it is anecdotical to evaluate any further benefit in terms of referral timings. In fact, it is extremely relevant from the patient and the health system perspective. So, our results are, however, relevant.

3. On the other hand, both cohorts were similar in terms of protocols and referral processes. We have included this information in the methods section: "During the implantation of the CRC screening program no change was performed in the diagnostic pathways for CRC diagnosis in symptomatic patients." Besides, we also made a comment on this respect in the discussion: "Recently, implementation of the faecal immunochemical test to triage patients with gastrointestinal symptoms in primary healthcare has improved diagnostic referral pathways.[21,22] In the health area of Ourense, faecal immunochemical test was implemented as a triage test seven years ago, so we cannot attribute the decreases in delay to this modification.[17]"

(1) Science editor: 1 Scientific quality: The manuscript describes a study on effects of implementation of a CRC screening program may increase the awareness of primary care physicians and, thus, reduce the diagnostic delays in CRC detected outside the screening program and improve prognosis. The results appear to confirm that the

implementation of the program reduced the diagnostic delays, but the overall result had no effect on the stage at diagnosis or in the two-year survival. The topic is within the scope of the WJG. (1) Classifications: Grade B, Grade C, and Grade D; (2) Summary of the Peer-Review Report: In this study, the investigators present an analysis on two cohorts of patients diagnosed with CRC in a Spanish region before and after the implementation of an institutionalized screening program. In this retrospective intervention study with a pre-post design, the authors confirmed the hypothesis that implementation of a CRC screening program may increase the awareness of primary care physicians, reducing the diagnostic delays in CRC detected outside the screening program. However, their study demonstrated that such reduction in the delay had no effect on the stage at diagnosis or in the two-year survival according to the multivariable Cox regression analysis. This topic is of potential interest to the Journal's readership. The manuscript was rated by the three reviewers in a wide range from B (very good), C (good), to D (fair). Together, they raised several questions that should be answered; (3) Format: There are 3 tables and 4 figures; (4) References: A total of 27 references are cited, including 10 references published in the last 3 years; (5) Self-cited references: There are at least 5 self-cited references (18.5%); the self-referencing rate should be less than 10%. Please keep the reasonable self-citations (i.e. those which are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; 2 Language evaluation: Classifications: Grade B, Grade B, and Grade B. A language editing certificate was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Approval Form from Institutional Review Board Committee. No academic misconduct was found by the Google/Bing search. 4 Supplementary comments: This is an invited manuscript, and the work was supported by Spain's Carlos III Health Care Institute by means of project PI17/00837 (Co-funded by European Regional Development Fund/European Social Fund "A way to make Europe"/"Investing in your future"). 5 Issues raised: (1) This study needs clarification in terms statistical methods. Cox multivariate regression analysis was used to determine which variables were independently related to survival after diagnosis. Prior to this, univariate regression analysis was not performed to screen variables. Due to the correlation between the included variable, this approach may produce much confounding bias. Please, explain the rational for the approach chosen, or

add some more data to statistical analysis. (2) The conclusion that reducing in referral delay had no effect on CRC staging at diagnosis seems to be controversial. Through the analysis of this study, the conclusion seems to lack evidence, because it did not confirm the impact of referral delay on CRC staging. Please, add discussion on this issue. (3) The major goal of this study was to demonstrate whether the screening could "reduce health system delays and improve CRC staging at diagnosis and long-term survival". However, the authors do not report any survival data, and the follow up is way too short to analyze the long-term survival. Please, explain why the results are still relevant, in the discussion. (4) The investigators do not present sufficient data to demonstrate any significant benefit or impact on the CRC population. CRC screening programs have been successfully implemented in many countries across the World, and it is unlikely that this scenario will be reverted, because of the numerous benefits of the screening and the good general acceptance by the populations. It may sound anecdotal to evaluate any further benefit in terms of diagnostic and referral timings, that are probably not comparable since the 2 population of this study are from different time periods, when protocols, pathways, referral processes and diagnostic/therapeutic capacity could have been modified and improved over time. Please, add some more discussion to defend the relevance of your study, or offer an alternative methodological approach. 6 Re-Review: Required/Required/Not required. 7 Recommendation: Conditional acceptance.

Answer to the science editor
1.All the comments made by the reviewer are answered previously.
2.With respect to the self cited references I am afraid our group has a problem since CRC diagnosis and prevention and the use of fecal immunochemical test as a diagnostic biomarker is our area of interest. So, our research is key in this point. I have reviewed all the citations and I have managed to delete one of them (Vega et al World Journal Gastrointestinal Oncology). The rest of them are required to justify the methods and the discussion.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for

Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".