



May 19th, 2022

**University of Chile**  
**Faculty of Medicine**  
**Basic and Clinical Oncology Department**

**Lian-Sheng Ma**  
Company Editor-in-Chief  
World Journal of Gastrointestinal Oncology

This letter is to submit the revision of the manuscript entitled "**Liquid biopsy to detect resistance mutations to anti-EGFR therapy in metastatic colorectal cancer**" to be considered for publication in the Journal as a review article, for the invitation received with the NO: 76514.

I would like to provide a detailed response to each of the comments made by the manuscript reviewers. All these changes are highlighted within the text.

**Reviewer #1:**

1.1 Some references should be updated

**Response:** References have been updated in the final manuscript.

1.2 Some abbreviations should be defined the first time they appear in the text: FOLFOX, FOLFIRI, FIRE-3

**Response:** We add a definition of abbreviations in the final manuscript.

1.3 Several typing errors are found, for instance "utilises", "harbouring", "characterise", "analised". I recommend Grammarly free software to quickly screen and correct these simple mistakes

**Response:** We will provide an English certificate in the final revision.

1.4 I recommend to include a short description of anti-EGFR therapy in the Introduction

**Response:** We include a brief introduction to anti-EGFR therapy in the introduction.

1.5 Is there any relevance in CTNNB1 gene mutations related to resistance to anti-EGFR therapy that could be detected through liquid biopsy?

**Response:** We searched in PubMed " $\beta$ -catenin AND anti-EGFR" and we only found 13 results. Only one paper discusses resistance to anti-EGFR (DOI: 10.3892/ol.2021.12470) and reports a potential in vitro fusion between AKT1/ $\beta$ -catenin which produces

chemoresistance. However, from a clinical oncologist's view, It would be necessary to find a correlation between these findings of chemoresistance with a clinical failure to treat. Therefore, we consider that this work would not be a candidate to add to the final manuscript.

1.6 An illustrative figure of the key pathways involved in CRC resistance to anti-EGFR that could be detected through liquid biopsy, as well as the involved drugs in this process, could be included

**Response:** We will include a figure that illustrates the mechanism of resistance.

**Reviewer #2:**

2.1 [...] My concern is that except of CTCs and ctDNA, tumor-derived exosomes could be detected by liquid biopsy, however, this part is missing. I suggest the author add this part in revised MS

**Response:** We will add a small part about tumor-derived exosome liquid biopsy in the "Advances in liquid biopsy detection technology" section.

**Reviewer #3:**

3.1[...] However, the mutation spectrum of KRAS, NRAS and BRAF shall be showed in Figure or Table. Moreover, the other mutation shall be shown in the Figure

**Response:** We will include a figure that illustrates the mechanism of resistance.

3.2 [...] The progression of detection technology in this field shall also be described in this review.

**Response:** We will add a new section called "Advances in liquid biopsy detection technology ", which includes the review's suggestion.

**Reviewer #4:**

4.1 We appreciate the review's positive feedback.

**Reviewer #5:**

5.1 We appreciate the review's positive feedback.

**Reviewer #6:**

6.1 Due to some error, the uploaded file completely lacks the list of References

**Response:** We correct this error soon as we could it, and we include the references list in a corrected manuscript.

6.2 In contrast, the Japanese Society of Medical Oncology clinical guidelines recommend the use of anti-EGFR for the usefulness and monitoring of this therapy[62]." -> "In contrast, the Japanese Society of Medical Oncology clinical guidelines recommend the use of anti-EGFR antibodies (???)

**Response:** We reformulate this sentence because had an error. The final sentence is "In contrast, the Japanese Society of Medical Oncology clinical guidelines recommend the use of liquid biopsy due to the usefulness in monitoring of anti-EGFR therapy"

**Science editor:**

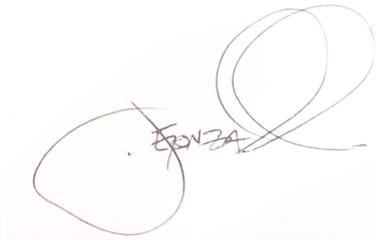
- 1) Please add a figure to summarize key pathways involved in CRC resistance to anti-EGFR, 2) add a section on detection technology evolution, 3) there are numerous typos throughout the text, authors are strongly recommended to contact a professional English editing company to polish your paper.

**Response:** We included all suggestions by reviews and science editor. Also, we attach an English editing certificate from a specialist company.

We hope that our responses and adjustments to the manuscript will be liked by the reviewers and the Editorial Board

I look forward to hearing from you at your earliest convenience.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'JAIME GONZALEZ-MONTERO', with a large, stylized flourish extending to the right.

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