

Reviewer's code: 00070916

SPECIFIC COMMENTS TO AUTHORS

This systematic review by Vacante et al. gives an overview of the current use of the different genetic and epigenetic biomarkers - mostly from a clinical point of view. I have only minor comments which can be considered suggestions for the most part. If introducing abbreviations, use them consequently thereafter.

Thank you for your comments. We checked and modify the whole manuscript for abbreviations according to the comment.

In the CIMP paragraph, there is one mistake: "Interestingly, in stage II and II CRC patients ..." must be II and III.

We corrected the mistake in the CIMP paragraph

The Figure is the weakest part of the manuscript. The question is, if it is at all necessary. At least, I would not have "mutated KRAS" and "mutated BRAF" together - they are not observed together unless a selective pressure is applied.

We modified the Figure according to the comment, specifying that mutation in KRAS or in BRAF are mutually exclusive

Since fact that this is not the first review of his kind must still be considered when judging the scientific quality.

Reviewer's code: 00227433

SPECIFIC COMMENTS TO AUTHORS

This review article outlines biomarkers in colorectal cancer, and has been structured by specific mutations and/or epigenetic changes, such as BRAF, KRAS, APC or methylation. I appreciate that the authors have attempted to provide an overview in this way, however further work could be done to improve the presentation and summary of evidence, and to discuss more novel work relating to these. Comments on the article are

below:

Thank you for your comments

1. There has been little discussion or focus on whether these biomarkers are being studied in the context of being predictive or prognostic.

We included more discussion on the predictive or prognostic role of each biomarker (also included this information in the tables)

2. In general, there has been very little critical appraisal of study designs, sample sizes or strength of evidence conveyed throughout the article. Quite rightly, there is a concentration on meta-analyses, but are these meta-analyses of single centre studies with high selection bias, for example? Was there heterogeneity in the pooled estimates identified?

We included more information on study designs, sample size and strength of evidence of the studies discussed in the paper. Also, we added information about the meta-analyses as regards possible selection bias, publication bias and heterogeneity of the studies.

3. Although I appreciate that molecular subtypes are not biomarkers per se, it seems remiss to not have a section on the overarching Consensus Molecular Subtypes; or the more recent CRIS-subtypes of colorectal cancer, and what this means for potential stratified medicine.

We added a section on the CMS and the CRIS subtypes of CRC, and discussed the implications for potential stratified medicine.

4. Many novel studies or trials are ongoing in precision medicine, for example an aspirin trial that stratifies on the basis of PIK3CA mutation is underway in the UK, and these have not been highlighted.

We modified the manuscript and discussed trials on the potential role of aspirin in

CRC patients with PIK3CA mutation.

5. Summary tables of evidence may aid presentation of information for the reader – the current format is very text-heavy in long paragraphs.

We included summary tables of evidence (Table 1 and Table 2).

6. In the conclusions, IGF1-R is introduced as a target for new therapies, but this has not been discussed before this point. IGFBP3 is mentioned earlier in the review, but further discussion would be needed to explain this conclusion.

We added further discussion in the manuscript on the role of IGF1-R and IGFBP3 as targets for new therapies .

Reviewer's code: 03317017

SPECIFIC COMMENTS TO AUTHORS

I hope the paper will be published to guide more researchers.

Thank you for your comment, we hope that our work will be useful.