

## Response to the Reviewers

Firstly, we would like to thank all the Reviewers for their valuable suggestions. In addressing their comments, we feel that the revised manuscript has been significantly improved. A detailed reply to the comments is included below.

### Reviewer #1

*This is an extensive review on nuclear medicine investigations in IBD, for diagnosis and follow-up. The authors nicely reported also in tables the large existing literature.*

**1) The text requires a review of the English style and grammar (e.g. "it may seem"..) and correction of some spelling errors.**

A deep revision of grammar has been performed and many errors have been corrected. Furthermore, many statements have been rephrased to improve the readability of the paper.

**2) Please delete granulomatous from inflammatory condition since only applies to CD**

Done as suggested.

**3) The authors should better and more extensively report in the conclusions, the limitations of nuclear medicine techniques: radioisotopes which make unfeasible their frequent use over time; lack of specificity; cost, access to specialized centers on the community; waiting list given their extensive use in oncology. As a matter of fact, given their accuracy, the small sample size studies available in the literature are strictly related to these limitations as compared to the plenty of studies using US and MRI.**

We agree with the Reviewer that the first version lacked a streamlined discussion about the main limitations of molecular imaging in the management of patients affected by IBD. Following the Reviewer's suggestions, we expanded on this important aspect in the relevant section (Discussion, page 31-bottom and page 32-top).

### Reviewer #2

The manuscript is well written and well structured

### Reviewer #3

The Authors reviewed the current literature on the potential of functional molecular imaging as diagnostic and prognostic tool in the management of adult and pediatric patients with IBD. However, there are a few minor issues that need to be addressed to improve the manuscript presentation and understanding.

**1) The manuscript should be reviewed for English grammar, style, typos and superscripts of atomic mass number.**

As also stated in the comments to the first Reviewer, a deep revision of the text has been performed.

**2) The Authors included Tables that should be cited in the text. Also at the end of the manuscript two Figures are included that should also be cited and commented in the text.**

As suggested, we added references to figures and tables in the text.

**3) In both text and Figure 2 legend WBC-scintigraphies should be corrected with 99mTc-HMPAO-WBC scintigraphy. Please delete granulomatous from "...Inflammatory bowel disease (IBD) is a chronic granulomatous inflammatory condition" which is not a correct definition of IBD.**

Both done as suggested.

**4) In the manuscript the Authors should underline the advantages and/or limitations of the reported studies to strengthen the potential of nuclear medicine in IBD diagnosis and prognosis.**

We thank the Reviewer for this suggestion, which partially overlaps that of the first Reviewer. Accordingly, we streamlined the discussion in order to highlight more clearly advantages and limitations of molecular imaging. To that end, we also reported the results of recent meta-analyses.

**5) It will be useful to add a comment on the effect of molecular imaging on cumulative radiation exposure in children.**

We agree with the Reviewer. Accordingly, we expanded on the discussion about radioexposure, suggesting some practical methods to reduce ionizing radiation and keep the total radioexposure into acceptable limits in case of repeated examinations over time.

## Reviewer #4

The authors reviewed the value of several imaging methods (PET, SPET, etc) in diagnosing IBD and in follow-up (i.e. response to therapy, post-op recurrence)

**1) Overall the review is too long and is a mere listing of studies.**

We agree that the first version of our Review needed to be streamlined. Accordingly, we shortened the text and rephrased many sentences to avoid giving the impression of a long list of studies. The results of each paper has been now reported as a part of a more streamlined description.

**2) The language must be revised.**

This comment overlaps those of the other Reviewers. A deep revision of the text has been performed.

**3) In order to shorten the paper older studies, i.e. studies where "new" imaging techniques are compared with small bowel follow-through or other obsolete techniques should be excluded.**

We thank the Reviewer for this suggestion. Accordingly, we only kept papers in which the newest techniques were compared to other methods which still play an important role in clinical practice or to new experimental tracers.

**4) What's about radiation exposure with repeated measurements?**

This comment also overlaps those of the other Reviewers. A more detailed discussion about this important aspect has been added in the relevant section.

**5) Are you sure that these techniques are really better than MRI?**

The Reviewer is correct in that the first version of our Review gave the impression that molecular imaging was considered superior to MR, which is not the case. Accordingly, we toned down statements on the comparison between MR and molecular imaging.

**6) Some terms are used improperly: fulminating colitis = fulminant last intestinal ansa (?) you mean terminal ileum?**

All terms have been corrected.

**7) In INTRO you state that endoscopy is a procedure with a high risk of bowel perforation, I don't agree; endoscopy remains the key-procedure also diagnosis, follow-up, and for detection of dysplasia.**

We agree that the first version of the introduction needed to be toned down. We rephrased the sentence, underlying that endoscopy remains the gold standard in the management of patients with IBD and that its contribution in clinical practice is invaluable.

**8) Abstract and INTRO first sentence Inflammatory bowel disease (IBD) is a chronic granulomatous inflammatory condition, only Crohn's is granulomatous not UC**

The error was corrected.

**9) In your search strategy you state that articles were selected only when dealing with IBD patients, but in your paper you include also animal studies, this is methodologically incorrect**

We agree that the description of the methods was incorrect. Accordingly, we added a statement about the selection of a selection of papers about experimental tracers in the relevant section. The paragraph about experimental tracers and new development has also been considerably shortened and streamlined.

**10) There are errors within the references (Bicik = ref 17 not 25 in text)**

Errors have been checked and corrected.