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Reviewer 1 (00004594)

Medical therapy of IBD is not so much different for Crohn's disease (CD) and ulcerative colitis (UC): if 5-ASA are essentially active in UC but not in CD, the rest of the treatment is the same for UC and CD; corticosteroids, immunosuppressants, anti-TNF and anti-integrins (Vedolizumab) have been validated for both diseases.

Introduction has been altered to say "response to medications, surgical indications…" as these points differ between the two types of IBD.

Monitoring of IBD is clinical, biological, morphological (ultrasonography, CT scan, MRI, endoscopy). Fecal calprotectin is a very useful tool that we currently use in practice (diagnosis, therapeutic follow-up, post-operative recurrence for CD…). Endoscopic procedures are important for the initial diagnosis but patient are more and more reluctant to endoscopies and noninvasive imaging such as ultrasonography and/or MRI are more and more used.

I agree with the points raised and patients certainly have a preference for less invasive procedures, hence the strong need for diagnostic tests that may be equal to or better than endoscopy.

CRP is not a good marker for UC and is normal in 20-30% of CD.

Table 1 has been edited to include the difference in CRP for UC and CD.

Fecal calprotectin is more accurate for the colon than the small bowel. - If "proteomics could play a potentially significant role towards improving the clinical management of IBD" the tools that we have presently are very interesting and have improved the clinical diagnosis and management of IBD. - As stated by the authors IBD proteomics remains in its infancy and requires further investigations. The cost, availability, reproducibility… is also a matter of debate. At the time where the management of IBD is more and more personalized (e.g. treatment), IBD proteomics should be of interest.

Thank you for your time in reviewing this article and providing feedback.

Reviewer 2 (00009064)

Very comprehensive review and well written.

Grade B: minor language polishing

Thank you for reviewing this article and your feedback, the article has been further proof-read.

Reviewer 3 (02520845)

This review provides an overview of current and possible proteomic biomarkers in the diagnosis and evaluation of therapeutic responses in the inflammatory bowel disease (IBD). The author methodically described the process of introducing biomarker candidates in pre-clinical and clinical management, described the mass spectrometry, and its application to IBD. Further, they described the current biomarkers in IBD management and gave a list of proteomics studies for discovering IBD diagnostic biomarkers and pathogenesis of IBD. Finally, they offer future guidelines for verification and validation of IBD proteomic biomarkers. The text is accompanied by appropriate tables. **References are not completely written according to the WJGP guidelines (journal abbreviations instead of the full name of journal).** In conclusion, this is a very interesting review which provides a view of the problem in screening and testing new proteomic biomarkers in the diagnosis and management of IBD.

Thank you for reviewing this article and for your feedback. The references have been edited according to WJGP guidelines.

Reviewer 4 (00038879)

Thank you for taking the time to review this article and the helpful feedback. Please find comments below regarding the points raised.

In this review Dr.Chan and colleagues examine the current status of IBD proteomics research especially as it relates to clinical applications such as diagnosis, disease activity, disease course and therapeutic response. The field of proteomics is rapidly growing. At least in theory, in the future it could potentially provide tools to improve IBD diagnosis and management. These are my comments:

1. By contrast with the authors' premise that "proteomics provides a powerful means of addressing major challenges in IBD today…" (page 2) the overall impression from their review is that:

a. No conclusions of relevant clinical or scientific meaning can be drawn from current studies.

b. By the authors' admission (page 19) most of these studies are small and not properly designed.

c. Even supposing that the current findings in the field – highlighted by the authors – are confirmed by future studies none of these discoveries seem to be superior to current noninvasive markers, most notably stool markers.

Please refer to the last comment for my response to these comments. Thanks

2. In addition to deal with a field which currently has no clinical impact the reader is dealing here with a paper that is not well written and organized.

a. The English is often incomprehensible. These are just some examples:

1. Abstract: "…improve diagnostic and management…"

2. Core tips: "…disease biomarkers for numerous disease…" this mistake is not a typo since it is repeated many times (page 3: "…many disease…") (page 9: "…biomarkers are present…and becomes…") and many more

3. Page 6: description of MS (fifth line from top) comes out of the blue, without a premise. 4. Page 8: "…the application of proteomics…accumulating at the discovery phase…" This is totally unclear.

5. Page 9: "…biological fluid that is closer to the diseased tissue…" Closer than what?

6. Page 9 "..examining for protein variations…" what do you mean?

7. Page 10: "…governed by an scoring…"

8. Page 11: "…an area that has yet been addressed…"

9. Page 11: "…additional investigation into validity…"

Thank you for identifying some of these, I have edited these and further proof-read the entire article.

b. The abbreviations are an option in this manuscript – sometimes they are present most often they are not (see figure 2, figure 3 and all the tables)

c. The paragraph on MS should be re-written in a more comprehensible way for the standard clinician (e.g.one wonders what is a "triple quadrupole")

d. Tables and figures: table 1 appears to be a summary of a summary (i.e. reference 10) whilst it really should list the individual references.

Figure 1 should be labeled as "ideal or potential uses of biomarkers in IBD" not "application of biomarkers" – especially as it relates to pre-clinical screening.

Figure 2 is entitled "Quantitative methods in proteomics" when it should really be labeled "quantitative (word mispelled in the artwork) MS".
Figure 3: Verification: "selected"; 2DE: abbreviation; "number of candidate markers" is this a proportion or an absolute number? It is unclear to the reader.
e. The paragraph and the entire table 4 epitomizes the confusing presentation of this paper – we don't discuss this… no,actually we do, in part…but only with the table... In my opinion either you discuss it properly or you eliminate paragraph and table.
The points above have been addressed and marked in the comments section in the document

f. Perhaps even more importantly the authors fail to draw any attention on the findings they discuss – no reference at all to any mechanist aspect of these discoveries. The reader is essentially left with a dry list of studies and authors – and hardly any take home message
Whilst I have identified that there are indeed barriers and limitations towards utilizing proteomics in IBD, it is difficult to discount the application of proteomics in IBD whilst it is in its infancy. Translating basic science and clinical research is notoriously difficult (for example, genomics research faces similar issues but has made great strides in our understanding of disease processes and our management). Whilst yes, the current candidate markers in IBD proteomics may not seem superior to current non-invasive methods, the fact remains that there is an ongoing need for better tools and also that proteomics may aid in this process and its research should be further supported. This is the take home message I hoped to convey, that these studies have provided only a glimpse of the wealth of information that the 'proteome' can provide and this is a worthwhile endeavor for others to investigate. As mentioned in the paper, the OVA1 panel is an example of markers discovered by proteomic discovery experiments which has now been validated to assess the risk of malignancy in patients with an adnexal mass.
I have also added on a recently published paper reporting a number of markers in IBD which have been validated using MRM mass spectrometry, lending weight to their potential clinical utility. I hope that this addresses some of your concerns about this paper.

Reviewer 5: 02520738
To: Professor Lian-Sheng Ma Editor board World Journal of Gastroenterology Title: "Current Application of Proteomics in Biomarker Discovery for Inflammatory Bowel Disease" Dear Editor, We have read through the manuscript and we think that the paper is good and well written as it stands.
Thank you for your time in reviewing this manuscript.

Reviewer 6: 00009530
The paper deals with a very interesting issue and is well documented and well written.
Only minor comments, mostly related to table 1:

- there are no data on sensitivity and specificity of ANCA; **- ANCA data included**

- the word "fecal" lacks both for lactoferrin and for calprotectin in the section "Marker of disease activity"; **- edited to include "fecal"**
- in the section "predicting course" I would add that pANCA may predict aggressive course and risk for pouchitis after surgery in UC and a "UC-like" behavior in CD. **– added into the table**
- In the section "predicting relapse" I would cite the combined Brignola score (Brignola et al, Gastroenterology 1986). – **I have added this to the discussion as a good example of using multiple parameters in assessing IBD**
- In Table 2 I would put Kanmura paper at the second position, similarly to what is in the text. **– Changes have been made accordingly**

In the discussion, it should be underscored that almost no spontaneous experimental model of IBD exist and that cell cultures as well are quite far from disease pathophysiology.
Last: there are typographical errors here and there.
The points have been addressed, thank you for your comments and time.

Reviewer 7: 00035901
The authors reviewed recent advances of proteomic biomarkers in diagnosing and managing IBD, especially in the clinical field. The present paper was well written and will give us important information. I have no claim in the present form.
Thank you for your time in reading this manuscript
Reviewer 8: 00004011
Very interesting and well documented manuscript
Thank you for your time in reading this manuscript