**March 28, 2020**

**Ruo-Yu Ma**
Science Editor, Editorial Office
Baishideng Publishing Group Inc.
**Re:** Manuscript Revision (World Journal of Gastroenterology No 05118157)

Dear Editor,
Thank you for the Editor and Reviewers for considering our manuscript "**Hepatocellular Adenoma in the Paediatric Population: Molecular Classification and Clinical Associations**." We have made some revisions based on the reviewers' suggestions. The response for each question or suggestion is listed below. The changes in the manuscript are highlighted in yellow. We hope you will find the revised manuscript acceptable for publication. Thank you again.

Sincerely,

**Juan Putra, MD**
Division of Pathology
Department of Paediatric Laboratory Medicine
Hospital for Sick Children
555 University Ave Rm. 3119
Toronto, ON M5G 1X8, Canada
Email: Juan.Putra@sickkids.ca
Telephone: 1-416-813-5966
Fax: 1-416-813-5974

**Reviewer 1**

The authors have provided a review of pediatric HCA. Overall a nice review of a rare topic.

1. In the introduction, the last sentence 1st paragraph seems out of place with the rest of the introduction. maybe separate histology and IHC as a different idea. (removed from introduction.)

2. The introduction subtype information seems like it could be made more succinct since this is not the focus ultimately of your article. (the introduction has been reduced to 1 paragraph.)

3. The order you selected to review the subtypes is different than usual. Usually inflammatory adenomas are considered and reviewed before b-catenin ones. Any reason you decided to cover b-catenin second? (The order of the subtypes has been revised.)

4. I think the information on the molecular categories (before you get to pediatric tumors) could be condensed. This is reviewed in many articles and doesn't need such a detailed analysis here. Maybe a short summary with the table would be enough on this topic, rather than reviewing all the molecular subtypes. Keep in mind that your main topic - pediatric cases - is quite unusual so that is the interesting part of your article and the one that should be elaborated on. The information prior to that is well-known, easily found in other review articles, and can't be done justice here. So I would make it even shorter and get to the point of your article faster (we decided to keep the molecular classification section; see #5.).

5. If you choose to keep a lengthy section on each molecular subtype, you need to clean up the writing a bit because it gets challenging to follow the genes, associations, and then pathogenesis on each subtype (thank you for your suggestion; the paragraphs were reorganized. Hopefully they are clearer now.).

6. Under HHCA, is MODY3 a germline mutation? not clear at the end of first paragraph. (the sentence was modified.)

7. HHCA second paragraph. Feels repetitive and not tightly written between the genes, associations, etc (see #5, this section was reorganized and partly rewritten.).

8 Under sex hormone dysregulation, I would tighten the language around OCP and other associations. For instance, " Besides OCP, sex hormone dysregulation in the pediatric population can occur with obesity, Pcos, etc." (revised.)

9. Under FA. "Patients with FA can develop HCAs spontaneously, and have an...." this is an awkward way of phrasing this. I guess you mean that patients with FA are at risk of developing HCA at baseline, but this is compounded by their being treated with androgen therapy and their iron overload? or something like that. (revised.)

10. Under GSD, I found the section on B-catenin types didn't flow because in the middle of that topic, there is this cases Hosp of Sick children and Caldereros' paper. Maybe unify b-catenin topic and rephrase the other items. (revised.)

11. The sentence describing caldrero's paper is confusing. (removed.)

12. In the next paragraph, it is unclear why you seem to be describing histology of GSD. Has nothing to do with HCA, or does it? (the sentence describing histology of GSD type III has been removed.)

13. I am not clear why you have elected to photograph figure 2 - which seems to be background liver in GSD? That isn't the subject of this review. If there is nothing else of interest that you can demonstrate in pediatric HCA, then we don't need figure 2. But if there is anything else worth demonstrating then I would illustrate that, rather than GSD. (Thank you for your suggestion; figure 2 has been removed)

**Reviewer 2**

Authors comprehensively reviewed molecular subtypes of hepatocellular adenoma and characteristics of hepatocellular adenoma affecting children and adolescents in terms of clinical settings, genetic predisposition, and various syndromes. I think that the quality of review is satisfactory for publication in the Wold Journal of Gastroenterology and that this review will improve reader's understandings about hepatocellular adenoma in pediatric patients. A few minor comments:

1) Figure 1 and Figure 2 illustrate the pathologic features of hepatocellular adenoma (Figure 1) and its adjacent non-neoplastic liver parenchyma (Figure 2). It would be better to combine the two figures into one figure. Also, I would recommend to give a title for the unified figure. (Based on the Reviewer 1's suggestion, we decided to remove Figure 2 since the background liver is not the focus of this research; thank you for your kind suggestion.)

2) Page 13, Paragraph 2, Line 2: 1 in 30 000 -> 1 in 30,000 (corrected.)

**Reviewer 3**

1.The manuscript deals with the molecular basis, subtypes without detailing other aspects of Hepatic Adenomas in children. The title to be suitably modified (the title was modified to "hepatocellular adenoma in the paediatric population: molecular classification and clinical associations.)

2. The review does not include solitary / multiple adenomas (included in the hepatocellular adenomas in children section – paragraph 3.)

3. The role of imaging in diagnosis and management is not outlined (included in the hepatocellular adenomas in children section – paragraph 3).

4. Differential diagnosis of adenoma in pediatric age group can add another dimension for the review (included in the hepatocellular adenomas in children section – paragraph 4; however the detailed information is not provided because it's beyond the scope of this review).

5. When and how to intervene is a vital question which is not addressed (thank you for your suggestions but it's beyond the scope of our review, and currently the practice is heterogeneous as there is no mainstay guidelines in children).

6. Do all adenomas require biopsy evaluation or only imaging for management? (thank you for your suggestions but it's beyond the scope of our review, and currently the practice is heterogeneous as there is no mainstay guidelines in children)