

Letter: Responses to the editors and reviewers

Lian-Sheng Ma, Editorial Office Director, Company Editor-in-Chief, Editorial Office

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Dear Dr. Ma

We would like to thank you, editors and reviewers for the favorable comments and excellent suggestions. The manuscript has been modified to include the valuable suggestions as detailed in the attached sheet.

Thank you again for your considerations!

Sincerely,

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Our point-to-point responses to the comments**A) EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

I find it a well-structured interesting study. Nevertheless, there are a number of points that may deserve some revisions.

1. The table should be in three-line format.

Our response: Thank you for the comments. The Tables have been modified with the standard three-line format.

2. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Our response: Thank you for the comments. The manuscript has been revised with no more than 3 references from the same journal.

3. The manuscript is comprehensive, but there seems to be no innovation.

Our response: Thank you for the comments. This review aims to provide a comprehensive update on the diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms (NENs), including the most up-to-date information on WHO classification, molecular genetics, and novel therapeutic approaches. This review also provides high-quality photos of NENs with typical and unusual clinical presentation.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Our response: Thank you for the comments. We have revised the Figure Legend to make a uniform presentation with the suggested format. We have also prepared decomposable Figures through a single PowerPoint file. To keep the higher resolutions of the figures, we would like to submit the 5 figures to Dr. Jia-Ping Pan, the scientific editor, through separate emails.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Our response: Thank you for the comments. The Tables have been modified with the standard three-line format.

Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend:
<https://www.wjgnet.com/bpg/gerinfo/240>.

Our response: Thank you for the comments. We have provided English Language Certificate from the American Journal Experts (AJE).

B) REVIEWERS'S COMMENTS

Reviewer #1:

Specific Comments to Authors: *The present review, titled “New insights in Diagnosis and Treatment of Gastroenteropancreatic Neuroendocrine Neoplasms” aimed at reviewing the main clinical and biological characteristics which determine the management of neuroendocrine neoplasms. Although this issue is very interesting and actual, the study has important limitations*

- First of all, the review is not innovative and does not add anything new to what is already known in the literature

Our response: Thank you for the comments. This review aims to provide a comprehensive update on the diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms (NENs), including the most up-to-date information on WHO classification, molecular genetics, and novel therapeutic approaches. This review also provides high-quality photos of NENs with typical and unusual clinical presentation.

- Moreover, it lacks citations of important papers that represent milestones for NEN therapy and management, such as some randomized studies in this area, as the pivotal trials PROMID, CLARINET FORTE and some RADIANT trials (i.e. Arnold R, et al. Placebo-controlled, double-blind, prospective, randomized study of the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol. 2009 or Caplin ME, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014. Or Pavel M, et al. 1162MO Efficacy and safety of lanreotide autogel (LAN) 120 mg every 14 days in progressive pancreatic or midgut neuroendocrine tumours (NETs): CLARINET FORTE study results. Ann Oncol. 2020. or Yao JC, et al. Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, Phase III RADIANT-3 study) as well as important reviews (i.e. Pavel M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(7):844–60. Or Mohammed Dawod et al. Antiproliferative Systemic Therapies

for Metastatic Small Bowel Neuroendocrine Tumours. *Curr Treat Options Oncol.* 2021 Jun 29;22(8):73. or Massironi S, et al. Somatostatin analogues in functioning gastroenteropancreatic neuroendocrine tumours: literature review, clinical recommendations and schedules. *Scand J Gastroenterol.* 2016;51(5):513-23.)

Our response: Thank you for the comments and excellent suggestions. We have included all the above-mentioned literatures in the revised manuscript (Reference #82-#87). Specifically, we stated that *“The treatment options for advanced and metastatic GEP-NENs have significantly expanded during the past two decades[82, 83]. Some important clinical studies, including PROMID[84] and CLARINET[85] trial, have demonstrated a significant efficacy of SSA in the control of tumor growth in patients with metastatic GEP-NETs. A recent CLARINET FORTE phase 2 clinical trial further supports the clinical benefit of the SSA lanreotide autogel (LAN), which led to significantly improved progress free survival (PFS) and Disease control rate in patients with GEN-NETs, especially in cases with Ki67 ≤ 10%[86]. Besides SSA[87], novel therapeutic approaches, including PRRT, targeted therapy and immunotherapy, have demonstrated promising clinical benefits[88-90].”*

- The author correctly used the most recent definition of neuroendocrine tumors namely “neuroendocrine neoplasms” (NEN), reserving the term “tumor” for well-differentiated forms only (G1 according to last WHO edition). But, throughout the manuscript, they create a sort of confusion in the use of both NEN and NET; please check and be more clear.

Our response: Thank you for the comments. The manuscript provides a comprehensive update on the diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms (NENs), which include well-differentiated neuroendocrine tumor (NET) and poorly-differentiated carcinoma (NEC). We have specified the terminology in the “Histopathologic Classification”, and clearly presented throughout the revised manuscript.

- English language needs to be reviewed and checked by an English native speaker. Only as an example, on page 3- Introduction, the authors wrote “. Majority (> 95%) of the GEP-NENs are sporadic, but some (~5%) could be part of a syndromic presentations”: The indefinite article a may not be required with the plural noun presentations. Also, the formatting was not correct (i.e. spacing, citations, abbreviates, etc).

Our response: Thank you for the comments. We have finished professional language editing services for this manuscript, and the English Language Certificate from the American Journal Experts (AJE) has been submitted together with the revised manuscript.

Reviewer #2:

Specific Comments to Authors: The manuscript entitled 'New insights in Diagnosis and Treatment of Gastroenteropancreatic Neuroendocrine Neoplasms' provides an overview of gastroenteropancreatic neuroendocrine neoplasms by the site of origin, histological classification, Ki-67 proliferation index, and genetic background. The authors also presented the clinical picture of different types of NENs accompanied by imaging and their diagnosis and treatment options. The manuscript is very detailed but also systematically written, and there is no need to add anything.

Our response: Thank you for the comments. We greatly appreciate the positive feedback from the expert reviewer.



Editing Certificate

This document certifies that the manuscript

New insights in Diagnosis and Treatment of Gastroenteropancreatic Neuroendocrine Neoplasms

prepared by the authors

Jinping Lai, Zihao Wu, Feng Yin

was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at AJE.

This certificate was issued on **January 3, 2022** and may be verified on the [AJE website](https://www.aje.com) using the verification code **A486-6626-5194-9CEE-OFC1**.



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