

Nicosia, 14/12/2016

Dear Dr Fang-Fang Ji,  
Science Editor,

on behalf of my co-authors I would like thank you for your reply and your thorough instructions.

I would also like to thank the reviewers for their interesting comments. Following you could find a point-by-point summary of how we dealt with each of the comments of the reviewers.

**Reviewer #1:** -

**Reviewer #2:**

“This is a review of CgA and its potential use in various situations. From the section on GEP NETS, the authors seem to suggest that it has a well established role in diagnosis although the conclusions suggest that there is a need to search for better biomarkers. it might be confusing for readers who are not so familiar with the topic. In general, because there are so many benign and common situations like hypertension and use of PPI that can cause CgA elevations, its role as a biomarker for NET and other tumours is very limited and needs to be properly explained in the manuscript. It is precisely for this reason that many investigators are exploring other biomarkers for NETs, and at this current time, the use of CgA in NETs is primarily limited for use of treatment response if there happens to be a pre-treatment elevation”

Answer:

- CgA limitations they are further explained in the text as requested

**Reviewer #3:**

“This is a good review. To be more helpful, remember that your readers will be getting labs back and get a number, not just "elevated" It would really help to put down observed ranges of CGA for each of the conditions in table 1,2. NET can easily surpass 30,000 ng/ml- the other conditions not so much. If your reader has a value of 30,000 ng/ml in a patient with renal failure, is this still indicative of NET, or can renal disease cause elevation to that degree, etc. It would be useful to mention a range of variation when following an individual. I've certainly seen patients with NET vary up and down several thousand ng/ml without an observable change in clinical status. "It is produced by the human myocardium and exerts negative inotropic effect"- This statement needs a reference page 3 spelling error -extend should be extent You used both tumour and tumor in the text- please use one form only”

Answer:

- Regarding CgA levels (ranges) in various conditions, there are broad ranges in the literature. For that reason it is mentioned in the text 'Summarizing, in non malignant diseases and conditions, CgA values may reach values of hundreds (ng/ml), but it is very uncommon to reach levels of several thousands that could be consistent with cancer diagnosis'.

- CgA limitations, as no relation between increased levels and clinical status, are mentioned in the text as requested
- Reference is added as requested
- Correction was made as requested: extent instead of "extend"
- "Tumour" is used within the text, as requested.

In addition:

-Proper revision of references style was performed

-All changes in the text are marked in red

We would like to thank you for your thoughtful consideration of our manuscript.

Please contact me if any further information is required.

Sincerely Yours

P. Kountourakis MD, PhD