Dear reviewer,

Thank you for taking the time to review our Letter to the Editor submission, titled "Commentary: A Closer Look at Malignant Glioma Biomarkers" (manuscript ID 73633). We addressed all the helpful comments discussed in the review, and now present a revised manuscript, titled "Commentary: Evaluating Potential Glioma Serum Biomarkers, with Future Applications." Below, please read how we addressed each of the comments. We also apologize for the delay in returning the revision.

"However, there exists some concerns in this manuscript. Most of the similar and controversial results from previous literatures proposed in this manuscript have been discussed in Gandhi et al' s article. For example, Gandhi et al. have discussed Adams et al. 's and Zhai et al. 's studies focused on kynurenine and attributed the contradict between their studies to the small number of patients. Therefore, they performed the analysis based on a relatively larger cohort."

Thank you for this helpful comment, as we tried to independently find sources to support and contrast Gandhi et al.'s claims. We should have initially cross-referenced our sources with those of Gandhi et al.'s manuscript. We have updated the current version of the manuscript with more sources that were not addressed by Gandhi et al. In the second paragraph, we added research by Du et al. and Mitsuka et al. to support kynurenine metabolism claims by Gandhi et al. In the third paragraph (previously was part of the second paragraph), we added 7 studies to further support NLR as an effective tool in distinguishing glioma grade, distinguishing IDH-mutant vs wild type status, and predicting survival. In the same paragraph, we added evidence by Zachariah et al. (23) to contrast Gandhi et al.'s finding of hTERT increasing with IDH-wild type status. In the subsequent paragraph, we present three new sources (24,25,28) to support IL-6 as a predictive biomarker, including differentiating IDH status. Meanwhile, we also added cell-based (26) and clinical/serum-based evidence to oppose IL-6 (31).

"The previous literatures the authors mentioned in the manuscript were mainly based on glioblastomas, while most of the patients in Gandhi et al. 's study were astrocytic and oligo-component, which have different biological behaviors with glioblastomas. Besides, one of the applications for Gandhi et al. 's panel is to differentiate patients of the IDH wt/mut status. The authors may need to supple related literatures to give a comprehensive comment to Gandhi et al. 's work."

Thank you for making this comment, as we didn't realize we were biased toward GBM research. To address this, we added a multitude of studies (7, 9, 14-15, 18-19, 24-26, 28, 31, 37-39) that include a variety of gliomas, and not just GBM. To address the IDH wt/mut status point, some newly added sources (9, 17, 28, 37-39) were included. We also now mentioned in the final sentence of the second paragraph that we were unable to discover other evidence supporting Gandhi et al.'s finding of tryptophan metabolism predicting IDH status. We hope these additions accomplish the objective of comprehensively commenting on Gandhi et al.'s work.

"The new application the authors suggested for Gandhi et al. 's panel to differentiate tumor progression from radiation necrosis and the potentially important molecules IL-33 they proposed may be meaningful promotion for Gandhi et al' s work. But these hypotheses still lack statistical data to support."

Thank you for this comment. We added two additional source (42,43) toward the radiation necrosis point in the penultimate paragraph. However, there is not much data on serum based biomarkers in identifying radiation necrosis. We included this original paragraph to present a useful future direction that Gandhi et al. may address. Regarding IL-33, we originally included several studies that implicated IL-33 as an important contributor in glioma pathogenesis. Thus, this paragraph was meant to also serve as a useful future direction for Gandhi et al., in that they may find IL-33 a useful addition/replacement in their panel. Furthermore, in the fifth paragraph, evidence

surrounding a urinary based biomarker (2-HG) that distinguishes IDH status was newly discussed, which may be useful for Gandhi et al. to explore.

"The title of the manuscript may need to be more specific."

Thank you for this point, which we agree with. The title was changed to "Commentary: Evaluating Potential Glioma Serum Biomarkers, with Future Applications"