

## RESPONSE TO REVIEWERS

1. Citations are required: “Early studies were based on the analysis of specific slide regions, such as the tumor center, margins, stroma or others.”

*RE: proper citations have been added*

2. Citations are required: “More recently, with the ability of the computational analysis of higher digital dimension, automated analysis of whole HE-stained tumor tissue slides has been possible.”

*RE: proper citations have been added*

3. A figure presentation is recommended to better explain machine learning detection of “hand-crafted” features of the cells.

*RE: a figure representing Machine learning with hand-crafted features has been added*

4. Citations are required: “Shape and orientation of cancer cells are among the most commonly assessed variables to predict patient outcome.”

*RE: proper citations have been added*

5. Full terminology of pT1 has to be provided.

*RE: pT1 has been explained*

6. There is only one example in “Assessment of shape and organization of cancer cells” and more examples should be given if more literature support can be found to make this section solid.

*RE another example has been added*

7. In the section of "Assessment of tumor infiltrating lymphocytes", citations in several sentences are missing.

*Re: citations have been added*

8. More details of machine learning application should be discussed instead of focusing on the outcome as the readers to this review are more likely to be interested of how machine learning approaches were designed and applied.

*RE: details in the application of ML have been provided (pag2)*

9. In the section of "AI for identification of peculiar molecular subgroups", citations in several sentences are missing.

*RE: citations have been added*

10. The trained features of Resnet18 should be discussed instead of simply describing "very large cohort of gastrointestinal cancer". More examples should be included in this section if available.

*RE: trained features of resnet18 have been clarified and another example has been included in this section*

11. In the section of "AI for the quantification of stromal tissue", how deep learning was used? How training was performed? What is "TCGA"? What do you mean "similar results"? It is quite hard to understand the only example in this section and more details should be included.

*RE: more details have been included as per request*

12. In the section of "Biology-agnostic machine learning", the CNN example is very interesting, but the authors should improve the descriptions and writing to make the entire section easier to understand. For example, what is "biological background"? Why

no biological background was fed? Why was “DoMore-v1-CRC” used and how it related to CNN? How was “non-distinct outcome” defined?

*RE: description of this section has been improved according to the reviewer's suggestion.*

**13.** Abstract needs major modification. Considerable information not given.

*RE: abstract has been improved*

**14.** Introduction need proper structure.

*RE: introduction has been improved*

**15.** Methodology not clear for the technologies mentioned here regarding AI.

*RE: artificial intelligence methodology has been better explained throughout the entire review and an additional figure has been included and the table enriched*

**16.** A review paper should have challenges, their solutions and future directions.

*RE challenges, solutions and future directions are now present in the discussion*