DEAR EDITOR,

We have completed the manuscript revision

According to your decision:

1. We provided 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 conform to the editing specifications, and the lines of each row or column of the table are aligned. We did not use carriage returns or spaces to replace lines or vertical lines and did not segment cell content.

Comments of the Reviewer #1 :

1. it is criticized that some of the recent studies were not included for instance, World J Gastroenterol. 2021;27(31):5232-5246. The proposed study is very interesting, and the authors evaluated the application of AI models on gastrointestinal polyps. However, this is about endoscopy, not pathology. Therefore, many valuable studies on AI models in the gastrointestinal tract were unfortunately not included in the review because they are related to medical disciplines other than pathology.
2. English language is revised.
3.

Comments of the Reviewer #2 :

1. The full form of GI is requested

   The expression "gastrointestinal cancer", previously abbreviated as GC in the abstract, is used both in the titles on page 6 and page 8 ('AI-based applications for prognostication of GI cancer and AI-based applications for genetic and molecular testing in GI cancer) is spelled incorrectly. Therefore, the abbreviation GI was removed and the abbreviation "GC" was used instead.
2. It is commented that the drawbacks of each conventional technique should be described clearly in the introduction section. Accordingly, the following new statements have been added with new references (refs 12, 13) (on page 4, last six lines): ''While the traditional supervised ML allows the production of data output from previously labeled training sets that can be corrected by the users, labeling big data can be time-consuming

and challenging [12]. Besides, the accuracy depends heavily on the quality of feature extraction. In contrast, the unsupervised ML is a time-saving model as it provides automatic detection of patterns[13]. However, input data that is not labeled by the users pose challenges during interpretation leading to varying results.'' The following phrase on the first form of the manuscript '' Compared to expert systems and handcrafted ML models, DL is simpler to conduct, has higher precision, and is more cost-effective[9,12].'' has been revised as ''On the other hand, DL extracts features directly from the raw data and utilizes multiple layers of hidden data for the output[14-16].''

3. To further clarify this study's position, it was stated that the difference between the other methods should be emphasized. Accordingly, we have prepared a new table (Table 1) summarizing the advantages and disadvantages of each method and the statement ''The strengths and weaknesses of typical ML methods are summarized in Table 1.'' has been added at the end of the first paragraph on page 5.
4. Since it is stated that the wide range of applications should be addressed in the introduction, on page 5, the following statements have been placed with their respective new references: '' Proscia, DeepLens, PathAI, and Inspirata are DL-based applications for the detection, diagnosis, and prognosis of several cancer subtypes[21-25]. Inspirata and PAIGE.AI are spending substantial time and resources on creating large libraries of digital WSI for use in training AI algorithms[21,24]. Interestingly, the landscape of DP is, in parallel, also undergoing important innovation and rapid changes[10].''
5. It was stated that the advantages of the proposed system should be included in a single quote line to justify the proposed approach In the introduction. Therefore, the statement "Nonetheless, AI-based approaches have the potential to contribute to pathological practice by improving workflows, eliminating simple errors, and increasing diagnostic reproducibility." has been added at the end of the 3rd paragraph on page 5.
6. It was commented that the current work should be compared with recent work in the same field to claim the contribution made, and a few references should be provided to substantiate the claim made in the abstract. Accordingly, the statements '' There have been few studies in the recent past that have addressed the effectiveness of AI models in

GC [8,30]. However, effective implementation of these methods in real-life pathology practice requires further reviews comparing the results of previous studies and highlighting the challenges to be overcome.'' have been added. (last two lines on page 5 and first two lines on page 6)

7. It was suggested that we refer to some of the latest related works from reputed journals like IEEE/ACM Transactions, Elsevier, Inderscience, Springer, Taylor & Francis, and others. New references have been added based on the referee's comments. However, not all references to suggested publishers were included.
8. The contributions and organization of the article were requested to be listed in the Introduction section. There is no organization that contributes to our article. It is stated on the title page that you have not received any support. No organization has contributed to our article. It is stated on the title page that we have not received any support.

4- **Food and Drug Administration**. (2017) IntelliSite Pathology Solution (PIPS, Philips Medical Systems) https://www.fda.gov/drugs/resources-informationapproved-drugs/intellisite-pathology-solution-pips-philips-medical-systems (accessed 29/9/2020).

12- Saxena S, Gyanchandani M. Machine Learning Methods for Computer-Aided Breast Cancer Diagnosis Using Histopathology: A Narrative Review. ***J Med Imaging Radiat Sci*** **2020; 51:182-193[PMID: 31884065 DOI: 10.1016/j.jmir.2019.11.001]**

13- **Gurcan MN, Boucheron LE, Can A, Madabhushi A, Rajpoot NM, Yener B. Histopathological image analysis: a review. *IEEE Rev Biomed Eng* 2009; 2: 147–171 [PMID: 20671804 DOI: 10.1109/RBME.2009.2034865]**

14- **Wang X, Chen H, Gan C, Lin H, Dou Q, Tsougenis E, Huang Q, Cai M, Heng PA. Weakly supervised deep learning for whole slide lung cancer image analysis. IEEE Trans Cybern 2019; [Epub aheadof print] doi: 10.1109/TCYB.2019.2935141**

15- **Silva-Rodríguez J, Colomer A, Naranjo V. WeGleNet: A weakly-supervised convolutional neural network for the semantic segmentation of Gleason grades in prostate histology images. Comput Med Imaging Graph. 2021; 88: 101846 [PMID: 33485056 DOI: 10.1016/j.compmedimag.2020.101846]**

21. **Fuchs TJ**, Wild PJ, Moch H & Buhmann JM Computational pathology analysis of tissue microarrays predicts survival of renal clear cell carcinoma patients. Med. Image Comput. Comput. Assist. Interv. 11, 1–8 (2008).

22. **Proscia**. Proscia digital pathology. Proscia.com https://proscia.com (2019).

23. **Lens Deep**. Digital pathology cloud platform. Deeplens.ai https://www.deeplens.ai (2019).

24. **PathAI.** PathAI. Pathai.com https://www.pathai.com/(2019).

25. **Aifora.** WebMicroscope. Big pictures. Deep Diagnosis. Aiforia.com https://www.aiforia.com/

28. **Baxi V,** Edwards R, Montalto M, Saha S. Digital pathology and artificial intelligence in translational medicine and clinical practice. *Mod Pathol* 2021; **5**: 1-10 [PMID: 34611303 DOI: 10.1038/s41379-021-00919-2]

29. **Bernstam EV**, Shireman PK, Meric-Bernstam F, N Zozus M, Jiang X, Brimhall BB, Windham AK, Schmidt S, Visweswaran S, Ye Y, Goodrum H, Ling Y, Barapatre S, Becich MJ. Artificial intelligence in clinical and translational science: Successes, challenges and opportunities. *Clin Transl Sci* 2021; Online ahead of print. [PMID: 34706145 DOI: 10.1111/cts.13175]