

Round-1

Answering Reviewers

Name of Journal: *Artificial Intelligence in Gastroenterology*

Manuscript NO: 63298

Manuscript Type: MINIREVIEWS

Artificial Intelligence in gastrointestinal diseases

Tanabe S *et al.* AI in gastrointestinal diseases

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Comments from Reviewer 1:

This paper summarizes the AI applications for gastrointestinal diseases treatment. I think, a sufficient amount of literature has been surveyed as a mini-review. However, the way the paper is written is merely a list, which is not a review. At the very least, the authors should classify the systems presented in each of the papers surveyed. (Examples of elements that should be used for classification) Disease of interest, use (diagnostic or screening), user (specialist or non-specialist), limitations of use (legal, functional, etc.)

Answers to Reviewer 1:

Thank you very much for your constructive comments and suggestions. The manuscript has been revised to classify the systems in each of the papers surveyed, according to the reviewer's comments. The table and figure were added to include the elements for classification as disease of interest, use (diagnosis or screening), user (specialist or non-specialist), and limitation of use (functional matter or legal matter have been described in sentences) as follows:

Figure Legends

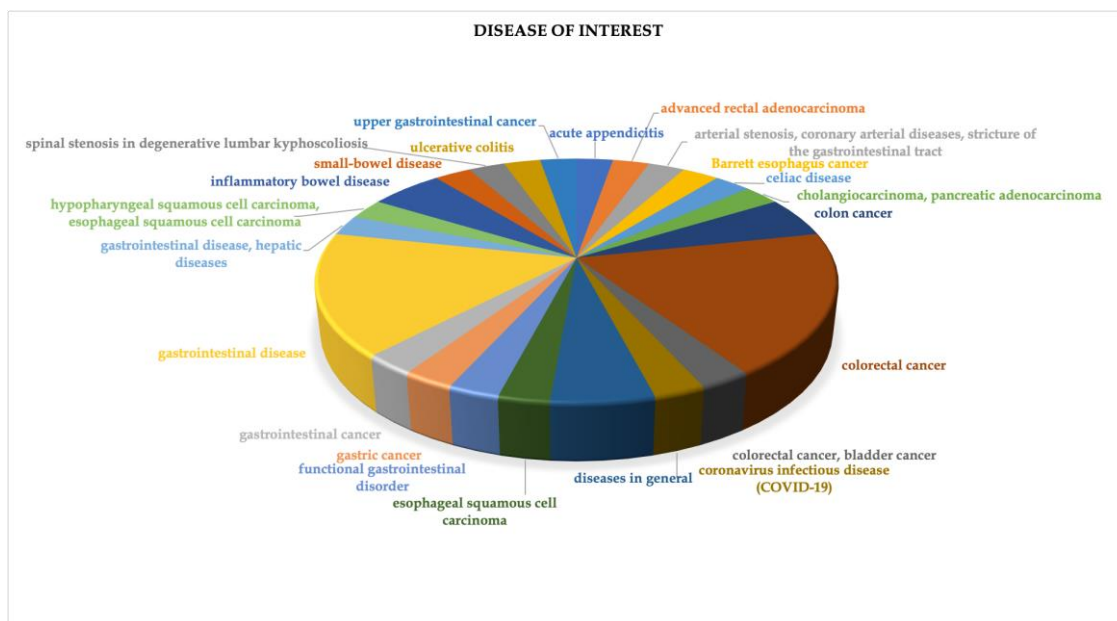


Figure 1 Disease of interest in references surveyed in AI-oriented disease management. Diseases of interest in references surveyed in AI-oriented disease management are shown.

Table 1 Classification of references surveyed in AI-oriented disease management

Disease of interest	Use	User	Limitation of use	Reference
acute appendicitis	diagnosis	specialist	The study is designed in retrospective nature.	4
colon cancer	diagnosis	specialist	The design of the analysis is post hoc and the number of patients is limited.	5
ulcerative colitis	diagnosis	specialist	Long-term clinical prognosis is not clear.	6
spinal stenosis in degenerative lumbar kyphoscoliosis	surgery navigation	specialist	The number of patients is limited. The long-term follow-up data is needed.	8
coronavirus infectious disease (COVID-19)	screening , diagnosis	specialist	Privacy of the patient data should be considered.	9
diseases in general	diagnosis	specialist	The burden on specialists may increase.	10

diseases in general	screening	specialist	Careful and thorough investigation is necessary.	11
gastrointestinal disease	diagnosis	specialist	There is a difference in the definition of anomaly detection between the area of computer science and medical domain.	12
gastrointestinal disease, hepatic diseases	diagnosis	specialist	High-quality datasets are needed.	13
colorectal cancer	diagnosis	specialist	The quality of previous study designs is limited, and practical usefulness of computer-associated diagnosis systems is unknown.	14
colorectal cancer, bladder cancer	prediction of anti-cancer drug efficacy	specialist	Further molecular layer profiling in organoids may be needed.	16

hypopharyngeal squamous cell carcinoma, esophageal squamous cell carcinoma	identification of diagnostic and therapeutic targets	specialist	Further studies are needed to validate the findings of the study.	17
arterial stenosis, coronary arterial diseases, stricture of the gastrointestinal tract	guiding of balloon catheter	specialist	The systemic performance needs to be improved.	18
gastrointestinal disease	diagnosis	specialist	Further studies are needed to improve the performance.	19
colorectal cancer	prediction of liver metastasis	specialist	The investigation of another dataset is needed.	20
colon cancer	diagnosis	specialist	The change of protein expression level needs to be investigated.	21

gastrointestinal disease	diagnosis	specialist	Investigation and development of newly improved methods are encouraged.	22
gastrointestinal disease	diagnosis	specialist	Further development is needed.	23
upper gastrointestinal cancer	diagnosis	specialist	Only high-quality endoscopic images for the training and validation analyses were used.	24
gastric cancer	diagnosis	specialist	The associations of the quality or the number of training images and the CNN accuracy needs to be examined.	25
gastrointestinal disease	diagnosis	specialist	The possibilities to improve the medical performance, to reduce the medical cost, and to improve the satisfaction of the patient and	26

			medical staff are unknown.	
functional gastrointestinal disorder	diagnosis	specialist	Evaluation of the feasibility of AI on studies on the gut-brain- microbiome axis is needed.	27
colorectal cancer	diagnosis	specialist	The uncertainty about the true efficacy of CAD in "real-world" practice remains.	28
colorectal cancer	diagnosis	specialist	Further accumulation of lesion images for training is needed.	29
small-bowel disease	diagnosis	specialist	Further multicenter, prospective studies and external validation are needed.	30
colorectal cancer	diagnosis	specialist	Complaints of system malfunctions and reports of patient injuries could lead to	31

			lawsuits against stakeholders.	
cholangiocarcinoma, pancreatic adenocarcinoma	diagnosis	specialist	Case-control and single-center design, and the lack of an independent validation cohort should be considered.	32
colorectal cancer	screening	specialist	The applicability to other types of cancer needs optimization.	33
gastrointestinal disease	diagnosis	specialist	Most studies were designed in retrospective manner. Ethical issues on misdiagnosis or misclassification need to be handled.	34
gastrointestinal cancer	prediction of microsatellite instability for	specialist	Larger training cohorts are needed.	35

	immunot			
	herapy			
colorectal cancer	diagnosis	specialist	The CNN architecture needs to be improved for colonoscopy.	36
Barrett esophagus cancer	diagnosis	specialist	The number of patients is limited. Further optimization is needed.	37
celiac disease	diagnosis	specialist	The preliminary results need to be followed-up with a real clinical setting.	38
esophageal squamous cell carcinoma	prediction of prognosis	specialist	Further experimental studies to verify the results are needed.	39
advanced rectal adenocarcinoma	prediction of response to neoadjuvant chemora	specialist	The size of the cohort is limited. The confirmation of the findings with another data set is needed.	40

	diotherap			
	y			
inflammatory bowel disease	prediction of prognosis	specialist	Interventional study to confirm the efficacy of the stratifying therapy is needed.	41
inflammatory bowel disease	mapping	specialist	The application of advanced natural language processing algorithms to the text- mining step may improve the current process.	42

Round-2

Name of Journal: *Artificial Intelligence in Gastroenterology*

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MINIREVIEWS Artificial Intelligence in gastrointestinal diseases

Authors Responses to Reviewers' comments

Reviewer 1: Some minor revisions are required as follows; P.4: Why authors mentioned to Agriculture here? In table 1: "Use" might be "Usage" or "Purpose"? There are some grammatical errors. In abstract: stateof -> state of bothdiagnosis -> both diagnosis In P. 5: patient'stranscriptome -> patient's transcriptome In P. 6: Kather et al.found -> Kather et al. found

Response: Thank you for your comments. P.4: The description "but are already being applied in many medicine and agriculture situations." has been changed into ", which are already being applied in medicinal situations."

The term "Use" has been changed into "Purpose of AI" in Table 1.

Some grammatical errors have been corrected as follows. Thank you so much.

Abstract: stateof -> state of, bothdiagnosis -> both diagnosis

P.5: patient'stranscriptome -> patient's transcriptome

P. 6: Kather et al.found -> Kather et al. found

Reviewer 2: The paper is logically organized and well written.

Response: Thank you very much for your respectful comment.

Reviewer 3: The authors showed a big title of the paper, but the manuscript does not seem to be a qualified review. The logical relationship of the full text is chaotic, and there is no corresponding sequence or connection within each part, which seems to be just a pile of documents. It should be possible to summarize the current state of AI applications from so many references. For example, in the section of "introduction", is there any connection between RNA edition and AI application? In the part of "APPLICATION OF ARTIFICIAL INTELLIGENCE (AI) IN DIAGNOSIS OF GASTROINTESTINAL DISEASES", AI seems to be applied to almost all GASTROINTESTINAL DISEASES. Why not make some separate discussions on inflammatory diseases, tumor diseases, and other diseases? Or according to specific AI application models or application methods, such as endoscopy, pathological analysis, etc.? In the "APPLICATION OF

ARTIFICIAL INTELLIGENCE (AI) IN THERAPEUTICS OF GASTROINTESTINAL DISEASES" section, there is almost no clear specific content of AI in terms of therapy. By the way, words in the table cannot give readers a clear or clean information about AI application in gastrointestinal disease.

Response: Thank you very much for your time and comment.

A reference has been added to connect and RNA editing and AI as follows: The RNA editing has been recognized as potential prognostic biomarker for cancer and prediction models have been developed with machine learning^[4].

Reference #4: Chen SC, Lo CM, Wang SH, Su EC. RNA editing-based classification of diffuse gliomas: predicting isocitrate dehydrogenase mutation and chromosome 1p/19q codeletion. BMC Bioinformatics. 2019 Dec 24;20(Suppl 19):659. doi: 10.1186/s12859-019-3236-0. PMID: 31870275; PMCID: PMC6929429.

Sub-sections for "APPLICATION OF ARTIFICIAL INTELLIGENCE (AI) IN DIAGNOSIS OF GASTROINTESTINAL DISEASES" has been created as follows: *AI application in inflammatory diseases, AI application in tumor, AI application in other diseases and endoscopy*

"APPLICATION OF ARTIFICIAL INTELLIGENCE (AI) IN THERAPEUTICS OF GASTROINTESTINAL DISEASES" has been changed into **APPLICATION OF ARTIFICIAL INTELLIGENCE (AI) IN THERAPEUTIC STRATEGY OF GASTROINTESTINAL DISEASES**, and the following descriptions and references have been added:

Since the responsiveness toward drug alters in cancer cell phenotypes such as epithelial-mesenchymal transition in diffuse-type gastric cancer, the AI application in the

identification of cancer subtype would lead to establish therapeutic strategy^[44,45]. The machine learning algorithms may be applied into the therapy of the gastrointestinal diseases in terms of gut-brain axis^[46].

References

#44 **Tanabe S**, Quader S, Cabral H, Ono R. Interplay of EMT and CSC in Cancer and the Potential Therapeutic Strategies. *Front Pharmacol* 2020; **11**: 904 [PMID: 32625096 DOI: 10.3389/fphar.2020.00904.]

#45 **Tanabe S**, Quader S, Ono R, Cabral H, Aoyagi K, Hirose A, Yokozaki H, Sasaki H. Molecular Network Profiling in Intestinal- and Diffuse-Type Gastric Cancer. *Cancers (Basel)* 2020; **12**: 3833 [PMID: 33353109 DOI: 10.3390/cancers12123833]

#46 **Mukhtar K**, Nawaz H, Abid S. Functional gastrointestinal disorders and gut-brain axis: What does the future hold? *World J Gastroenterol* 2019; **25**: 552-566. [PMID: 30774271 DOI: 10.3748/wjg.v25.i5.552]

The title of Table 1 has been updated into Classification of systems in AI-oriented disease management. The “Use” has been changed into “Purpose of AI” in the column head.