Dear Lian-Sheng Ma,

Please find enclosed the revised solicited manuscript entitled, ERCP: Current Practice and Future Research. We appreciate the well thought out revisions and feedback.

We have responded to the four reviews. The necessary grammatical, formatting, and content revisions have been made to the article.

Sincerely,

Richard Kozarek MD

Dear Editors,

Please find in this letter, the point-by-point responses to reviewer comments/queries for Manuscript No: 66036 titled – ERCP: Current Practice and Future Research.

Feedback provided is bolded. Responses are below.

Reviewer #1: Number ID: 05429162

Specific Comments to Authors: Summary Sanders et al. reviewed current status and future perspectives of the Endoscopic Retrograde Cholangiopancreatography (ERCP). The article includes multiple points of view, such as diagnostic ERCP, combination technique of ERCP and EUS. The manuscript gives valuable information for readers, however, there are some points to be revised.

Major points
[Introduction] 1) Page 4; The sentence shown below does not seem essential for drafting the manuscript. Also the sentence is difficult to understand for non-native English speaker. Please consider to delete or change the sentence: As endoscopists and physicians, we are humbly reminded of the adage from Hercalitus that "the only constant in life is change."

Response: Thank you very much for your constructive suggestions. We have changed the sentence to "The evolution in endoscopic retrograde cholangiopancreatography (ERCP) has been more gradual, but certainly there have been periods of innovation punctuated by rapid change".

The sentence "As endoscopists and physicians, we are humbly reminded of the adage from Hercalitus that "the only constant in life is change"." has been removed.

[1. INFECTION PREVENTION AND QUALITY IMPROVEMENT] [A) Disposable duodenoscopes] 1) Page 5: The following sentence may be confusing for non-native English speaker. Please reconsider the sentence: this past year was a somber reminder of our oath of "primum non nocere."

Response: This sentence has been changed to "While some practice changes in ERCP have been adopted because of an enthusiasm for technologic advance and the opportunity to treat complex problems, this past year was a somber reminder of our oath to do no harm". The latin translation has been changed to English.

2) Page 5-6: Indeed, the disposable duodenoscopes has an advantage for prevention of patient-to-patient transmission of infections. However, the information of working channel diameter, up lifting angle of working channel, viewing angle should be described.

Response: The following sentence with information regarding working channels, lift angle and viewing angle has been added to the manuscript - "The endoscope has a 4.2 mm working channel, LED light, and conventional four-way steering. The current model D has a similar elevator lift angle and viewing angle when compared to the available reusable duodenoscopes."

[B) Periprocedural management: Anesthesia involvement and propofol use in ERCP] 1) In the periprocedural management for propofol anesthesia, the respiratory depressant action can be

problematic in certain situation. Please describe pros and cons for using anesthesia comparing with another sedative drugs, such as midazolam or diazepam.

Response: The paragraph has been changed to - "Propofol is a sedative and hypnotic medication with a shorter duration of action compared to midazolam and fentanyl. Benefits of propofol include improvements in patient satisfaction, procedural outcome, and quicker recovery when compared to procedural sedation [18-20]. Propofol can cause significant hypotension and rapid respiratory depression. Further study was required to clarify propofol's safety in endoscopy."

[C) Future directions: Reducing post ERCP pancreatitis] 1) The use of the indomethacin has certain benefits preventing post-ERCP pancreatitis. However, the dose of indomethacin in the manuscript shown in this article is relatively high (100mg). Please describe the dose of indomethacin and potential side effects.

Response: The following line has been added: The dose of rectal indomethacin used in the study was 100 mg.

The following sentence has been added: Side effects of long-term NSAID use include renal impairment and peptic ulcer disease. A single dose of indomethacin did not result in a significant risk of acute renal impairment or clinically significant gastrointestinal bleeding [27].

[2. CANNULATION, BILIARY ACCESS, AND ALTERED ANATOMY] [B) Overtube-assisted enteroscopy (OAE) and laparoscopic surgery-assisted ERCP] Page 8: The author described "patients with a roux-en-y with gastric bypass had a successful ERCP in just 70% of cases". Please describe this successful rate described whether the technical success or clinical success. (Cai et al. Surg Endosc. 2017 Jul;31(7):2753-2762. doi: 10.1007/s00464-016-5282-2.)

Response: This is technical success. This has been changed.

[C) EUS-directed transgastric ERCP (EDGE)] Page 10: The adequate interval from EUS placement of a translminal stent to subsequent ERCP should be described. Please discuss the interval duration from EUS to subsequent ERCP.

Response: Although an EDGE procedure can be done at the time of LAMS placement, stent migration and free perforation can occur and most endoscopists wait 4-6 weeks prior to proceeding to ERCP. This has been added to the manuscript.

[4. PANCREATIC DISEASE: PANCREATIC STONES AND PANCREATIC LEAKS] [B) Pancreatoscopy, pancreatic stones, and pancreatic leaks] 1) Page 14: The usefulness of the Spyglass is referred in this section. Please describe the manufacturer and location of the manufacturer should be described as in the disposable duodenoscope.

Response: The manufacturer and the location - (Boston Scientific Corporation, Marlborough, MA, USA) has been added to the manuscript.

Minor points [C) EUS-directed transgastric ERCP (EDGE)] 1) Page 9: The term "Roux-en-Y" should be used consistently. The term "Roux-en-Y" was described as "roux-en-y" in the previous section. Please be consistent with the terms you use.

Response: Thank you. This has been changed to Roux-en-Y.

Reviewer #2: Number ID: 05710028 Saburo Matsubara

Specific Comments to Authors: I have read this review article with a great interest. Authors described current status and future perspectives regarding ERCP citing newest evidences. I think this article is worth of publication. However, I will indicate a few points to be revised.

#1 2. CANNULATION, BILIARY ACCESS, AND ALTERED ANATOMY A) EUS assisted biliary access Authors mention about EUS-guided biliary drainage with a LAMS. However, a LAMS can be used for EUS-guided choledochoduodenostomy (CDS) for distal biliary obstruction alone. It looks strange to state only distal biliary obstruction. Authors had better describe all of EUS-guided biliary drainage (including hepaticogastrostomy) using various stents, or delete this part regarding EUS-guided transmural biliary drainage.

Thank you very much for your comments.

Response: The paragraph has been changed to following to address EUS guided biliary drainage options.

"In addition to EUS rendezvous, EUS directed transmural bile duct drainage is an alternate option. Transmural options for biliary drainage include hepaticogastrostomy (for proximal biliary obstruction) and choledochoduodenostomy (for distal biliary obstruction). While hepaticogastrostomy is performed using tubular metal stents, choledochoduodenostomy can be performed using tubular stents or LAMS based on bile duct size. A recent RCT compared EUS guided transmural biliary drainage vs ERCP for distal malignant obstruction and reported similar technical and clinical success."

#2 B) Overtube-assisted enteroscopy (OAE) and laparoscopic surgery-assisted ERCP In 1st paragraph "The pooled rates of enteroscopy and technical success of double-balloon enteroscopy ERCP (DBE-ERCP) in 4 studies was higher at 83.5% (95% CI 68.3-92.2) and 72.5% (95% CI 52.3-86.4), respectively." cannot be understood. Please reconsider this sentence.

Response: This paragraph has been reformatted.

"The pooled rate of enteroscopy success with a double-balloon enteroscope in the 4 available studies was 83.5% (95% CI 68.3-92.2). Importantly, technical success of double-balloon enteroscopy ERCP (DBE-ERCP) was also higher at 72.5% (95% CI 52.3-86.4). The pooled rate of adverse events with DBE-ERCP was 9.0% (95% CI 5.4-14.5) [^{40}]."

#3 3. ERCP AND ITS ROLE IN THE DIAGNOSIS AND MANAGEMENT OF BILIARY DISEASE B) ERCP in strictures and cholangiocarcinoma: Diagnosis and management In the last paragraph, "....if the patient received a biliary stent-only alone (8.3 months ± 0.5 P < 0.001). " I think "stent-only alone" should be corrected.

Response: This sentence has been rephrased to:

In 21 months of follow-up, the mean survival time was significantly higher in the RFA and stent group (13.2 months ± 0.6) than if the patient received a biliary stent alone (8.3 months ± 0.5 $P < 0.001$).

#4 Ref. 85 and 97 are same.
Response: Thank you for picking this up. The error has been corrected. Reference 97 has been changed to:

El Hajj II, Brauer BC, Wani S, Fukami N, Attwell AR, Shah RJ. Role of per-oral pancreatoscopy in the evaluation of suspected pancreatic duct neoplasia: a 13-year U.S. single-center experience. Gastrointest Endosc. 2017 Apr;85(4):737-745. doi: 10.1016/j.gie.2016.07.040. Epub 2016 Jul 26. PMID: 27473181.

#5 Two "Figure 4" are present. Latter one should be changed to "Figure 5", including in the text.

Response: We apologize for the error. The latter figure has been changed to Figure 5 and has been changed in the text as well. Thank you.

Reviewer #3: Number ID: 00503834
1. Present duodenoscpe disinfection was good. Worry about the spread of multidrug resistant organism was a little bit overemphasize.

Response: Thank you for your feedback. Inter-patient cross-infection with multi-drug resistant organisms and multiple studies demonstrating residual MDRO organisms after high level disinfection, led to a directive by the US FDA that required industry to redesign duodenoscopes to improve disinfection of the elevator channel or consider development of a disposable duodenoscope.

2. Disposable duodenoscope was very expansive. People of underdevelope , developing country and even nonrich person in USA cannot affort it.

Response: We agree that disposable duodenoscopes prove an insurmountable financial burden in many developing as well as developed countries, their development and availability is one mechanism to eliminate the well-documented and sometimes fatal infections that can occur between patients when using conventional duodenoscopes.

3. There are mant way to minimize post-ERCP pancreatitis. I strongly believe that well training and experience ERCPscopist was most essential. They can avoid or minimize barometric and thermal injury the pancreas and resulting in absent pancreatitis or signifiantly reduce severity of pancreatitis. So ERCPscope should be work independently after well training.

Response: We support your view that clinical experience and expertise are important components of clinical care in patients undergoing an ERCP.

4. Well trained ERCPscopist and experience ERCP-team can shorten time for ERCP, so mild to moderate sedation was suffience for patient to tolerate ERCP procedue. I perform ERCP for more than 30 years with mild to modrate sedation only.

Response: We agree that there is no substitute to excellent clinical training. Although many patients can undergo ERCP with midazolam and fentanyl, a subset require propofol or even general anesthesia.

5. Your review paper was general and detail. Ideas was reasonable. Congraduation.

Response: Thank you.

Reviewer #4: Number ID: 02537509

Specific Comments to Authors: Very interesting and instructive review about the recent advances in the prevention of ERCP infection, quality improvement, biliopancreatic access, and management of biliopancreatic diseases. The review has been clearly presented and is easy to read. In my opinion, this paper can be accepted for publication. Congratulations!

Response: Thank you very much for your comments.

Thank you for your time a thoughtful feedback.

Dr. David Sanders for Dr. Richard Kozarek