To the Editor-in-Chief and Reviewers,

We would like to thank you on the good review and comments that have been made by you on our article, which is entitled "***Helicobacter pylori retreatment: When clinical guidelines meet patient reality***". The manuscript has also been re-written in response to the recommendations of the reviewers as well as the editorial requirements of an **Opinion Review**. This new version of the manuscript was enhanced in terms of clarity, balance, terminology and critical analysis of evidence upon which it is based. The modifications are indicated with yellow in the edited manuscript.

Reviewer 03713791:

1. In the present editorial article Ren et al commented on a recently published article on WJG, addressing the problem of H. pylori re-treatment and loss of follow up after failure. I believe that the point of view reported in the Editorial is fully shareable. nevertheless, the comments are quite witty and shed a new light on the problem described in the article by Cantu-Germano. Maybe, the only issue that can be commented on by Ren, is that compliance may be influenced also by the presence of a "caregiver", especially in older patients (paragraph "The asymmetry of adverse events...").

Response: We thank the reviewer for suggesting this. Access to caregiver/family support impacts treatment completion and retreatment decisions, particularly for older patients and those with substantial logistical or caregiving needs. In the revised manuscript, we have discussed this under the context of treatment capacity and care planning after treatment failure rather than as a separate explanatory variable. For example, we have stated that decisions about whether or not to pursue retreatment in older adults should be made in the context of frailty, comorbidities, polypharmacy, goals of care, and practical support required to complete therapy and follow up. This is more in keeping with the evidence base and limitations of the registry data

Reviewer 07985371:

Specific Comments to Authors, This editorial addresses an important and often underrecognized aspect of *Helicobacter pylori* management, namely the clinical gap that may occur after eradication failure has already been documented. The manuscript highlights the practical issue that a considerable proportion of patients do not proceed to retreatment despite confirmed eradication failure, which is a relevant problem in daily gastroenterology practice. The topic is timely and the manuscript is generally clearly written, with an appropriate selection of references. A strength of the manuscript is that it shifts the focus from eradication regimens alone toward the broader clinical pathway after treatment failure. The discussion on patient follow-up, adherence, and communication between clinicians and patients provides a useful perspective and expands the discussion beyond pharmacologic considerations.

However, several points could be clarified to improve the manuscript.

1. First, the abstract appears somewhat similar to the structure used for original research articles. Since this manuscript is an editorial commentary based on previously published registry data, the

abstract could be simplified to better reflect the nature of the article.

Response: I would like to thank you for this remark. We have made the abstract more in a manner of an opinion review and not as an original research report but as an abstract of a clinical issue, new developments in the field of rescue therapy, issues that still remain on management once it fails and the view that rescue therapy is part of the pathway of care following failure.

2. Second, in some parts of the discussion the wording seems slightly stronger than what can be directly inferred from the underlying data. The interpretations offered by the authors are reasonable, but it may be helpful to present them more clearly as possible explanations rather than firm conclusions.

Response: We agree with the reviewer and are grateful to him or her for this useful suggestion. In the revised manuscript, we have softened the language in a number of sections of the Discussion to clarify that these interpretations are put forward as possible explanations or clinically informed guesses rather than causal statements. The statements about non-retreatment, patient- and physician-related influences, and the implications of the registry findings have been changed accordingly. These changes better separate the observations reported in the index study from interpretations that remain inferential.

3. Third, the section discussing potential patient-related reasons for not pursuing retreatment is interesting but somewhat speculative. As the underlying data do not directly capture patient motivations or physician-patient discussions, this limitation could be acknowledged more explicitly.

Response: We appreciate the reviewers comment. Health literacy, prior treatment experience, risk perception, personal values, and practical barriers are potential contributors but were not documented explanations. This point has been further emphasized in the revised **Future Directions and Limitations of Current Evidence** sections where we now ask for patient-reported reasons for not wanting retreatment and standardized measures of treatment burden.

4. Finally, the manuscript occasionally uses different terms to describe similar concepts (such as retreatment gap or post-failure management). Using more consistent terminology throughout the text may improve readability.

Response: We are thankful of this suggestion and have revised the manuscript to use terminology in a more consistent manner. The term post-failure management is now used as the main term to refer to the broader clinical process after established eradication failure, and the term retreatment gap is only used when referring to specific instances where patients did not advance to rescue therapy.

Reviewer 05038439: This editorial provides a thoughtful commentary on a European registry-based study examining patterns of non-retreatment following confirmed H. pylori

eradication failure. The authors effectively frame a "second gap" in the H. pylori eradication pathway, the failure to initiate rescue therapy even after documented treatment failure, and consider it within the broader context of gastric cancer prevention. The manuscript is well-structured, clinically relevant, and supported by an appropriate range of references.

Major Comments

1. The authors did not critically evaluate the limitations of this registry study. Key methodological concerns of the study, such as the voluntary registry design, potential selection bias, and the absence of standardized patient-reported outcome measures, are not discussed. An editorial commentary is most valuable when it both contextualizes and critically interrogates the index paper. It is recommended to organize at least one paragraph to the inherent limitations of registry-based evidence in this context, and explain how these limitations affect the generalizability of the conclusions drawn.

Response: Thank you to the reviewers for this comment. We have provided a part of our work with the title Limitations of Existing Evidence as an explicit critical analysis of the evidence used in the manuscript. This chapter is concerned with the interpretative challenges of data generated by registries, including clinical selection, the unmeasured socioeconomic and access factors, and the lack of knowledge about clinician decision making, and the absence of validated patient reported outcomes. It also points out that there are very few studies on implementation in this area. The addition of such information assists in placing the registry results in the context of a more reasonable setting and it becomes evident that the associations presented should not be regarded as causal explanations.

2. The section "Gender differences and the 'silent decline' after failure" attributes male non-retreatment to sex differences in preventive care engagement and risk appraisal, citing a 2003 sociological reference (Williams DR, Reference 13) that is now over two decades old. The field of gender medicine has evolved considerably, and relying on a single dated sociological source to contextualize clinical registry findings is insufficient. The authors acknowledge that the registry did not capture the specific reasons patients declined, which further undermines strong interpretive claims about sex-linked behavior. This section should either be supported by more contemporary and clinically relevant references or reframed as a hypothesis-generating observation warranting prospective investigation.

Response: We are grateful to the reviewers perceptive and essential remark. We recognize that our first interpretation of sex-related differences was not completely supported by the registry data and did not refer to recent or clinical enough evidence. In the revised manuscript, we have removed the discussion of sex-specificity. The manuscript now defines non-retreatment in general terms like treatment burden, past negative experiences, communication, and health care delivery. This description is more consistent with the data and does not imply a sex-specific explanation that cannot be substantiated by the current evidence.

Minor Comments

3. The manuscript uses both "compliance" and "adherence" inconsistently. Contemporary clinical and behavioral literature strongly favors "adherence" as it reflects a collaborative, patient-centered

relationship rather than a hierarchical one. The authors themselves note the importance of shared decision-making and supported care. The term "compliance" (used in the context of the ≥90% medication threshold) should be clarified as a registry-defined metric, while the broader behavioral concept should be uniformly referred to as "adherence" throughout.

Response: We agree with the reviewer that this is an important point. In the revised manuscript we have predominantly used adherence when referring to the general behavioural construct of patient engagement with treatment, retaining compliance only where needed to preserve the terminology or threshold reported in the cited registry-based literature.

4. The brief mention of potassium-competitive acid blockers (Reference 11) in the second section reads as a digression. The index study does not specifically address PCAB use, and the editorial's central argument concerns patient engagement, not pharmacological optimization. This passage should either be expanded with discussion of how newer regimens might specifically affect retreatment acceptance, or condensed to a single sentence to avoid distracting from the editorial's core thesis.

Response: We thank the reviewer for this helpful comment. Vonoprazan-based therapy is now mentioned less, and as an example of emerging rescue options, to avoid an independent pharmacologic digression.

ROUND 2

This manuscript addresses a clinically relevant but often overlooked aspect of *Helicobacter pylori* management, namely the gap between confirmed eradication failure and the initiation of rescue therapy. The topic is important, particularly in the setting of increasing antimicrobial resistance and the growing preventive focus of *H. pylori* eradication. The manuscript is well organized and offers a useful clinical perspective that goes beyond regimen choice alone. A major strength of the manuscript is that it shifts the discussion from rescue regimens themselves to the broader issue of post-failure management. This is a valuable perspective.

1. However, in some parts of the discussion, the interpretation of registry-based findings remains somewhat stronger than the available data directly support. I would suggest maintaining a cautious tone throughout, especially when discussing the reasons for non-retreatment.

Response: We are grateful to the reviewer on this crucial remark. We concur that registry-based results must be taken with a grain of salt. We corrected the pertinent parts so as not to overstate causality and adopted more tentative language, including “may contribute, are consistent with, and hypothesis-generating”. We also explained that registry data is able to detect a post-failure gap but not determine the exact causes of non-retreatment.

2. The addition of the limitations section improves the manuscript. Still, the authors may further emphasize that registry-based data are subject to selection bias and unmeasured confounding, including differences in healthcare access, treatment cost, local practice patterns, and patient-related barriers. These issues are important when interpreting the broader clinical meaning of the reported retreatment gap.

Response: We agree. We added to the limitations section, selection bias and unmeasured confounding in registry-based studies. In particular, we included healthcare access, treatment cost, local practice patterns, availability of susceptibility testing, health literacy, transportation difficulties, comorbidity and patient preferences as possible unmeasured variables that can affect retreatment decisions.

3. The abstract has improved, but it still reads somewhat like the abstract of an original article. Since this is an Opinion Review, a more concise and clearly narrative abstract may be more suitable.
Response: Thank you for this valuable suggestion. We have rephrased the abstract.

4. Another strength of the manuscript is that it highlights eradication failure as not only a microbiological problem but also a care-delivery issue. This is an important point. At the same time, some sections discussing resistance patterns and newer regimens could be tightened to keep the focus more clearly on implementation, follow-up, and patient-centered care.
Response: We are grateful to the comment. The updated text is shorter on these regimens and it relates them better to application, patient tolerance, the ability to complete a treatment and also the eradication confirmation.

5. The discussion of patient-related barriers is clinically meaningful, but because these factors were not directly captured in the cited registry data, they should be presented as possible contributors rather than firm explanations.
Response: We are of the same opinion as the reviewer. The patient barriers were modified in their discussion to indicate that they could be possible causes but not definite explanations. We also included a statement that was on the level of patients including health literacy, risk perception, and previous bad experiences, and practical constraints were not directly captured by the analysis of the registry.

6. The manuscript is generally readable, although there are still some minor language and stylistic issues in a few sections, especially in the abstract and early parts of the text. A final language edit would be helpful.
Response: Thanks. We did a final language edit, focusing mainly on the abstract and the first parts of the manuscript. We changed a few sentences to make them more concise, clear and with a consistent tone.

7. The tables are clear, useful, and add value to the manuscript. In summary, this is a relevant and well-conceived Opinion Review that draws attention to an important gap in real-world *H. pylori* care. With minor revision for tone, emphasis, and language polishing, the manuscript would be suitable for publication.
Response: We thank the reviewer for his/her positive assessment of our manuscript and tables, which we have kept with light language polishing, and modified the manuscript following the suggestions of the reviewer about the tone, the emphasis and the language.

We thank the reviewers' comments that have greatly improved the manuscript in terms of clarity, balance, critical assessment and overall readability..

Sincerely,
Le Liu