The authors reviewed the scientific background of IBD comprehensively and then developed a DNAm pipeline tool that can be useful for epigenetic studies of IBD in Vietnam. Thanks to the authors' efforts in writing the paper. Please see some suggestions below.

Major comments

1. To further reflect the value of this manuscript, we suggest this manuscript as an Original Article, not a Review. This is because the authors have proposed a DNAm pipeline tool related to IBD, not just done a review. According to the DMR's Author Instruction, the format and content should be refined further, including Introduction, Highlight box, Discussion et al. Please refer to https://cdn.amegroups.cn/static/public/2.1-Structure%20of%20Original%20Articles-template-V2022.11.4.docx

2. The two subtypes of IBD, ulcerative colitis and Crohn's disease, have different clinical phenotypes and pathological features. Can they be developed under the same genetic, environmental, and intestinal flora conditions?

3. Line 74, it's highly suggested that the authors revise it as "1.2 Epigenetic Mechanism of IBD". Then please add more comments about the relationship between epigenetics and IBD, instead of merely describing the general information of epigenetic mechanisms. This would obviously be of interest to the reader.

4. Please consider providing more details of the DNAm pipeline development and data processing and placing them in the "Methods" section, and if applicable, the literature search strategy can be added. Besides, relevant statistical analysis methods should be described, such as data in Fig3.

5. Please add a Result section and reallocate these key findings to it, including the key literature review findings, and a case study of the DNAm pipeline.

6. If possible, authors may consider giving thoughts on future studies in the context of current advances in epigenetics.

7. We recommend including a separate section on the strengths and limitations of this paper to promote a more intellectual interpretation.

8. Please consider a more concise conclusion which is a scientific extrapolation of the results available.

9. We encourage authors to cite more up-to-data references, which is also in line with our journal aim and scope-"to deliver up-to-date authoritative coverage of basic, translational, clinical research and operative techniques in digestive diseases"

10. Similarity: Some statements need paraphrase, especially source 1. Please see the similarity report.

Minor comments
11. We suggest authors make a more informative title to highlight the significance of the DNAm pipeline in IBD research.

12. Please don't use abbreviations in the title.

13. Abstract
(1) Background: This paragraph is incomplete and the authors should clearly specify the objective of this study.
(2) "we reviewed the concept of IBD and epigenetic...", If authors consider preserving this sentence, it is advised to describe the literature search strategy in Methods and specify the key findings during this process in the Results.
(3) We suggest authors provide specific data to support this sentence-"DNAm is a great data point to explore the phenotype of age and cell type".

14. Authors should also highlight the objective of this paper after the sentence-"From the overall situation...lacks comprehensive investigation in Vietnam".

15. References are not cited or are inadequately cited in some places. For examples, "Epigenetic factors have been proven to be involved in the pathogenesis of a variety of disorders..."
"more and more studies reported promising results in using DNAm for colorectal cancer screening in IBD patients [54]."

Please check the FULL text and further add the citations.

16. Please define ALL abbreviations mentioned the first time, such as SNP. Lines 284-286, no need to define these abbreviations here.

Reviewer B:

Thanks for the authors' careful revision. It's good for authors to change the type of manuscript. There are some minor issues that suggest addressing.

Comment 1. The running title should be adjusted based on the TEXT, which should highlight the DNA methylation analysis model rather than just epigenetic studies.
Reply 1: We have modified the running title following your suggestion.

Comment 2. Lines 33-36, "this model was...(R2=0.96) and cell type deconvolution (highest R2=0.99 in neutrophils)", which should appear in the Abstract-Results. Authors can mention corresponding statistical methods in Abstract-Methods.
Reply 2: We have moved this part into the Abstract-Results.

Comment 3. Highlight Box
1) The "key findings" fail to show what was done (use DNAm pipeline to validate against public datasets of age prediction) and how did it turn out (significantly correlated with the ground truth and cell type deconvolution).
Reply 3.1: We have added these key results into highlight box
2) We kindly suggest to point out the knowledge gap about DNAm in IBD and then specify what this manuscript adds to current studies.
Reply 3.2: We have inserted the knowledge gap and what we supply in the highlight box.
3) Before talking about future actions, the authors is advised to specify the DNAm pipeline implications.
Reply 3.3: We have added the implications of DNAm pipeline

Comment 4. It's good to see authors give details of DNA methylation and demethylation. Of note, The DNAm and its relation with IBD should be the focus of this study. It's a bit confused about why authors use such a lengthy section to describe RNA methylation, histone modification, and non-coding RNAs. Please consider making this content concise.
Reply 4: We have shortened this part.

Comment 5. Apart from the exploration of age and cell types in the immune system, are there else factors that have been studied? As the authors said that numerous factors are involved in the development and progression of IBD, why authors choose those two factors in this work? We would prefer to see other factors' results if authors have done, which can enrich the study content.
Reply 5: We also want to evaluate more different factors related to IBD pathogenesis. Sadly, we did not find more other appropiate dataset for applying in IBD context, so we could only provide results regarding age and blood cell types. Other factors such as microbiome analysis, diet compositions, family history are now recruited in some studies and we hope in the near future our dataset will be enriched.

Comment 6. Lines 325-333, "For the next step...", this content would be more appropriate in the discussion.
Reply 6: We have moved this part into Discussion.

Comment 7. Please avoid reporting "P=0.00", which can be reported P<0.001.
Reply 7: We have change these to p<0.001

Comment 8. Discussion

1) The key results (result of Fig 3) should also be highlighted and explained at the beginning of the discussion.

Reply 8.1: We have added these information in the beginning part of discussion.

2) Line 367, "Besides, the changes of diet after diagnosis are also an important factor in managing flare-ups of both diseases". Please add a reference to substantiate this claim.

Reply 8.2: We have add the citation for this.

Comment 9. Conclusion

"Our proposed DNA methylation was potential foundation for the development of a screening and early diagnosis approach by using epigenetic information in Vietnam". The DNA methylation should be revised as DNA methylation pipeline.

Reply 9: Yes, we have fixed it