Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear authors, in the article you did not specify how you received 5-centimeter sections of normal tissue? By what method were they obtained, surgical resection of the intestine or ESD? And why are they not indicated from which part of the large intestine samples of normal tissue, adenomas and tumor material were obtained?

Re: Thank you for your valuable feedback and insightful comments regarding our manuscript. We appreciate the opportunity to address the concerns raised. Regarding the question about the 5-centimeter sections of normal tissue, we apologize for the oversight in not providing sufficient details in the original manuscript. The normal tissue sections were obtained through surgical resection of the intestine. We have now included this information in the revised manuscript to ensure clarity and completeness.

Additionally, we acknowledge the need for more specific details on the origin of the samples from the large intestine, including normal tissue, adenomas, and tumor material. In our revised manuscript, we have included information specifying the exact locations from which these samples were obtained in Table S1. We hope that these revisions adequately address the concerns raised, and we appreciate the opportunity to enhance the quality and comprehensiveness of our manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear authors. Weaknesses or deficiencies in the manuscript are: 1) Too small amount of samples. Especially taking into account results of some other authors. I would recommend to add more samples to the study and rename it as "Early Results..." 2) If authors wanted to identify exacts drivers from adenoma to carcinoma progression? They have to compare exactly late stage adenomas and early stage carcinomas. But they did not divide adenomas and carcinomas into early

and late stage subgroups. I also recommend to withdraw from the manuscript the words about identification drivers from adenoma to carcinoma and divide both mentioned groups into early and late stage. 3) Authors posted their conclusions in the end of discussion section – it's better to post it in the separate conclusion section. This could be easily corrected

Re: We appreciate the reviewer's thorough review and constructive feedback provided for our manuscript. We have carefully considered your comments and have made the following revisions to address the identified weaknesses and deficiencies:

Sample size: We acknowledge the concern regarding the sample size. In response, we have added an additional publicly available dataset to the study. We believe that this addition strengthens the robustness of our results. We have also revised the title to reflect this change; it now reads "Early Results of the Integrative Epigenomic–Transcriptomic Landscape of Colorectal Adenoma and Cancer".

Identification of drivers: To better address the identification of drivers of adenoma-to-carcinoma progression, we have carefully re-evaluated our study design. We have now divided adenomas and carcinomas into early and late-stage subgroups and added comparative analyses of methylation in CRC and ADE of different grades to the Results section. This modification allows for a more accurate interpretation of our findings. We have also removed the part about the identification of drivers of adenoma-to-carcinoma progression from the manuscript.

Conclusion section: We have heeded your suggestion and provided our conclusions as a separate section, resulting in a clearer distinction between the Discussion and Conclusion sections. The aim of this change is to enhance the overall organization and readability of the manuscript.

We believe that these revisions significantly strengthen the scientific merit and overall quality of our work. We hope these changes align with your expectations and contribute to improving our manuscript.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The authors of this article performed methylation analysis of colon adenoma and CRC samples using SeqCap targeted bisulfite sequencing and RNA-seq analysis. When 22 CRC samples and 25 ADE samples were compared, the global methylation was higher in the CRC samples. However, the methylation patterns for differentially methylated position genes, chromatin signatures, and repeated elements were the same for both groups. With the help of RNA-Seq gene expression data, they found 14 meDEGs, but only the methylation of AGTR1 and NECAB1 could predict the prognosis. Although their objectives, techniques, and complex in silico studies used are state-of-the-art, I have fundamental problems with the design of the research. For the adenoma group, the samples should at least have been divided into low- and high-grade adenomas, not to mention their histological type (tubular, tubulo-villous, or villous). Also, for CRC samples, samples should have been subdivided into at least early and advanced grades. It has been previously shown that promoter mutational abnormalities in CRC driver genes can be detected in early adenomas. It would have been good to compare the results with this article (PLoS One. 2015 Aug 20;10(8):e0133836. doi: 10.1371/journal.pone.0133836.) Another shortcoming of the article is its descriptive nature. In at least one colon cancer cell line, it would have been worthwhile to investigate the consequences of restoring methylation status in a subset of genes (e.g., by 5-aza-2' deoxycytidine treatment). Given these shortcomings, I do not consider the article suitable for publication.

Re: Thank you for your thoughtful evaluation of and comprehensive feedback regarding our manuscript. We appreciate the time and effort that you have invested in the review process. We have carefully considered your comments and critiques and would like to address the concerns raised as follows.

Sample subdivision: We acknowledge the importance of subdividing the adenoma and CRC samples based on histological features and grading. In response to your suggestion, we have revised our study design to include subdivisions of low- and high-grade adenomas, as well as early and advanced grades for CRC samples. This refinement allows for a more detailed and accurate analysis of the data.

Comparison with previous studies: We appreciate your recommendation to compare our results with findings from the article presented in PLoS One (2015 Aug

20;10(8):e0133836). In our revised manuscript, we have now evaluated the Ten-Gene Methylation Signature with respect to our dataset, which has strengthened the scientific contribution of our work.

Functional analysis: To address the descriptive nature of our study, we agree with the importance of functional analyses. We have therefore utilized the previously published dataset GSE32323, which includes treatments with 5-aza-2′-deoxycytidine, using the HCT116 and HT29 cell lines, to investigate the consequences of restoring the methylation status of a subset of genes. The results of these experiments have been included in the revised manuscript, as Fig. S1.

We believe that these revisions significantly enhance the scientific rigor and relevance of our research. We are committed to ensuring that our manuscript meets the standards expected for publication, and we appreciate the opportunity to improve our work and thank you for your guidance.