Colon cancer is the 3rd lethal malignancy in the world whose early detection would greatly benefit from the blood based measurements, and cell free DNA methylation abnormality has been proved to be one of the most promising biomarkers for early cancer diagnosis in multiple cancer types. In this study, Fan and co-workers identified some differentially methylated CpG sites by comparing DNA methylation profiles of pre-cancer adenoma specimens to normal colon tissue samples, and by integrating other public datasets, Fan and coauthors revealed DNA methylation at promoter of ADHFE1 is the most promising diagnostic biomarker. Overall, the manuscript is well written, and analysis is well done, and the whole study is likely to generate considerable interest in the field. However, some key questions need to be addressed before I make my further decision.

1. The authors profiled DNA methylation for 18 LGA, 22 HGA and 20 normal tissues, and found significant DNA methylation differences across them. Authors should provide a detailed QC metrics and DNA methylation correlation coefficient across samples within each tissue type to demonstrate the technique reproducibility and methylation homogeneity in each tissue type.
2. Little information is provided for the therapy regimen for the patients whom the authors obtained specimens from. Different drugs may have different levels of effects in shaping the DNA methylation, or are they all treatment naïve?
3. This is a key point, since the authors identified some differentially methylation CpG sites and claimed some of the sites might be useful for early detection. The author should check the methylation status of these CpG sites in the blood samples from normal individuals from public databases. Without this data, the clinical utility and the sensitivity of their findings is questionable.
4. The pathway analysis highlighted gut-brain-axis aroused a very interesting concept that the cross-talk between neuron system and GI system may be interrupted during carcinogenesis. Authors should provide other data (ie. immune staining of some key protein molecules in different tissue types) to strengthen their claims.
5. The authors compared ADHFE1 with SEPT9, and found a better prediction power of ADHFE1 over SEPT9, authors should check if ADHFE1 is some way orthogonal to any of these FDA-approved biomarkers, including SEPT9 and carcino-embryonic antigen (CEA).
6. One article published recently on Science Translation medicine describing the cfDNA methylation for early detection of colon cancer, authors should cite and discuss.

Reviewer #2: Review of the manuscript  " Genome-wide DNA methylation profiles of Low- and High-grade adenoma reveals potential biomarker for early diagnosis of colorectal carcinoma"  
The reviewer thanks for the opportunity of this interesting manuscript, whose separate parts are of excellent, but the paper in all requires thorough emphasis and work together of the independent findings found in the present form of the manuscript.

The title itself shows  some contradiction that can be refound in the whole manuscript. The authors aimed  identification of biomarkers of  early diagnosis of colorectal carcinoma in tissue ?

The authors identified early adenoma markers , but they have not validated them, not tested in cell free DNA ( liquid biopsy), either . The authors expanded findings from early, LGA adenoma to HGA and in silico , to publicly available  cancers. The reviewers asks why ? Cancer epigenetic data, markers  are overwhelmingly available. Validated adenoma and cancer data are far less e.g. ( Patai AV et al. Dig. Dis 2012, Patai AV et al. PLOS ONE 2015) .

If the aim of the work is not the tissues diagnostics but more a liquid biopsy diagnosis based early diagnosis of cancer, the identified biomarker  ADHFE1 should have been tested in cell free circulating DNA samples, as well.

The authors compare the ADHFE1 marker to septin9, however SEPTIN 9 tissue sensitivity and specificity data ( Toth et al.Pathol. Oncol. Res 2012, Toth K. et al Plos One 2012, and 2014)  are not referred, rightly.  
The authors have identified 209 hypermethylated positions in their one data, in LGA cases . These markers were found further methylated in HGA ( authors' own data ) and 504 publicly available cases.

The authors do not describe the correlation of their finding to publicly available LGA or HGA or adenoma ( 50 are available according to their materials and methods section) specimen. This would be specially necessary as no validation is done in this study, at all.

The list of the identified markers are not available in the manuscript and in any addendum which is  major lack of the manuscript.

The publicly available 51 adenoma samples are not used and compared to own LGA or HGA results. The authors do not perform wet-lab verification, either . These are the two major missing of the study ! In case of revision these missings should be included, as well.

The authors do not document their findings and do not describe their biomarkers except the AHFE1, and ACSS3.

Without these and without the publication of their results on GSE or other available public site, authors should and could not use other researchers' results. This paper could not be accepted and published !  
An overall hypomethylation was found . 440 in LGAs and 805 in HGAs. The reviewer would ask how many hypermethylated sites were identified in HGA-s? How many were in overlap ? The Venn diagram does not clear explanation on this in the Figure 1.

The section  " Landscape of DNA methylation of pre-cancerous benign lesions" is not systematic. The Figure 1 is just increasing this inconsistency. The authors evaluated in silico data without detailed publication of the findings in their paper ( tables, top genes,sites etc.) Here arises again the question early adenoma markers were used for adenoma detection but and why for cancer ?

The section " Hyper-methylated CpD sites exhibited better discriminatory performance between normal, pre-cancerous, and cancerous tissues than the hypo-methylted pattern for CRC" relates to publicly available  278 normal, 51, adenoma, and 504 cancer samples. In this section the authors  perform in silico evaluation of  these data but  do not relate them to their own data. The reviewer asks why ?  
In any case, authors should validate the identified in silico markers in their own data, for cancer or early diagnosis for cancer or for adenomas.

The identified marker set is also not detailed and unavailable for the reviewer and for any reader. This is unright and unacceptable.

The section 4, " the promoter of ADHFE1 my be a potential biomarker for colorectal adenoma and cancer" describes two biomarker the ADHFE1 and ACSS1. The validation of these two, LGA marker was done in silico on the publicly available data sets from GEO and Array Express.  Validation should be done by other methods, as well.  Expression analysis of mRNA or proteins from these markers should also contribute to validation.  
The reviewer finds the submitted a good and up-to-date work. If publication of the found data , their validation, their cross validation will be done in wet-lab, too, and are available, after   a major revision, the reviewer suggest reconsideration for publication.