Author's response to reviews

Title: Aberrant methylation of NPY, PENK, and WIF1 as a promising marker for blood-based diagnosis of colorectal cancer

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Author's response to reviews:

Referee 1

1) We did not test the CIMP status, and rather assessed the predictive power of our markers per se. We agree that it will be very interesting to assess whether the CIMP status would add new information to that of the methylation of those markers.

2) To show the results of the selection, we have added a Venn diagram with the relative intersections of the markers selected on each sample type (tissue, urine, serum) and showed the obtained markers.

3) We agree on the point and modified the statement with suggested use with patients where the risk of CRC is present but difficult to assess (e.g. mild symptoms with no CRC family history) and who would therefore not necessarily choose to go for further examination. We also added the referee's point that the method we present can be used as noninvasive effective screening tool for the detection of asymptomatic cancer patients for colonoscopy.

4) We agree that the selection of WIF was not well presented. We rephrased the section referring to that point.

5) We agree and added a comment in the Conclusions on the possible indications for non CRC patients who would be positive to the test.

Discretionary:

1. Thanks for noting the typo, we corrected.

2. We have also results for stool, but with more noise.

Referee 2.
We have added the ROC curve of the other cancers series, as requested.

1) We have added a Venn diagram of the relative intersections of the markers selected on each sample type (tissue, urine, serum) and showed the obtained markers.

2-6) Done.

7) We clarified that point by adding the references. WIF was not in the Illumina Goldengate.

8) Done.