Comments to the Authors,

In this manuscript, Dr. Thorlacius-Ussing conducted a comprehensive diagnostic biomarker evaluation to a large DNA methylation gene panel in 181 pancreatic adenocarcinoma related and control blood samples from Denmark population. The study identified at least 8 hyper-methylated genes which are useful in the diagnostic prediction model. This study is quite timely since majority of the previous study were focusing on solid tissue and ctDNA has been demonstrated as potential and important medium for early cancer diagnosis. However, there are still several small defects in current manuscript.

**Major Revisions**

1, Could you provided the ctDNA yield of cancer and normal plasma samples? Could you find the increased ctDNA yield in cancer plasma? And how about the plasma in pancreatitis patients? It would be nice if the authors could make some correlation analysis between the methylation status and ctDNA yield.

2, Between Line 20 and 25, the authors claimed that Routine analyses (C-reactive protein,leucocytes, alanine aminotransferase, alkaline phosphatase, amylase, bilirubin) were performed immediately afterwards. However, there is no any related statistical analysis to these variables, why?

3, Two-step PCR is a quite smart idea to be applied in low level ctDNA methylation detection, however, the author detected 28 genes at the same time, I hope to find some evidence that this technique could be stable, high sensitivity and uniformly to each genes, especially in the 1st round PCR. In addition, please provide some evidence to guarantee the specificity of the MSP technique.

4, The authors applied MSP in the current study, it is disappointed since MSP is not quite stable and the sensitivity (false negative), even the specificity (false positive) would be lower compared with other methods, such Methylight or Pyrosequencing. The authors have mentioned that they lacked sufficient power to conduct a quantitative analysis. I just don’t understand why they could not conduct Methylight to the production of 1st PCR.

5, The authors didn’t detect the methylation level in the solid tissues. I thought the authors might assume that these regions should be hyper-methylated in solid pancreatic adenocarcinoma since these regions were collected from previous Review paper. However, I hope the authors should give some evidence about it. For examples, in the previous volume of Clinical Epigenetics 6 (1), 18 (PMC4177372), genome-wide aberrantly methylated targets in pancreatic adenocarcinoma has been identified, I’d like to know how many genes among 28 genes could be overlapped? It is quite important since we should be sure about these targets should be pancreatic adenocarcinoma hyper-methylation, rather than some other cancer, such as lung cancer et al.

**Minor Revisions**

1, In the page 8 and page 9(line 59 and line 22, respectively), Additional file 1should be replaced as Additional file 2.

2, The order how to eliminate the variables in Figure 2 should be explained.

3, Why Model 13 was determined as the model with the best performance should be explained.

4, I recommend move the supplementary Table 1 to the main body, since this information would provide more details about the MSP result.

5, Frankly speaking, when I saw the AUC, sensitivity and specificity, I was a little disappointed since these index is not good enough for the clinical application. Compared with other methylation related diagnosis performance, it seems the current study have a little worse performance.

6, please provided the genomic position for the primers, except the primer sequencing.