**Question 1**: The work described in this manuscript is very similar to the one published before: Zhong YH, Peng H, Cheng HZ, Wang P, Quantitative assessment of the diagnostic role of CDH13 promoter methylation in lung cancer, Asian Pac J Cancer Prev. 2015;16(3):1139-43. The authors should mention this work in the manuscript, and discuss why their work is novel and important. It it not good to make readers think the work is completely new by not mentioning the work people have done before.

**Answer 1**: Thanks for your suggestion. In our revised manuscript, we have revised our introduction part, and we have added the sentence as the following:

“Although, Zhong and colleagues have conducted a meta-analysis to evaluate the association between CDH13 promoter methylation and NSCLC [[29](#_ENREF_29)], only published case-control studies were included.” In Line 78-80.

**Question 2**: Besides, due to the fact that the majority work described in this manuscript is what have published before, I recommend the authors to submit this work as a Short Research Communication rather than a Research Paper.

**Answer 2**: Thanks very much for your suggestion. We will communicate with the editor and discuss your idea with the editor and make the last decision.

**Question 3**: Overall, this is an interesting study to conduct a meta-analysis on the methylation status of the CDH13 promoter in non-small cell lung cancer (NSCLC) diagnosis, and four independent TCGA and GEO lung cancer datasets were used to validate the results. However, the study was still not very convincing for its claims because it did not explain why the aberrant methylation of CDH13 could be a potential biomarker in the lung adenocarcinoma diagnosis, while the ORs of the non-diagnosis groups were significantly higher than that of the diagnosis groups.

**Answer 3:** Thanks very much for your question. In our research, although a slight difference occurred between diagnosis subgroup and non-diagnosis subgroup (p = 0.047), a significant difference in CDH13 promoter methylation between cases and controls was observed in both diagnosis and non-diagnosis group and this result were confirmed by non-publication-biased microarray data. In our opinion, diagnosis subgroup analysis is more creditable since the samples are autogenous samples (cancer tissue and adjacent normal tissue from same patient) while non-diagnosis subgroup analysis includes large number of non-paired samples and therefore, in some way, the accuracy would have a little high variability compared with diagnosis subgroup. Meanwhile, some other factors like races, methods, sample sizes and sample quality and disease stages etc. might contribute to it. In conclusion, we believe that the heterogeneity between the subgroups of diagnosis and non-diagnosis will not impair the robustness of our conclusion and aberrant methylation of CDH13 can be a potential biomarker in the lung adenocarcinoma diagnosis

**Question 4**: There was actually thirteen studies included not fourteen ones mentioned in the abstract, making the strategies of the meta-analysis inexplicitly.

**Answer 4**: Thanks very much for your correction. Actually, we have corrected this mistake in our last revision according to the reviewers’ suggestions.

**Question 5**: In “results” of the “abstract” part, the authors claimed, “Fifteen studies, including 2109 samples were included in this meta-analysis”. However, in the “results” part, the authors said, “13 studies with data on the relationship between CDH13 gene promoter methylation and NSCLC were pooled for analysis”. According to table 1, it seems to be thirteen studies in the analysis. It is very confusing. The authors should clarify the actual number in the meta-analysis.

**Response 5**: Thanks very much for your correction. We have corrected this discordance in our last revised manuscript. And in “results” of the “abstract” part (Line 33), we have replaced the sentence with “thirteen studies, including 1850 samples were included in this meta-analysis”.

**Question 6**: Background: It seems the authors often mixed up past tenses and present tenses, and used active tenses in the passive tenses sentences or vice versa. Singular and plural of the nouns should be correctly used. E.g. “Lung cancer is often silent in its early stages and difficult to diagnose in the early stages” should use passive voice as “to be diagnosed”. The mixed active tenses and passive tenses examples are like “Evidence showed that promoter methylation, which inhibits CDH13 gene expression, is mediated by DNA methyltransferases Dnmt3A”. “In the past decades, a large number of DNA methylation based cancer diagnostic biomarkers have been identified in NSCLC. The diagnostic or risk associations for several of them have been quantitatively evaluated … status of CDH13 in NSCLC has not been investigated” and etc.

**Answer 6**: Thanks very much for your correction. We have checked them again and made corresponding change in current version.

**Question 7**: The correct font format should be used correctly. E.g. sometimes the “CDH13” was used as italic, and used as standardized form from time to time.

**Answer 7**: Thanks very much for your correction. We have corrected such typo in our revised version.

**Question 8**: All the similar problems in the OVERALL text should be possibly checked and rephrased.

**Answer 8:** Thanks very much for your correction. In this revised manuscript, we have carefully checked all of the similar problems you mentioned previously.

**Question 9**: The sentence of “Lung cancer is often silent in its early stages and …” seems to be weird and it would be better eliminating this phrase and just point out “lung cancer is poorly diagnosed in the early stages”.

**Answer 9**: Thank you for your correction. In the revised version, we have replaced the sentence in Line 51 with “lung cancer is currently poorly diagnosed in the early stages”.

**Question 10**: The authors asserted “Non-small cell lung cancer (NSCLC) comprises the majority of lung cancer and has an increasing incidence and mortality in the last two decades in China and in the world”, and the relative references should be added.

**Answer 10**: Thanks for your suggestion. In the revised manuscript, we have added three references describing the lung cancer statistics in China as well as in the world in Line 54.

**Question 11**: The author introduced “The CDH13 (cadherin 13) gene, an atypical member of the cadherin superfamily, was isolated recently and has been mapped to 16q24, and which was devoid of a transmembrane domain and anchored to the exterior surface of the plasma membrane via a glycosylphosphatidylinositol anchor”. The “which” here was clearly not indicating “16q24”, and the sentence should be rephrased.

**Answer 11**: Thanks for your suggestion. In the revised manuscript, we have rephrased the sentence as “The CDH13 (cadherin 13) gene was isolated recently and has been mapped to 16q24. CDH13 gene is a unique member of the cadherin superfamily due to the devoid of a transmembrane domain. Instead, it uses the glycosylphosphatidylinositol (GPI) anchor to attach to the exterior surface of the plasma membrane” in Line 64-67.

**Question 12**: Results: The authors found there was “significant differences between the diagnosis and non-diagnosis subgroup” and they conducted further research in the non-diagnosis subgroup. It is very interesting, as it seems to be one meta-analysis on a diagnostic biomarker according the title, not the investigation on the non-diagnostic biomarker. What about the difference between the subgroups of the proportion of adenocarcinoma <70% and that of >70% subgroup in the diagnosis subgroup?

**Answer 12**: Thank you for your suggestion. In order to assess the diagnostic ability of CDH13 methylation test in NSCLC, we conducted this meta-analysis. And after searching the literature databases, we obtained 13 studies with data on the relationship between CDH13 gene promoter methylation and NSCLC. Of the 13 studies, we found that the main purposes of some included papers are not in diagnosis of NSCLC. For example: \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*. However, these papers actually provide the necessary and useful information for us. We can still combine these data to get a more robust and unbiased conclusion on the diagnosis ability of CDH13 gene promoter methylation in NSCLC.

As to the second question, among diagnosis subgroup which consists of 5 studies, we found that there is only one study’s Ad% is less than 65%, while the other 4 studies’ Ad% are higher than 65%. That makes the subgroup analysis unreliable due to the imbalance of sample sizes and the extremely few studies in the subgroup of Ad% <65%. As a result, we didn’t perform the subgroup analysis in the diagnosis subgroup.

**Question 13**: Moreover, the author should clearly clarify why they focus on the potential of using CDH13 as a biomarker for NSCLC diagnosis, not NSCLC prognoses and etc.

Answer 13: Thanks very much for your question. The potential of using CDH13 as a biomarker of NSCLC diagnosis and prognoses are both what we care about. And we have searched the papers focusing on the association of CDH13 promoter methylation and NSCLC prognosis through PubMed and Web of Science, and found too few papers are focused on this area and thus not enough for drawing a robust conclusion. On the other hand, as we mentioned in the introduction section that around 70% of lung cancer patients will survive for at least a year if diagnosed at the earliest stage compared to around 14% for people diagnosed with the most advanced stage of disease, the early diagnostic biomarker is quite important to decease the mortality of NSCLC. As a result, we focused on the potential use of CDH13 as a biomarker for NSCLC diagnosis.

**Question 14**: Results & Discussion, For the “relatively inconsistent results”, the author supposed it might be the MSP and qMSP method or the sparseness of CpG sites. Yet it seems they did not compare the differences between different stages of NSCLC. The progress of the cancer might be an important reason resulting in different methylation status of the CDH13 gene. It would be very interesting to know the difference between different stages in the subgroups and present the forest plots to show the difference, not only in the diagnosis and non-diagnosis group.

**Answer 14**: Thanks very much for your suggestion. In our manuscript, we have divided the samples into different groups according to the cancer stages in Table 2. We found no significant heterogeneity between Stage I <49.3% subgroup and Stage I >=49.3% (P-value = 0.14). No significant heterogeneity was also found between subgroups of Stage (I+II) <75.2% and Stage (I+II) >=75.2% (p-value = 0.90). And 49.3% and 75.2% was the median stage percent in all the studies and thus taken as the criteria for dividing the studies. As a result, we didn’t show the forest plot of the subgroups with different cancer stages due to the insignificant heterogeneity.

**Question 15**: In Figures & Tables, the necessary abbreviations of the terminology should be added below the figures and the table, like the methylation detection methods and the types of cancer and etc.

**Answer 15**: Thanks very much for your correction. We have added the abbreviations of the terminology in Figure 2-3 and Table 1-3 in our revised manuscript.

**Question 16**: In Figure 1, the title of “Combined estimates for the association between CDH13 promoter hypermethylation and non-small cell lung cancer (NSCLC) with forest plot” sounds a little bit weird. It should be rephrased.

**Answer 16**: Thanks for your correction. In our revised manuscript, we have rephrased the title of Figure 1 as “Forest plot of Meta-analysis for association between CDH13 promoter hyper-methylation and non-small cell lung cancer (NSCLC)” in Line 513-514.

**Question 17**: In Figure 2, All the figures should be annotated separately, instead of an inexplicit combined subtitle (A-D).

**Answer 17**: Thanks very much for your correction. We have corrected this mistake in the revised manuscript with detailed annotation of Figure 2 in Line 527-534