**Cover Letter**

Dear Executive Managing Editor,

On behalf of my co-authors, I am submitting the enclosed material “*Diagnostic Role of APC Promoter Methylation in Non-Small Cell Lung Cancer (NSCLC): A Integrate-Analysis of Published Articles and Microarray Data*” for possible publication in *Clinical Cancer Research*. It has not been submitted for publication nor has it been published in whole or in part elsewhere. I attest to the fact that all authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to *Clinical Cancer Research*.

APC has been considered one of most important biomarker for early diagnosis of cancer while there was still not yet any quantitative assessment for the sensitivity and specificity in NSCLC. We systematically integrate 3298 NSCLC and its counterparts from published articles and DNA methylation microarray data to discover the association between DNA methylation and NSCLC. A significant association was observed between APC promoter methylation and Lung cancer, with an aggregated odds ratio (OR) of 3.79 (95%CI 2.22, 6.45) in random effect model. Pooled sensitivity and specificity were 0.548(95%CI: 0.42-0.67, P<0.0001) and 0.776(95%CI: 0.62-0.88, P<0.0001), respectively. The area under the curve (AUC) of the methylation test in NSCLC was 0.82. And we found the specific of CpG site, proportion of adenocarcinoma to squamous cell carcinoma and heterogeneous or autogenous control were most important heterogeneity sources. Gender, TNM stage, methylation detection methods, tissue or serum showed no significant associations with APC methylation in NSCLC diagnosis. What's the most important is that we compared the performance of APC methylation test in NSCLC and prostate cancer diagnosis (Chen Y, etc. 2013, EJHG, 1-7), therefore it provide more comprehensive assessment of the diagnostic role for APC methylation test.

We certify that we have participated sufficiently in the work to take public responsibility for the appropriateness of the experimental design and method, and the collection, analysis, and interpretation of the data.

Best Regards.

Yours Sincerely,

Name of the corresponding author : Juncun Wang

May 12, 2013