Author’s response to reviews

Title: Blood Test Shows High Accuracy in Detecting Stage I Non-Small Cell Lung Cancer.

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Response is also attached a supplemental

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Rossano Lattanzio
Editor, BMC Cancer
https://bmccancer.biomedcentral.com/

Dear Dr. Rossano Lattanzio,

Enclosed, please find a revised manuscript (BCAN-D-19-03455R1) entitled "Blood Test Shows High Accuracy in Detecting Stage I Non-Small Cell Lung Cancer" by Cherylle Goebel, Christopher L. Louden, Robert Mckenna Jr., Osita Onugha, Andrew Wachtel, and Thomas Long.

We are honored that you have considered our publication to be potentially accepted. As you have indicated in your email dated January 21, 2020, I am submitting this revised manuscript for further review. Sections that were modified or added are underlined in the revised manuscript. The comments
Liping Dai (Reviewer 1): The manuscript titled 'Blood Test Shows High Accuracy in Detecting Stage I Non-Small Cell Lung Cancer' by Cherylle Goebel et al has been revised by the authors according to the reviewer's comments. However, there still are several issues should be addressed clearly for the understanding.

Comment 1: The article stated that the LCDT1 model greatly improves accuracy and the LCDT1 algorithm was developed with slight modifications using a smaller subset of biomarkers from the 21 biomarkers. However, the authors did not describe which or how many biomarkers were included in the LCDT1 model. The authors should add some contents about the LCDT1 model.

Reply: Respectfully, in the Results Section, Page 9, Line 55-58, it is indicated that the information requested was proprietary and a patent application was filed; We do recognize and expect that others will want to know the 21 biomarkers. Unfortunately, at this time we are unable to disclose that information. We hope that Reviewer 1 understands.

Comment 2: In the page 10 line 14, it is showed 'IL-2 and IL-7 showed greater than a 50% reduction in signal (Supplementary Figure 2)'. However, in Supplementary Figure 2, I found the median concentration of IL-7 in NSCLC was higher than other three groups, the result in figure and the explanation is inversed. The authors should check it carefully and address it correctly.

Reply: We thank Reviewer 1 for catching that mistake. The reference should have stated “Table 4” and not Supplementary Figure 2.

The Results Section, Page 10, Line 16-17 has been corrected to: “….signal (Table 4).”

Furthermore, The Supplementary Figure 2, Page 31-37 has been removed as it was from a previous feasibility data1 that consisted of Russian and US samples; I have included a separate file Supplementary Figure 2 with the correct figures for this publication which include samples that originated from the United States only. However, this was not referred to in the publication and will not be attached in the manuscript; it will be available upon request.

As a preview, we plan to submit a future publication that evaluates the difference of biomarker expression in samples originating from Russia vs. the United states which can affect algorithm development for evaluating diagnostic capabilities and may be important to consider for future studies in disease development and diagnostics using biomarkers.

J Lu (Reviewer 2): The search of this kind is very important and the quality of overall work is excellent. But I do have following suggestions:

Reply: We thank the reviewer for the comment.

My main concerns are about your controls: You have included cancer types other than NSCLC like breast cancer, pancreatic cancer and colon cancer, and non-cancer types such as smokers, healthy individual and asthma patients etc. I think you missed inclusion of other types of lung cancers in your controls such as small cell carcinoma and metastatic adenocarcinoma to the lung as well as other nodular lung lesions in non-cancer groups.
It is very important to include small cell carcinoma and metastatic adenocarcinoma to the lung in your cancer controls, otherwise, one cannot reach the conclusion of its specificity as claimed for non-small cell lung cancer (NSCLC). Also, I think it is important to include some nodular lesions (non-cancer) such as pulmonary Langerhans cell histiocytosis etc. since this would be scenario to be encountered in differential diagnosis for early lung cancer, which is often presenting as a small nodule.

Reply: We agree with the Dr. Lu and thank the reviewer for the input. This study was in continuation of a previous study and the goal was to provide clinical validity that the algorithm and markers detected Stage I-II NSCLC specifically.

To elaborate, feasibility studies and additional unpublished internal studies did include Small Cell Carcinoma (SCLC) and late stage NSCLC (metastatic LC); They were detected with our algorithm using the 33 plex (as mentioned in the Methods Section, Page 8, Line 4-12); In past studies, we observed certain biomarkers to be more elevated in late stage versus early stage LC (as noted in the Discussion Section, Page 12, Line 52-60);

In this study, we wanted to focus on Stage I-II NSCLC, -as detection of early stage NSCLC allows for intervention and possibly cure; Hence, given previous observations, we narrowed and optimized our markers and algorithm accordingly for the study covered in this publication. We limited our LC cohort to Stage I-II NSCLC to obtain data to support our clinical validity study in detecting early stage NSCLC. We hope that this addressed Reviewer 2’s concern.

To further add, we are currently conducting a multi-site, prospective, blinded clinical trial to show clinical utility; We are looking at nodule size, LC type, cancerous vs non-cancerous nodules, histopathology and CT results; Here we will have an opportunity to follow-up with the patient's medical history and initial assessment stage and provide a more expansive analysis.

To the Editor, Dr. Lattanzio, and in regards to Reviewers 1 comment, our legal counsel has recommended not to release the list of the 21 biomarkers until our patent has been granted. We hope that this manuscript offers sufficient valuable and novel data to other scientists and medical professionals that withholding the list of 21 biomarkers would not automatically disqualify our manuscript from being published with BMC Cancer.

In accordance with BioMed Central editorial policies and formatting guidelines, a clean version of the manuscript is attached.

A copy of the updated Supplementary Figure 2 is also attached for your reference only.

A submission agreement from each author is also attached.

Please let me know if I can provide further information to address the Reviewer’s comments. Thank you for your consideration and time. I look forward to your response.

Respectfully,

Cherylle Goebel