1. Introduction to the Revised Application

The initial application was reviewed by the BMIT-B study section and scored in the 37th percentile. The resume and summary of the review discussion commented positively on the potential high impact of the "excellent application" as well as the team"s expertise in both lung imaging and software development. Concerns were also raised regarding the lack of certain project details (vis-a-vis both hardware and data) and the expected application areas. Additionally, issues were raised concerning the dynamic nature of the lung and the potential difficulties with the proposed project. This revised application addresses these concerns and includes additional details to motivate reconsideration.

Lack of details for hardware, data, and method descriptions. We agree and have added text detailing hardware requirements for the proposed project including additional discussion concerning the GPU hardware component. We have also expanded our proposed documentation deliverables to include hardware platforms employed and benchmarking of computational times (Critique 1). Also, we have expanded descriptions for the methodologies proposed in the revised application and removed items that were deemed "trivial."

Lack of PET imaging. We agree concerning the importance of PET imaging in the lung and have included discussion of possible data and algorithmic contributions to be included in this project. Based on recent work done by our group, we have added a related contribution concerning quantification of pulmonary blood perfusion parameters which we have added to this revised application (Critique 1).

Lung motion not addressed. *Jim to add.*

Excessive number of external collaborators (Critique 2). It was suggested that the number of proposed external collaborators is potentially excessive and possibly redundant. We agree with this assessment and have limited the number of beta testers to research groups at the core institutions (i.e., the University of Pennsylvania and the University of Virginia). As the other groups continue to have an interest in the outcome of this project, we plan to maintain the proposed relationships but intend to scale back the direct assistance for individual projects that we had originally planned.

Lack of novelty (Critiques 2 and 3). Despite the admitted lack of *algorithmic* innovation, we believe that significant novelty lies in the fact that an open-source package for lung image analysis has yet to be offered which is analogous in functionality as the various brain packages. As we pointed out in the original appliation, according to a prominent figure in lung image analysis, such lack has been one of the "major hinderances to more widespread usage of such [lung] imaging biomarkers."

Preexisting lung image analysis software (Critique 2). Already existing softwares were mentioned as obviating factors for the proposed project. It is true that "investigators have been assessing pulmonary images of tumors/nodules, interstitutal disase, and pulmonary embolism for decades" yet public availability of such work continues to be a critical problem. Specific mention was made of available software accompanying the LIDC and RIDER lung imaging databases. However, the only software we found were limited to functionality involving interpretation and translation of the XML files describing the nodule annotations of those specific databases. Such software certainly does not comprise a part of the generic processing utilities that we envision. Similarly, we looked at the various lung-based image processing competitions that have been held over the years (VOLCANO09–nodule detection, EMPIRE10—motion estimation, and LOLA11—lung and lobe segmentation challenges) and it appears as though the majority of proposed algorithms are not publicly available. Also, the reviewer asserts that "many of the feature indices (Table 2) already exist in generic form in Brain packages, etc." We are unaware of such availability in the major brain packages (e.g., FSL, SPM, FreeSurfer) although we are aware that a significant number of them do exist in the Insight Toolkit as we created the corresponding software and put them in there. Part of ITK-Lung would be targeting these features to lung images.

Naivety on the part of the investigators (Critique 2). The concern is raised regarding the necessary level of sophistication of the investigators to fulfill the project deliverables. Although the reviewers point out the software expertise of our team and our success in the neuroimaging domain, it is assumed that we are "too naïve with respect to the difficulty and complexity of creating [targeted pulmonary image analysis] software." Based on our publication record in the field, we find this assessment to be a significant undervaluing of our research contributions where much of our showcased "preliminary" software has been used in large studies. We thank the reviewer for pointing this out and have added a section outlining these publications.

General usage issues.

Reduction of algorithmic scope. (Critique 2) Concerns describing the scope of the project as being too large were made in light of the extensive methodological depth of the field. It should be noted that we have no intent of implementing a fraction of these methods. We have revised our application to sharpen the delineation of our contributions. Additionally, we have dropped nodule detection from the set of lung-specific algorithms targeted in this application although such an implementation might be made available during the course of our interaction with our external collaborators.