1. Introduction to the Revised Application

We would like to thank the reviewers for a careful critique, the resume and summary of which commented positively on the "potential high significance" of the "excellent application" as well as the "expertise [of the team] in [both] lung imaging and software development." We are equally grateful for the reviewers' helpful suggestions, all of which were incorporated in this resubmission as described below.[1]

Lack of details for hardware, data, and method descriptions (Critiques 1 and 2). We agree and have expanded descriptions for all elements of the project, including new discussion concerning GPU development, and hardware platforms employed and, where applicable, publicly available competition data for performance benchmarking. We have also removed "trivial" items as per reviewer suggestions.

Lack of PET imaging (Critiques 1 and 3). We agree concerning the importance of PET imaging in the lung and have now included this modality in the project, as well as a related contribution in pulmonary blood perfusion quantification based on recent work from our group.

Dynamic nature of the lung environment and heterogeneity of applications/equipment not addressed (Critiques 1 and 3). The unique dynamic nature of the multi-modality lung imaging environment indeed poses significant challenges to acquiring high quality images of the lung. Although acquisition protocols continue to improve—in part due to precisely the kinds of image registration/processing innovations that we propose to make available through ITK-Lung, the current state-of-the-art is sufficient to allow effective quantitation of lung structural and functional parameters in multi-modality studies. The major caveat, however, is that sophisticated and extensive pre- and post-processing of the images may be required depending on the type and degree of distortions and artifacts introduced during acquisition. Enabling such preprocessing is exactly one of the major goals of this project. To achieve this objective, given the additional complexity introduced, as noted in critique, by the heterogeneity of applications and equipment in lung imaging, flexible and tunable (i.e., open and programmable) tools are needed, with manifold capabilities carefully curated to cover essential analysis and processing tasks, all of which ideally integrated within a single coherent toolbox—this is precisely the overall goal and deliverable of the proposed project.

Excessive number of external collaborators (Critiques 1 and 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 primary beta testers to research groups at the project sites (i.e., the University of Pennsylvania and the University of Virginia). However, we plan to maintain the proposed relationships with the external groups but will scale back the direct assistance to them. The use of separate, independent testing sites will increase the value of the tools produced by ensuring that their success is not specific to the particular source of data. This will increase the generality of the developed resources and thus ease dissemination to the wider community.

Lack of novelty (Critiques 2 and 3). Indeed, this project does not seek to invent new algorithms and is motivated instead by the lack of access to methods that define the current state-of-the-art, in particular, within a comprehensive, integrated framework. Thus, in spite of the relatively modest degree of algorithmic innovation, we believe that significant novelty lies in the proposed "initiation of a new general toolkit focused on lung imaging" as noted in Critique 1.

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, interstitial disease, 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 that is publicly accessible appears to be limited to interpretation and translation of the XML files describing the nodule annotations of those specific databases. In contrast, the COPDGene study has given rise to the Chest Imaging Platform software, which does not yet appear to be fully available to the public and whose focus and scope (CT imaging primarily of COPD) are significantly more narrow than those for this project. Similarly, we looked at the various lung-based image processing competitions that have been held over the years and, to the best of our knowledge, the vast majority of proposed algorithms are not publicly available. Critique asserts that "many of the feature indices (Table 2) already exist in generic form in Brain packages, etc;" however, we are unaware of such availability in the major brain packages (e.g., FSL, SPM, FreeSurfer), although we do know that a number of them exist in the Insight Toolkit because our group developed and contributed the corresponding software. This project would target these available features—as well as create additional ones specialized—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. Based on our publication record in the lung imaging field (now documented in the revised application), we respectfully submit that this assessment represents a significant undervaluing of our contributions, where much of our showcased "preliminary" software has been used in large studies. A new letter from Eric Hoffman, an acknowledged authority in the field, attests to our group's reputation in lung image analysis methods and software development. Moreover, Dr. Hoffman has joined the project team, further strengthening feasibility of the project.

Reduction of algorithmic scope (Critique 2). Concerns describing the scope of the project as being too large were raised in light of the extensive methodological depth of the field. We agree and have revised our application to sharpen the delineation of our contributions.

Budget (Critique 1). This has been reduced as per review suggestions and includes further cuts to reflect the more limited support of external collaborators in the revised project.

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[1] Changes to the Research Plan in response to reviewers' concerns are identified by vertical sidebars.