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). Lung imaging analysis is indeed made more difficult by the inherent challenges posed by the dynamic nature of the lung environment in acquiring high quality images. This is compounded by the wider range of imaging signal characteristics in the chest due to the appearance of air, fat, soft tissue and bone, together with their interfaces, in the images. The complexity of lung images and diversity of protocols and equipment/modalities used for their acquisition, therefore, demand flexible and tunable (i.e., open and programmable) tools, 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). As the external groups continue to have an interest in the outcome of this project, we plan to maintain the proposed relationships but will scale back the direct assistance to these groups. 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 algorithms 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. 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—registration and motion estimation, LOLA11—lung and lobe segmentation, and VESSEL12—vasculature segmentation) 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. Although the reviewers highlight 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 lung imaging field (now documented in the revised application), we respectfully submit that this assessment represents a significant undervaluing of our research contributions, where much of our showcased "preliminary" software has been used in large studies. A new letter from one of the foremost authorities in the field, Eric Hoffman, attests to our group's international 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

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

of our contributions. Additionally, we have removed nodule detection from the project in the interest of avoiding redundancy as this seems to be a major developmental effort of the Chest Imaging Platform.

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.