Reply to: Hierarchical CT Scoring Systems Cannot Discriminate Between Reversible Bronchiectasis and Mucus Plugs

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On behalf of the authors of: Improvement in Lung Clearance Index and Chest Computed Tomography Scores with Elexacaftor/Tezacaftor/Ivacaftor Treatment in People with Cystic Fibrosis Aged 12 Years and Older - The RECOVER Trial.

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From the Authors:

In the letter to the *Journal* by Dournes *et al*., referring to our recent paper (1), the authors state that hierarchical CT scoring systems cannot discriminate between reversible bronchiectasis and mucus plugs. This is not correct. Existing scoring systems cannot determine whether structural abnormalities in specific airways switch from one hierarchical tag to another between scans, however scoring systems assess changes for the whole lung or at a lobar level as opposed to a selected bronchus/artery (BA) pair. PRAGMA-CF has been well validated and proven to be more sensitive to detect and track airway disease in many longitudinal cohort studies compared to the older, less developed scoring systems referred to by the authors (2). RECOVER involved pre-study standardization of scanner imaging outputs from all sites and spirometry control during scanning to standardize lung volumes. Intra-class correlation coefficients in our study for measurements of %Bronchiectasis, %wall thickening, and %Mucous plugging were excellent (>0.8).

More sensitive image analysis systems are clearly needed. Recently an AI-based fully automated analysis system was developed that measures BA-dimensions of a large number of BA pairs on each CT scan. These measurements replace subjective human judgement using the artery as reference structure. This BA-analysis has been validated in three external cohorts and in two clinical studies(3, 4). These studies confirm that in response to drugs that improve mucociliary clearance, airway wall thickening reduces, the internal diameter increases, but that the mean ratio between outer bronchial diameter and artery does not change significantly(3, 5). As we showed, ETI therapy is effective in reducing airway wall thickness, which results in lower numbers of visible BA pairs that can be evaluated. This likely also results in less visible widened (bronchiectatic) airways. In our opinion this contributes to the conclusion in the referenced studies that bronchiectasis is reduced.

The authors argue that studies have demonstrated improvements in CF related bronchial dilatation with ETI. These studies did not employ spirometry control and use older, less sensitive or unproven

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methodologies on which their claims are based. Spirometry control and the PRAGMA-CF scoring system were introduced specifically to improve the sensitivity and reliability of CT imaging to detect structural changes. We feel it's important however to be open-minded on this issue and accept that current studies are still of limited duration. Sensitive automated AI based image analysis on longitudinal datasets will be needed to answer this question - an approach we are currently engaged in.

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