Reply to: When adopting Global Lung Function Initiative reference values, can we also adapt them to a local context as needed?

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Reply to S. Verbanck and co-workers:

We thank S. Verbanck and co-workers for their insightful response to the recent official European Respiratory Society technical standards for Global Lung Function Initiative (GLI) reference lung volumes [1]. The data presented highlight the real-world impact of using published equations and how equipment or protocol offsets can impact clinical interpretation. We generally agree with S. Verbanck and co-workers that more precise approaches are ideal, and that is the ultimate goal of the GLI Network.

For all diagnostic tests, there is a need to balance precision and generalisability. The GLI Network aims to apply consistent methodology to data from many laboratories to produce reference equations that balance these concerns. Of course, differences may arise because of differences in study methodology, reference population and equipment. These, however, do not necessarily indicate true or meaningful differences in lung function. Sampling variability, particularly when study sample sizes are small, can contribute to the observed heterogeneity between populations. For spirometry, sample sizes smaller than 1000 individuals can lead to observed differences as large as 0.4 z-scores [2, 3]. Within the lung volumes data, we have also observed that within the same study population (single centre), the between-subject variability of lung volume indices was much wider than for spirometry. Therefore, there is an urgent need to further standardise equipment and measurement protocols for lung volume indices before we can take further efforts to produce reference equations that are more precise.

It is also relevant to highlight that reference equations (at least not at the present time) do not reflect a reference standard or representation of ideal lung function. Reference equations for lung function provide an indication of where an individual's lung function lies relative to a wider, representative, otherwise healthy population. The GLI approach makes every effort to ensure data included in the published equations are collected under the same standardised conditions. We do agree that the individuals included in the reference population, the protocols and equipment, and quality control applied within each centre will all impact the accuracy and precision of the final reference equation. It is difficult to unequivocally say whether a population-level difference is meaningful at the individual level. Stratification of equations by equipment type or creating offsets would potentially account for these differences insofar that other centres also used the same equipment model and protocol. This approach will not eliminate the potential for misclassification and would limit the generalisability of results. The potential for misclassification goes in both directions, in that while having a wide range of values may miss the detection of the early signs of pathology, an unduly narrow range of values based on limited observations would pathologise normal lung function.

The uncertainty of lung function interpretation should not be understated. The observations reported by S. Verbanck and colleagues and wide limits of normal within the GLI should encourage physicians to consider the uncertainty in their decisions, rather than to rely on these limits as fixed cut-offs of abnormality. Thus, we acknowledge that the differences observed in the re-analysis of data from S. Verbanck and colleagues constitute a large enough difference to warrant further investigation. The GLI

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Global Lung Function Initiative reference equations help to standardise interpretation of pulmonary function tests; however, there is a need to balance precision and generalisability with the uncertainty of interpretation https://bit.ly/3iheRFv

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are committed to continued efforts that will help to further standardise the interpretation of lung function measurements.

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