with asthma (14, 15). These findings are pivotal, particularly in the light of sustaining discussions with regard to the role of ambient NO_2 concentrations on population health. It emphasizes the need to have strategies that not only reduce exhaust particulate but also scavenge NO_2, particularly within congested urban areas, where diesel vehicles make up a significant proportion of the fleet. ■

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Validation of Imaging Measures in Chronic Obstructive Pulmonary Disease

Imaging provides an amazing opportunity to glean *in vivo* insights into acute and chronic diseases. The imaging community has described many features that can be used to detect disease and stratify its severity, predict outcomes, and even assess disease progression. These typically begin with the identification of a novel structural aspect of an organ, obtaining a range of measures of that feature and then demonstrating that those measures remain statistically significantly associated with an outcome of interest despite exhaustive multivariable adjustment. These approaches are not wrong, but they are often accompanied, appropriately, by disclaimers in the limitations section of the discussion or even a modification of the name of the feature to communicate an appropriate degree of uncertainty as to what is actually being measured. Few of the imaging-based measures reported in the literature are backed by histopathology or knowledge of what is occurring on the microscopic level.

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In this issue of the *Journal*, Vasilescu and colleagues (pp. 575–581) report the results of their investigation linking data collected using both clinical computed tomography (CT) and micro-CT (1). Their features of interest were derived by a technique called parametric response mapping (PRM) (2) and their goal was to demonstrate that the application of their approach to clinical CT scans could noninvasively disambiguate the contributions of emphysema and small airway disease to gas trapping observed on expiratory images. To do so, they collected explanted lungs from 14 subjects, inflated and then froze them before sectioning and taking 1.5-cm core samples. They then performed micro-CT scanning on these core specimens (33 from patients with COPD and 22 from control subjects), and assessed the resultant images for features indicative of emphysema, such as airspace size and alveolar surface area, as well as those suggestive of small airway disease, including wall thickening, decreased circularity, and obstruction of the terminal bronchioles.

The core samples from COPD lungs had increased airspace size, greater airway obstruction, and decreased numbers of terminal bronchioles compared with cores from control lungs. The authors also found that the PRM-based measures of emphysema (PRM^{Emph}) were highly significantly associated with the corresponding tissue destruction observed on micro-CT. These findings are not surprising given work by this group linking the loss of small airways to COPD (3, 4), as well as the more extensive body of older literature linking densitometric assessments of the lung parenchyma to airspace dilation observed on direct assessment of the explanted lung tissue (5, 6). Although these findings establish the overall validity of their experiment, the true novelties in this work are the links established between the tissue-based measures of small airway disease and the PRM^{fSAD}.

Greater amounts of PRM^{fSAD} were associated with lower numbers of terminal bronchioles as well as reduced lumen area, circularity, and more frequent obstruction of those that remained. What is equally compelling but elicited little comment is the lack of association between the fSAD measure and both the mean linear intercept and alveolar surface area. These measures were uniquely associated with the PRM-based measure of emphysema. This lack of association between PRM^{fSAD} and measures of emphysema on micro-CT must have elicited relief from the investigative team. This allows them to state that the technique has some degree of specificity and can appropriately classify these processes as either emphysema or airway disease.

Where does this leave us? The first place to look may be back on the increasing body of literature focused on the application of these measures in smokers. One important clinical validation is the finding that PRM^{fSAD} was associated with a faster FEV_1 decline, and contributed more to FEV_1 decline than PRM^{Emph} (7). Another interesting finding is the use of PRM measures in longitudinal imaging, and a recent paper by Labaki and colleagues reported something quite interesting (8). In a cohort of 725 smokers spanning a range of COPD severities, those with predominantly normal tissue on CT tended to have the greatest increase in PRM^{fSAD} (and not PRM^{Emph}), and those with higher amounts of emphysema and fSAD at baseline tended to have the greatest subsequent increase in emphysema. This suggests that PRM^{fSAD} and PRM^{Emph} are measures of distinct COPD phenotypes with different (and important) implications for disease progression. Considering what Vasilescu and colleagues just reported, one may conclude that they reflect pathologic phenotypes as well.

The imaging community has greatly benefitted from the deployment of software libraries that enable deep learning approaches to image postprocessing. These tools have led to a divergence of efforts surrounding image analytics. Unlike those focused on hypothesis-driven approaches that involve segmentation and quantification of anatomic features believed to be related to the condition of interest, deep learning–based efforts may converge on a clinical signal without human input. One thing that is generally common to both is the belief that the validation of these techniques requires a demonstration of clinical association. Although such findings may substantiate the methods being presented, we cannot conflate substantiation with true validation. With imaging, the latter can really only be done with tissue. Vasilescu and colleagues should be congratulated for taking on such a challenging study long after the medical community had accepted PRM, and establishing this link between noninvasive imaging features and pathologic findings in severe COPD. Future work may help establish these measures in early or mild COPD, from which conclusions about pathologic contributions to disease progression in COPD may be better inferred. For now, at the very least, we can drop the word "functional" and embrace this as a metric for small airway disease in smokers. ■

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