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Review

Imaging in alpha-1 antitrypsin deficiency: a window into the disease

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Yuh-Chin Tony Huang, Marion Wencker and Bastiaan Driehuys

***Abstract*:** Imaging modalities such as plain chest radiograph and computed tomography (CT) are important tools in the assessment of patients with chronic obstructive pulmonary disease (COPD) of any etiology. These methods facilitate differential diagnoses and the assessment of individual lung pathologies, such as the presence of emphysema, bullae, or fibrosis. However, as emphysema is the core pathological consequence in the lungs of patients with alpha-1 antitrypsin deficiency (AATD), and because AATD is associated with the development of other lung pathologies such as bronchiectasis, there is a greater need for patients with AATD than those with non-AATD-related COPD to undergo more detailed assessment using CT. In the field of AATD, CT provides essential information regarding the presence, distribution, and morphology of emphysema. In addition, it offers the option to quantify the extent of emphysema. These data have implications for treatment decisions such as initiation of alpha-1 antitrypsin (AAT) therapy, or suitability for surgical or endoscopic interventions for reducing lung volume. Furthermore, CT has provided vital insight regarding the natural history of emphysema progression in AATD, and CT densitometry has underpinned research into the efficacy of AAT therapy. Moving forward, hyperpolarized xenon gas (^{129}Xe) lung magnetic resonance imaging (MRI) is emerging as a promising complement to CT by adding comprehensive measures of regional lung function. It also avoids the main disadvantage of CT: the associated radiation. This chapter provides an overview of technological aspects of imaging in AATD, as well as its role in the management of patients and clinical research. In addition, perspectives on the future potential role of lung MRI in AATD are outlined.

Keywords: alpha-1 antitrypsin, alpha-1 antitrypsin deficiency, computed tomography, densitometry, emphysema, lung imaging, magnetic resonance imaging, xenon-129

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Introduction

As part of the diagnostic workup of chronic obstructive pulmonary disease (COPD), patients will often receive a plain chest radiograph, the primary purpose of which is to rule out alternative diagnoses that might cause shortness of breath and/or cough, such as bronchiectasis, fibrosis, focal lesions, pneumonia, lung cancer, and tuberculosis.[1–3] Chest radiographs provide some information on the presence of lung pathologies of COPD, including more advanced emphysema,[4] which is often sufficient to guide further diagnostic and therapeutic steps. While more sophisticated imaging technologies such as computed tomography (CT) should be limited to justify the resource expenditure,[5] it is warranted for the assessment of alpha-1 antitrypsin deficiency (AATD)-related lung disease, where it addresses the need to provide more detailed spatially resolved information. As previously discussed in the first chapter of this series of reviews,[6] emphysema is the principal pathological process in AATD, and establishing its extent and morphology, in addition to identifying the presence of other pathologies such as bronchiectasis, can influence monitoring and treatment decisions. The present review provides an introduction to the technology underpinning imaging modalities

Correspondence to:
Yuh-Chin Tony Huang
Department of Pulmonary, Allergy, and Critical Care Medicine, Duke University School of Medicine, Durham, NC, USA
yuhchin.huang@duke.edu

Marion Wencker
Conresp, Loerzweiler, Germany

Bastiaan Driehuys
Department of Radiology, Duke University School of Medicine, Durham, NC, USA

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that have been used in AATD and how these technologies are crucial to the characterization of an individual's disease state in routine clinical practice. The contribution of these technologies to new avenues of research in AATD and the creation of several key clinical trials, in addition to the potential of emerging imaging modalities, are also reviewed.

CT and the characterization of lung pathologies in AATD

CT scanners utilize focused X-rays that are rotated around the patient and their transmission is digitally reconstructed to produce a 3-dimensional (3D) image consisting of stacked "slices."[7] CT scanning provides static images and lung density measurements generated from digital data collection. Stacked images generated by CT scanners consist of volume elements (voxels) that can be compiled to show a picture of the scanned region; the attenuation (or loss of radiation detection due to absorption in the body) of each voxel is related to the density of the tissue it represents. Tissue density is expressed numerically in Hounsfield Units (HU),[4] and then assigned a gray color tone to enable visualization. A HU of 0 represents the density of water, negative values are less dense (e.g. the lungs) and positive values are more dense (e.g. bone). A value of −1000 HU represents the density of air. Healthy lungs typically display attenuation values between −750 and −850 HU (mean of −789 HU), while emphysematous lungs are often determined using cutoffs of −910 to −960.[8,9] Several large clinical studies in non-AATD-related COPD have used −950 HU;[10–12] this threshold method is also known as the voxel index (VI).[8] Measuring the area of the lung that is below the cutoff attenuation value allows the burden of emphysema to be quantified as a percentage of the total area of lung tissue.[13] Additionally, emphysema can also be expressed as a percentile density (PD); typically as the 15th percentile density (PD15)—the HU density value at which 15% of voxels are below the cutoff.[8] Investigators comparing the VI and PD quantitative methods have found that PD15 is a more consistent measure of lung density change across a wide range of physiological impairments,[14] and so PD15 has been widely adopted as a standard to assess the extent and progression of AATD-related emphysema.[8]

In AATD, a greater burden of emphysema on CT imaging has been shown to correlate with more symptoms, poorer health status, and increased risk of death.[15,16] With regard to AATD treatment, CT densitometry is not necessary to initiate treatment, but has been established as the most specific and sensitive surrogate endpoint for the evaluation of the therapeutic benefit of alpha-1 antitrypsin (AAT) therapy (AAT augmentation).[17] The management of patients with AATD and the different treatment options are described in more detail within a separate chapter of this review series, authored by Barjaktarevic and Campos.[18]

As with plain chest radiographs, a conventional CT scan delivers a dose of radiation; however, due to the higher intensity of X-rays required, the radiation dose from a chest CT scan is more than 100 times higher than that from a plain chest radiograph (8.2 mSv *versus* 0.065 mSv).[19] This limited how often CT scans could be employed, as each CT scan added to a patient's lifetime cancer risk (commonly reported to be a 1:2000 increase per CT scan).[19] Therefore, routine/serial CT scanning, for example, annually, was usually not recommended;[20] instead, CT scanning was usually based on clinical need or guided by clinical study protocols. However, CT densitometry with lower radiation dose protocols, as with those used in lung cancer screening studies (~2 mSv),[21] is now being used in the field of AATD, and like conventional CT scanning, is well correlated with clinical features of the disease.[22] To put these radiation doses into perspective, the average dose from naturally occurring background radiation in the United States (US) is 3 mSv per year.[23]

Within the field of AATD, it is recommended that newly diagnosed patients with symptoms of COPD and/or impaired lung function receive a baseline CT scan.[20] CT scanning in clinical practice [typically high-resolution CT (HRCT)] is used to assess disease presentation, specifically to characterize the extent and distribution of emphysema and bullae, in addition to assessing the presence/extent of bronchiectasis. HRCT is superior to conventional CT scanning for visual identification of small areas of emphysema due to its decreased volume averaging and higher spatial resolution, and therefore, unlike conventional CT, HRCT is able to accurately detect emphysema at a relatively early stage.[24,25]

Studies have shown that HRCT data are closely related to physiological changes in patients with emphysema and AATD.[22,26] Specifically, the degree of HRCT scan abnormality has been shown to be significantly correlated with forced expiratory volume in 1 s (FEV_1), specific airway conductance, residual volume/total lung capacity, and transfer factor of the lung for carbon monoxide, as well as patient health status as assessed by the St. George's Respiratory Questionnaire and the Short-Form health survey ($p < 0.001$ for all).[26] It was originally suggested that HRCT was associated with considerably higher radiation doses in comparison to conventional CT scanning; however, studies have shown that this is not the case, and a combination of HRCT and low-dose protocols results in an average dose comparable to that associated with chest radiography.[27–29]

To assist in the analysis of visual imaging from CT scanning, quantitative CT (QCT) methods have been developed to assess the severity of several lung diseases,[30] and can provide a more precise, reader-independent estimate of disease extent and severity compared with conventional CT.[8] Software that automatically recognizes and traces contours of the lungs, and produces histograms of lung attenuation values, which are then used to distinguish emphysematous tissue from non-emphysematous tissue, is available.[31] QCT is considered by some physicians to be more suited to AATD studies rather than clinical practice, but should be used to confirm the presence, severity, and distribution of emphysema in patients with severe AATD and an FEV_1 above the historically recommended range for treatment (35–60% predicted).[32] QCT has demonstrated that changes in lower lung zone CT densitometry relates to survival in patients with AATD; in a study of patients with severe AATD in the United Kingdom (UK), lower zone lung density decline was significantly associated with subsequent mortality ($p = 0.048$).[33] Upper zone lung density decline demonstrated a similar trend, but this was not significant ($p = 0.072$).[33] Furthermore, those who experienced a normal age-related decline in FEV_1, that is, those who exhibited no significant decline in FEV_1 between two successive QCT scans, did show a decline in lung CT density.[33] This suggests that serial CT densitometry would be the most reliable way of identifying progressing high-risk patients, adding support to the clinical use of QCT.[33]

Assessing the type, distribution, and extent of radiological changes of patients with AATD needs to be confirmed before initiation of pharmacological intervention in the form of intravenous AAT augmentation,[20] as earlier initiation of treatment reduces irreversible lung tissue loss.[34] As previously discussed in the chapter by Tejwani and Stoller,[6] studies have found that the majority of patients with AATD have panlobular emphysema, that is, the permanent destruction of the entire acinus (typically with basal predominance), as opposed to centrilobular emphysema, that is, affecting the portion of the acinus proximal to the bronchioles (typically with upper-lobe predominance).[35] Although a subsection of AATD patients have a more centrilobular-predominant phenotype,[36] panlobular emphysema is one of the hallmarks of AATD (Figure 1).[37,38] However, the AATD genotype and its impact on anti-elastase concentrations in the lungs may also play a role on the type, distribution, and extent of emphysema in patients with AATD. A study from the UK found that patients with a less severe protease inhibitor (PI) genotype (i.e. PI*SZ) generally have more apical and less basal involvement than individuals with the most severe genotype (PI*ZZ).[37]

By HRCT, panlobular emphysema appears as uniform expansion of air spaces from the bronchioles to the alveoli.[39] In advanced disease, the lumen around alveoli are slightly enlarged compared with normal alveoli, which is less apparent in early emphysema.[39] This can make early panlobular emphysema difficult to discern by CT, which poses a key diagnostic challenge and can limit the ability of physicians to initiate appropriate pharmacological intervention, that is, AAT augmentation therapy early in the disease course.[40]

Knowledge of emphysema morphology has other important functions as a prognostic indicator and in helping to guide suitability for surgical intervention in AATD. Lung volume reduction surgery (LVRS), a palliative treatment option for advanced lung disease with significant hyperinflation, is generally thought to be more suitable for patients with more heterogeneous emphysema (more often associated centrilobular emphysema).[35] Recently, CT has become more widely used to guide target lung regions for LVRS, with the procedure increasingly being performed endoscopically with use of

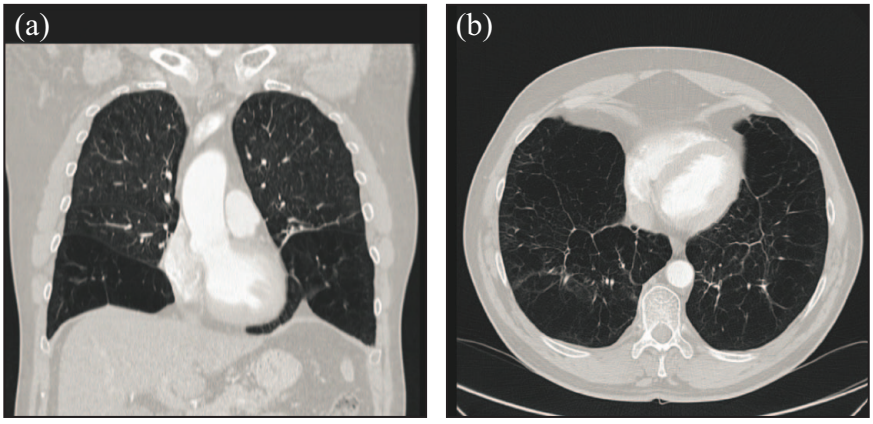

Figure 1. Typical presentation of emphysema in AATD. Chest CT scan (a) coronal cut; (b) axial view of an AATD patient with basal-predominantly emphysema.
AATD, alpha-1 antitrypsin deficiency; CT, computed tomography.
Reproduced with permission from Newell *et al*.[38]

implanted valves instead of surgical lung resection.[41] Surgical approaches to disease management in AATD is further discussed within the chapter by Barjakterevic and Campos.[18] When pharmacological and non-pharmacological treatment options are no longer viable, lung transplantation may be necessary, which is the focus of the chapter by Zamora and Ataya.[42]

The role of CT in AATD research

Although CT is better known for producing visualization of organs, as previously discussed, the images produced by CT scans directly relate to tissue density.[8] Thus, in a similar manner to dual energy X-ray absorptiometry (DEXA) scans used to measure bone density in the field of osteoporosis, chest CT scans can provide quantitative measures of tissue density, and, therefore, an indicator of emphysema progression in longitudinal assessments. Due to the challenges associated with clinical trials in rare diseases (e.g. difficulties with recruitment/small sample sizes), the higher sensitivity of lung densitometry *versus* other endpoints including spirometry, mortality/survival, and patient-reported outcomes, makes lung densitometry more suited to investigating the clinical efficacy of therapies aimed at slowing progression of emphysema in AATD.[43–45] Early work to validate the use of lung densitometry in AATD demonstrated correlations with change in health status and spirometry,[14,46] in addition to patient survival.[15,33,47] Initial clinical trials (the Dutch-Danish and EXACTLE trials), explored and refined the use of CT densitometry for determining the efficacy of AAT therapy in the setting of a double-blind placebo-controlled trial.[44,48,49] Although these trials were underpowered to determine a statistically significant effect, observed trends were suggestive of a lower rate of lung density decline. In the later RAPID clinical trial program, which was sufficiently powered, the clinical efficacy of AAT therapy was demonstrated using CT densitometry.[50,51] These trials are discussed in more detail in the later treatment chapter by Barjakterevic and Campos.[18]

Due to a lack of standardization of CT densitometry technology, methodology, software, calibration methods, and limited experience for analysis and interpretation of data in most clinics, the technique is not often implemented in routine clinical assessments.[8] A procedure for standardizing image analysis has been proposed,[52] but there is still a need for standardization of the technology and methodology.[8] As the technical abilities of modern CT scanners is evolving at a rapid pace, standardization of image acquisition protocols is likely to be a continuous task.[52] Nevertheless, an important advantage of densitometry is that it provides a numerical classification of the degree of emphysema, avoiding reliance on the subjective interpretation of CT scans by clinicians. However, while CT scanning best captures the pathological changes associated with pulmonary emphysema and has been shown to be the most sensitive parameter to detect emphysema progression,[17] the use of CT lung densitometry as an endpoint for clinical studies

has been a matter of debate with regulatory bodies for some time and has not been formally accepted in the field of AATD. For investigating the effects of AAT therapy, the US Food and Drug Administration (FDA) mandates the use of other clinically meaningful endpoints, such as FEV_1, serious exacerbations, exercise capacity, and symptoms as primary endpoints.[53] Due to the high variability of these endpoints and the slow deterioration of pulmonary emphysema in AATD, this would require a large number of patients in a placebo-controlled trial with a study duration of several years, which is deemed impossible. Therefore, determination of a minimal clinically important difference (MCID) is an important step in the validation of CT densitometry and links an endpoint to patient-related parameters. For CT densitometry, the MCID has been proposed as −2.89 g/L.[54]

New methodologies on the horizon: lung magnetic resonance imaging

Magnetic resonance imaging (MRI) is a fundamentally different technology to CT; rather than using ionizing radiation, MRI utilizes magnetic fields to align the magnetization of hydrogen nuclei in the structure being scanned.[4] Until recently, the use of lung MRI scans has been limited due to the high proportion of air, and therefore, low levels of hydrogen in lung structures. This has changed with the introduction of inhaled hyperpolarized contrast agents [^{3}He (helium) and ^{129}Xe (xenon)] that can directly reveal regional function without any background signal.[55]

Although a more expensive technology than CT,[56] a major advantage of MRI is that it does not use ionizing radiation, making it more suited to serial scanning. Thus, MRI removes a key ethical barrier to the use of lung imaging in epidemiological studies, potentially opening up new avenues of research. However, at present, the spatial resolution of lung MRI is fairly limited compared with HRCT, and HRCT is therefore superior in terms of visualization of small structural changes.[57] Nevertheless, visualization of function imposes less stringent resolution requirements as spatial discrimination at the level of an acinus is usually sufficient. Furthermore, whereas function must be inferred from CT, it can be interrogated directly by hyperpolarized gas MRI. For example, both helium and xenon report on ventilation and apparent diffusion coefficient (ADC). The latter is an established marker for alveolar structure and emphysema progression that correlates with traditional measures of gas transfer.[58,59] The ability of lung MRI to provide such functional information regionally is a significant advantage over standard pulmonary function tests (PFTs).[60]

As ^{3}He supply is limited due to the small amount of helium in the atmosphere, and because ^{3}He is required by the US Department of Homeland Security for neutron detection,[61] alternative agents are required to sustain functional lung MRI. Recently, ^{129}Xe has emerged as the most prominent alternative to ^{3}He MRI.[62–64] In addition,^{129}Xe MRI appears to more readily detect ventilation defects than ^{3}He MRI, likely due to its higher density and lower diffusivity in distal airways.[65] Unlike ^{3}He, ^{129}Xe is soluble in tissues and freely diffuses from alveoli through barrier tissues, including cells of the alveoli, interstitium, capillaries, and finally to the red blood cells (RBCs). When ^{129}Xe enters these compartments, it exhibits unique resonance frequencies that enable it to be separately detectable in each,[66] allowing ^{129}Xe MRI to quantify ventilation, membrane diffusing capacity, and regional capillary blood volume with very good resolution and sensitivity.[59,60] Furthermore, it has been shown that emphysema and chronic bronchitis have specific ^{129}Xe MRI signatures, which can be useful information for clinical phenotyping.[67] The clinical utility of lung MRI will likely be a supplement to traditional PFTs, especially when regional gas exchange function is needed. The technology is currently undergoing FDA approval and should be approved for clinical use in the next few years; costs are likely to be higher than standard MRI but a ^{129}Xe MRI is substantially quicker to perform and can be completed in approximately 10 min rather than 60 min; thus xenon MRI has the potential for scanning a larger number of patients.

The literature pertaining to use of lung MRI for characterizing emphysema progression in AATD is limited at present. However, early studies have shown promising results. A Danish pilot study on the progression of emphysema by ^{3}He MRI over 2 years in nine patients with AATD revealed a high correlation between time trends in diffusing capacity of the lungs for carbon monoxide

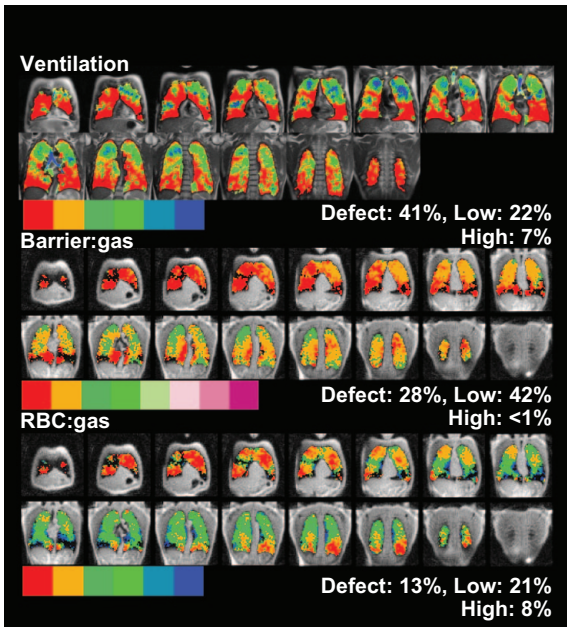

Figure 2. Quantitative 3D functional maps of ventilation, barrier uptake and RBC transfer in a patient with AATD (PI*ZZ). The ventilation image (top panel) shows significant regions of ventilation defect in red, comprising 41% of the thoracic cavity; defects predominate in the basal regions of the lung. Similarly, barrier uptake (middle panel) is significantly reduced (red and orange regions), suggesting a loss of surface area for gas exchange associated with emphysema. Finally, transfer or ^{129}Xe to RBCs is also reduced, suggesting a loss of capillary blood volume in the red and orange regions (bottom panel).
3D, three-dimensional; AATD, alpha-1 antitrypsin deficiency; PI*ZZ, protease inhibitor homozygous for the severe Z mutation; RBC, red blood cell.

(DLco) and MRI ADC ($p < 0.001$).[68] A later study from Canada compared ^{3}He MRI parameters (including ADC), CT lung area, and DLco between eight patients with AATD, eight ex-smoking patients with non-AATD COPD, and a healthy control group of five never smokers.[34] Results showed that only MRI parameters were significantly different between AATD and non-AATD COPD patients, with the former group showing worse ventilation and ADC, indicating higher levels of parenchymal destruction, particularly in the basal regions.[59] This suggests that lung MRI is able to detect lung disease earlier in disease pathogenesis than CT. In addition, signals from barrier uptake and RBC transfer provided by ^{129}Xe roughly correspond to membrane diffusion and pulmonary capillary blood volume in the Roughton and Forster equation for pulmonary gas diffusion.[69] The ability to assess these two components of lung diffusion can provide novel insights into the pathophysiology of lung diseases, including emphysema, which show increased barrier defects (Figure 2, red zone, middle panel) and RBC transfer defects (decreased capillary blood volume; Figure 2, red zone, lower panel).

Ongoing work at Duke University in the US is investigating the use of ^{129}Xe MRI in patients with AATD (Figure 2).[70] In addition, an ongoing pilot study is investigating whether early signs of lung disease can be discerned with use of ^{129}Xe MRI in individuals who are heterozygous for AATD,[71] that is, patients with the PI*MZ genotype. Initial results of the study in four PI*MZ individuals with normal lung function by standard PFTs showed regional abnormalities not detectable by CT, which may reflect early signs of lung disease.[71] Several clinical trials are also underway to determine the utility of ^{129}Xe MRI in evaluating pulmonary function in a variety of lung conditions such as asthma, COPD, cystic fibrosis, and pulmonary hypertension, in addition to AATD.[72,73] The inability to view regions of the lung with ventilation impairment may be a limitation of ^{129}Xe MRI as the gas exchange function in those regions cannot be assessed. However, this would alternatively

provide information on which areas of the lung have ventilation impairment. ^{129}Xe MRI is currently under review by the FDA as a diagnostic method to assess *in vivo* lung function, but only time will tell as to whether this method will become a clinically recognized biomarker to clinically assess lung function.

Alternative imaging methodologies

Another type of imaging that has been used in studies of AATD is positron emission tomography (PET), which measures gamma rays emitted from radiolabeled markers to create an image of where the markers are most concentrated. Imaging using ^{18}fluorodeoxyglucose PET-CT (^{18}FDG PET-CT) can provide quantitative and spatial data of pulmonary glucose uptake by pulmonary neutrophils, providing a noninvasive biomarker of pulmonary neutrophilic inflammation. The ECLIPSE-AATD study utilized ^{18}FDG PET-CT, demonstrating that ^{18}FDG uptake by pulmonary neutrophils was greater in patients with non-AATD COPD compared with patients with severe AATD (PI*Z phenotype), and that in patients with non-AATD COPD there was a correlation between ^{18}FDG uptake and clinical measures of disease severity.[74] However, it was expected that ^{18}FDG uptake by active inflammatory neutrophils would be greater in AATD than non-AATD COPD, which is inconsistent with the conventional understanding that neutrophilic inflammation in AATD is comparable in nature but more severe than in non-AATD COPD.[74] An alternative explanation is therefore required to account for the reported findings. ^{18}FDG PET-CT was also used as an outcome measure for augmentation therapy in patients with AATD, but there were no significant differences in ^{18}FDG uptake after 12 weeks of treatment.[74] Overall, PET shows a potentially useful role in quantitative imaging in AATD; however, a different radiolabeled marker that monitors a key biochemical process in AATD is required for this imaging method to be truly useful in studies of AATD.[75]

Optical coherence tomography (OCT) is a minimally invasive technique that can produce ultra-high-resolution images of the lung in real time, without exposure to ionizing radiation.[76] However, although OCT is limited to imaging of the airways, OCT measurements of airway dimensions do have a strong correlation with CT measurements.[77] There is also a strong correlation between OCT measurements and FEV_1, although the slope was not sufficiently steep enough to detect subtle FEV_1 changes that are likely to have clinical relevance.[77] Although OCT has been used in several studies of non-AATD COPD,[77,78] there are yet to be any studies specifically in AATD.

Conclusions

CT is an essential tool in the clinical management of patients with AATD and has been central to research efforts in the field. Standardized protocols are required to support the more widespread use of CT densitometry, and low-dose radiation CT scanning may facilitate the use of serial scanning in the future. In the longer term, ^{129}Xe shows the most promise as a diagnostic method by providing a greater level of information regarding regional functional lung defects, and potentially lung pathophysiology related to AATD at a very early stage. However, due to costs, limited availability, and pending regulatory approval, the technology will likely initially be limited to answering specific research questions.

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Author contributions

All authors contributed to the writing of the manuscript, reviewed the manuscript, and approved the manuscript for submission.

Conflict of interest statement

Y-CTH reports no conflicts of interest. MW reports personal fees for consultancy from CSL Behring. BD is founder and shareholder in Polarean, Inc., a company established to commercialize hyperpolarized ^{129}Xe magnetic resonance imaging technology.

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