Imaging approaches to understand disease complexity

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REVIEW | *Imaging in Metabolic Research*

Imaging approaches to understand disease complexity: chronic obstructive pulmonary disease as a clinical model

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Sanders KJ, Ash SY, Washko GR, Mottaghy FM, Schols AM. Imaging approaches to understand disease complexity: chronic obstructive pulmonary disease as a clinical model. *J Appl Physiol* 124: 512–520, 2018. First published July 27, 2017; doi:10.1152/japplphysiol.00143.2017.—The clinical manifestations of chronic obstructive pulmonary disease (COPD) reflect an aggregate of multiple pulmonary and extrapulmonary processes. It is increasingly clear that full assessment of these processes is essential to characterize disease burden and to tailor therapy. Medical imaging has advanced such that it is now possible to obtain in vivo insight in the presence and severity of lung disease-associated features. In this review, we have assembled data from multiple disciplines of medical imaging research to review the role of imaging in characterization of COPD. Topics include imaging of the lungs, body composition, and extrapulmonary tissue metabolism. The primary focus is on imaging modalities that are widely available in clinical care settings and that potentially contribute to describing COPD heterogeneity and enhance our insight in underlying pathophysiological processes and their structural and functional effects.

body composition; chronic obstructive pulmonary disease; imaging; lung

INTRODUCTION

The clinical manifestations of chronic obstructive pulmonary disease (COPD) reflect an aggregate of multiple pulmonary and extrapulmonary processes. It is increasingly clear that full assessment of these processes is essential to characterize disease burden and to tailor therapy (23, 39). Examples of these COPD-associated features include emphysematous destruction and fibrosis of the lung parenchyma, cardiovascular disease, sarcopenia, abdominal adiposity, and osteoporosis (20, 23, 48, 58, 84). Highly effective therapies are available for many of these conditions, and yet their prevalence and role in the mortality and morbidity of those with chronic respiratory diseases is often underappreciated (22, 23, 39).

Although no imaging study is critical to the initial diagnosis and management of COPD, many patients with COPD undergo imaging for other reasons, such as lung cancer screening, screening for osteoporosis, or acute changes in their clinical status. Although these medical images are often used principally for the indication that prompted their acquisition, they also provide the opportunity to obtain in vivo insight into the presence and severity of these and other conditions (3, 15, 56, 58, 91). Exciting new areas of imaging research are focused on singular aspects of these comorbidities; however, such specialization often causes us to lose a larger view of efforts in this field. Thus, although we do not advocate the routine use of imaging in COPD without another indication, extraction of morphological information and comorbidity patterns from already available medical images acquired in routine clinical care may provide new opportunities to better characterize patients and individualize treatment in the future.

In this review, we have brought together the available information on structural and metabolic imaging with regard to its potential usefulness in improving the understanding of COPD and with particular emphasis on quantitative techniques. More specifically, we focus on the structural information obtained using routine computed tomography (CT) imaging as well as on the information on body composition from both CT imaging and dual-energy X-ray absorptiometry (DEXA). Furthermore, we briefly discuss the potential of

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metabolic molecular imaging using the standard positron emission tomography (PET) radiopharmaceutical fluordeoxyglucose (FDG) in COPD when available for additional scientific purpose. These three imaging modalities allow the noninvasive characterization of many of the underlying pathophysiological processes in COPD and their structural and functional effects. Of note is that although magnetic resonance imaging and optical coherence tomography have been and continue to be investigated as potential imaging techniques in COPD, none have yet found a place in routine clinical care and so are beyond the scope of this review. In addition, although ultrasound is increasingly useful in the diagnosis of acute chest diseases such as pneumothorax, and endobronchial ultrasound has been widely adopted for procedures such as lymph node biopsy, neither has been routinely used in COPD, and so they have also been excluded.

LUNG STRUCTURE

Functional, structural, and molecular imaging of the lungs, using a variety of modalities, has revealed new information regarding the complexity of COPD. This discussion will focus primarily on the role of imaging in understanding COPD, but it should be noted that there is extensive work in this area on lung cancer, interstitial lung disease, asthma, pulmonary hypertension, and other chronic lung diseases.

Computed Tomography

Contributions to phenotyping. CT imaging utilizes X-rays to acquire a three-dimensional (3D) attenuation image of the body. The images themselves are comprised of 3D pixels or voxels, each of which has a density, typically measured in Hounsfield units (HU), that distinguishes water from air, enabling the characterization of various tissue types to that particular area. These voxels are then reconstructed to using various gray values to create the overall CT image. Although CT imaging is not indicated for the routine diagnosis or clinical staging of COPD due to the overlapping risk factors and clinical manifestations of COPD with other chest diseases such as lung cancer, it is frequently obtained for other reasons in these patients (5, 60). There are a multitude of processes evident in CT imaging of the lungs, which may be grouped by anatomic compartment, namely those that affect the parenchyma, the airways, and the vasculature.

With regard to the lung parenchyma, emphysema is the most prominent anatomic and radiological COPD-associated process (Fig. 1*A*), and the volume, distribution, and subtype of emphysema on CT have yielded insights into the clinical management and physiology of COPD (14, 46). For instance, in the National Emphysema Treatment Trial, 1,200 COPD patients with hyperinflation were randomized to either lung volume reduction surgery (LVRS) or optimal medical therapy. Although there was no overall survival benefit to LVRS, a nonprespecified subgroup analysis based on the combination of baseline CT emphysema distribution and exercise testing identified a subset of patients who responded differently to LVRS compared with medical treatment. Subjects with upper lobe or upper zone predominant emphysema and low exercise capacity had significantly lower mortality than subjects randomized to medical treatment (32). Subsequent work suggests that such clinical differences between those with upper lobe predominant

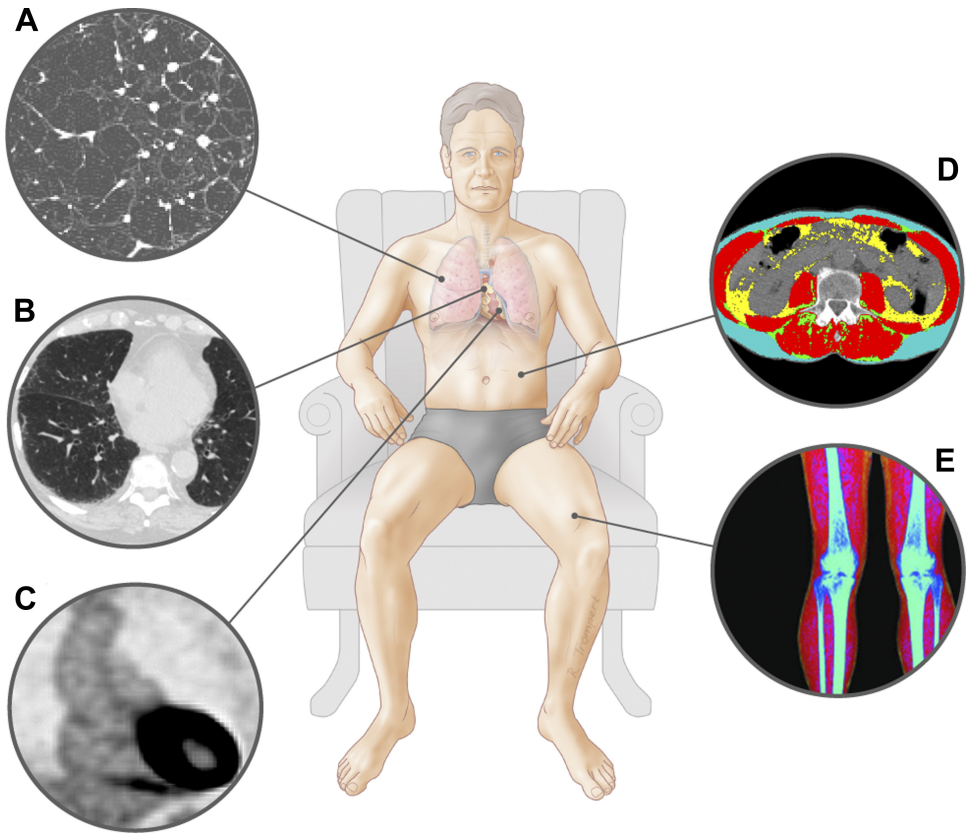

Fig. 1. Imaging techniques. *A*: thoracic CT image of patient with emphysema. *B*: thoracic computed tomography (CT) image of patient with interstitial lung abnormalities. *C*: positron emission tomography image displaying fluordeoxyglucose uptake in the aortic wall (image courtesy of Dr. Jan Bucerius). *D*: abdominal CT with different body composition compartments at the 3rd lumbar vertebra. *E*: dual-energy X-ray absorptiometry scan leg with different body composition compartments.

or heterogeneous emphysema and more homogeneous emphysema may reflect not only anatomic differences but physiological ones as well. For instance, those with homogenous emphysema have been shown to have a greater degree of dynamic hyperinflation during exercise than those with upper lobe predominant disease, suggesting potential differences in their lung mechanics and differences in the underlying pathophysiology of their disease (11). Perhaps more importantly clinically is the role of CT in identifying patients for endobronchial lung volume reduction procedures, which are bronchoscopic alternatives to surgical LVRS, including endobronchial valves, coils, glue, and other devices. The effectiveness of endobronchial valves in particular may be limited by collateral ventilation in the setting of incomplete interlobular fissures. Collateral ventilation prevents the valves from fully deflating the target area, thus limiting their effectiveness. Small studies have suggested that CT imaging may be sensitive, albeit not necessarily specific, for the detection of the interlobular fissures, and new automated techniques may improve its performance in this area, making it an important tool for the preprocedure planning of patients undergoing endobronchial lung volume reduction (68, 69, 78).

Although less immediately clinically applicable, the CT identification of emphysema subtypes provides a noninvasive window into the pathophysiology of the disease and thus opens the door to additional treatment options. Smoking, the most frequent cause of emphysema, is most commonly associated with centrilobular disease and to a lesser but still significant extent with paraseptal emphysema (6, 38, 50). Additional subtypes include panlobular disease, which tends to be rare, except in patients with α1-antitrypsin deficiency or who have used certain intravenous drugs (6). Recent investigations suggest that these subtypes, including both the lobular distribution as well as severity, may have differing clinical associations (17, 18). For instance, whereas nearly all emphysema subtypes are associated with respiratory function, dyspnea, physical capacity, and annual number of exacerbations in COPD, paraseptal emphysema may be a marker of more severe clinical manifestations of the disease (18). Further CT-based investigation has shown that there may be genetic and pathophysiological reasons for such disease heterogeneity. For instance, emphysema matrix metalloproteinases (MMPs), which are proteolytic enzymes that can break down the extracellular matrix, have been shown to be potentially important in the development of emphysema. Although some MMPs, such as MMP-3 and MMP-10, are associated with most emphysema subtypes, others, such as MMP-3 and MMP-10, have been shown to be associated with both paraseptal emphysema and more severe centrilobular disease (63). In addition, genome-wide association studies have suggested that each of the emphysema subtypes may have a somewhat unique set of genetic determinants (17). Taken together, these findings suggest the importance of CT imaging for the understanding of both the clinical manifestations and pathophysiology of the emphysematous component of COPD, especially in terms of identifying specific phenotypes of the disease.

It is increasingly clear, in large part thanks to CT imaging-based studies, that tobacco smoke exposure results in not only emphysematous but also interstitial changes in the lung, such as interstitial lung disease. In the extreme, such changes manifest radiologically and clinically as pulmonary fibrosis, but more subtle changes, often termed interstitial lung abnormalities (ILA), are as highly prevalent as ever in smokers (Fig. 1*B*) (8, 25, 67, 87, 88). Clinically, smokers with ILA tend to have less COPD, greater respiratory impairment, shorter 6-min walk distances, and less emphysema as measured by standard densitometry (24, 26, 87, 88). Furthermore, these abnormalities are associated with a decline in lung function and are strongly predictive of all cause and respiratory specific mortality (2, 67). Finally, ILA have been shown to be associated with a specific single-nucleotide polymorphism in the promoter region of the gene encoding mucin 5B, which has been strongly linked to the presence of more advanced idiopathic pulmonary fibrosis (41, 74). These clinical and genetic associations do not necessarily imply that all ILA will progress to idiopathic pulmonary fibrosis but rather highlight the potential role of CT in identifying those COPD patients at the greatest risk for adverse events as well as its importance for understanding the complexity of smoking-related lung disease. Further work in this area could ultimately lead to the use of novel therapies such as anti-fibrotic agents in those patients with combined emphysema and early stage fibrosis.

The other lung compartment classically affected in COPD is the airways. Although usually described as being the location of chronic bronchitis, the distal small airways are likely the site of airflow limitation for COPD more generally (1, 40). These airways are below the resolution of standard clinical CT imaging; however, quantitative CT analysis of more central airways in smokers has revealed that those with smaller airway caliber and thicker airway walls tend to have lower lung function and more frequent exacerbations (37, 59, 61, 83). Although these findings are not yet clinically applicable, they may prove especially important in future phenotyping of COPD. For instance, recent work by Lange et al. (47) has shown that some individuals with COPD developed airflow limitation in early adulthood, followed by a slow decline in lung function rather than due to a rapid decline from a higher or more normal peak lung function, and it may be that those smokers who have a smaller airway caliber on CT in young adulthood are those more likely to develop COPD (4, 47).

The last lung compartment with changes evident on the CT scans of smokers is the intraparenchymal pulmonary vasculature. Pruning of the vasculature and dropout in regions of severe emphysema have long been recognized on angiographic studies, and improved CT scan resolution has made it possible to detect and quantify such changes on CT (42, 70). These changes typically include pruning of the distal vasculature and dilation of the more central vessels (30, 89, 90). Although not yet clinically available, 3D analysis of the distal pulmonary vasculature has shown that pruning of the distal vessels is associated with increased respiratory symptoms, reduced exercise capacity, impaired diffusing capacity, and multicomponent predictors of mortality (30). Further work is now ongoing to determine how metrics of pulmonary vascular morphology may be further integrated into clinical care to predict outcomes such as patient response to lung volume reduction. Of more immediate clinical importance is the appearance of the central vasculature on CT in patients with COPD. More specifically, Wells et al. (90) has shown that pulmonary artery enlargement as defined by a ratio of the diameter of the pulmonary artery to

the diameter of the aorta of >1 is associated with an increased risk for severe respiratory exacerbations in patients with COPD, potentially identifying patients who will benefit the most from strategies to reduce exacerbation risk.

Advantages. CT imaging is almost universally available in clinical care settings. It provides high-resolution insight into lung structure, and there are a multitude of methods published on the standards of image interpretation.

Limitations. The greatest limitation to the broad utilization of CT imaging is ionizing radiation. There is an ongoing debate in the medical community about what is a safe level of such exposure. Because of this, CT manufacturers have invested a tremendous amount of resources to reduce the dose of radiation while maintaining or even improving image quality.

Clinical applications. CT is increasingly becoming a common component to the clinical care of patients with COPD. Despite the reason for image acquisition, the biomedical community is obliged to obtain as much data as possible from these images to improve our understanding of disease and improve patient care.

BODY COMPOSITION

Alterations in body composition frequently occur in COPD, contributing to increased morbidity and mortality. In fact, up to 25% of patients with COPD have a significant loss of skeletal muscle, which has been associated with impaired exercise performance and increased mortality independent of the primary lung impairment (76, 79). However, in overweight and obese subjects, low muscle mass may not be recognized without assessment of body composition (80). Furthermore, Beijers et al. (9) recently demonstrated in normal-weight COPD patients a high prevalence of low muscle mass combined with abdominal obesity. Notably, these patients were characterized by an increased cardiometabolic risk. Clinically available imaging modalities to visualize body composition include dual-energy X-ray absorptiometry (DEXA) and CT.

DEXA Imaging

Contribution to phenotyping. Originally designed for osteoporosis assessment, DEXA can also be utilized to measure body composition (Fig. 1*E*). The underlying concept for DEXA estimation of body composition is based on assumptions regarding the difference in chemical constituents. Briefly, DEXA utilizes the variable absorption or attenuation of high- and low-energy X-ray photons to estimate the fraction of tissue occupied by fat mass (FM) and fat-free mass (FFM) (43, 65). Although the details of how these measurements are made are beyond the scope of this review, it is important to note that increased tissue thickness is associated with a greater attenuation of low-energy photons than-high energy photons regardless of the tissue composition, the effect of which is a tendency for the underestimation of FM in obese subjects (36).

Recently, the European Respiratory Society task force on nutritional assessment and therapy in COPD has designated DEXA as the most appropriate tool for combined screening of osteoporosis, sarcopenia, and adipose tissue redistribution (71). Although two-compartment screening methods such as bioelectrical impedance analysis and skinfold thickness can discriminate whole body FM from FFM, DEXA is able to analyze tissue depletion and redistribution at regional levels. This is particularly useful in COPD, in which appendicular FFM has been found to be more predictive for exercise performance than whole body FFM (80). Moreover, DEXA analyses have also provided insight into some of the clinical complexity of COPD. For example, despite similar decreases appendicular FFM, whole body and trunk FFM reductions have been found to be more altered in COPD patients with CT-based emphysema compared with those without (28, 29).

In addition to differences in truncal and whole body distribution, recent advances in DEXA imaging have allowed for the differentiation between and the ratio of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) (45, 52, 57). SAT and VAT differ in metabolic and inflammatory characteristics and the corresponding metabolic risk profile (31, 49, 77). Smoking cigarettes is a main cause of both COPD and cardiac disease, but other causes may increase the risk. For instance, cardiac disease in COPD associates with VAT (21, 51). DEXA measurements of SAT and VAT have thus far only been validated in patients without COPD. Other limitations of DEXA include the insensitivity of appendicular FFM for the detection of small loss of muscle fiber CSA, which may limit its role in monitoring subtle changes after intervention (62).

Advantages. DEXA is particularly attractive due to low ionizing radiation, which is comparable to 1 day of normal background radiation (10). With ~10 min of scan time, DEXA is very time efficient and convenient. It enables noninvasive insight into body composition and its potential metabolic associations.

Limitations. Although the errors are relatively small, one has to keep in mind that the results may be influenced by conditions in which the ratio of extracellular water and intracellular water varies (e.g., severe malnutrition, edema, diuretics, aging) (66). Furthermore, this technique provides only two-dimensional projections of the body, thereby being unable to gain information about muscle groups or quantification of fat depots in the muscle. Regarding DEXA-based VAT analysis, more validation studies are warranted, as there seems to be a tendency toward overestimation of VAT (45, 52).

Clinical applicability. DEXA is used in clinical routine care for evaluation of osteoporosis in COPD.

CT Imaging

Contribution to phenotyping. As discussed above, CT imaging provides a wealth of information regarding lung structure and its implications for lung function in patients with COPD. Extrapulmonary findings on CT in COPD are of great scientific utility as well. Similarly to DEXA imaging, CT can also be utilized beyond its "field" to measure body composition in addition to the more traditional lung measures discussed above. This is done by measuring muscle cross-sectional area (CSA) on CT imaging, and although the standard site to measure CSA is the third lumbar vertebra (L3), this is typically outside the field of view of clinically acquired CT imaging in patients with chest diseases (Fig. 1*D*) (9, 73, 75, 79).

Therefore, other levels, such as L1, have been evaluated. Although single-slice CSA L3 and L1 result in significantly different whole body estimates of muscle mass, the latter may be useful to detect changes during the disease course or after

intervention (73). Other sites that have been evaluated include the pectoralis muscles, where muscle CSA assessed by CT has been correlated with both objective and subjective measures of COPD severity and midthigh muscle CSA, which has been found to be strongly related to increased mortality risk (55, 56). Although such measures are not yet routinely clinically available, advances in CT segmentation technology that allow the automated detection of specific radiographic features may soon enable their more routine use.

CT is also able to quantify and evaluate the distribution of fat. For instance, CT-based analysis at the L4–L5 level revealed significantly increased VAT in the elderly with obstructive lung disease than in nonobstructive subjects, despite a comparable SAT and BMI. This adipose tissue distribution also correlated to higher interleukin-6 levels in elderly with obstructive lung disease (81), suggesting that VAT might contribute to increased plasma IL-6, which was also shown to be a strong predictor of all-cause and respiratory mortality.

Finally, patients with chronic diseases such as COPD are known to have ectopic depots of fat beyond the major subcutaneous and visceral fat storage locations, such as intramuscular adipose tissue (IMAT). Although data concerning muscle lipid content in the elderly and patients with muscle wasting disease have initially relied on muscle biopsy studies, improved resolution of CT scanners makes it now possible to noninvasively quantify IMAT (33, 35, 44). CT-derived data concerning IMAT have shown fat infiltration in intercostal muscles and midthigh muscle in normal to overweight COPD patients. This infiltration in intercostal muscles in particular is correlated with COPD severity, and patients with high midthigh IMAT tended to have lower physical activity levels (54, 64).

Advantages. An advantage of CT is that information about body composition can be collected at the time of routine clinical imaging.

Limitations. Muscle CSA and adipose tissue quantification may be subject to a multitude of factors, such as manufacturer, slice thickness, and pixel spacing, although their exact influence on body composition quantification is unknown. Furthermore, the radiation exposure of CT limits longitudinal research applications.

Clinical applicability. Although CT imaging is not independently indicated for the diagnosis and management of isolated COPD, images are widely available due to their implementation in excluding other underlying pathology. Measurements of muscle CSA and adipose tissue are not yet routinely performed, but new automated techniques may enable their introduction into clinical care in the near future.

TISSUE METABOLISM

Metabolic alterations are reflected not only by body composition but also by underlying changes in tissue metabolism. [^{18}F]fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET) may improve understanding of the biological processes of tissues.

[^{18}F]FDG-PET imaging

Contribution to phenotyping. Although DEXA and CT are informative in tissue mass quantification and distribution, they are limited in monitoring tissue metabolic activity. Standard PET imaging uses a radiolabeled glucose derivate fluordeoxyglucose (FDG) to give a 3D information on glucose metabolism in the body, enabling evaluation of local or tissue-specific metabolic features (7). There is a wide range of classical and novel radiopharmaceuticals (tracers) evaluated in (pre)clinical and experimental settings using PET. However, here, we focus on FDG-PET because of its universal availability in clinical care settings. Although PET imaging is not routinely used in the workup of COPD assessment, this method allowing quantification of tissue metabolism may be useful in scientific research to contribute to better understanding of different clinical phenotypes, as illustrated below.

FDG reflects the metabolic rate of glucose, a process reinforced in inflamed tissue, and this distinctive characteristic enables PET to evaluate adipose tissue activity in vivo. One study showed that COPD patients exhibited increased FDG uptake in visceral adipose tissue (VAT) compared with subjects without COPD. Furthermore, FDG uptake in VAT was found to predict aortic wall FDG uptake, even when adjusted for sex, age, BMI, and smoking (Fig. 1*C*) (12, 13, 85). It is well known that smoking tobacco is the main risk factor for development of both COPD and vascular inflammatory processes. Nevertheless, these data suggest a possible contributing role of VAT in augmenting atherosclerotic processes in COPD (84). However, further research is needed, including histological confirmation of VAT biological activity.

Several studies confirmed the presence of metabolically active brown adipose tissue (BAT) in the neck and supraclavicular region and the mediastinum as well as along the spine in healthy adults, using FDG-PET scanning and biopsy verification (19, 82). BAT activity is inversely correlated to body fat percentage in healthy adults (82). In addition, in several BAT-associated pathological conditions, such as pheochromocytoma (86) and hyperthyreoidism (53), energy expenditure is increased. Recently, it has been shown from in vitro experiments that lactate stimulates the browning of adipocytes, which is mediated by intracellular redox modifications (16). Given the hypermetabolic state observed in COPD particularly in the emphysematous phenotype (72), mitochondrial dysfunction (34, 92), and early lactate acidosis during exercise (27), increased BAT activity may be involved in energy homeostasis in COPD. However, no clinical studies that assessed BAT activity in COPD are yet available.

Advantages. Whereas DEXA and CT provide information about structures, PET is a unique imaging tool that provides molecular imaging information. Using FDG noninvasive quantitative information of metabolic activity of tissues in vivo is acquired.

Limitations. FDG-PET uses ionizing radiation, is not broadly available, and is more expensive than the other modalities. It is important to mention that the radiation burden is lower than in conventionally used whole body CT protocols. Additionally, factors influencing the amount of FDG uptake, such as overexpression of glucose receptors, might induce false-positive or false-negative results (7).

Clinical applicability. F-FDG-PET imaging is not integrated in standard clinical care of COPD patients.

CONCLUSION

Over the past century, imaging has become critically important in the routine clinical care of patients, and the

technologies used have advanced dramatically. The use of new analytic techniques applied to traditional imaging modalities and the development of novel imaging techniques have greatly improved the clinical care and understanding of complex diseases like COPD. These approaches, including CT, DEXA, PET, or hybrid PET-CT already aid in the noninvasive characterization of COPD phenotypes and severity, and ongoing and future work has the potential to improve our understanding of and care for this disease and the patients it affects even more. We acknowledge that, at least in the short term, some of the methods discussed above are limited to the research setting. They may improve phenotyping for clinical observational studies and clinical trials and contribute to better risk stratification and personalized medicine.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.J.S., G.R.W., and A.M.S. prepared figures; K.J.S., S.Y.A., G.R.W., F.M.M., and A.M.S. drafted manuscript; K.J.S., S.Y.A., G.R.W., F.M.M., and A.M.S. edited and revised manuscript; K.J.S., S.Y.A., G.R.W., F.M.M., and A.M.S. approved final version of manuscript.

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