

# Artificial Intelligence in COPD: New Venues to Study a Complex Disease

Raúl San José Estépar, PhD

*Applied Chest Imaging Laboratory, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*

## ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease that can benefit from novel approaches to understanding its evolution and divergent trajectories. Artificial intelligence (AI) has revolutionized how we can use clinical, imaging, and molecular data to understand and model complex systems. AI has shown impressive results in areas related to automated clinical decision making, radiological interpretation and prognostication. The unique nature of COPD and the accessibility to well-phenotyped populations result in an ideal scenario for AI development. This review provides an introduction to AI and deep learning and presents some recent successes in applying AI in COPD. Finally, we will discuss some of the opportunities, challenges, and limitations for AI applications in the context of COPD. (BRN Rev. 2020;6(2):144-60)

Corresponding author: Raúl San José Estépar, rsanjose@bwh.harvard.edu

**Key words:** Artificial Intelligence. COPD. Emphysema. Deep learning. Imaging. Machine learning.

## Correspondence to:

Dr. Raúl San José Estépar

Applied Chest Imaging Laboratory, Department of Radiology,

Brigham and Women's Hospital

1249 Boylston St, Boston, MA, 02115

Email: rsanjose@bwh.harvard.edu

Received in original form: 18-07-2020

Accepted in final form: 02-09-2020

DOI: 10.23866/BRNRev.2019-0014

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex pathological condition characterized by an admixture of small airway inflammation, obliteration, and parenchymal injury leading to its destruction. Those processes are complicated by an aberrant inflammatory response that has spill-over effects to other systems leading to a complex comorbidities relation<sup>1</sup>. Although COPD is clinically characterized by expiratory airflow obstruction, the complexity of the different endotypes that conform the disease defines the heterogeneity in symptoms, therapeutic responses and outcomes<sup>2</sup>. This marked heterogeneity makes COPD a syndrome more than a single condition that requires a multidisciplinary approach to understand the basis of the disease and divergent trajectories to discern the different endophenotypes that could lead to more homogenous groups of patients exhibiting common mechanisms.

Artificial intelligence (AI) has revolutionized how we can use clinical, imaging, and molecular data to understand and model complex systems. This has led to an explosion of applications across multiple disciplines, including healthcare. Although applied AI still is an emerging field in many areas, it has shown exciting and impactful results in the diagnosis of different conditions using raw data sources like diagnostic images<sup>3,4</sup>. COPD has not been “immune” to this trend, and the research community has embraced AI as a novel modeling paradigm to harness COPD heterogeneity. This review focuses on the emerging AI applications in COPD that enable new venues for its characterization, diagnostication, and prognostication. A brief initial introduction to AI

and fundaments of deep neural networks will be provided as the prelude to a review of emerging applications of AI.

## What is AI and why now?

Artificial intelligence dates back to the mid-'50s and the beginning of the digitalization of the information. It refers to a wide range of techniques aimed at mimicking and enhancing some aspects of human cognitive capabilities like vision or speech recognition. Much of the clinical data that we handle in digital form is amenable to be exploited by modeling techniques to determine relations between inputs and an outcome or discover the internal structure of the data without explicit knowledge of those relations. The power of AI to uncover new relationships in complex datasets has driven the high interest in healthcare and medical science. The power of AI is better realized when applied to multi-contextual/multi-dimensional information: electronic medical records, laboratory and functional testing, imaging, and multi-omics data. Within those complex data scenarios, AI has shown a remarkable capacity to deliver unprecedented capabilities to recognize trends that can be translated into complex tasks like a diagnosis or derived new knowledge from the discovery relations.

Although the theoretical bases for AI methods have been established during the last decades, AI applications have exploded over the previous five years, driven by multiple factors. First, the maturity of the approaches that can exploit non-linear relation in the data has been vital. The most significant example is the resurgence of deep neural networks, a

type of machine learning based on a computation model inspired in the neural brain architecture with millions of interconnected computational units. Second, advances in optimization and regularization techniques have made tractable to fit models with a large number of parameters to a limited set of training data points. Third, the consolidation of methods in well-maintained open-source libraries has empowered the use of AI techniques to a broader community, including non-experts in the field with multidisciplinary skills. Finally, specialized computing architectures based on Graphics Processing Units (GPUs) have delivered the necessary computing power to train advanced models within reasonable amounts of time.

## Deep neural networks

Machine learning is the subfield of AI devoted to the development of computational constructs to capture data relations that can be used to make autonomous decisions. Machine learning covers a wide range of techniques from Bayesian methods to decision trees techniques. Deep learning, a type of machine learning, is revolutionizing domains from computer vision and image understanding to speech recognition<sup>5,6</sup>. Deep neural networks are one of the main techniques behind the explosion of AI. One of the most notable applications has been the emergence of autonomous driving solutions built on top of this new breed of approaches. Deep learning allows an algorithm to “program” itself by learning the underlying features that are required for the task at hand, unlike conventional methods in which a model is learned on pre-design features. The predecessors of

these new approaches were neural networks inspired by the computational construct of a biological neural system<sup>7</sup>. The neuron acts as a generalized linear model regressor. Complex modeling beyond linear regression is achieved by connecting multiple neural layers effectively creating a hierarchical model. The most interesting mathematical property of neural networks is that they can approximate any continuous function, known as the universal approximation theorem<sup>8</sup>. The implications of this theorem were profound as it creates the theoretical basis to design a system that can map a complex input (a chest computerized tomography [CT] image or an RNA expression panel, for example) to a continuous target (for example, a functional measurement like forced expiratory flow in one second [FEV<sub>1</sub>] or a probability of diagnosis) in a non-linear fashion. Unlike traditional biostatistical modeling that is based on linear relationships between independent variables and an outcome, neural networks can describe complex non-linear relations, therefore providing a powerful and flexible modeling tool, albeit with a significant loss of interpretability. Original neural network approaches, although revolutionary, fell out of favor in the AI community due to their simplistic architectures that limited their learning capabilities. New developments in massively parallel computing infrastructures using GPUs have unlocked this limitation allowing more complex network designs (deep networks) with multiple stacked layers that interconnect between each other to render models with millions of parameters that can be fit in a reasonable amount of time. Advances related to the optimization of the networks and the avoidance of overfitting to the data that prevents the generalization of the results to external

datasets are also responsible of the renewed interest in applying neural networks.

Convolutional neural networks (CNNs) is a type of deep learning method that can define relations in complex multidimensional datasets like images<sup>9</sup>. These networks drew their inspiration in the human visual system architecture that integrates the activations from photonic stimuli across multiple layers (V1, V2, and V3) with a kernel of neurons that slide across each dimension of the data<sup>10</sup> (Fig. 1).

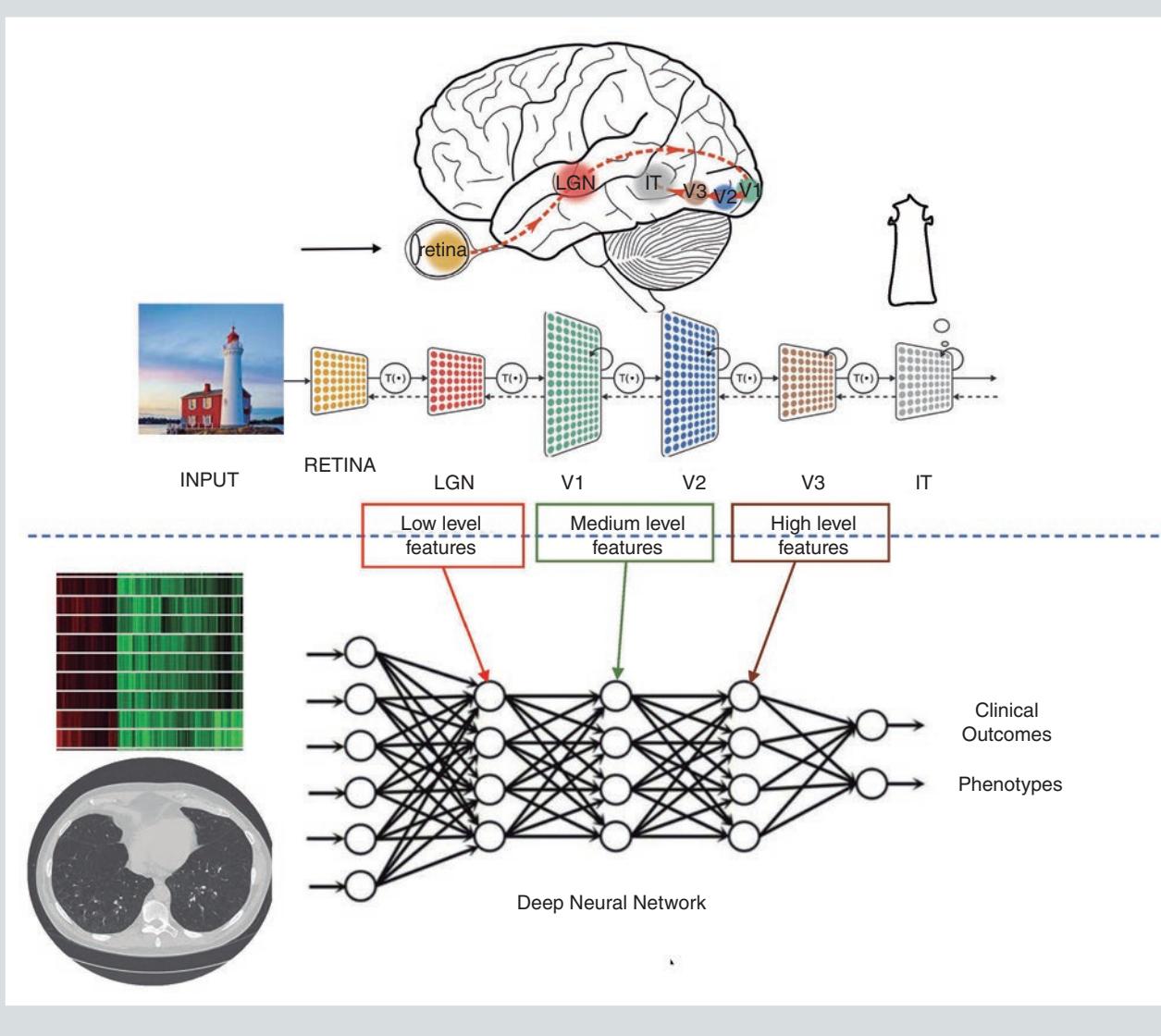
## APPLICATION OF AI IN COPD

### Empowering pulmonary function testing

Pulmonary function testing (PFTs) has been at the forefront of the clinical diagnosis and management of COPD patients. The assessment and interpretation of these tests follow international guidelines<sup>11</sup> to discern the different patterns. Despite the multiple decades of experience with PFT, the recognition of various disease patterns in PFTs is variable<sup>12</sup>. In this study, 120 pulmonologists evaluated 50 cases with various pulmonary diagnoses to identify PFT patterns (obstructive, restrictive, mixed and normal). Their interpretation was compared to a machine learning technique based on a decision tree. The decision tree used functional parameters and basic patient characteristics as inputs and was trained with data from 1,430 subjects<sup>13</sup>. The accuracy of the interpretation of pulmonary pattern among specialists was 74.4%, with an interrater variability of kappa = 0.67 reflecting the difficulty of this clinical task. The automated method had a 100% and 82% accuracy in PFT pattern identification

and its corresponding diagnosis. These impressive results suggest the role that AI can play as a decision support tool within the clinical workflow. Despite the outstanding results, the method was tested in a single center, and large-scale prospective studies are needed to support the evidence that machine learning can outperform experts.

Beyond support to clinical interpretation, one of the most exciting aspects of AI is the ability to extract opportunistic relations in the data beyond the primary diagnostic intended use. Flow-volume loops provide a unique signature to discern different structural information based on the intimate relationship between structure and function<sup>14</sup>. Bodduluri and colleagues<sup>15</sup> explored this question and proposed a one-dimensional fully convolutional neural network (CNN) to identify CT-derived COPD phenotypes (emphysema predominant, airway predominant and mixed) as a multiclass classification from flow-volume curves. The network was trained and tested using 8,980 smokers from the COPDGene cohort with and without COPD. 80% of the data was used from training, and 20% was held out to validate the performance. The network system provided better discrimination between emphysema and small airway phenotypes than FEV1% predicted (FEV<sub>1</sub>pp) and FEV<sub>1</sub>/forced vital capacity (FVC) (area under the curve [AUC] 0.91 versus 0.80). However, the neural network only showed incremental discrimination performance to detect a mixed emphysema-airway phenotype. These initial studies indicate that deep learning approaches can establish new relations between physiological and structural phenotypes of COPD to provide novel insight to develop new diagnostic criteria of COPD.



**FIGURE 1.** Convolutional neural network representation. Multiple layers of neurons are interconnected to extract feature information from the input stimulus. This concept can be applied to digest multidimensional information from chest computed tomography scans or gene expression panels to predict a clinical outcome.

LGN: lateral geniculate nucleus.

## Unraveling lung structure

Thoracic CT imaging is the primary diagnostic tool to investigate the pathological determinants of COPD by enabling an *in vivo* detection of underlying disease endophenotypes. Imaging can be the primary driver to provide personalized management of COPD<sup>16</sup>. Although

imaging has been widely used to phenotype COPD in research cohorts<sup>17,18</sup>, uses in clinical practice are still limited. The limited use of imaging is partially motivated by the lack of automated approaches to provide actionable information within the variable imaging conditions commonly encountered in the day-to-day clinical work.

The definition of the lung field, lobar compartments, fissures, and the broncho-vascular tree are essential steps to quantify the phenotypic information that CT conveys. AI is transforming and consolidating the upstream set of automated operations necessary to resolve the diseased lung's structural components. Rule-based approaches to segment the lung and the lobes are being replaced by more reliable and precise deep learning methods based on CNN<sup>19,20,21</sup>. Rule-based methods propelled some of the early research applications of CT-based phenotyping<sup>22,23,24,25,26</sup>, however, these approaches lack of generalization and tend to under- or over-segment regions without well-demarcated edges.

Convolutional neural networks have enabled image interpretation at different scales. In particular, the use of U-nets, a specialized neural network architecture for semantic segmentation, has provided a new modeling paradigm that is consolidating approaches for automated lung image segmentation and interpretation. These approaches are trained with large databases of annotated or segmented images by experts or semi-automated methods. Figure 2 shows lobar, airway, and vascular structure variability in two COPD subjects with similar degrees of emphysematous destruction obtained with an AI feature detector trained to detect lung structures<sup>20</sup>.

Lung anatomical extraction has enabled the phenotyping of both emphysema and airway wall thickening in COPD<sup>27,28</sup>. Reliable structural interpretation is enabling the quantification of that lobar-specific emphysema and fissure completeness metrics as part of the routine patient selection planning for endobronchial lung volume reduction<sup>29</sup>. Also, robust

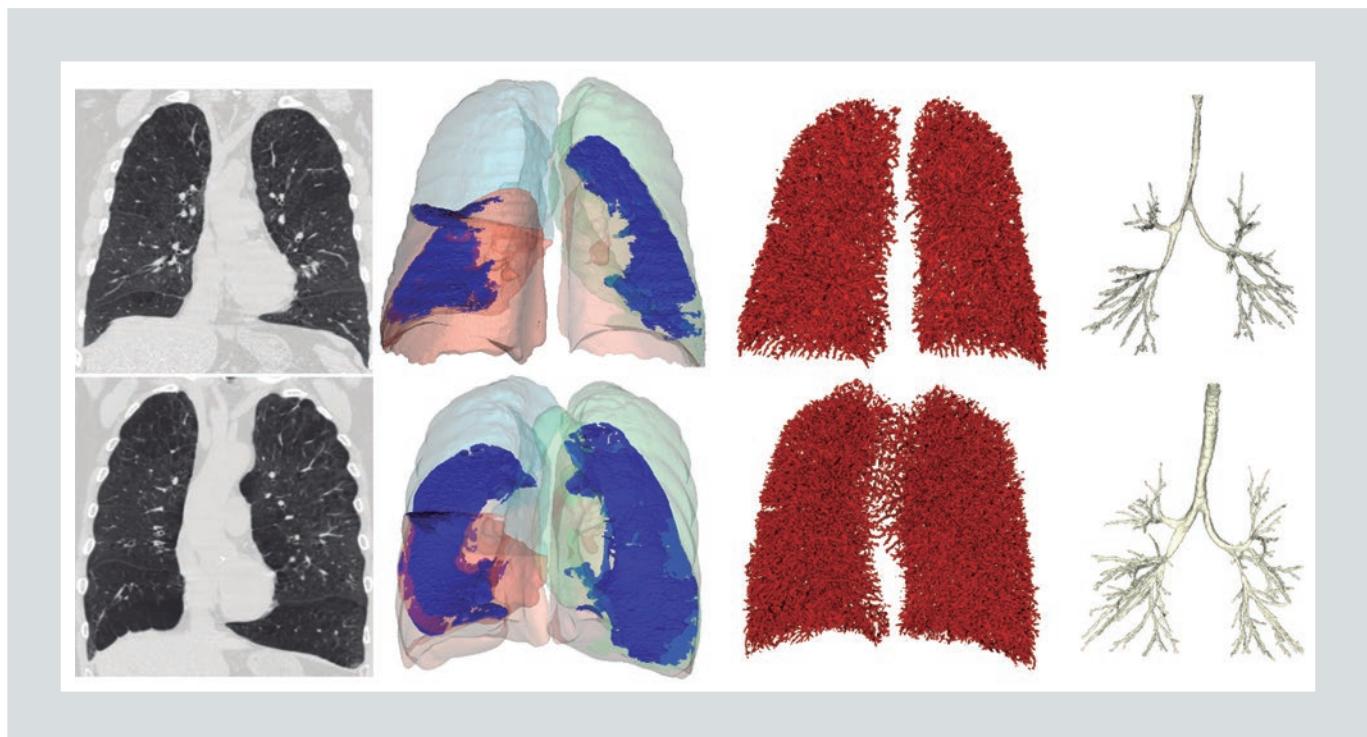
airway tree reconstruction has facilitated the postulation of novel phenotypes of airways disease based on tree fractality measurements that aim to detect the tree simplification and the small airway destruction that is characteristic of the early onset of the disease<sup>30,31</sup>. An airway fractality index computed from airway tree CT reconstructions was positively associated with FEV<sub>1</sub>, FEV<sub>1</sub>/FVC as well as exercise capacity, quality of life and 5-year decline in FEV<sub>1</sub> in subjects from COPDGene. Subjects with the unique phenotype of low fractality (tree simplification) and peribronchial emphysema had a higher mortality risk than those that did not present tree simplification but still have emphysema<sup>32</sup>. These findings suggest the implications of advanced phenotyping beyond traditional wall thickness measurements and how AI is critical to its translation.

## Parenchymal injury

Parenchymal injury and its destruction due to repeated and unregulated inflammatory response to noxious particles is one of the primary mechanisms for the development of COPD<sup>33</sup>.

## EMPHYSEMA SUBTYPING

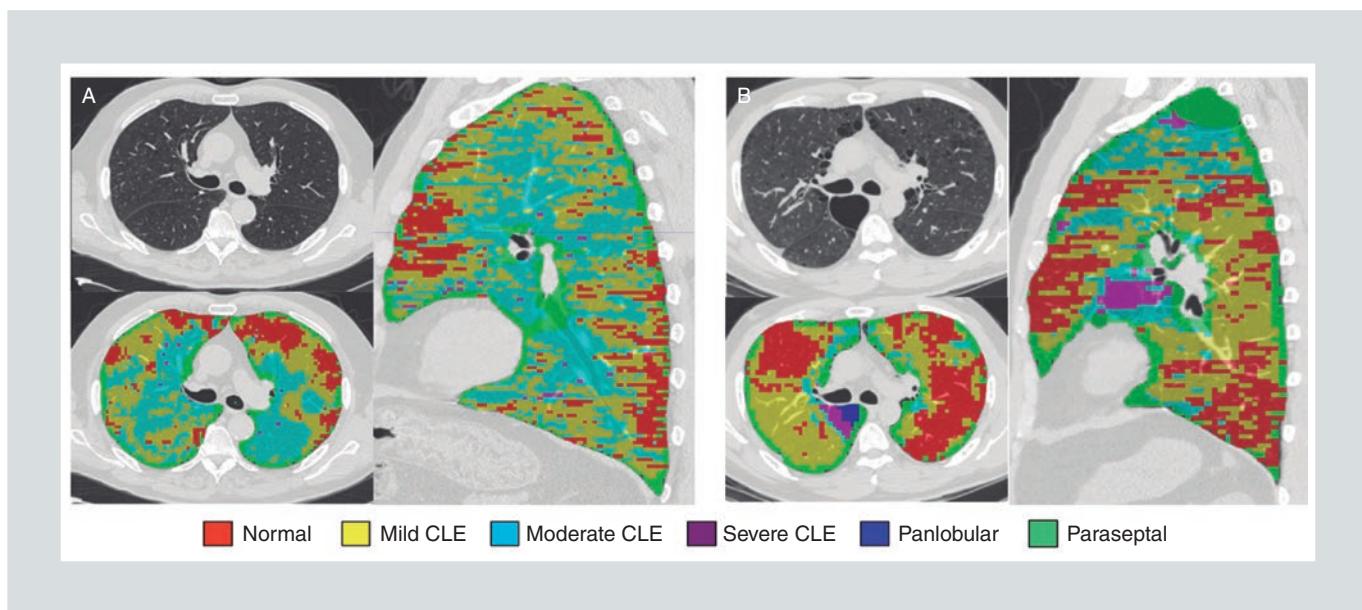
Quantification of emphysema on CT is probably today the most employed and reliable image-based biomarker<sup>16</sup>. But the nature of the destruction at the secondary lobule follows different microscopic patterns that can define distinct phenotypes<sup>34</sup>. Emphysema is classified into three major histopathological patterns<sup>35,36</sup>. Centrilobular emphysema (CLE) is the result of dilatation and destruction of



**FIGURE 2.** Coronal computed tomography (CT) view, lobar, fissures (blue overlay), vascular and airway fissure morphology in two COPD subjects with similar levels of emphysema score (LAA-950% = 15%) and hyperinflation (FRC ~6.4 liters) from the COPDGene study. (Top) Male, BMI = 31.99, GOLD 3, FEV<sub>1</sub>pp = 34.9, TLC = 7.5 liters, FRC = 6.44 liters. (Bottom) Male, BMI = 20.01, GOLD 4, FEV<sub>1</sub>pp = 15.6, TLC = 7.8 liters, FRC = 6.33 liters. The lung morphology was extracted using automated AI image analysis methods. Differences in fissure integrity are noticeable in the right oblique fissure. AI enables quantification of lung morphology destruction that can be used to personalized treatment. AI: artificial intelligence; BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in one second; FRC: functional residual capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LAA: Low Attenuation Area; TLC: total lung capacity.

the respiratory bronchioles; panlobular emphysema (PLE) results from more uniform damage of all of the acini within the secondary lobule, and paraseptal emphysema (PSE) is the localized destruction in the subpleural region. Their radiographic appearance is distinctive, and their functional characteristics are unique<sup>34,37</sup>, suggesting that they are not the results of identical pathobiological mechanisms. Visual classification of emphysema patterns as defined by the Fleischer classification system has been an independent predictor of mortality after adjusting for the severity of emphysema<sup>38</sup>, suggesting the importance of emphysema subtyping as a prognostic tool.

Machine learning has been employed to classify emphysema radiographic patterns, exploiting unique densitometry and textural characteristics of the tissue density at a local level<sup>39-41</sup>. A general observation has been that the local distribution of CT intensities in the secondary lobule can be a distinctive enough feature<sup>40</sup>. The local histogram technique has been shown to provide differential, and incremental associations between physiological and functional metrics of disease as emphysema patterns evolve from mild-to-moderate/severe centrilobular and panlobular<sup>42</sup>. Figure 3 shows an example of emphysema subtyping using the local histogram technique. Differences in emphysema



**FIGURE 3.** Emphysema subtyping recognition in two COPD using the local histogram approach in two subjects with similar global emphysema scores (LAA-950% ~10%). **(A)** GOLD 1,  $FEV_1/FVC = 0.66$   $FEV_1,pp = 94.6\%$ . **(B)** GOLD 0,  $FEV_1/FVC = 0.73$ ,  $FEV_1,pp = 95\%$ .

Emphysema subtyping reveals potential different endotypes despite having a similar emphysema score.

CLE: Congenital lobar emphysema; COPD: chronic obstructive pulmonary disease;  $FEV_1$ : forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LAA: Low Attenuation Area.

patterns suggest potential different underlying endotypes with variable courses of disease. Of note, Castaldi and colleagues<sup>42</sup> also showed that mild centrilobular disease patterns in smokers without COPD were associated with reduced  $FEV_1$  and worse functional status. This functional implication of early parenchymal injury detected by automated methods can help to better understand parenchymal changes in early COPD before the damages become deleterious and irreversible. Genome-wide association analysis on the local histogram subtypes identified novel loci for moderate and severe centrilobular and panlobular emphysema with enhancer regions of pulmonary fibroblast showing the stronger enrichment<sup>43</sup>. Recently, the same group was able to link further the functional role of emphysema subtype detected loci, in particular, a locus near genes in the transforming growth factor-beta (TGF-beta) family that

regulates the expression of fibroblast in lung cells<sup>44</sup>. This mechanistic discovery empowered by machine learning subtyping of emphysema highlights the advantages of using machine learning tools to further understand the genetic and molecular basis of the COPD.

Feature-driven subtyping methods, as described above, have been recently augmented by deep learning approaches based on convolutional neural networks that have shown an increased performance in quantifying emphysema centrilobular<sup>45</sup> and paraseptal<sup>46</sup> patterns. Humphries and colleagues<sup>47</sup> also showed that deep learning could emulate the visual scoring of emphysema patterns, not only replicating results but also providing better classification than visual scores in terms of mortality differentiation across groups. The increased association with mortality can be explained by

the increased reliability and consistency of AI systems despite being trained with human labels that are subjective and imperfect. The classification performance beyond human expertise to tackle a recognition task is at the core of the transformation that AI is delivering.

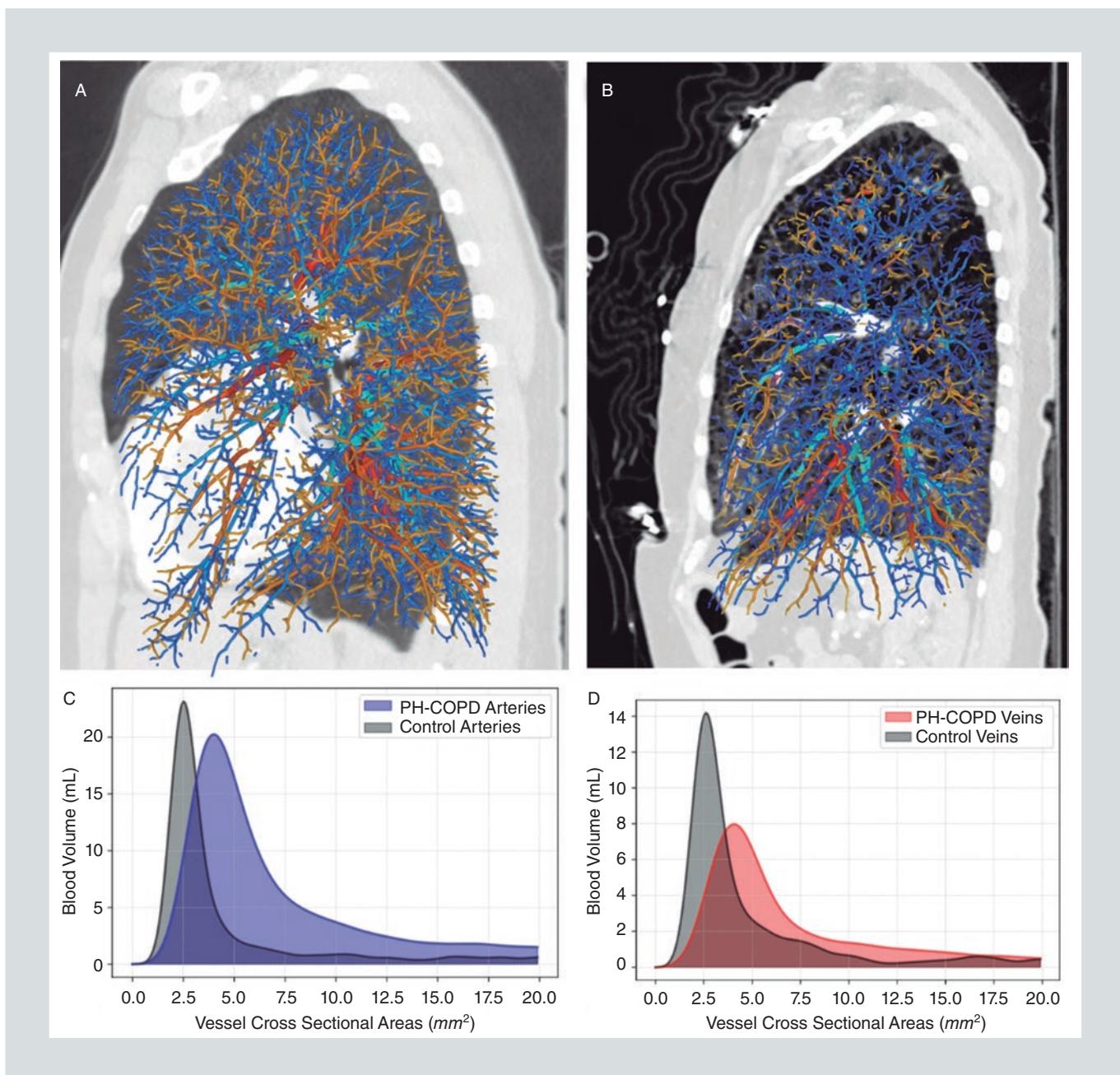
## DISCOVERING EMPHYSEMA SUBTYPES

Supervised emphysema subtyping classification rests upon the premise that distinct and well-known characterize subtypes exist. Although there are very compelling reasons to believe so, one exciting application of machine learning approaches revolves around discovering new patterns hidden in complex data. Yang and colleagues<sup>48</sup> explored the hypothesis of applying texture learning to define new emphysema-specific lung texture patterns (sLTPs) that could be related to yet undefined emphysema subtypes with unique clinical characteristics. Advanced clustering of emphysematous region textons in the MESA COPD cohort<sup>49</sup> was used to discerned 12 distinct sLTPs. One interesting aspect of this approach is that integrated spatial information as regional distribution of emphysema has been recognized as an important phenotype<sup>50</sup>. Almost all the sLTPs showed reasonable associations with dyspnea and exercise capacity, but more work is needed to better understand the pathological meaning. Similarly, Binder<sup>51</sup> proposed a generative latent Bayesian modeling to define six distinct data-driven subtypes. One of the challenges of data-driven discovery approaches is the need to strike a trade-off between revealing very specific, but irrelevant, patterns while preserving invariant and consistent characteristics across the general population to ensure that capture meaningful biological

traits. Striking this balance requires rigorous modeling with large databases where data is carefully aggregated and normalized.

## Heart-lung interaction

The vascular and cardiac implications of smoking have been well described<sup>52,53</sup>. Endothelial dysfunction and arterial remodeling have been reported in both patients with mild-to-severe COPD as well as smokers with normal lung function<sup>54</sup>. The pulmonary vascular implications of COPD are not well understood, but they can provide an alternative mechanistic view of the development of COPD. Image-based phenotyping of the small vessels has shown to be associated with the decline of lung function, reduced exercise capacity, and worse quality of life<sup>55</sup>. The exploration of vascular injury is being propelled by new methods to classify and quantify pulmonary vessels based on AI. Arterial and venous stratification is key to understand the pre-capillary and post-capillary effects of vascular remodeling in COPD as seen in figure 4. Arterial and venous separation of the pulmonary vessels have been challenging and initial attempts were based on graph matching and partitioning techniques<sup>56,57</sup>. Nardelli et al.<sup>58</sup> proposed a CNN to compute an “arterialness” probability for each vessel location based on cropped image sections of a vessel. Those probabilities were used to further divide the vascular tree in a connected arterial and venous size. Although the technique was trained with a limited number of subjects, the validation showed that the sensitivity and specificity in classifying arteries and veins are comparable despite the emphysema level in COPD subjects.



**FIGURE 4.** Vascular representation in a smoker control without COPD (A) and a COPD subject with pulmonary hypertension (B) showing arterial (blue shades) and venous (orange shade) phases color-coded by vessel size. Deep learning techniques are enabling the phenotyping of complex tree structures like the vasculature with unprecedented resolution. Remodeling of small vessels can be quantified by means of the blood volume distribution as a function of vessel cross-sectional area (C and D). Arterial (C) and venous (D) remodeling reflected as vascular pruning with volume loss are observed in COPD. Other quantifiable traits like increased tortuosity can also be observed in the vascular tree architecture of the case with PH.

COPD: chronic obstructive pulmonary disease; PH: pulmonary hypertension.

The definition of vascular phenotypes in COPD that can be potentially sensible to remodeling relies on an accurate estimation of the vessel

size, particularly in small vessels. This is technically challenging as the CT scanner's resolution compromises the ability to resolve

small structures. Similar resolution issues are encountered in the quantification of small airways that have limited the utilization of wall thickening as a reliable phenotype. The development of new methods is further complicated by the lack of ground truth as histology samples with corresponding imaging are challenging to obtain. Advanced deep learning techniques that leverage generative adversarial networks<sup>59</sup> to synthesize real looking CT scans of airway and vessel with known characteristics have been employed to train accurate regressors of vessel and airway morphometric characteristics<sup>60</sup>. This approach has been shown to provide accurate airway and vessel metrics while preserving high precision to variations in imaging protocol (Fig. 4). This new kind of techniques can enable the exploration of small structural changes to define more sensitive phenotypes of vascular and airway remodeling. This further demonstrates that AI-driven *in silico* models of lung pathology could provide a new paradigm to define endophenotypes under control conditions. This is probably one of the most exciting and novel areas of AI that could emerge in the near future.

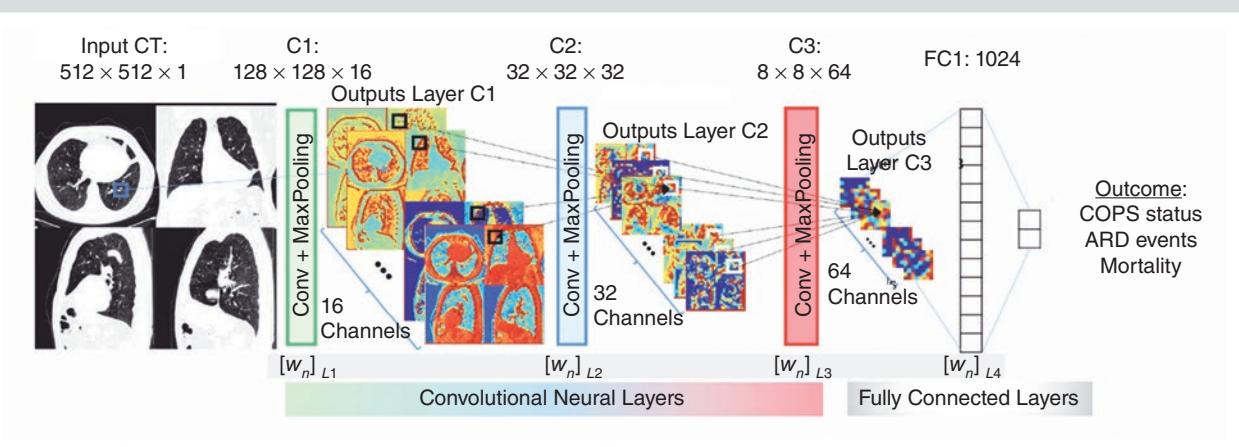
One recent application of these advanced techniques for pulmonary vascular subtyping has been in the understanding of the complex lung-heart interaction in COPD. Epicardial assessment on CT is not optimal, but computational imaging techniques have shown to provide a reasonable correlation with cardiac magnetic resonance imaging (MRI)-derived volume metrics<sup>61</sup>. Cardiac dysfunction is common in COPD and better understanding of lung determinants is necessary. Washko and colleagues<sup>62</sup> explored the determinants of right ventricular (RV) remodeling using AI-driven tools for

vascular and cardiac assessment on CT. Although COPD subjects showed a decreased RV volume as disease advances in severity, RV enlargement was associated to higher mortality. However, the effect was modified by arterial small vessel remodeling, death risk was 63% higher in patients with RV enlargement and arterial pruning. The investigators also explored the effects on left ventricular (LV) volume<sup>63</sup>. LV volumes were also reduced as COPD progresses. Emphysema, venous vascular pruning and pectoralis muscle wasting was directly associated to this reduction. However, smaller left ventricles were associated with better outcomes and lower mortality rates. Competing effects in ventricular enlargement due to tobacco smoke suggest that a well-defined cardio-vascular phenotype may exist in COPD.

## Diagnosis and outcome prediction

Probably one of the most direct uses of AI in healthcare is the ability to define new diagnostic and prognostic models based on multidimensional clinical data without a minimal set of "a-priori" hypothesis. AI relevance in healthcare has exponentially increased after practical demonstrations on large datasets of how deep learning could help diagnose diabetic retinopathy and melanoma from diagnostic images<sup>34</sup>.

Gonzalez et al.<sup>64</sup> used a three-layer CNN on chest CTs from the COPDGene and Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohorts to determine whether this methodology could detect and stage COPD as well as predict acute respiratory events and mortality among smokers (Fig. 5)<sup>64</sup>. The training was performed in



**FIGURE 5.** Convolutional neural network (CNN) to diagnose and prognosticate COPD outcomes. The input of the CNN is a composite image of four canonical views of the computed tomography scan: an axial slice at the level of the mitral valve, a coronal slice taken at the level of the ascending aorta, and two sagittal slices at the level of the right and left hilum. The image is analyzed with a CNN consisting of three convolutional layers (Conv) followed by max-pooling operations, each reducing the image size fourfold in each direction. At the end of the convolutional layers are two fully connected networks, the first one of 1,024 neurons and the second one of variable size depending on the problem at hand: classification, multiclass classification, or regression (*reproduced and modified from González Serrano G, et al.<sup>64</sup> with permission*).

ARD: acute respiratory disease; COPD: chronic obstructive pulmonary disease; CT: computed tomography.

7,983 COPDGene subjects, and testing and replication were conducted in 1,000 and 1,672 COPDGene and ECLIPSE participants, respectively. Using a montage of four canonical CT slices at different anatomical levels, the authors showed that the CNN can predict COPD GOLD status (74.0% one-class-off accuracy), mortality (C-index = 0.72) and acute exacerbations (C-index = 0.61). These results hold in the replication cohort, although there was a reduction in performance characteristics suggesting the complexities in generalizing the results across cohorts due to imaging and population differences. This performance, although only slightly better than known indexes like Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) and other diagnostic models based on known image phenotypes, highlights the power of CNNs in extracting meaningful features from

CT images without prescribing potential factors involved in the prediction. The ability to operate with minimal hypotheses around a prediction task defines the pragmatism of current AI approaches. Recent work by Tang and colleagues further shows that residual neural networks can effectively diagnose COPD (AUC = 0.88) using data from the PanCAN cohort with stable replication results in ECLIPSE based on a subset of slices<sup>84</sup>. In addition to that, advanced machine learning using random survival models was used to exploit imaging and clinical phenotypes to predict mortality in COPD and outperforming the BODE index<sup>85</sup>. Although these results are fascinating, they are somehow of limited impact in understanding disease pathogenesis due to the lack of introspection into the rules that the network finds. Further work

is necessary to understand better how AI operates.

Machine learning approaches can also exploit the richness of gene expression data to assist in COPD diagnostic and prognostic tasks. In recent work, a random forest was used to classify airway transcriptomic data from 15 pre-selected candidate genes to define a COPD risk score<sup>65</sup>. Although the ability to discriminate COPD subjects was very limited, active research in exploiting omics data with machine learning may offer new insights about disease pathogenesis.

Finally, acute exacerbations are one of the primary drivers in COPD healthcare utilization. The development of prognostic models is an active area of research where different clinical parameters and biomarker are being integrated<sup>66</sup>. Initial attempts using Deep Belief Networks and clinical factors have shown an accuracy of 92%, which is superior to prior attempts to predict exacerbations using support vector machine classifiers<sup>67</sup>. These kinds of approaches could augment and support more standard models that have been recently proposed from pooled clinical trials<sup>68</sup>.

## COPD progression and trajectory discovery

A progressive decline of lung function characterizes the natural history of COPD. However, the traditional view of a continuous lung decline has been challenged by recent works that highlighted early life effects contributing to COPD development<sup>69-71</sup>. Machine learning tools have been used to shed light on the patterns of decline in functional

progression and endotype variability. A Bayesian mixture model approach was able to identify four trajectories of lung function decline in a data-driven manner using subjects from the Normative Aging Study and COPDGene<sup>72</sup>. These trajectories had unique genetic contributions suggesting biologically plausible paths of disease evolution. Alternatively, Young et al.<sup>73</sup> used another machine-learning tool called “Subtype and Stage Inference” (SuStaIn) to identify two trajectories of disease progression in COPD, one where small airway disease and emphysema progress to involvement of larger airway disease, and a second where larger airway disease is followed by emphysema and small airway disease. These findings provide evidence of new paths of COPD progression that warrant further investigation.

Several other studies have provided evidence for machine-learning driven COPD subtypes that have consolidated the understanding of COPD as both discrete and continuum processes with unique biological characteristics<sup>74,75</sup>. These examples show how data-driven approaches can be used to postulate new hypotheses related to the natural history of COPD.

## FUTURE APPLICATION OF AI

It is clear that AI continues to evolve at a fast pace as greater and greater interest has been created around its applications, and public and private initiatives are rapidly emerging to catalyze this field. The COPD community can benefit from this frenetic activity as novel approaches to redefine disease from rich datasets are proposed. Better phenotypes are essential to grasp disease heterogeneity. Mostly

empowered by imaging, COPD phenotypes continued to be investigated and proposed, however its translation to clinical practice is limited by the need of additional testing or complexity in their extraction. AI approaches that could regress or predict those phenotypes from available clinical data or simpler modalities, like chest X-Rays, could transform COPD management in the clinic<sup>76</sup>.

AI can also be used to capture disease processes that were recognized but could not be estimated. For example, airway cartilage loss has been described in COPD since the late sixties; however, there is no specific metric to characterize this process that can modify how airway obstruction is understood. Preliminary studies based on generative deep learning techniques have shown the ability to quantify airway cartilage<sup>77</sup>. Results in this direction are auspicious and raise the field to a new level in terms of the quality of the question that can be explored and, potentially, answered.

One of the main aspects of AI is its ability to define undescribed relations between data points. Connecting the imaging phenotype with genetic and molecular features in a hypothesis-free way can enable the exploration of novel endophenotypes that could lead to exploring the disease in new directions that can be hard to elucidate with our current understanding of the disease<sup>2</sup>. Although these venues are highly speculative, they hold much promise as the integration of information has been an effective way to improve the understanding of diseases<sup>75</sup>. The same way the advent of imaging changed how many diseases were approached from the research end to the clinical side, AI offers a new paradigm for data integration in COPD with potential ever lasting effects.

## AI LIMITATIONS AND CHALLENGES

Despite all the compelling preliminary evidence that could advocate for a more extensive AI role in medicine and COPD in particular, several challenges remain that need to be carefully evaluated and addressed. AI is essentially a data-driven approach. Models are derived by training with specific samples of a population. How well those models generalized to other populations or disease stages with slightly different endotypes is unknown. Careful replication studies and reevaluation of the model are needed to define the model's true performance. The need for the replication of findings is common to any discovery approach like genome-wide association studies. Lessons from those fields could be extracted to avoid missteps<sup>78</sup>.

Model explainability and interpretation are major concerns that could hamper the adoption and assimilation of AI in COPD. Many AI approaches, particularly those based on deep neural networks, are often considered "back-boxes". Although that term is not completely accurate as the model parameters are available and can be inspected, the reality is that those parameters are hard to explain, and it is difficult to translate their meaning into general principles and rules that can be understood by humans. The ability to draw a line between the inference that the network derives from the data and understandable governing principles is an area of active research in the AI community that needs to mature<sup>79</sup>.

Another important issue related to the application of AI in COPD is the potential for biases and their implications in terms of equity use of AI<sup>80,81</sup>. Biases and disparity in COPD diagnosis and treatment may be translated into AI

systems trained with clinical data in which those underlying biases exist. Artificial intelligence might be more susceptible to those biases as it might assimilate them as key distinctive features to derive a decision. Understanding the specific performance characteristics and new methodological approaches to avoid disparities by recognizing differences between data domains or populations<sup>82</sup> are fundamental. Those new approaches will need to be adopted and iteratively revised and refined.

Finally, the intrinsic data-driven nature of AI approaches requires careful consideration of data sharing infrastructures and patient privacy. AI approaches thrives on large streams of data that sometimes surpass the limits of single institutions or a study. Infrastructures that preserve data integrity and privacy need to be created to exploit pan-institutional data-sets that can maximize the potential of deep learning. Federated solutions that are being proposed to develop models in a de-centralized fashion will be necessary components of the AI lifecycle in the near future<sup>83</sup>.

## CONCLUSIONS

Artificial intelligence is an emerging field that is transforming how clinical and imaging data can be consumed to explore determinants of complex diseases like COPD. Machine learning models that link imaging, functional, biomarkers, and multi-omics data can advance our understanding of disease subtypes and trajectories beyond our current limited phenotypic understanding of the disease. The translation of the models that can be obtained with AI to clinical practice

requires careful consideration and extensive validation.

## DISCLOSURES

Dr. San Jose Estepar reports grants from NHLBI during the conduct of the study. Outside the submitted work he also reports personal fees from LeukoLabs and Chiesi, grants from Boehringer Ingelheim, Lung Biotechnology, and NHLI. He is also a founder and co-owner of Quantitative Imaging Solutions which is a company that provides image based consulting and develops software to enable data sharing.

## FUNDING

Dr. San José Estépar receives funding support from the National Heart, Lung, and Blood Institute of the NIH under awards number R01HL149877, R01 HL116473, and R21 HL140422.

## REFERENCES

1. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J*. 2009;33:1165-85.
2. Agusti A, Celli B, Faner R. What does endotyping mean for treatment in chronic obstructive pulmonary disease? *Lancet*. 2017;390:980-7.
3. Gulshan V, Peng L, Coram M et al. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. *JAMA*. 316:2402-10.
4. Esteva A, Kuprel B, Novoa RA et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542:115-8.
5. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature*. 2015;521:436-44.
6. Schmidhuber J. Deep learning in neural networks: An overview. *Neural Networks*. 2015;61 :85-117.
7. McCulloch WS, Pitts W. A logical calculus of the ideas immanent in nervous activity. 1943. *Bull Math Biol*. 1943;5:115-33.
8. Cybenko G. Approximation by superposition of sigmoidal functions. *Mathematics of Control, Signals and Systems*. 1989;2:303-14.
9. Lecun Y, Bottou L, Bengio Y, Haffner P. Gradient-based learning applied to document recognition. *Proc IEEE*. 1998;86:2278-2324.
10. Kravitz DJ, Saleem KS, Baker CI, Ungerleider LG, Mishkin M. The ventral visual pathway: an expanded neural framework for the processing of object quality. *Trends Cogn Sci (Regul Ed)*. 2013;17:26-49.

11. Rabe KF, Hurd S, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176:532-55.
12. Topalovic M, Das N, Burgel P-R et al. Artificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests. *Eur Respir J.* 2019;53.
13. Topalovic M, Laval S, Aerts J-M et al. Automated Interpretation of Pulmonary Function Tests in Adults with Respiratory Complaints. *Respiration.* 2017;93:170-8.
14. Weibel ER. It Takes More than Cells to Make a Good Lung. *Am J Respir Crit Care Med.* 2013;187:342-6.
15. Bodduluri S, Nakhmani A, Reinhardt JM et al. Deep neural network analyses of spirometry for structural phenotyping of chronic obstructive pulmonary disease. *JCI Insight.* 2020;5.
16. Washko GR, Parraga G. COPD biomarkers and phenotypes: opportunities for better outcomes with precision imaging. *Eur Respir J.* 2018;52.
17. Vestbo J, Anderson W, Coxon HO et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *Eur Respir J.* 2008;31:869-73.
18. Regan EA, Hokanson JE, Murphy JR et al. Genetic Epidemiology of COPD (COPDGene) Study Design. *COPD.* 2011;7:32-43.
19. Gerard SE, Patton TJ, Christensen GE, Bayouth JE, Reinhardt JM. FissureNet: A Deep Learning Approach For Pulmonary Fissure Detection in CT Images. *IEEE Trans Med Imaging.* 2018;38:156-66.
20. Nardelli P, Ross JC, San José Estépar R. CT Image Enhancement for Feature Detection and Localization. *Medical Image Computing and Computer-Assisted Intervention.* Vol 1496. 2017:224-32.
21. Yun J, Park J, Yu D et al. Improvement of fully automated airway segmentation on volumetric computed tomographic images using a 2.5 dimensional convolutional neural net. *Med Image Anal.* 2019;51:13-20.
22. Tschirren J, Hoffman EA, McLennan G, Sonka M. Intrathoracic airway trees: segmentation and airway morphology analysis from low-dose CT scans. *IEEE Trans Med Imaging.* 2005;24:1529-39.
23. van Rikxoort EM, Prokop M, de Hoop B, Viergever MA, Pluim JPW, van Ginneken B. Automatic segmentation of pulmonary lobes robust against incomplete fissures. *IEEE Trans Med Imaging.* 2010;29:1286-96.
24. Ross JC, San José Estépar R, Diaz A et al. Lung extraction, lobe segmentation and hierarchical region assessment for quantitative analysis on high resolution computed tomography images. *Med Image Comput Comput Assist Interv.* 2009;12(Pt 2):690-8.
25. van Rikxoort EM, van Ginneken B. Automated segmentation of pulmonary structures in thoracic computed tomography scans: a review. *Phys Med Biol.* 2013;58:R187-R220.
26. Mansoor A, Bagci U, Foster B et al. Segmentation and Image Analysis of Abnormal Lungs at CT: Current Approaches, Challenges, and Future Trends. *RadioGraphics.* 2015;35:1056-76.
27. Müller NL, Staples CA, Miller RR, Abboud RT. Density mask. An objective method to quantitate emphysema using computed tomography. *Chest.* 1988;94:782-7.
28. Nakano Y, Muro S, Sakai H et al. Computed Tomographic Measurements of Airway Dimensions and Emphysema in Smokers. *Am J Respir Crit Care Med.* 2000;162:1102-8.
29. Klooster K, Hacken ten NHT, Hartman JE, Kerstjens HAM, van Rikxoort EM, Slebos D-J. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. *N Engl J Med.* 2015;373:2325-35.
30. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med.* 1968;278:1355-60.
31. Hogg JC, Chu F, Utokaparch S et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350:2645-53.
32. Bodduluri S, Pulyakote ASK, Gerard SE et al. Airway fractal dimension predicts respiratory morbidity and mortality in COPD. *J Clin Invest.* 2018;128:5374-82.
33. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. *N Engl J Med.* 2009;360:2445-54.
34. Saetta M, Kim WD, Izquierdo JL, Ghezzo H, Cosio MG. Extent of centrilobular and panacinar emphysema in smokers' lungs: pathological and mechanical implications. *Eur Respir J.* 1994;7:664-671.
35. Thurlbeck WM. The Incidence of Pulmonary Emphysema. *Am Rev Respir Dis.* 1963;87:206-15.
36. Anderson AE, Foraker AG. Centrilobular emphysema and panlobular emphysema: two different diseases. *Thorax.* 1973;28:547-50.
37. Hogg JC. Chronic obstructive pulmonary disease - part 2: pathology and biochemistry of emphysema. *Thorax.* 2002;57:830-4.
38. Lynch DA, Moore CM, Wilson C et al. CT-based Visual Classification of Emphysema: Association with Mortality in the COPDGene Study. *Radiology.* 2018;172294.
39. Sørensen L, Shaker SB, de Bruijne M. Quantitative analysis of pulmonary emphysema using local binary patterns. *IEEE Trans Med Imaging.* 2010;29:559-69.
40. Mendoza CS, Washko G, Ross J et al. Emphysema Quantification in a Multi-Scanner HRCT Cohort Using Local Intensity Distributions. *Proc IEEE Int Symp Biomed Imaging.* 2012:474-7.
41. Nava R, Escalante-Ramírez B, Cristobal G, San José Estépar R. Extended Gabor approach applied to classification of emphysematous patterns in computed tomography. *Med Biol Eng Comput.* 2014;52:393-403.
42. Castaldi PJ, San José Estépar R, Mendoza CS et al. Distinct Quantitative Computed Tomography Emphysema Patterns Are Associated with Physiology and Function in Smokers. *Am J Respir Crit Care Med.* 2013;188:1083-90.
43. Castaldi PJ, Cho MH, San José Estépar R et al. Genome-Wide Association Identifies Regulatory Loci Associated with Distinct Local Histogram Emphysema Patterns. *Am J Respir Crit Care Med.* 2014;190:399-409.
44. Parker MM, Hao Y, Guo F et al. Identification of an emphysema-associated genetic variant near TGFB2 with regulatory effects in lung fibroblasts. *Elife.* 2019;8.
45. Bermejo-Peláez D, San José Estépar R, Ledesma-Carbayo MJ. Emphysema classification using a multi-view convolutional network. *Proc IEEE Int Symp Biomed Imaging.* 2018:519-22.
46. Bermejo-Peláez D, Okajima Y, Washko GR, Ledesma-Carbayo MJ, San José Estépar R. A SR-NET 3D-to-2D Architecture For Paraseptal Emphysema Segmentation. *Proc IEEE Int Symp Biomed Imaging.* 2019:303-6.
47. Humphries SM, Notary AM, Centeno JP et al. Deep Learning Enables Automatic Classification of Emphysema Pattern at CT. *Radiology.* 2020;294:434-44.
48. Yang J, Angelini ED, Balte PP et al. Novel Subtypes of Pulmonary Emphysema Based on Spatially-Informed Lung Texture Learning. *Arxiv.* 2020.
49. Smith BM, Austin JHM, Newell JD Jr et al. Pulmonary Emphysema Subtypes on Computed Tomography: The MESA COPD Study. *Am J Med.* 2014;127:94.e7-e23.
50. Boueiz A, Chang Y, Cho MH et al. Lobar Emphysema Distribution Is Associated With 5-Year Radiological Disease Progression. *Chest.* 2018;153:65-76.
51. Binder P, Batmanghelich NK, San José Estépar R, Golland P. Unsupervised Discovery of Emphysema Subtypes in a Large Clinical Cohort. In: Wang L, Adeli E, Wang Q, Shi Y, Suk H-I, eds. *Machine Learning in Medical Imaging. MLMI 2016. Lecture Notes in Computer Science, vol 10019, Springer, Cham,* 2016:180-187.
52. Peinado VI, Barbera JA, Ramirez J et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. *Am J Physiol.* 1998;274(6 Pt 1):L908-13.
53. Barr RG, Bluemke DA, Ahmed FS et al. Percent Emphysema, Airflow Obstruction, and Impaired Left Ventricular Filling. *N Engl J Med.* 2010;362:217-7.
54. Peinado VIV, Pizarro SS, Barberà JA. Pulmonary vascular involvement in COPD. *Chest.* 2008;134:808-14.
55. San José Estépar R, Kinney GL, Black-Shinn JL et al. Computed Tomographic Measures of Pulmonary Vascular Morphology in Smokers and Their Clinical Implications. *Am J Respir Crit Care Med.* 2013;188:231-39.
56. Jimenez-Carretero D, Bermejo Peláez D, Nardelli P et al. A graph-cut approach for pulmonary artery-vein segmentation in noncontrast CT images. *Med Image Anal.* 2018;52:144-59.

57. Charbonnier JP, Brink M, Ciompi F, Scholten ET, Schaefer-Prokop CM, van Rikxoort EM. Automatic Pulmonary Artery-Vein Separation and Classification in Computed Tomography Using Tree Partitioning and Peripheral Vessel Matching. *IEEE Trans Med Imaging*. 2016;35:882-92.

58. Nardelli P, Ross JC, San José Estépar R. Generative-based airway and vessel morphology quantification on chest CT images. *Med Image Anal*. 2020; 63:101691.

59. Goodfellow IJ, Pouget-Abadie J, Mirza M et al. Generative Adversarial Networks. *arXiv*. 2014;stat.ML.

60. Nardelli P, Ross JC, San José Estépar R. Generative-based airway and vessel morphology quantification on chest CT images. *Med Image Anal*. 2020; 63:101691.

61. Rahaghi FN, Vegas-Sánchez-Ferrero G, Minhas JK et al. Ventricular Geometry From Non-contrast Non-ECG-gated CT Scans: An Imaging Marker of Cardiopulmonary Disease in Smokers. *Acad Radiol*. 2017;24:594-602.

62. Washko GR, Nardelli P, Ash SY et al. Arterial Vascular Pruning, Right Ventricular Size, and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. A Longitudinal Observational Study. *Am J Respir Crit Care Med*. 2019;200:454-61.

63. Washko GR, Nardelli P, Ash SY et al. Smaller Left Ventricle Size at Non-contrast CT Is Associated with Lower Mortality in COPDGene Participants. *Radiology*. 2020;191793.

64. González Serrano G, Ash SY, Vegas-Sánchez-Ferrero G et al. Disease Staging and Prognosis in Smokers Using Deep Learning in Chest Computed Tomography. *Am J Respir Crit Care Med*. 2017;197:193-203.

65. Matsumura K, Ito S. Novel biomarker genes which distinguish between smokers and chronic obstructive pulmonary disease patients with machine learning approach. *BMC Pulm Med*. 2020;20:29-13.

66. Donaldson GC, Wedzicha JA. Prediction of Chronic Obstructive Pulmonary Disease Exacerbation Frequency. Clinical Parameters Are Still Better Than Biomarkers. *Am J Respir Crit Care Med*. 2017;195:415-6.

67. Ying J, Dutta J, Guo N et al. Classification of Exacerbation Frequency in the COPDGene Cohort Using Deep Learning with Deep Belief Networks. *IEEE J Biomed Health Inform*. 2020;24:1805-13.

68. Adibi A, Sin DD, Safari A et al. The Acute COPD Exacerbation Prediction Tool (ACCEPT): a modelling study. *Lancet Respir Med*. 2020; S2213-2600 (19)30397-2.

69. Lange P, Celli B, Agusti A et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2015;373:111-22.

70. Agusti A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med*. 2017;9:35-45.

71. Washko GR, Colangelo LA, San José Estépar R et al. Adult Life-Course Trajectories of Lung Function and the Development of Emphysema: The CARDIA Lung Study. *Am J Med*. 2020;133:222-30.e11.

72. Ross JC, Castaldi PJ, Chu MH et al. Longitudinal Modeling of Lung Function Trajectories in Smokers with and without COPD. *Am J Respir Crit Care Med*. 2018;198:1033-42.

73. Young AL, Bragman FJS, Rangelov B et al. Disease Progression Modeling in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2020;201:294-302.

74. Castaldi PJ, Dy J, Ross J et al. Cluster analysis in the COPDGene study identifies subtypes of smokers with distinct patterns of airway disease and emphysema. *Thorax*. 2014;69:416-23.

75. Castaldi PJ, Boueiz A, Yun J, San José Estépar R et al. Machine Learning Characterization of COPD Subtypes: Insights From the COPDGene Study. *Chest*. 2020;157:1147-57.

76. Iturrioz Campo M, Pascau J, San José Estépar R. Emphysema quantification on simulated X-rays through deep learning techniques. *Proc IEEE Int Symp Biomed Imaging*. 2018;273-6.

77. Nardelli P, Washko GR, San José Estépar R. Bronchial Cartilage Assessment with Model-Based GAN Regressor. *Lecture Notes In Computer Science*. 2019;11769:357-65.

78. Kraft P, Zeggini E, Ioannidis JPA. Replication in genome-wide association studies. *Stat Sci*. 2009;24:561-73.

79. Reyes M, Meier R, Pereira S et al. On the Interpretability of Artificial Intelligence in Radiology: Challenges and Opportunities. *Radiol Artif Intell*. 2020;2:e190043.

80. Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. *Science*. 2019;366:447-53.

81. Larrazabal AJ, Nieto N, Peterson V, Milone DH, Ferrante E. Gender imbalance in medical imaging datasets produces biased classifiers for computer-aided diagnosis. *Proc Natl Acad Sci USA*. 2020;24:201919012.

82. Ganin Y, Ustinova E, Ajakan H et al. Domain-Adversarial Training of Neural Networks. *arXiv*. 2015;stat.ML.

83. Kaassis GA, Makowski MR, Rückert D, Braren RF. Secure, privacy-preserving and federated machine learning in medical imaging. *Nat Mach Intell*. 2020;5:1-7.

84. Tang LYW, Coxson HO, Lam S, et al. Towards large-scale case-finding: training and validation of residual networks for detection of chronic obstructive pulmonary disease using low-dose CT. *The Lancet Digital Health*. 2020;2:259-67.

85. Moll M, Qiao D, Regan EA, et al. Machine Learning and Prediction of All-Cause Mortality in COPD. *Chest*. 2020;158:952-64.