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Early View

Review

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Exploring Computer-based Imaging Analysis in Interstitial Lung Disease: opportunities and challenges

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Abstract

The advent of QCT (quantitative computed tomography) and AI (artificial intelligence) using high-resolution computed tomography (HRCT) data has revolutionized the way interstitial diseases are studied. These quantitative methods provide more accurate and precise results compared to previous semi-quantitative methods, which were limited by human error such as interobserver disagreement or low reproducibility. The integration of QCT and AI and the development of digital biomarkers has facilitated not only diagnosis but also prognostication and prediction of disease behaviour not just in idiopathic pulmonary fibrosis (IPF) where they were initially studied but also in other fibrotic lung diseases. These tools provide reproducible, objective prognostic information which may facilitate clinical decision-making. However, despite the benefits of QCT and AI, there are still obstacles that need to be addressed. Important issues include optimal data management, data sharing and maintaining data privacy. In addition, the development of explainable AI will be essential to develop trust within the medical community and facilitate implementation in routine clinical practice.

Acronyms and Terminology

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

UIP: usual interstitial pneumonia

NSIP: non-specific interstitial pneumonia

CTD-FLD: connective tissue disease-related fibrotic lung disease

FHP: fibrotic hypersensitivity pneumonitis

ILA: interstitial lung abnormalities

REF: progressive pulmonary fibrosis

GGO: ground-glass opacification

QCT: quantitative computed tomography

AI: artificial intelligence

CT: computer tomography

CALIPER: Computer-Aided Lung Informatics for Pathology Evaluation and Rating

AMFM: Adaptive multiple features method

QLF: Quantitative Lung Fibrosis

FRI: Functional Respiratory imaging

SOFIA: Systematic Objective Fibrotic Imaging Analysis Algorithm

DTA: Data-driven texture analysis

Background

Interstitial lung disease (ILD) is a group of disorders characterized by lung tissue inflammation and or fibrosis. Overall, they represent complex clinical entities with non-specific pulmonary symptoms and functional findings. Patients present with progressive dyspnoea, dry cough, and restrictive patterns on pulmonary function tests. ILD is a broad term that encompasses many different conditions in which inflammation or fibrosis of interstitium is found in variable proportions affecting disease behaviour and response to treatment. At one end of the ILD spectrum is Idiopathic pulmonary fibrosis (IPF), a fibrotic disorder with an inexorably progressive course and poor prognosis (3-5 years) (1, 2). However, there are other ILDs that are mainly characterized by inflammation and have better outcomes with or without treatment and higher survival rates (3-6). Although there has been significant progress in treatment of these conditions in the last decade, in an addition to IPF, are other forms of pulmonary fibrosis which progress regardless of treatment and demonstrate and

IPF-like disease course. These non-IPF progressive forms of fibrosis have recently been collectively named, “progressive pulmonary fibrosis” (REF).High-resolution computed tomography (HRCT) of the chest is central to diagnosis in patients suspected of fibrotic lung disease by providing detailed cross-sectional images of lungs and evaluating disease distribution in three dimensions. HRCT may also play a prognostic role in fibrotic lung disease and given that it is routinely performed in most patients with suspected fibrotic lung disease, is an attractive target for biomarker research in these diseases (7, 8).

At the most basic level, a typical UIP pattern or probable usual interstitial pneumonia (UIP) pattern (so-called UIP-like disease) is associated with a poor prognosis based on recent antifibrotic therapy trials in IPF and progressive non-IPF disease (9-14). In addition to the HRCT phenotype, specific HRCT patterns can also be visually quantified (known as semiquantitative evaluation) and used as prognostic markers. Honeycombing, a cardinal sign of fibrosis on HRCT and a key pattern in the identification of UIP, is defined as clustered cystic air spaces, cysts of comparable diameters, and cyst diameters typically <10 mm surrounded by well-defined walls (15). When scored for extent visually, either alone or in combination with the extent of reticulation (sometimes called a “fibrosis score”), honeycombing has been consistently linked to mortality idiopathic fibrotic lung disease (IPF and idiopathic nonspecific interstitial pneumonia, “NSIP”), connective tissue disease-related fibrotic lung disease (CTD-FLD) and fibrotic hypersensitivity pneumonitis (FHP) over the past two decades (16-21). In one study involving 315 patients with IPF enrolled in a clinical trial of IFN-g1b, Lynch et al. reported that the overall extent of fibrosis, defined as the extent of reticular and honeycombing patterns combined, was the strongest predictor of mortality (21). It is noteworthy that in this study, HRCT was a better predictor of mortality than pulmonary function in IPF. The severity of traction bronchiectasis is also a strong predictor of mortality in multiple fibrotic lung disease subsets (17, 18, 20, 22) and may be a sensitive surrogate marker of disease progression in IPF (23). Most recently, changes in aortosternal distance and fissural displacement measured manually predict outcomes in patients with IPF (24). In contrast, the presence of certain patterns may be associated with a more favourable outcome. In fibrotic hypersensitivity pneumonitis (FHP), the presence of mosaic attenuation and air trapping may be associated with a more favorable survival (25). Since disease severity based on HRCT fibrosis extent and lung function decline have been reported as independent predictors of outcome, these variables have been combined to create staging systems in IPF, systemic sclerosis related ILD, and fibrotic sarcoidosis (21, 26-29).

Despite this large body of literature reporting consistent findings, semiquantitative evaluation of HRCT is associated with a number of well-documented limitations; it is, 1) liable to significant interobserver variability, 2) poorly reproducible, 3) insensitive to subtle changes in disease extent over short follow-up periods, 4) time-consuming, and 5) requires domain expertise which may not be available (7, 8, 30, 31). This provides the rationale for applying computer-based image analysis to HRCT for both diagnostic

support as well as reliable disease quantification also known as quantitative CT (Table 1).

Quantitative CT (QCT)

Early studies

The earliest move toward QCT in pulmonary fibrosis used simple measures of lung density based on density masks or whole-lung HRCT histogram analysis (8). Since the CT histogram provides a graphical representation of lung density per voxel in a CT image, it allows the mean lung attenuation, skewness, and kurtosis to be calculated. Kurtosis describes the sharpness of the peak of the histogram whereas skewness is a measure of the lack of symmetry of the CT histogram. Lung fibrosis increases the mean lung attenuation and reduces the kurtosis and leftward skewness of the histogram therefore these metrics may be used as surrogates of fibrosis extent on CT. In 144 IPF patients, Best et al. reported a correlation between kurtosis and physiologic decline and mortality. A key difficulty with this approach is that it cannot discriminate between different HRCT patterns commonly seen in patients with IPF (32). Recently, Ash et al. described local histogram-based objective quantification of different radiologic patterns of disease in 46 patients with IPF and found strong correlations between visual and objective histogram-based scores for disease extent as well as a poor prognosis in patients with higher fibrosis and honeycombing extent scores (33).

Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER)

CALIPER has been used to predict survival and future physiological decline in patients with IPF, using a computer vision-based technique based on volumetric local histogram and morphological analysis to characterize and quantify different HRCT patterns (8). Furthermore, CALIPER extracts the pulmonary vessels and provides an estimation of the vessel volume, reported as a novel 'vascular-related structures' (VRS) variable. In a landmark study published in 283 patients with IPF, Jacob et al demonstrated on multivariable survival analysis which included CALIPER and semiquantitative HRCT pattern scores, only the computer-based variables independently predicted mortality, with VRS being the strongest predictor among them (34). In a subsequent study, published in 2018, the same group used a VRS-threshold for cohort enrichment in an IPF drug trial setting to reduce the IPF drug trial population size by 25%. Importantly, the VRS score identified a subset of patients in whom antifibrotic therapy reduced FVC decline (35). What is important to understand from these data, is that CALIPER was not originally designed to evaluate the pulmonary vessels; this variable was generated as a by-product of the software image preprocessing pipeline, which extracts the lung parenchyma from the airways and vessels. This finding is early evidence that computer-based image analysis provides an opportunity to identify novel HRCT biomarkers including those that may not be accessible visually. CALIPER has also been applied to CTD-FLD and FHP. In a cohort of 203 all-comers CTD-FLD, Jacob et al

demonstrated that VRS was an independent predictor of mortality across all CTD-FLD subgroups (36). In addition, the authors stratified patients into three prognostically distinct groups based on CALIPER-related HRCT variables demonstrating the potential of this technology to identify novel outcome-based radiologic phenotypes in CTD. Likewise, in a cohort of 135 patients with a diagnosis of FHP, the same group (37) demonstrated stronger associations between restrictive functional indices and CALIPER-defined total ILD extent than semiquantitative scores. In a subsequent study, the authors applied a VRS threshold to identify a subgroup of patients with IPF-like disease behaviour among 103 patients with FHP. Similar results have been reported applying CALIPER to patients with unclassifiable fibrotic lung disease (38).

Adaptive multiple features method (AMFM)

AMFM identifies and quantifies HRCT patterns based on textural analysis, including normal lung, ground-glass opacification (GGO), emphysema, honeycombing, and nodules (8). Initially, this method was used to differentiate normal lung from the lung with emphysema. In the late 1990s, Hoffman et al. (39) compared AMFM with mean lung density (MLD) and histogram-based analysis and demonstrated high precision for the AMFM method in discriminating between normal and emphysematous lung. Later studies extended these experiments to patients with IPF and sarcoidosis, comparing the AMFM with these two methods to objectively characterize four groups of subjects; normal lung, emphysema, IPF, and sarcoidosis. In all four groups, the AMFM method demonstrated superiority over MLD and histogram-based analysis (40). In 2017 Salisbury et al. demonstrated in 199 IPF patients enrolled in the PANTHER-IPF treatment trial, that baseline fibrosis (measured as ground glass-reticular opacities (GGR)) measured by AMFM predicts disease progression. Interestingly, changes in GGR only weakly correlated with FVC changes suggesting that a combination of FVC change and GGR change, as measured by the AMFM software, may provide improved prognostic signal over either variable in isolation (41). (Figure 1)

Quantitative Lung Fibrosis (QLF)

QLF quantifies fibrotic reticular patterns (8). A total ILD extent composite of Quantitative Interstitial Lung Disease (QILD) is the sum of QLF, honeycombing, and GGO patterns. QLF has been shown to correlate well with lung function measurement in ILD patients and has been used to evaluate disease progression in IPF and scleroderma-related ILD treatment trials (42). In a study of cyclophosphamide versus mycophenolate in 142 patients with scleroderma related ILD, Tashkin et al. found that QLF scores did not change in the treatment arms of the study, while QILD scores did show a small improvement in both treatment arms (43). The incorporation of QLF/QILD scores in secondary outcomes of clinical trials demonstrates the utility of computer-based imaging analysis tools for providing complementary measures of disease progression to conventional lung physiology (i.e. FVC)(44, 45).(Figure 2)

Functional Respiratory Imaging (FRI)

Functional Respiratory Imaging (FRI) combines low-dose HRCT with computer-based flow simulations. Respiratory gating using a handheld spirometer is performed during the acquisition to ensure repeatable lung volumes (Figure 3). FRI allows regional quantification of lung structure and function and shows low variability (1–3%) for airway volumes, blood vessel volumes, and airway resistances (46). FRI can also assess airway volume and therefore can quantify the severity of traction bronchiectasis, a potent predictor of mortality based on several studies which applied semiquantitative airway assessments. Recent studies in IPF show that disease progression, as determined by FVC decline, is associated with a reduction in CT-measured lung volumes (R2= 0.80, P, 0.001) and an increase in relative airway volumes (R2=0.29, P, 0.001). Changes in FVC are correlated with changes in lung volumes (R2= 0.18, P, 0.001) and changes in relative airway calibre (R2=0.15, P, 0.001) (47). Lobe and airway volumes can already be significantly affected by IPF, whereas conventional measures such as FVC remain within the normal (healthy) range while FRI metrics capture early changes. Additional studies are needed to be done to determine minimal clinically important differences.

Deep learning

A key drawback of many of the QCT tools described above is that their development requires some degree of “feature engineering”; the computer is trained to identify and quantify specific HRCT patterns by human operators. This means that all of the limitations associated with visual HRCT assessment are in principle incorporated into the system. A second significant issue is that the features upon which the computer is trained need to be known *a priori*, negating the possibility that novel, visually inaccessible HRCT biomarkers, might be discovered. Both of these challenges can be overcome if the computer can learn to extract the most predictive features from the images in an autonomous fashion. This is the key advantage of deep learning.

Deep learning is a form of machine learning that has the capacity to autonomously identify patterns in high dimensional data (e.g., HRCT scans) and map these patterns to endpoints such as diagnosis and future disease progression(7, 48-50). Deep learning is very efficient at identifying subtle features within images that are important while at the same time, ignoring irrelevant variations between images including those introduced by different HRCT techniques. The key advantage of deep learning over many existing QCT techniques is that it simultaneously optimises feature extraction and classification during algorithm training; *a priori* knowledge of what image features to quantify for a given classification problem is not necessary. More concretely, deep learning bypasses the need to train computers on specific patterns; the computer learns itself, during training, which patterns on HRCT are most important for predicting a given task. This approach also has the added advantage of avoiding all of the limitations associated with visual HRCT assessment. Perhaps most importantly, since the computer learns autonomously without explicit programming, an opportunity is created for identifying novel HRCT biomarkers, including those that are not readily identified visually. In respiratory medicine, deep learning has been successfully applied

to lung cancer detection, predicting mortality in patients with chronic obstructive pulmonary disease and classifying fibrotic lung disease on CT scans (7, 48, 51).

Applications of Deep learning to fibrotic lung disease

Deep learning, in principle, can be applied to a number of unresolved research questions related to imaging in fibrotic lung disease. Two important unanswered questions relate to 1) predicting progressive fibrotic lung disease using baseline imaging and clinical data and 2) early detection of clinically significant fibrotic lung disease.

Identifying patients with progressive fibrotic lung disease

The reliable identification of progressive fibrotic lung disease using baseline imaging and clinical data is of immediate clinical importance (10, 52-58). Since antifibrotic therapy is currently only licensed in those patients that demonstrate progression (i.e., progressive pulmonary fibrosis), patients must first undergo a period of progression before they qualify for treatment, meaning that an opportunity to initiate early treatment and reduce functional decline, is missed. Based on published data coming from recent clinical trials, UIP and probable UIP, (UIP-like disease) in general exhibit progressive disease behaviour, but the progressive disease is not confined to patients with UIP-like disease and currently, we cannot accurately predict progression using baseline HRCT data, in this non-UIP group. (10, 59)

Recently, a deep learning algorithm, SOFIA (Systematic Objective Fibrotic Imaging Analysis Algorithm), trained to identify UIP-like features on HRCT and provide a "UIP probability" score was used to predict progression in a cohort of 504 suspected IPF patients, drawn from the Australian IPF Registry (7). This novel HRCT biomarker, the UIP probability score, was predictive of mortality, independently of disease severity (when expressed as a total fibrosis score on HRCT, or lung function). Furthermore, on subgroup analysis in patients whose HRCT was considered indeterminate (i.e., the HRCT was considered unhelpful based on visual assessment by two expert thoracic radiologists), the UIP probability score, again, was a strong predictor of mortality (RESULT: HR 1.73, P-value < 0.0001, 95% CIs). Finally, in patients who underwent surgical lung biopsy (n=86), the UIP probability score predicted mortality independently of guideline-based histologic diagnosis and total fibrosis extent, with both these latter variables failing to reach statistical significance (RESULT: HR 1.75, P-value < 0.0001, 95% CIs). It is important to point out, that radiologists can also provide a UIP probability score, and this outperforms guideline-based HRCT diagnosis in survival analysis (7). However, in this setting, radiologists tend to default to the extremes of this scale (i.e., they tend to assign a UIP probability of 0% or 100%) whereas SOFIA provides a granular probability score as a continuous variable, regardless of the HRCT pattern; subjective biases to which human assessment are vulnerable, do not exist. (Figure 4)

It is important to highlight that further work is needed to decode the outputs of SOFIA, particularly in cases where there is significant disagreement between the algorithm and the radiologists. More generally, a key challenge in deep learning is that the complexity that makes neural networks so efficient at identifying patterns in large datasets, can also make them difficult to interpret. Neural networks are often regarded as "black boxes" which is viewed as an obstacle to their implementation. Explainability is an increasingly important component of algorithm development particularly when algorithmic decision-making is based on features contained within the images which are invisible to human observers. Efficient deep learning also relies on being able to understand why an algorithm misclassifies certain images, making algorithm interpretability, crucial.

Deep learning based QCT has also been developed. Data-driven texture analysis (DTA) is a deep learning-based tool which utilises a convolutional neural network to classify image patches based on the presence of fibrosis and quantifies fibrosis extent on HRCT. DTA fibrosis score has demonstrated good correlation with lung function and visual quantification of fibrosis by experts and can stratify patients based on fibrosis extent (Figure 5). By quantifying baseline line fibrosis extent, it can also be used to predict disease progression (RESULT: HR 1.14, P-value < 0.0001, 95% CIs) (60-62). Humphries at el. reported in a cohort of 393 IPF patients (62) significant associations with FVC and DLco decline as well as statistically significant outcome prediction, independent of lung function.

Detection of early fibrotic lung disease

The second open research question, to which deep learning can be applied is the characterization of interstitial lung abnormalities (ILA). ILA are defined as interstitial abnormalities that exceeds 5% extent of the total lung volume on HRCT and they present thorny clinical problem. Data extracted from longitudinal lung cancer and cardiovascular cohort studies show shared clinical and genetic associations between incidentally detected ILAs on HRCT and IPF. ILAs are associated with aging and are more commonly seen in smokers. ILA are also seen in those expressing MUC5B promoter polymorphism positivity (63, 64) and ILA progression correlates to physiologic decline. But ILAs are common, seen in 7-9% of lung cancer screening subjects, exceeding the prevalence of IPF by almost two orders of magnitude (65). The current challenge is that it is not possible to predict which ILA will progress to clinically significant fibrotic lung disease and which will not. As with diagnosis in established fibrotic lung disease, the current ILA classification is based on visually defined morphology, rather than disease behaviour, which means that classification of incidentally identified ILA is associated with all the limitations associated with visual HRCT evaluation. Also, the current ILA definition represents an umbrella term encompassing a range of non-fibrotic and fibrotic patterns. This definition will need refinement if progressive ILA are to be reliably identified. As with predicting progressive behaviour when fibrosis is established, one solution might be found in

deep learning-based analysis; algorithmic training could be anchored to ILA behaviour with no *a priori* assumptions as to the importance of individual ILA patterns. A major challenge to this approach will be the collating of sufficiently large datasets to adequately power algorithm training.

Challenges to development and implementation

The use of QCT as biomarker in fibrotic lung disease faces several barriers. These include, access to high quality data in sufficient quantities to drive novel QCT development, recognising and minimising biases in algorithm training, improving algorithm explainability, ensuring equal access for patients to AI-based technology and establishing reference standards for training, testing and algorithm deployment.

The availability of large and diverse datasets is a critical factor in the development of effective machine learning models. Open-source datasets like The Open-Source Imaging Consortium (OSIC) (https://www.osicild.org) can help address these limitations by making data more accessible and secure, while also addressing privacy and ethical concerns. The multidisciplinary nature of OSIC, engaging radiologists, clinicians, computer, and data scientists as well as industry stakeholders helps to ensure the credibility and trustworthiness of the dataset and therefore, making it a valuable resource for the development of AI-powered healthcare solutions.

The integration of machine learning with pathogenetics can have a major impact on drug development. Machine learning can help identify patterns and correlations in large population data, allowing the testing of hypotheses on a larger scale. This can lead to more personalized and effective treatments, as well as a deeper understanding of disease mechanisms. By leveraging the power of machine learning, drug development can be more efficient and targeted, ultimately improving patient outcomes.

Deep learning algorithms come with unique risks because of they can reinforce biases in training data. Missing or unbalanced data can affect algorithm performance and amplify inequalities in healthcare in ways that are difficult to detect. Subgroups of patients with rare diseases may not see the benefit of these AI-based imaging analysis techniques because of insufficient data for algorithm development (66). Deep learning algorithms may also be manipulated to output conclusions that trend toward the use of specific third-party tests. Establishing ethical frameworks with by-in from all stakeholders and in particular, patients will be needed to foster trust in this technology. Bespoke governance frameworks which are tailored to address the unique challenges associated with AI will likely be needed. Preserving trust and transparency will be of paramount importance. Finding ways to encode ethical standards into AI training will be essential as well as preserving trust and transparency.

Encouraging the medical community to fully embrace AI and machine learning tools may be hampered by a lack of understanding and concerns about quality, safety, and accuracy. However, it’s important to consider that first the quantitative analysis

provided by these tools can offer more reliable and objective data for disease assessment and precision medicine (67-71). Second, this can aid in clinical decision-making and improve the accuracy of predictions about disease progression. It will also be important for all stakeholders to receive appropriate education and training on the use of these tools and how to appraise and overcome their limitations.

Conclusion:

Quantitative Computed Tomography (QCT) and Artificial Intelligence (AI) are increasingly being recognized as valuable tools in the diagnosis and prognosis of interstitial lung diseases (ILDs). Two key advantages are: first, they offer the advantage of being more precise and efficient compared to semi-quantitative methods, and second, can help in decision making for physicians. However, there are still challenges in terms of acceptance by the medical community and navigating technical and bureaucratic hurdles.

QCT The computer is trained to identify and quantify patterns in HRCT. Its development requires "function engineering", a human operator.	
Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER)	This tool uses volumetric local histogram and morphological analysis to characterize and quantify different HRCT patterns. Including the novel 'vascular-related structures' (VRS) variable, which has been shown to be an independent predictor of mortality and a potential tool to identify novel outcome-based radiologic phenotypes in various lung diseases.
Adaptive multiple features method (AMFM)	Identifies and quantifies HRCT patterns based on textural analysis (normal lung, GGO, emphysema, honeycombing, and nodules).
Quantitative Lung Fibrosis (QLF)	This tool quantifies fibrotic reticular patterns. A total ILD extent composite of Quantitative Interstitial Lung Disease (QILD) is the sum of QLF, honeycombing, and GGO patterns. It can provide complementary measures of disease progression to conventional lung physiology.
Functional Respiratory Imaging (FRI)	This technology combines low-dose HRCT with computer-based flow simulations. FRI enables precise quantification of lung structure and function, with low variability for airway volumes, blood vessel volumes, and airway resistances. It can also evaluate airway volume, making it useful for measuring the severity of traction bronchiectasis, which is a predictor of mortality.
Deep learning It has the ability to autonomously identify patterns in high-dimensional data features (for example, HRCT scans). It has no human operator.	
Systematic Objective Fibrotic Imaging Analysis Algorithm (SOFIA)	The algorithm is trained to identify usual interstitial pneumonia (UIP)-like features on high-resolution computed tomography (HRCT). It provides a "UIP probability" score. It can predict disease progression and mortality in patients with suspected idiopathic pulmonary fibrosis (IPF).
Data-driven texture analysis (DTA)	This technology classifies image patches based on the presence of fibrosis and quantifies fibrosis extent on HRCT. It can stratify patients based on fibrosis extent.

TABLE 1. This table summarizes the tools of QCT and deep learning.

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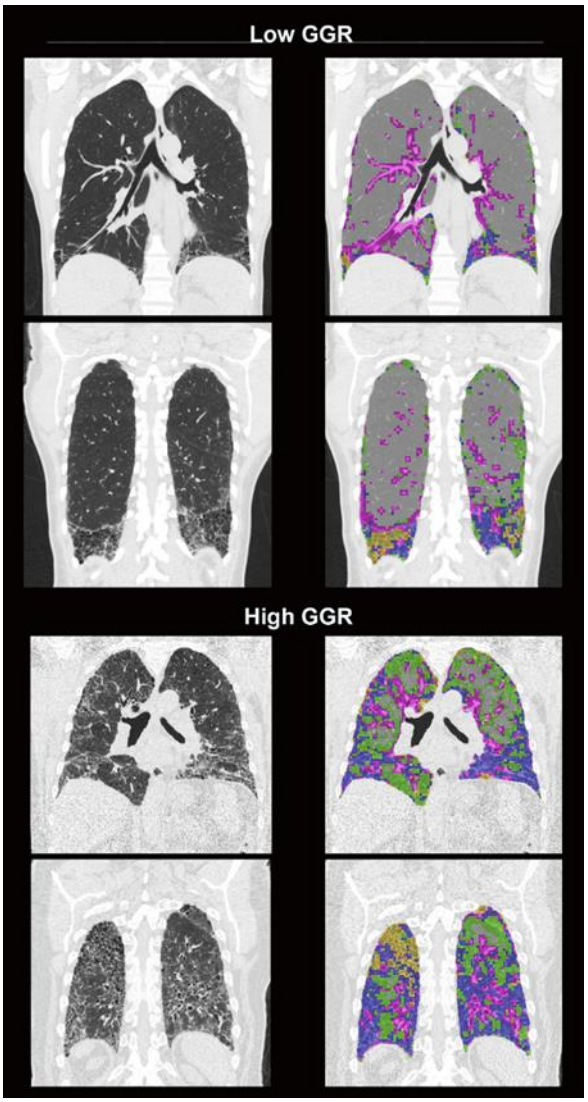

FIGURE 1. Adaptive multiple features method (AMFM). The image demonstrates a patient with low Ground Glass Reticular texture and a patient with high GGR. Colour coding: Grey (white overlay) = Normal; Pink= Broncho-vascular bundles; Yellow= Honeycombing; Green=Ground Glass; Purple/Blue= Ground Glass ReticularCourtesyReticular. Courtesy of Prof. Eric Hoffman.

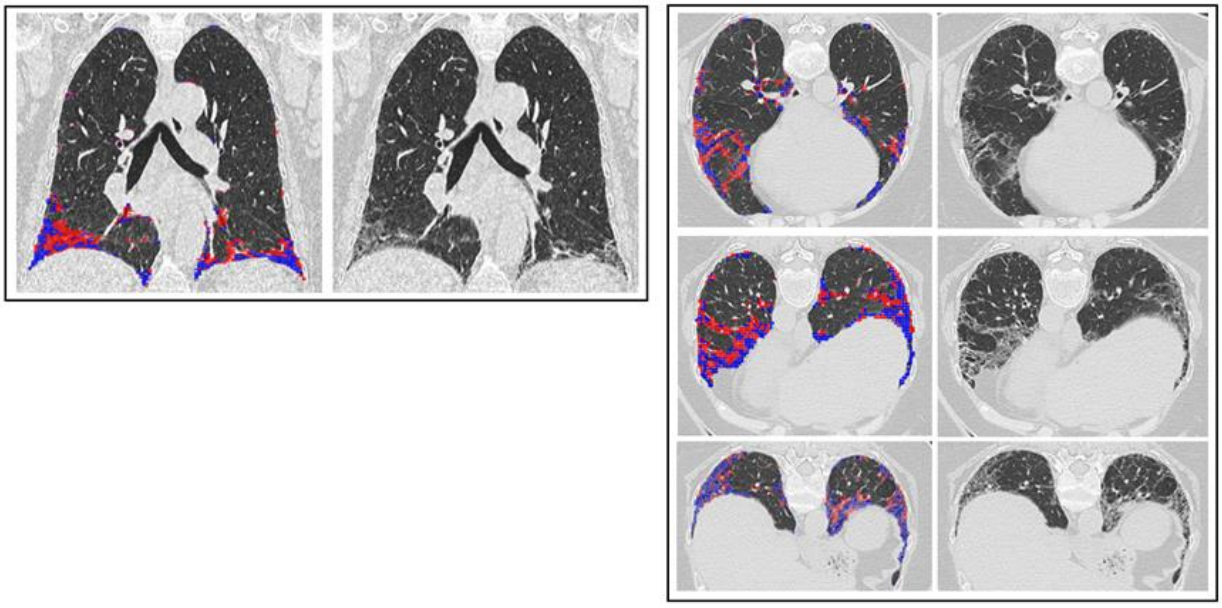

FIGURE 2. Coronal and axial computed tomography (CT) images with Quantitative Lung Fibrosis (QLF) characterization. Left: coronal (left) and original (right) coronal images. Right: Annotated axial high-resolution CT images with the classification of QLF (blue and red) and the corresponding original images. In whole lung, QLF extent is 10.6% and QLF score is 393 mL in volume. QLF scores in right and left lung are 11.5% and 9.5%, respectively. QLF scores were 20.1%, and 19.7% in the right and left lower lobes, which convert to 142mL and 105mL, respectively. QLF score quantifies the extent, and characterizes the distribution of pulmonary fibrosis as predominately lower lung disease. Courtesy of Prof. Grace Hyun J Kim and Prof. Goldin Jonathan.

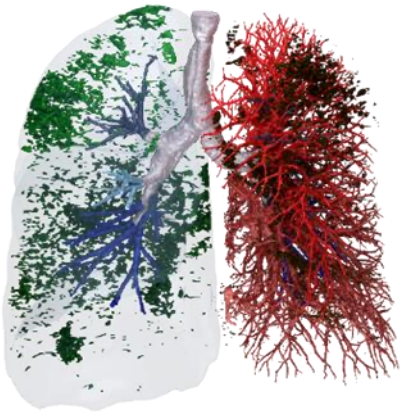

FIGURE 3. Functional Respiratory Imaging. Visualization and quantification of airway volumes (depicted in blue), lobe volume, fibrosis (depicted in green), and emphysema (depicted in black and blood vessel volume (depicted in red). Courtesy of Fluidda, Inc.

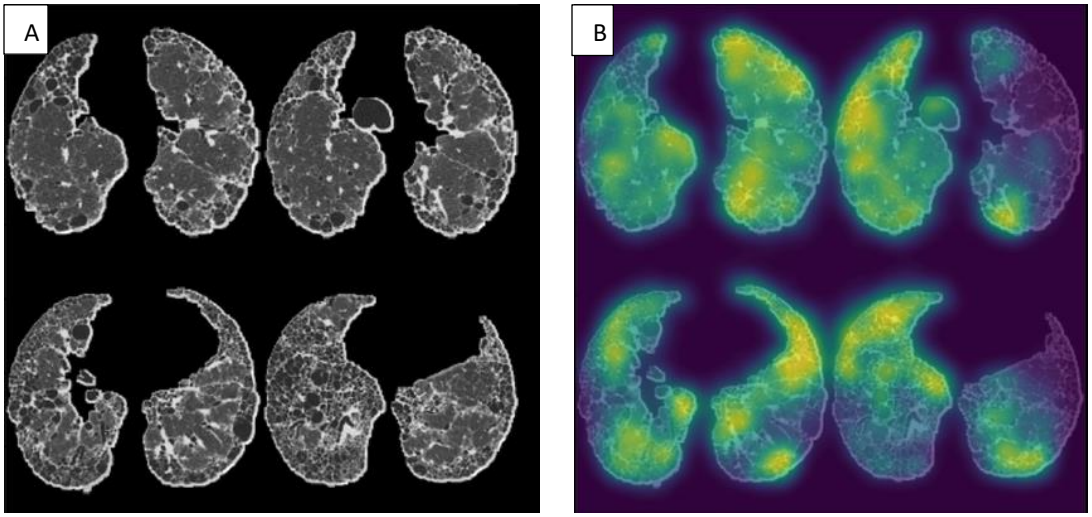

FIGURE 4. Systematic Objective Fibrotic lung disease analysis Algorithm. A) Four slice HRCT montage of segmented lung slices depicted peripheral honeycombing consistent with a UIP pattern. SOFIA (Systematic Objective Fibrotic lung disease analysis Algorithm) scores for this case were UIP: 0.9963, Probable UIP: 0.0036, Indeterminate: 0.0001, and Alternative diagnosis: 0.000. B) Saliency map for Figure A highlighting regions within the montage that were most influential algorithmic decision-making.

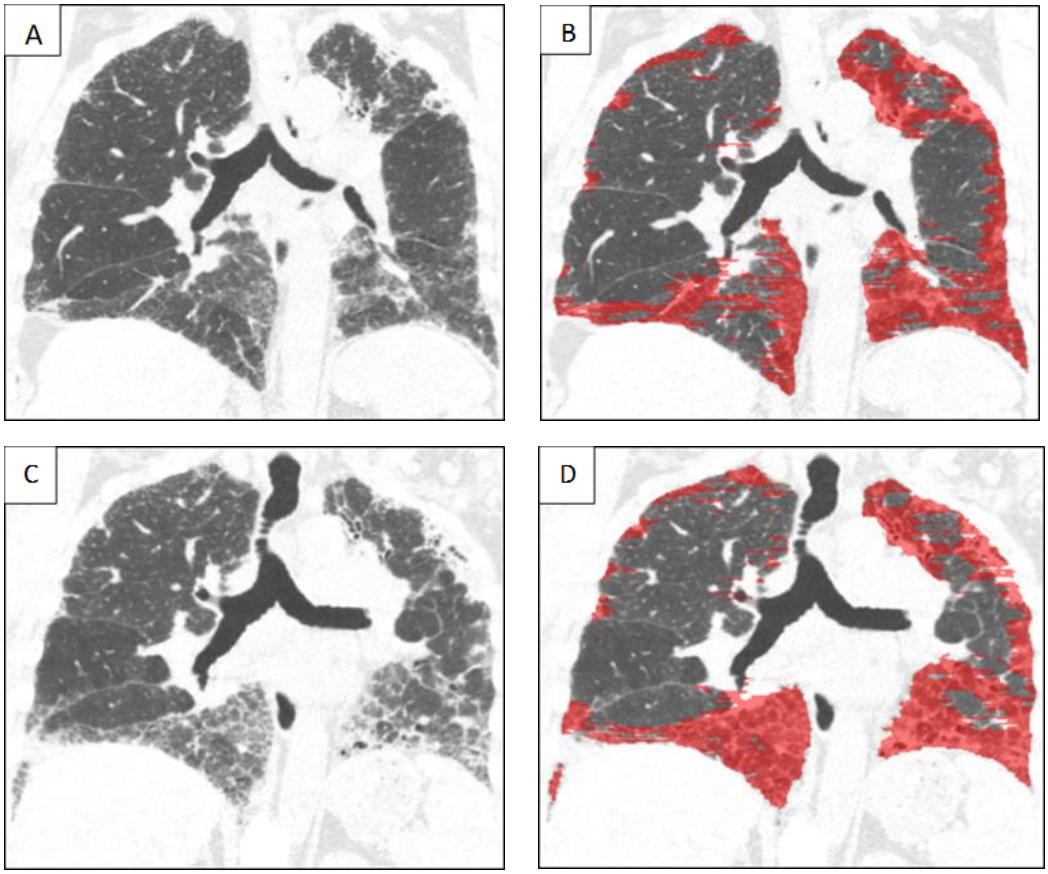

FIGURE 5. Data-driven texture analysis (DTA). Coronal CT sections on a 66-year-old female with IPF. Visual CT pattern was indeterminate for UIP. Baseline CT with B) DTA classification as red overlay. DTA score (calculated as percentage of lung volume classified as fibrosis) was 33.0 at baseline. C) Follow-up CT at 1 year and D) DTA classification as red overlay. DTA score increased to 39.0 at 1 year follow-up. Courtesy of Prof. Steve Humphries.