

# High resolution CT-based characterization analysis of idiopathic pulmonary fibrosis

Yuwen Zhang

Supervised by : Prof. Merryn Tawhai

Dr. Alys Clark

Dr. Haribalan Kumar

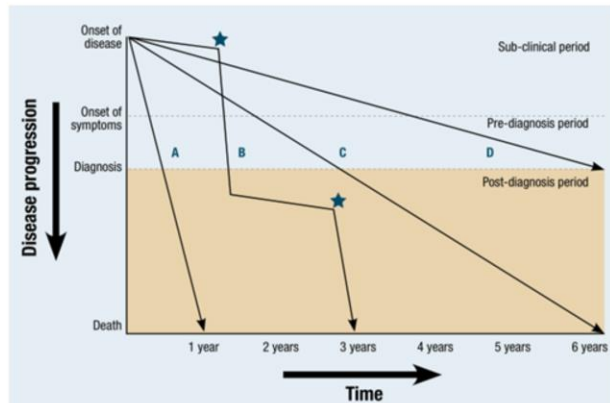


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Good morning, everyone, I'm Yuwen Zhang, from Auckland Bioengineering Institute. Thank you very much for coming to my presentation. Next, I will introduce my research project, it's about CT-based characterization analysis of idiopathic pulmonary fibrosis

## Background

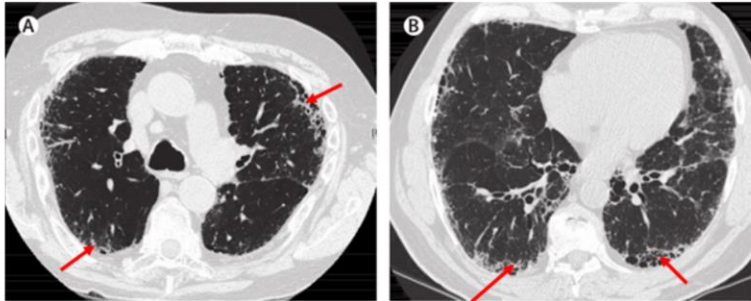
- Idiopathic pulmonary fibrosis (IPF) is a chronic and life-threatening disease
- Cause is unknown
- Etiology remains elusive
- Progression is variable and unpredictable



IPF is one of the most aggressive and frequent forms of idiopathic lung disease. Idiopathic means that the cause is unknown. For people more than 75 years old, IPF is estimated to occur in more than 200 cases per 100,000. That is a large number of people, and a mean survival of only approximately 3 years. The rate of progression of IPF is quite variable and unpredictable between patients. However, there are currently no reliable biomarkers that can indicate the likely progression of IPF disease.

## Background

- HRCT is an essential tool in evaluating lung disease
- Associated with the presence of a usual interstitial pneumonia (UIP) pattern on HRCT (ATS/ERS criteria)
- Honeycomb, reticular, ground-glass
- Combined IPF and emphysema (CPFE)



With the development of radiological imaging techniques, high-resolution computed tomography (HRCT) has played an essential role in evaluating lung disease. Based on the criteria set by members of ATS / ERS, the diagnosis of IPF usually associates with the presence of a usual interstitial pneumonia (UIP) pattern on HRCT. Honeycomb, reticular and ground-glass are all typical CT patterns of fibrosis disease. In addition, in the past ten years, some researchers suggest that combined IPF and emphysema (CPFE) should be regarded as a distinct clinical entity other than emphysema or IPF alone.

## Summary of published work

- Quantitative analysis of radiology:  
Adaptive multiple feature method (AMFM), mean lung attenuation (MLA),  
texture-based scoring systems
- Clinical functional measurements:  
Pulmonary functional tests (PFTs), airway resistance/tissue compliance,  
ventilation/perfusion ration



Limited research into combining spatial data with functional data.

No established quantitative tools to assess the progression of IPF

**Aim:** Develop a new method for quantitative assessment of the IPF lung bringing together volumetric imaging, pulmonary function tests, and computational models for lung function.

Renuka et al(1999), Alan et al (2008), Wang et al (2003, 2008), Hyun et al (2010, 2011, 2015)

In the past few years, there has been effort to provide quantitative analysis on CT scans of lung parenchymal abnormalities, and also some statistical analysis of clinical data from IPF patients, such as PFT data, airway resistance, tissue compliance and ventilation/perfusion ratio. But, currently, there are few researches involves in relating spatial distribution of abnormalities to the functional data. And there is no established quantitative tools exist to assess the progression of IPF. So the aim of our study is to develop a new method for quantitative assessment of the IPF lung that brings together volumetric imaging, pulmonary function tests, and computational models for lung function.

## Imaging and clinical data

Clinical data assessed in this study	
Age (years)	43-82
Females/Males	3/5
Slice thickness (mm)	1.25-3.00
Interval between scans (months)	5-20
Slice resolution	512x512
Number of slices	65-160

The clinical data used in this study comprised HRCT images and pulmonary function tests obtained from 8 patients diagnosed with IPF at Auckland City Hospital, Auckland, New Zealand.

5 patient → 1 time point

1 patient → 2 time point

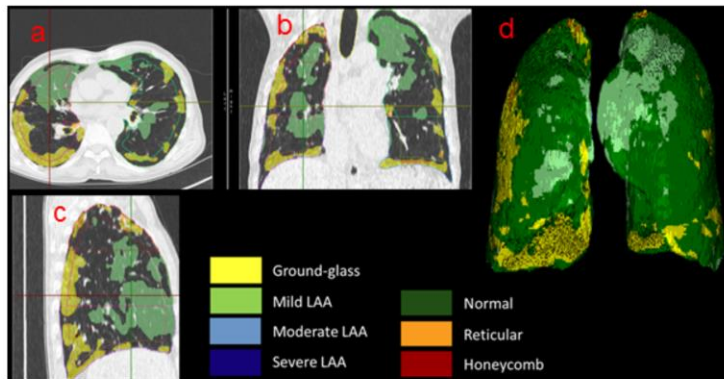
2 patient → 3 time point

The clinical CT data used in this study was acquired from 8 patients diagnosed with IPF at Auckland City Hospital. The slice thickness of these clinical CT images are from 1.25 to 3.00mm. Among these data, 5 patients have one time point, 1 patient has 2 time point data, 2 patients have time point data. The time interval between different time point is between 5 to 20 monts.

## Pulmonary parenchymal classification

CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Ratings) software.  
Mayo Clinic (Rochester, MN, USA)

Each parenchymal voxel was classified into the following characteristic CT patterns: normal (N), reticular (R), honeycomb (HC), ground-glass (GG), mild low attenuation areas (LAA), moderate LAA and severe LAA. Emphysema : Hounsfield Unit is under -950.

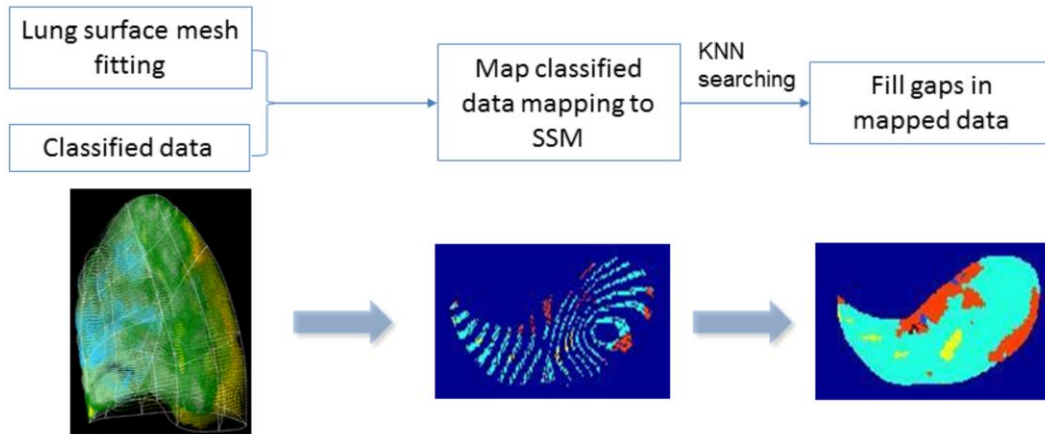


Color labelled classification result of case 7 on IPF HRCT by CALIPER. (a) Transverse plane. (b) Coronal plane. (c) Sagittal plane. (d) 3D color labelled lung.

Tissue regions were classified using CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Ratings) software, developed at the Mayo Clinic. This software is able to classify every lung parenchymal voxel into several kinds of CT patterns, including normal (N), reticular (R), honeycomb (HC), ground-glass (GG), mild low attenuation areas (LAA), moderate LAA and severe LAA. In addition, emphysema areas were extracted through detecting the voxels whose Hounsfield Unit is under -950.

## Normalization of classified data

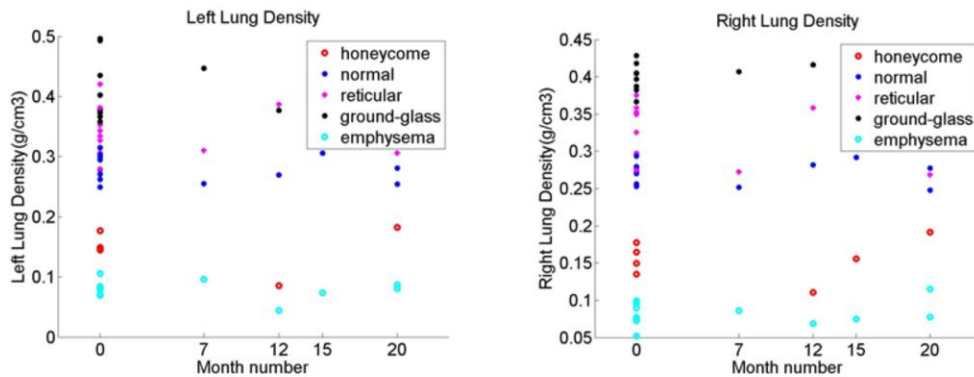
- Lung mesh : bi-cubic Hermite finite element surface mesh (left lung: 35 nodes and 44 elements; right lung: 50 nodes and 62 elements)
- Statistical shape model (SSM): 30 healthy normal subjects (15 males and 15 females), principal component analysis (PCA)



Lung surface data was extracted from the classified data and fissure surfaces were defined manually using the open-source visualization software CMGUI by an expert user. A bi-cubic Hermite finite element surface mesh was fitted to the shape of the lung and its fissures. Since there is lung shape variation between different subjects and often between clinical images obtained at different times. Classified volumetric lung data was then mapped to a statistical shape model (SSM) of the 'normal' older human lung. The statistical shape model was constructed based on principle component analysis derived from a set of training meshes. The gaps on the mapped data was filled using KNN searching to make it easier for the further quantitative analysis.

# Density analysis

- Fibrosis usually has a consistently higher tissue density (0.34/0.41 for reticular/ground-glass) compared to normal tissue (0.27) over time
- In contrast, emphysema has lower density (0.078)

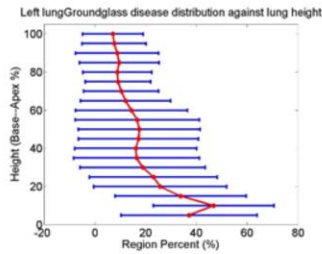


The average tissue density of each classified CT pattern was calculated. From the result, we can see fibrosis has a consistently higher tissue density (0.34/0.41 for reticular/ground-glass) over time compared to normal tissue (0.2752). In contrast, emphysema has lower density (0.0784).

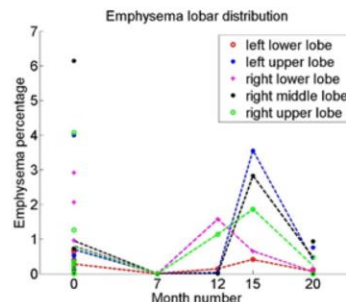
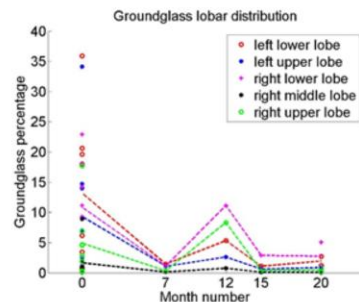
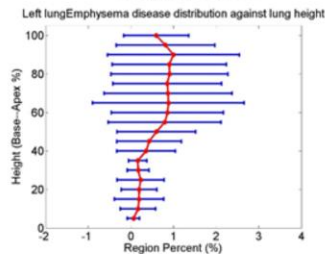


# Spatial distribution analysis

## Ground-glass



## Emphysema

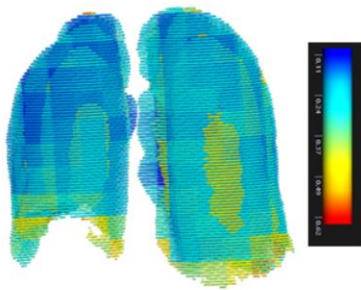


- Fibrosis mostly located in lower lobes (72%, 58%, 65% for honeycomb, reticular, ground-glass)

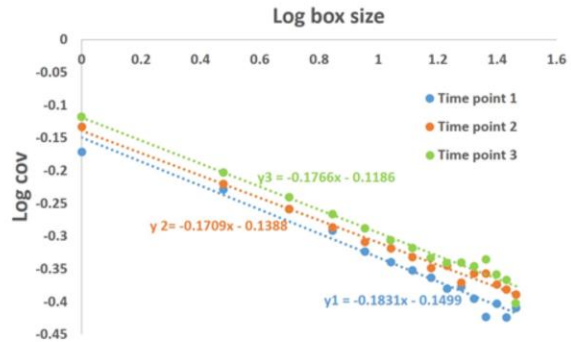
- Emphysema mostly located in upper lobes (73%)

In order to analyze the spatial distribution of abnormalities, the volume percent of each kind of disease pattern was averaged within 5% lung height in the direction from base to apex. Also, the volume percent of each disease pattern for each lobe was calculated to provide a lobar distribution of disease. We can see from the result that fibrosis mostly located in lower lobes (72%, 58%, 65% for honeycomb, reticular, ground-glass). In contrast, Emphysema mostly located in upper lobes (73%).

# Heterogeneity analysis



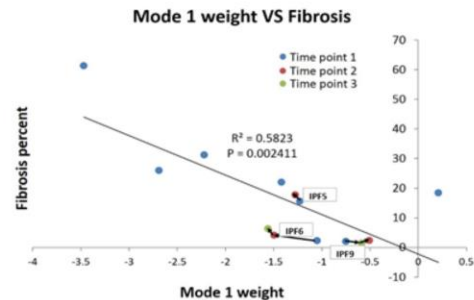
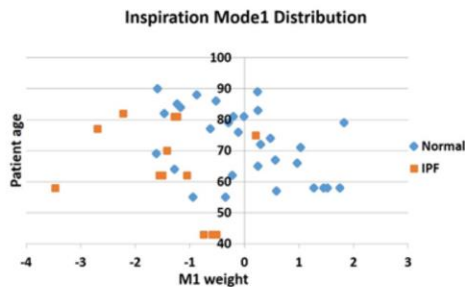
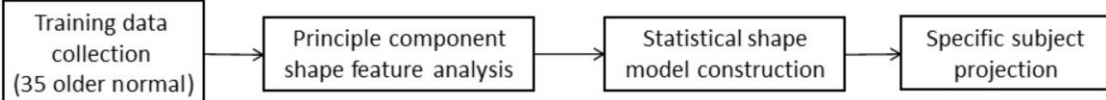
3D grid density visualization



- Fractal dimension for density: fitting a straight line for the relationship between coefficient of variance (COV) and sampling window size.
- $FD = 1 - \text{gradient of log-log curve}$
- Heterogeneity is relatively constant over time.

Next, we used fractal dimension as a measurement to analyze the heterogeneity of IPF lungs. A straight line is fitted to build a relationship between the coefficient of variance of density and the sampling window size. The fractal dimension equals to 1 minus the gradient of the fitted line. As we can see from the result, although the spatial position and percentage of abnormalities keep changing all the time, the heterogeneity seems not change too much with the development of the disease.

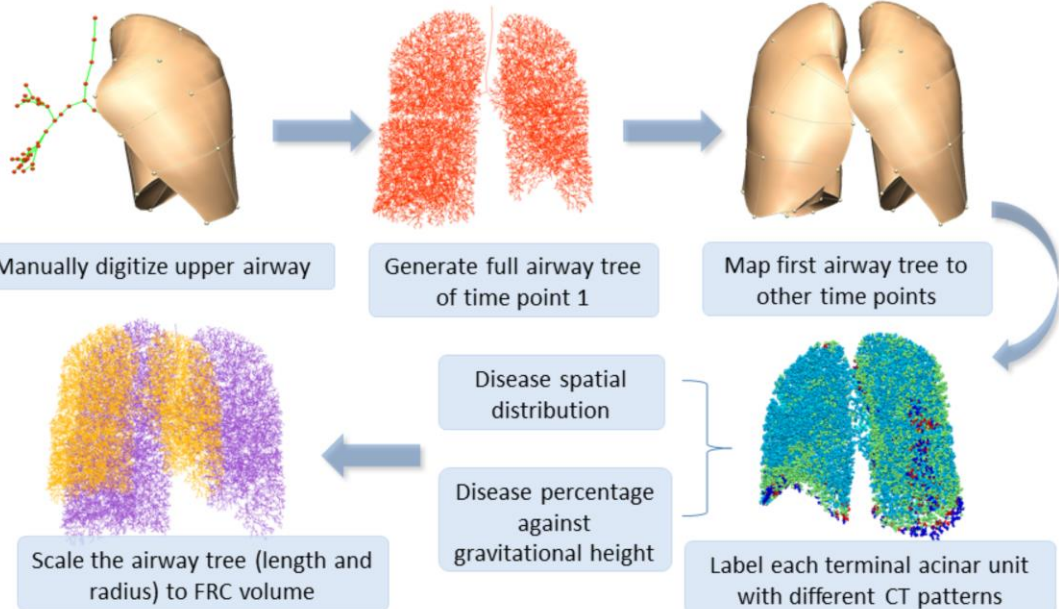
# SSM based shape analysis



- The first principal SSM mode relates to the anteroposterior diameter of the lung, and the ratio of apical and basal diameters
- The first principal SSM mode (>20% of the shape variation in normal lungs) is significantly different between IPF and normal .
- For IPF subjects, the first mode has a strong relationship with fibrosis percent.

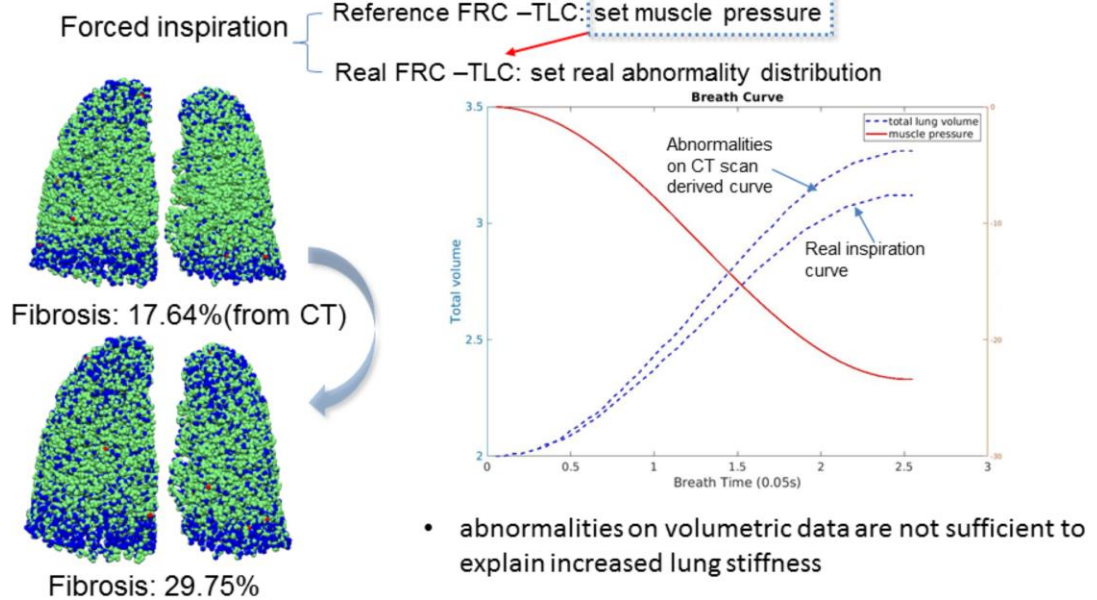
Next, we compared the IPF lung shape to the old normal ones. In order to analyze the lung shape difference, we also used the PCA-based SSM which is constructed using the same way as we introduced previously. The only difference is here we used 35 old normal subjects as the training set. By making use of PCA analysis, we are able to decompose lung shape into a set of mode, each mode represents a kind of shape variation. Here, we projected each IPF lung to the SSM, so that we can get the weight value for each mode. We found that there is a significant difference of the first mode between IPF lungs and old normal lungs. The first mode captures over 20% of the entire shape variation, it mainly describes the change of the anteroposterior diameter of the lung, and the ratio of apical and basal diameters. Also, there is a strong relationship between the first mode and the fibrosis percentage. That means with the progression of IPF, the abnormalities could cause a shape change of lung, and this kind of change has a relationship with the fibrosis overall percent.

## IPF patient-specific airway tree geometry



In the next stage, our work is to use the previous quantitative CT based analysis on our computational models. Before that, a patient-specific airway tree geometry is needed. Firstly, the upper airway tree was manually digitized. Then, generate full airway tree of the first time point, map this airway tree to the lung volume mesh of other time points. Next, the airway tree terminal acinar unit was labelled with different CT disease patterns. After that, scale the airway tree, from image volume to its FRC volume.

## IPF patient-specific ventilation analysis

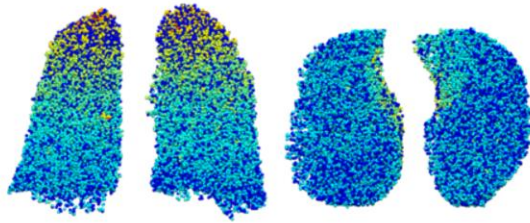


With the labelled and scaled airway geometry, we used our ventilation model to simulate forced inspiration from FRC to TLC. Simulate forced inspiration from reference normal FRC to TLC to set a driven muscle pressure, then use this muscle pressure to drive the disease forced inspiration on real FRC to TLC. Here, we decreased the compliance of the disease labelled acinar unit into a very small value, in order to make sure the disease region is stiff enough. We found, for most subjects, the fibrosis area extracted from CT image is not sufficient to match the real inspiration curve. There must be some tissue become stiffer on CT “normal” regions.

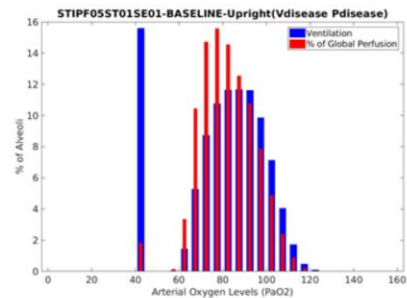
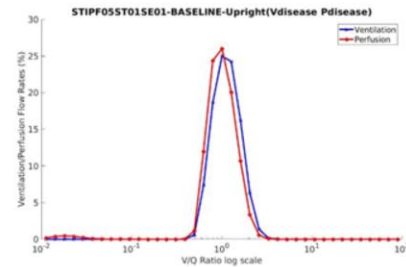
## IPF patient-specific gas exchange analysis

### Perfusion analysis:

- parameterize the model inputs
- generate vessel geometry
- reduce the vessel radius of disease labelled region



V/Q ratio distribution



For the patient-specific perfusion analysis, we generated the full vessel tree matching and surrounding by the airway tree. The vessel radius of the disease labelled region were decreased so that we can get a reduced perfusion of the abnormal regions. Using the ventilation and perfusion as input of the gas exchange model, we can get a V/Q ration distribution of IPF patient. We can observe from the result that V/Q mismatching could occur not only around the disease location but also happen on normal region. Currently we are still working on this part, more factor need to be taken into consideration, which leads to our future work.



## Future work

- Transfer factor: alveolar-capillary membrane area, thickness
- Forced expiratory model combined with FEV1, FVC results
- Tissue mechanical model combined with density and shape analysis results
- Predict IPF development at an early stage

In the next stage, we may take the transfer factor into consideration. As for emphysema regions, the alveolar-capillary membrane has a larger area, for fibrosis tissues, the membrane thickness will become bigger, both of them will influence the transfer factor. We also plan to use more PFT data to parameterize our model, e.g. use FEV1 and FVC value to parameterize the forced expiratory model. And use the density and shape analysis results on our tissue mechanical model to analyze the stress distribution of IPF lungs. Our further goal is to integrate all the analysis to make a prediction of IPF progression at an early stage in order to help with a clinical treatment.

# Thank you



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