Enhanced subgroup identification in heterogeneous clinical courses of disease burden using a machine learning score from CT images

HTA session on Monday, June 17, from 15:15 to 16:30

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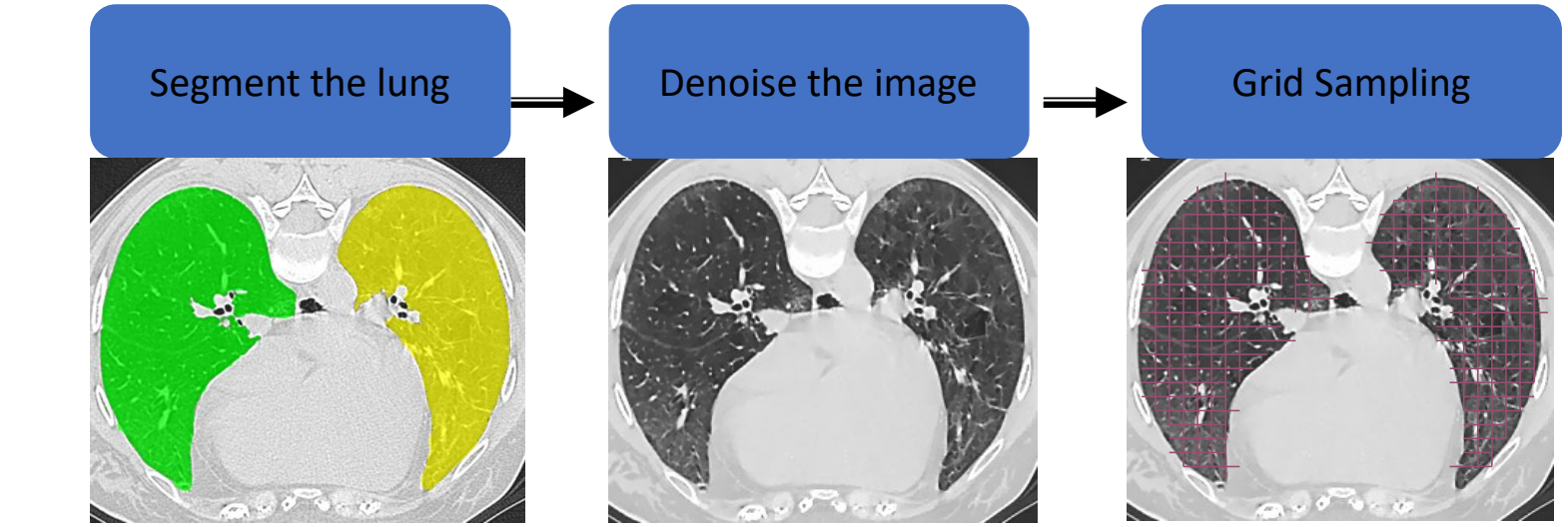
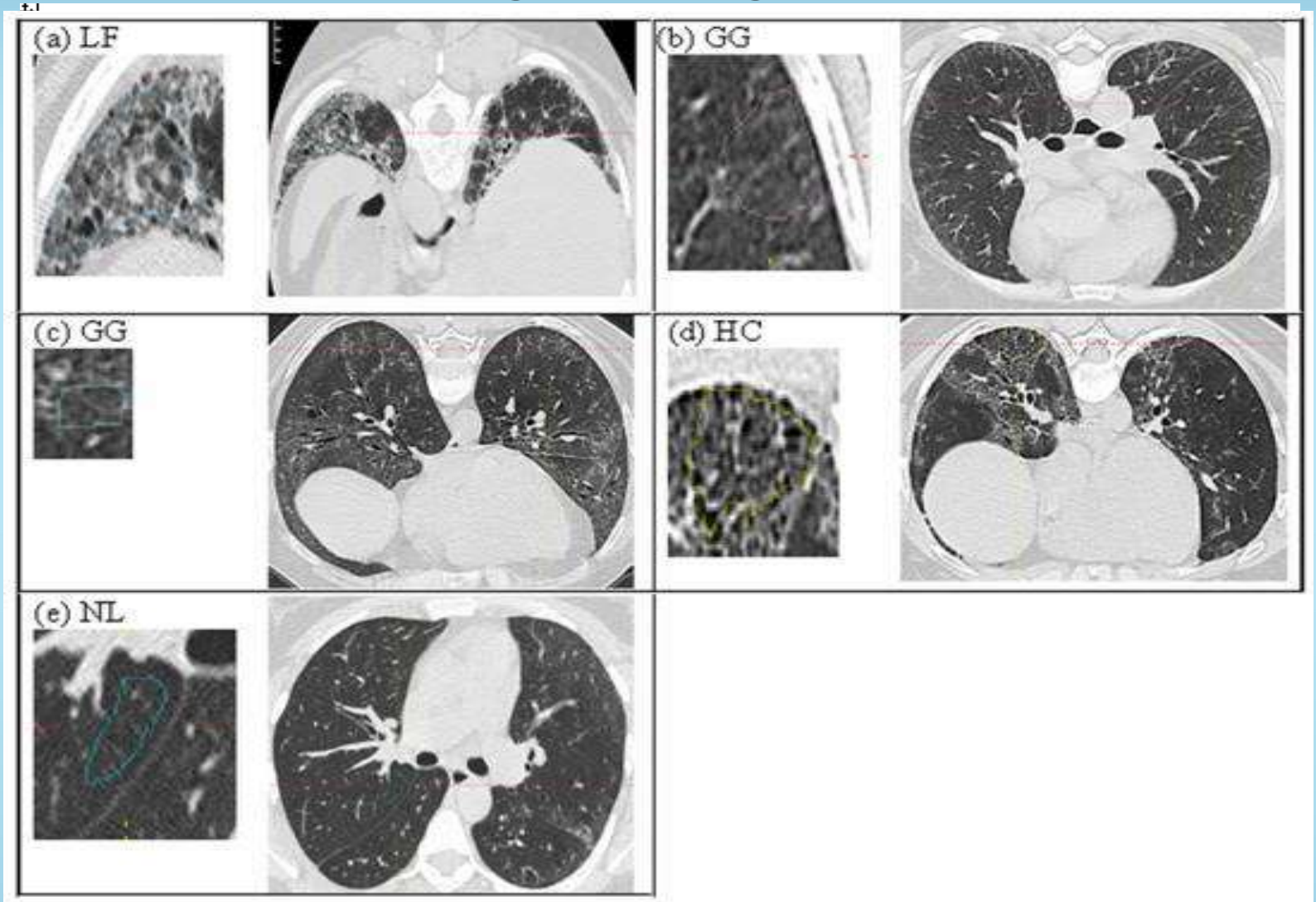
Background

- Quantitative lung fibrosis (QLF) score has been developed using non-contrast computed tomography (CT) by applying machine-learning (ML) algorithm with AUC=0.96
- The performance QLF score has been evaluated in clinical trials as a secondary or an exploratory endpoint
- However, the study visits of a clinical trial have the pre-specified visits to evaluate a study drug. Scans from clinical care/ real-world CT are used to test patient's response after initiating a new therapy or confirmation of worsening.

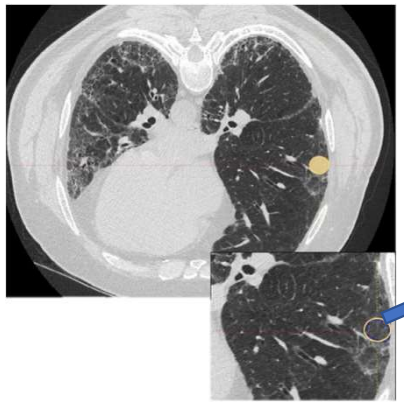
1. One Pipeline: Automated Fibrosis Classifier & Quantitative Lung Fibrosis (QLF) Score: *starts from 30 slices, now 300 slices, large cohorts, need to be faster*



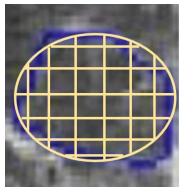
Denoised vs. Original Images



Radiomics (texture)



Window



Texture features calculation within a window (e.g. 12x12x12 for isotropic)

Convert to numerical dimension

- Histogram,
- Co-occurrence Matrix
- Run-Length Parameter
- Wavelet ..

Texture Feature calculation

energy	entropy	glcm_angl	glcm_angl	glcm_angl
5.865164	5.865164	0.015947	0.015165	0.017486
5.96621	5.96621	0.016151	0.014928	0.014076
5.363856	5.363856	0.024337	0.020833	0.020381
6.259505	6.259505	0.021769	0.019788	0.01808
6.386632	6.386632	0.017119	0.014879	0.015049
5.948896	5.948896	0.024202	0.018066	0.020272
5.753963	5.753963	0.022463	0.025277	0.021039
6.019739	6.019739	0.009215	0.0087	0.00785
5.753221	5.753221	0.010774	0.009624	0.009802
5.480691	5.480691	0.011027	0.013646	0.012877
5.858508	5.858508	0.010633	0.009141	0.009072
5.673742	5.673742	0.013358	0.010413	0.012204
5.405142	5.405142	0.015348	0.014205	0.01325
5.296464	5.296464	0.014323	0.014375	0.015625

Classification

Example) Co-occurrence Matrix: within a window, set a categorical level (bin size) of HU intensities and generate co-occurrence matrix (P). Here, HU intensities were set to 4 levels and P was generated for predetermined 0° with distance 1.

3	0	1	1
0	0	1	1
0	2	2	2
2	2	3	3

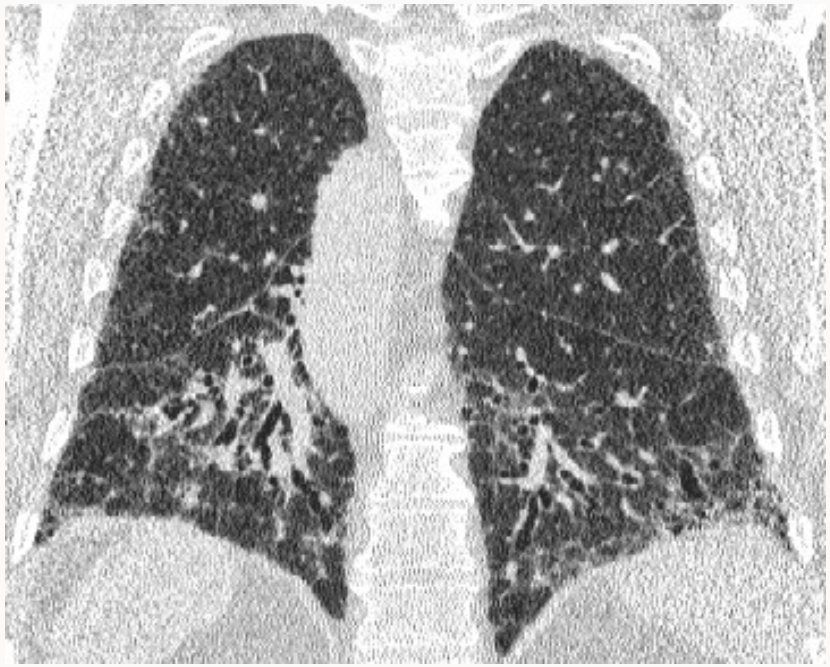
$$P_{0^\circ,1} = \begin{pmatrix} p(0,0) & p(0,1) & p(0,2) & p(0,3) \\ p(1,0) & p(1,1) & p(1,2) & p(1,3) \\ p(2,0) & p(2,1) & p(2,2) & p(2,3) \\ p(3,0) & p(3,1) & p(3,2) & p(3,3) \end{pmatrix} = \frac{1}{12}\begin{pmatrix} 1 & 2 & 1 & 0 \\ 0 & 2 & 0 & 0 \\ 0 & 0 & 3 & 1 \\ 1 & 0 & 0 & 1 \end{pmatrix}$$

$$Angular\ \ Second\ \ Moment: \quad f_1 = \sum\sum\{p(i,j)\}^2$$

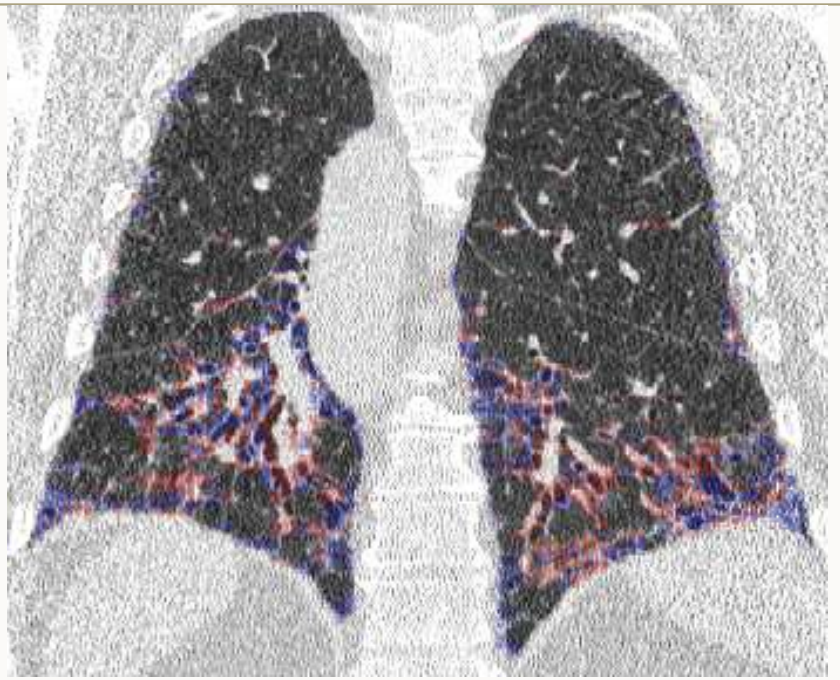
$$Entropy \quad : \quad f_9 = -\sum_i \sum_j p(i,j)\log\{p(i,j)\}.$$

$$Contrast: \quad \sum_i \sum_j (i-j)^2 p(i,j)$$

HRCT scans: QLF score

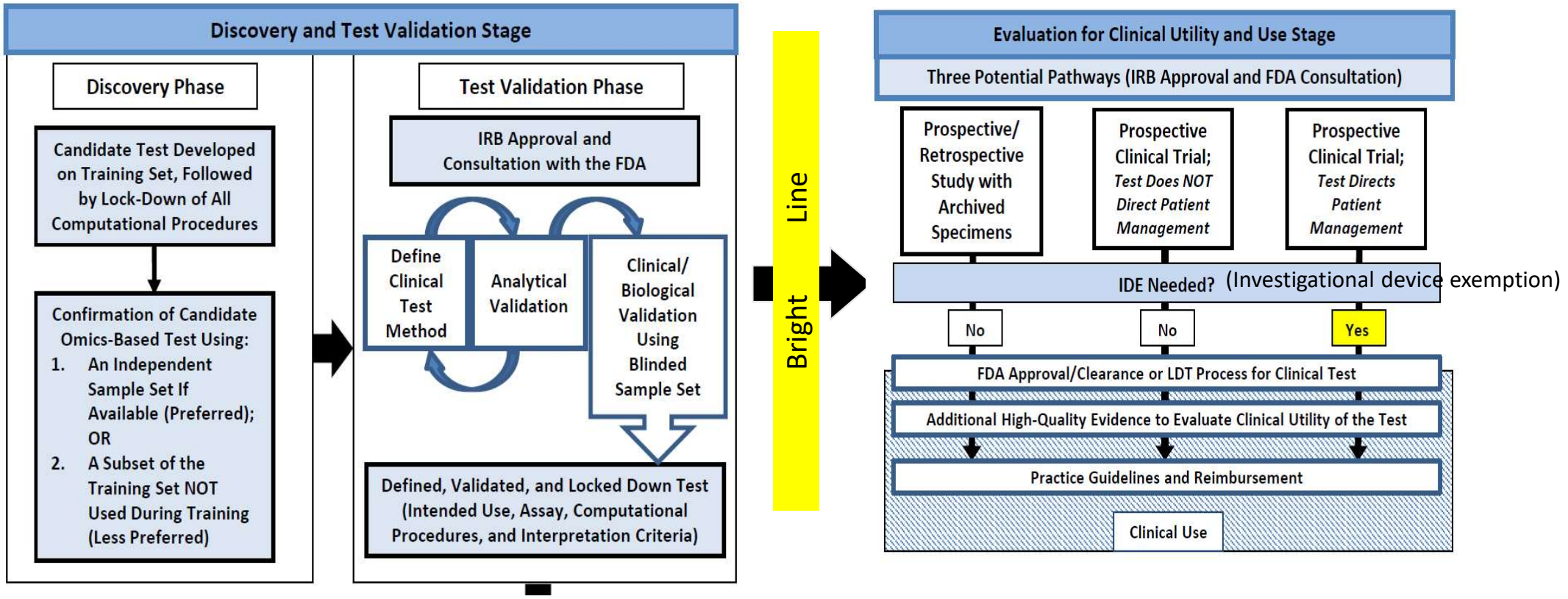


Coronal CT Image



QLF classifier: blue+ red dots

Omics-Based Test Development Process



Evolution of Translational OMICS lessons learned and the path forward (March 2012) by IOM (Institution of Medicine) report

Status of UCLA Quantitative Lung Fibrosis Scores

Discovery & Test Validation Stage

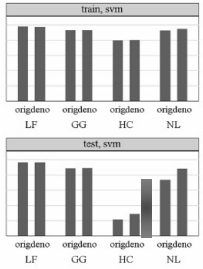
Discovery Phase

Table 1.0

Numbers	Patients	Contoured ROIs	Grid sample pixels
Training set	38+14*	148 (46 LF, 85 GG, 4 HC, 13 +74* NL)	5690 (3069 LF, 1994 GG, 348 HC, 339 +5991* NL)
Test set	33+14*	137 (44 LF, 77 GG, 4 HC, 12 +67* NL)	5045 (2665 LF, 1753 GG, 291 HC, 336 + 5638* NL)

ROI: Region of interests
* Data from Lung Image Data Consortium

(LF=lung fibrosis, GG=ground-glass, HC=honeycomb, NL=normal lung)



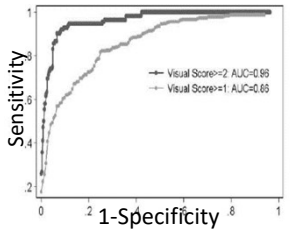
P<0.05

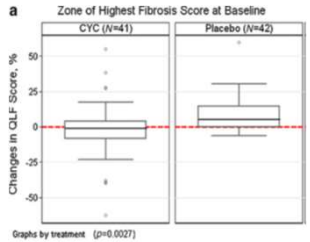
Active Learning in test set

Original: HC 0.735 (214/291)

Denoised : HC 0.701(204 /291)

Test Validation Phase





Kim et al. European Radiology 2011

Bright Line

Evaluation for Clinical Utility and Use Stage

Three Potential Pathways (IRB Approval & FDA Consultation)

2 phase 3 trials with 760 subjects, Study with Archived Specimens	8 Prospective Clinical Trial; Test Does Not Direct Patient Management	2 phase 2 (with visual override) Prospective Clinical Trial Direct Patient Management

IDE Needed?

No	No	Yes

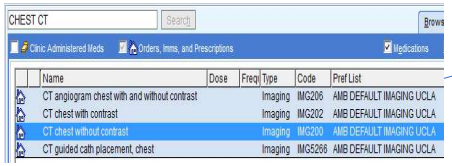
FDA Approval/Clearance or LDT Process for Clinical Trial

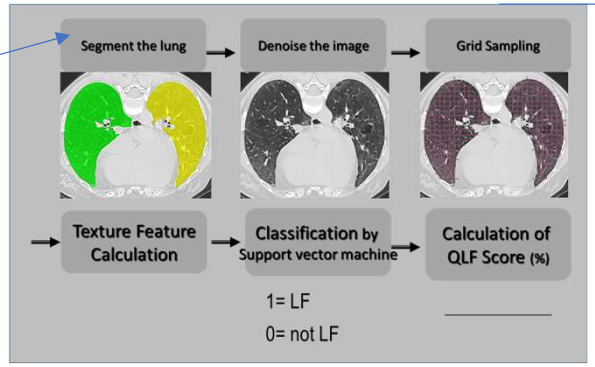
Additional High-Quality Evidence to Evaluate Clinical Utility of the Test

Practice Guidelines and Reimbursement

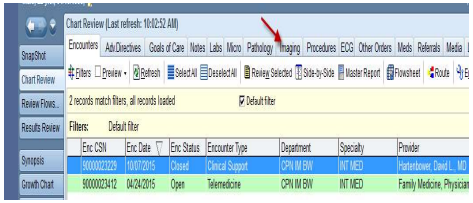
Clinical Use

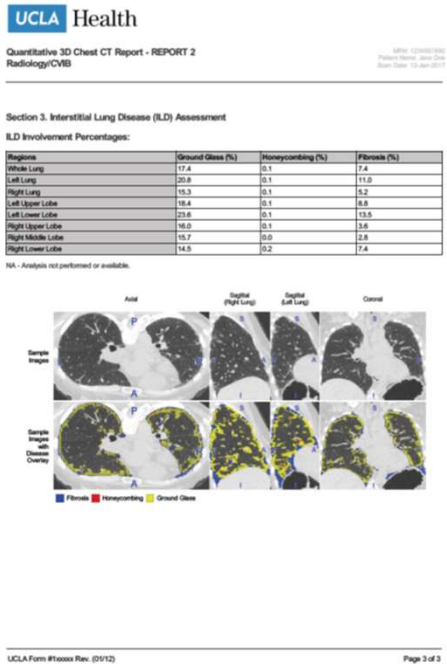
High-throughput : image QC/segmentation &=> Automated Fibrosis Classifier => Quantitative Lung Fibrosis (QLF) Score=> report: **Human in the loop**





reject /rerun





Approve

Modeling and its notation

1. $f(t) = e^{-dt} + e^{gt} - 1$

d represents a decrease pattern over time, ***g,*** represents an increase in QLF score, where initial decrease is followed by progressive increase.

2. $f(t) = (\phi)e^{-dt} + (1 - \phi)e^{gt}$

** When $\phi = 0$, this model is labeled as ***gx,*** and it describes consistent progressively increase pattern over time, with ***d*** being eliminated.

- ** When $\phi = 1$, this model is labeled as, with ***g*** being eliminated.

Examples) idiopathic inflammatory myopathy-associated interstitial lung disease: follow-up times are varied

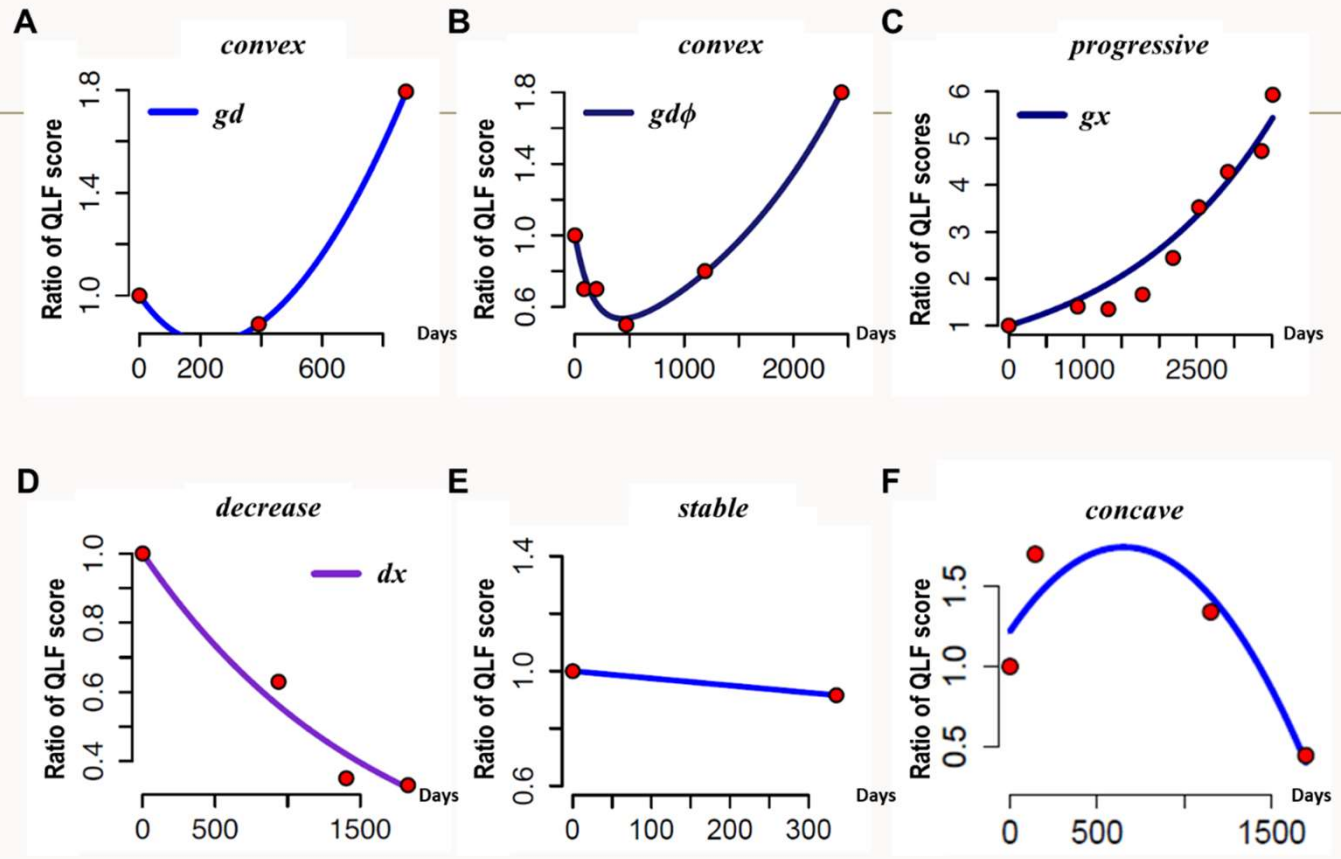
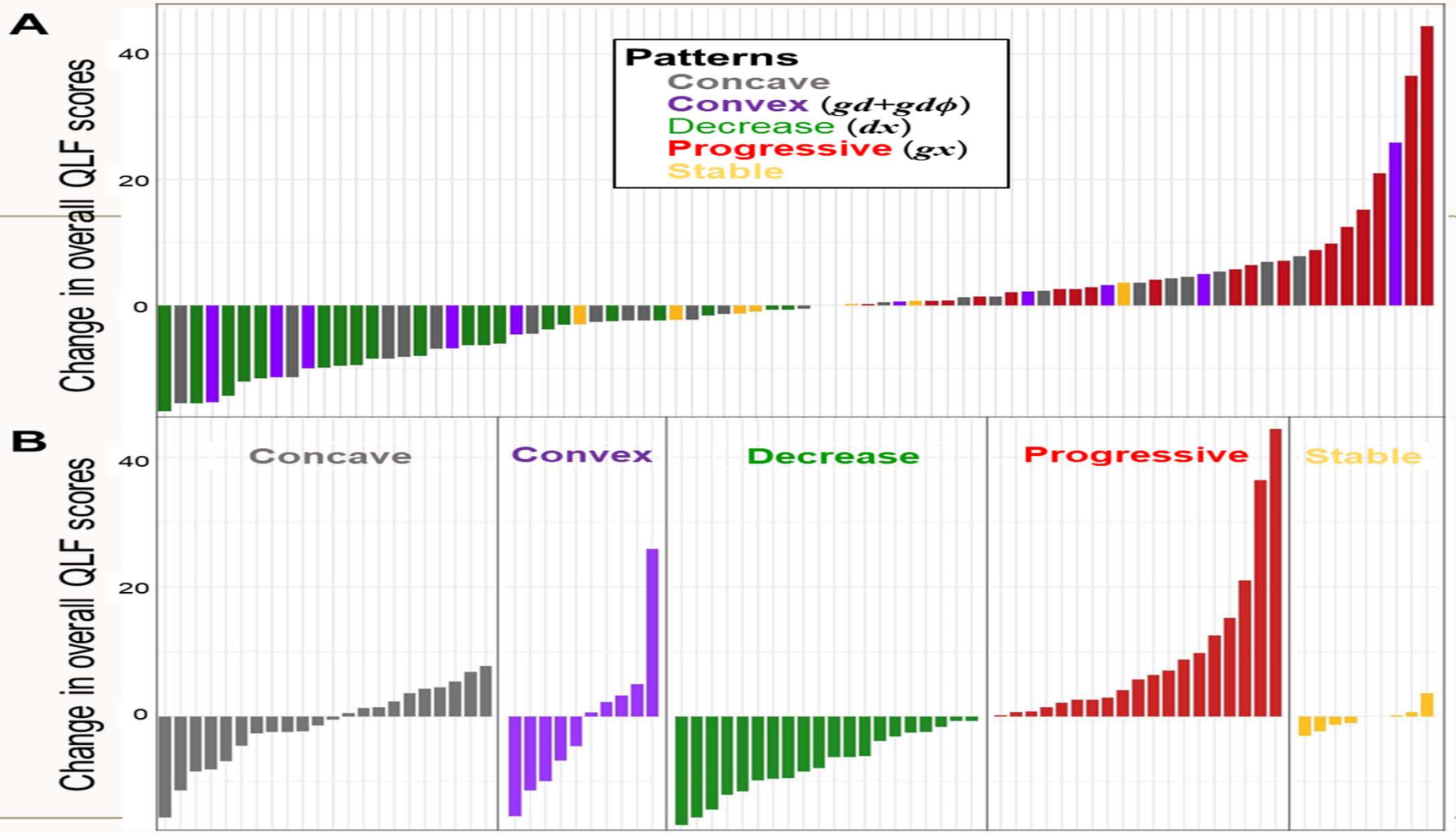


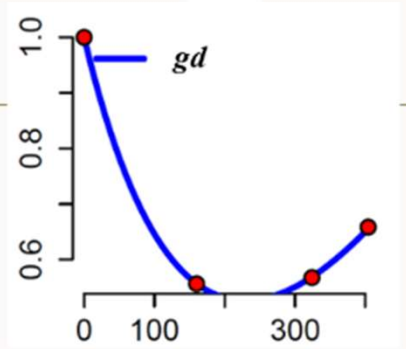
Table 1. Categorization of total subjects according to growth-rate model application

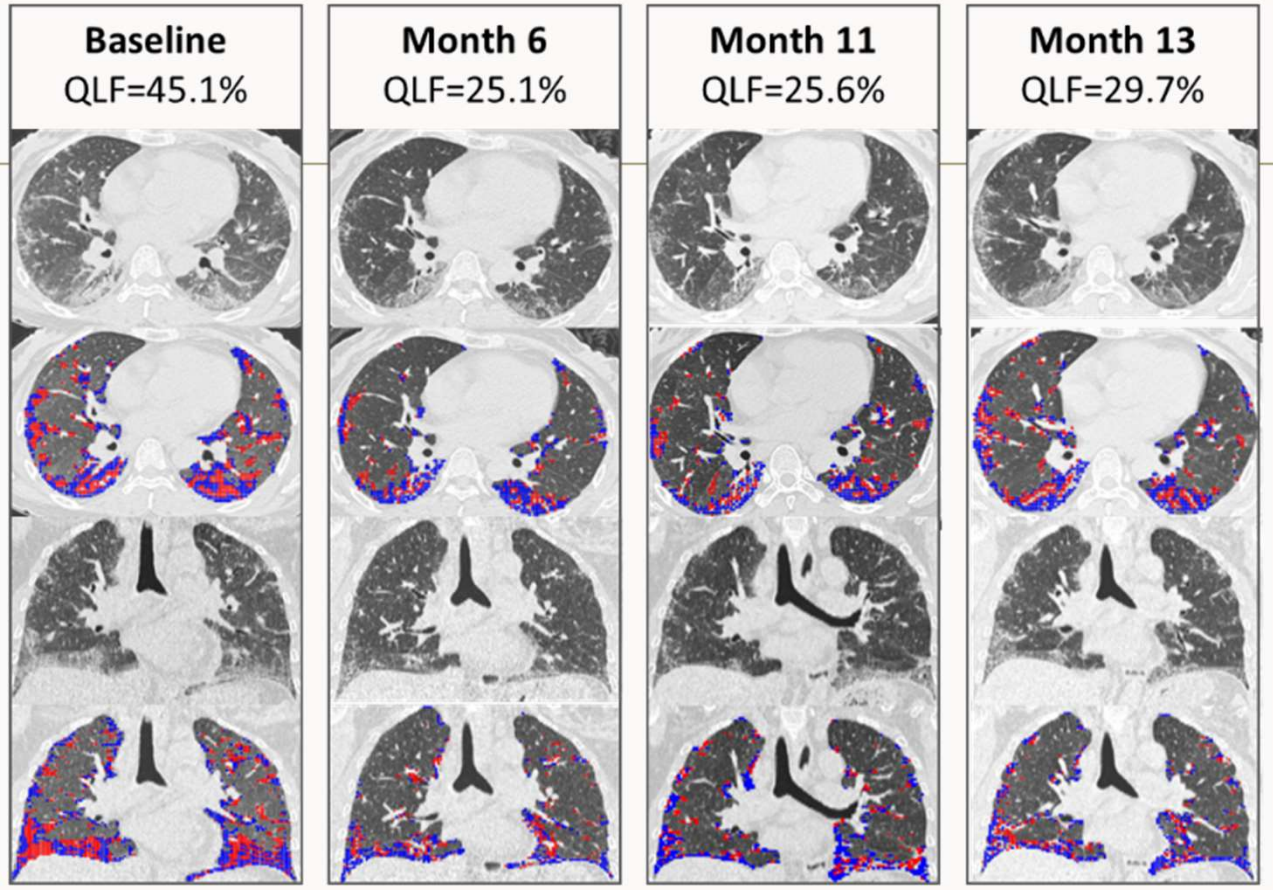
	Evaluable – Fitted			Evaluable – Not fitted by the AIC	Not evaluable by the model
Assigned patterns	**decrease** (*dx*)	**progressive** (*gx*)	**convex** (*gd* + *gdϕ*)	**concave**	**stable**
n (%)	20 (25.0)	19 (23.8)	10 (12.5)	22 (27.5)	9 (11.2)


A
Change in overall QLF scores
40
20
0
Patterns
Concave
Convex (gd+gdϕ)
Decrease (dx)
Progressive (gx)
Stable
B
Change in overall QLF scores
40
20
0
Concave
Convex
Decrease
Progressive
Stable

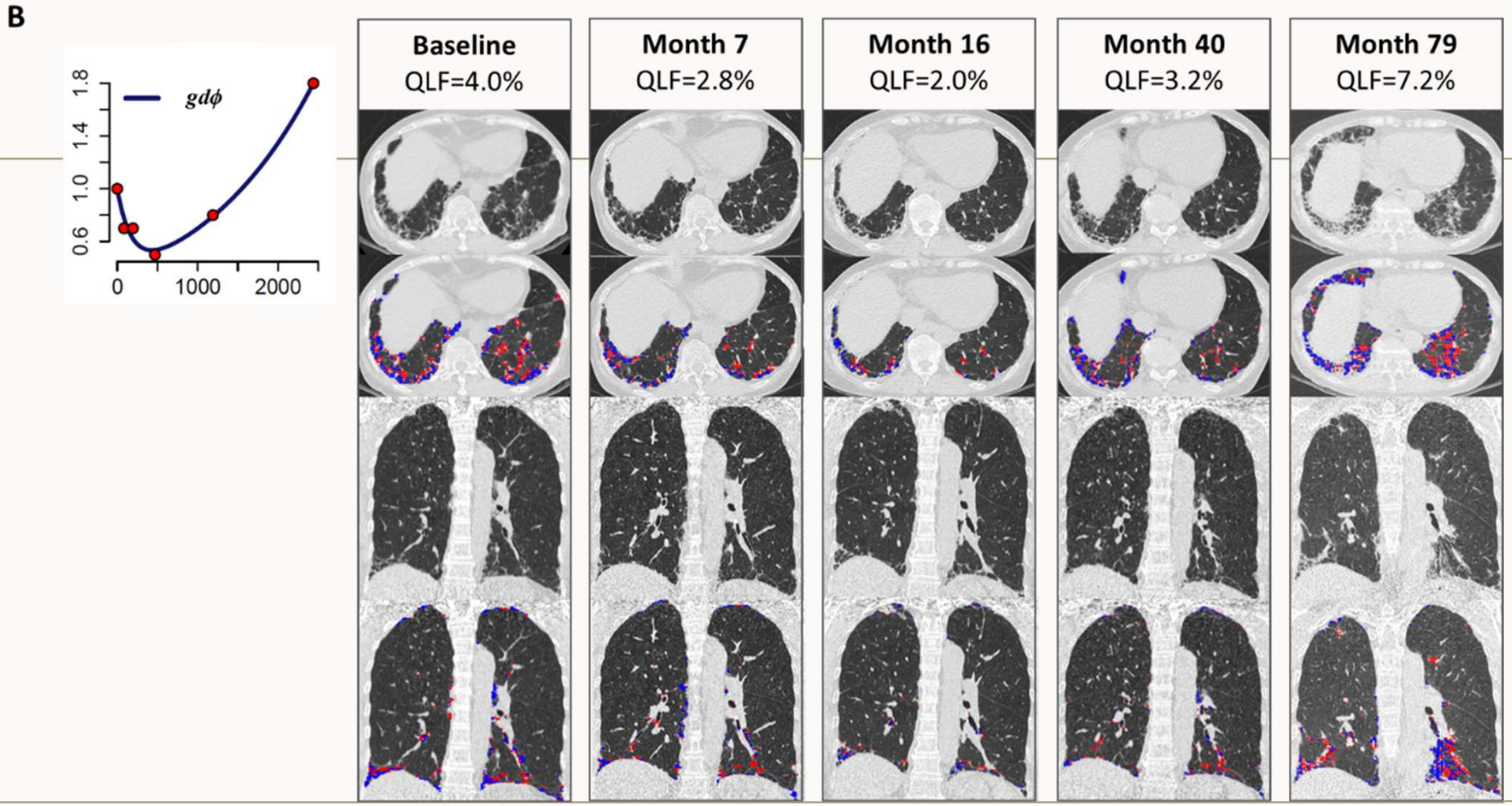
Longitudinal Changes

A





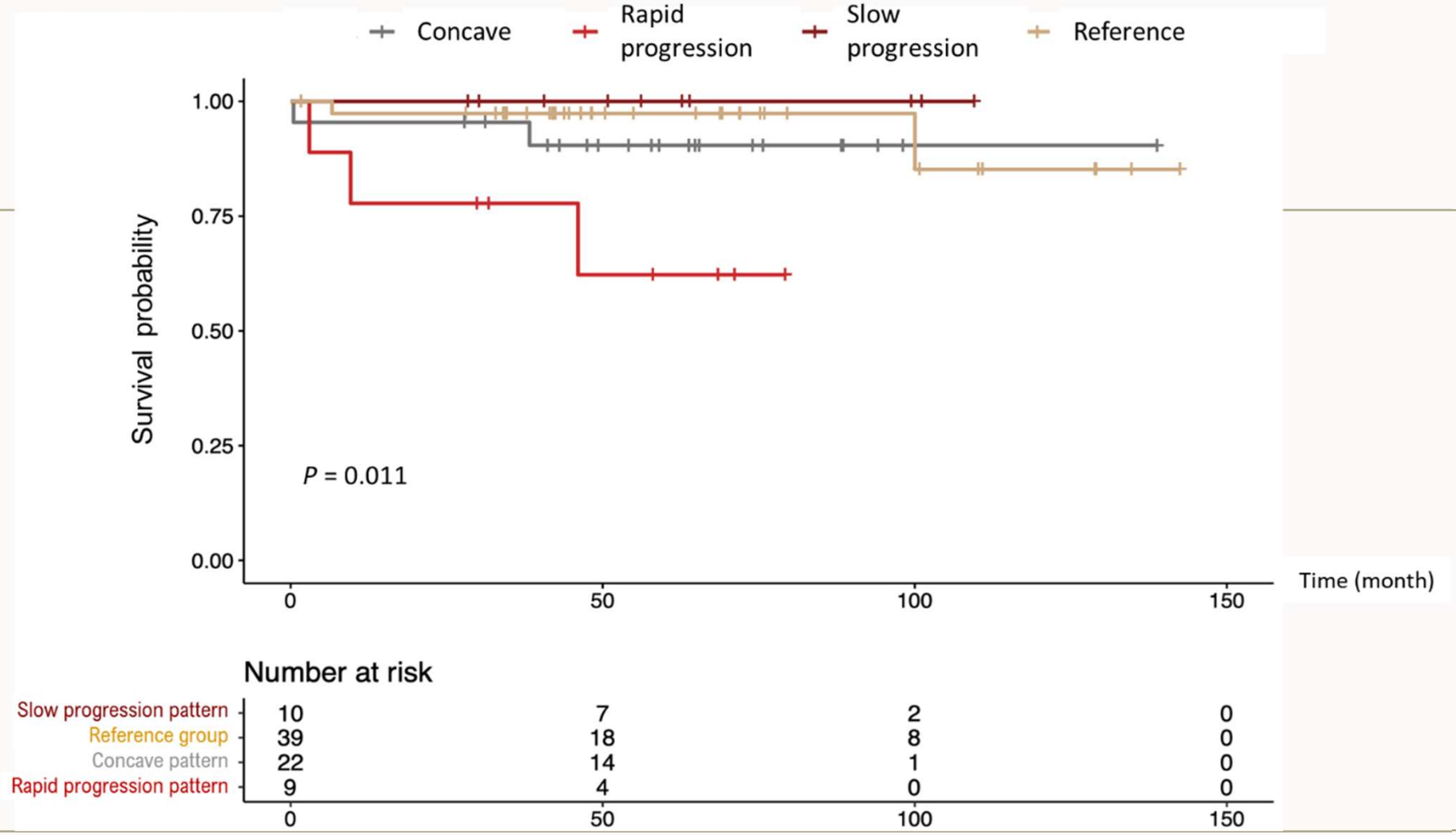
A:***gd***. The sum of red and blue dots represents lung fibrosis.



B: ***gdϕ***). The sum of red and blue dots represents lung fibrosis.

Cox proportional hazard regression analysis on mortality

Variables	Hazard Ratio	95% confidence interval	p-value
Age	1.052	0.968–1.169	0.253
ILD subtypes			
UIP	1.158	0.084–12.193	0.909
OP (organizing pneumonia)	0.376	0.027–2.801	0.365
NSIP and others	1	ref.	ref.
QLF (at landmark time)	1.042	0.981–1.109	0.162
Pattern groups			
Rapid progression†	**15.926**	**1.079–548.324**	**0.043**
Slow progression†	0.447	0.002–9.018	0.644
Concave	2.134	0.239–28.755	0.495
Reference*	1	ref.	ref.
Treatment group			
Intensive immunosuppression	2.385	0.398–15.864	0.337
Not intensive immunosuppression	1	ref.	ref.



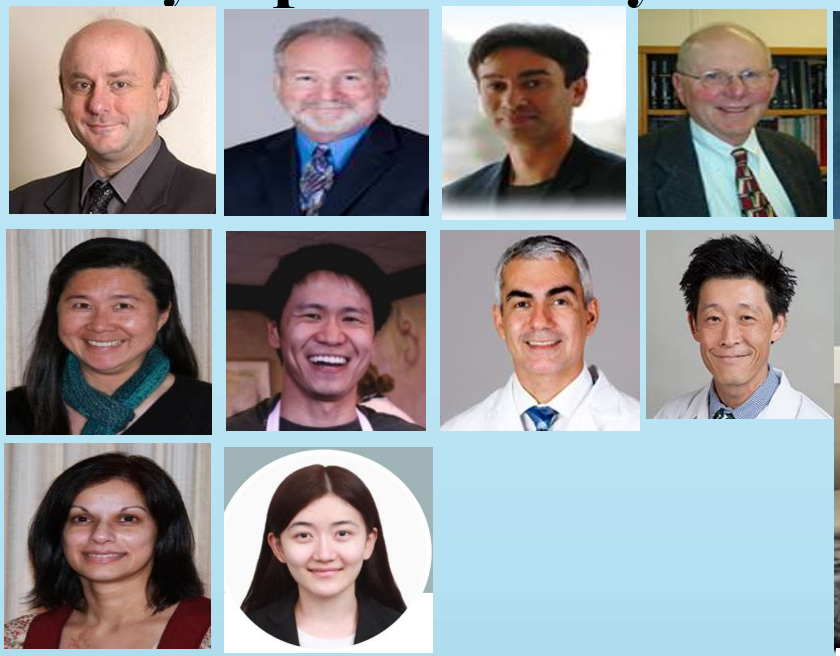
Kaplan-Meier survival plots demonstrating the probability of survival according to redefined four pattern groups.

Conclusion/Summary

- Growth-rate model can be practical approach, revealing five distinct patterns over time that substantiate the dynamic changes.
- By the pattern groups, characterizing and estimating a progression rate (***g***) is feasible
- Easy interpretation of complex data for the disease course, potentially contributing to more personalized treatment strategies and improved patient care.

Discussion

- Future research with larger datasets and adopting prospective registry may provide firm evidence for the efficacy of our approach and expand upon our findings.

Thank you

- **UCLA CVIB group, CTD-ILD for supporting this study. Special thank you Jiahao Tian, You-Jung Ha**