Genomic Classifier for Usual Interstitial Pneumonia Predicts Progression in Fibrotic Lung Disease Across a Range of Clinical Diagnoses

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RATIONALE

Fibrotic interstitial lung disease (ILD) is a heterogeneous group of diseases, the most common of which is idiopathic pulmonary fibrosis (IPF), a disease characterized by histologic features of usual interstitial pneumonia (UIP). Other fibrotic lung diseases can have pathologic UIP, and this is typically associated with progressive disease. The Genomic Classifier for UIP (GC UIP) (Envisia, Veracyte, Inc.) is a test that uses gene expression data in samples obtained by transbronchial lung biopsy (TBBx) to identify a genomic signature of UIP. The training of the classifier utilized advanced machine learning with the goal of optimizing specificity for pathologic UIP, and it was clinically validated in several independent cohorts. A recent meta-analysis (Kheir, et al. Ann Am Thorac Soc. 2022;19(5):827-32) showed an aggregate sensitivity of 68% (95% CI, 55-73%) and a specificity of 92% (95% CI, 81-95%). We hypothesized that a GC UIP(+) result would predict disease progression in patients with and without a clinical diagnosis of IPF.

METHODS

This was a retrospective analysis of data from patients enrolled in the BRAVE study in which patients were undergoing an evaluation for ILD and had samples obtained by clinically-indicated biopsy (surgical, cryobiopsy, or TBBx) as part of their clinical workup. Patients were included in this analysis if they had a baseline Forced Vital Capacity Percent of Predicted (FVC%) measurement collected within six months of enrollment and a follow-up FVC% approximately 12 months after their baseline FVC%. Data were collected on antifibrotic use and the treating physician's clinical diagnosis at the time of the follow-up FVC%. Physicians were blinded to the Envisia result. Statistical analyses were performed in R (version 4.1.3, https://www.r-project.org).

RESULTS

135 patients were eligible for this analysis. 73 (54%) were GC UIP(+) and 62 (46%) were GC UIP(-). Demographics, GC UIP result, absolute FVC% change over 12 months, and clinical diagnosis for both groups are shown in Table 1. Demographics were similar between groups except the GC UIP(+) group was significantly older. GC UIP(+) patients had a lower median baseline FVC% (64% vs 75%) and greater decline over one year (3% decline vs. 1% increase, p = 0.03) (Figure 1 and Table 2). The distribution of clinical diagnosis is also shown in Table 1. Patients with a GC UIP(+) result were more likely to have a clinical diagnosis of definite or probable IPF at 12 months (44% vs. 21%). The GC UIP(+) group also included patients with hypersensitivity pneumonitis (19%), nonspecific interstitial pneumonia (fibrotic, cellular, or mixed: 12%), connective tissue disease-associated ILD (4%), and unclassifiable (3%) (Table 1).

In both IPF and non-IPF subgroups, the GC UIP(+) group showed a greater 1-year decline relative to the GC UIP(-) group (Table 2 and Figure 2). GC UIP(+) patients diagnosed with IPF had a median FVC% decline of 2.5%, while GC UIP(-) patients diagnosed with IPF had a median FVC% increase of 7% (p=0.01). GC UIP(+) patients receiving a non-IPF or unclassifiable diagnosis had a median FVC% decline of 3%, while GC UIP(-) patients receiving a non-IPF or unclassifiable diagnosis had no change in the median FVC% predicted over the one-year duration (p=0.17).

TABLE 1
Demographic characteristics of study cohort by GC result.

	GC UIP(+), N = 73[1]	GC UIP(-), N = 62[1]	p-value[2]
Age	67 (61, 73)	64 (56, 70)	0.03
Sex			0.2
Female	29 (40%)	32 (52%)	
Male	44 (60%)	30 (48%)	
Smoking history			0.2
Current	2 (2.7%)	6 (9.7%)	
Former	34 (47%)	29 (47%)	
Never	37 (51%)	26 (42%)	
Unknown	0 (0%)	1 (1.6%)	
Clinical diagnosis			0.005
Definite or probable IPF	32 (44%)	13 (21%)	
Non-IPF	41 (56%)	49 (79%)	
Hypersensitivity pneumonitis	14 (19%)	8 (13%)	
Connective tissue disease-associated ILD	3 (4.1%)	5 (8.1%)	
Nonspecific interstitial pneumonia	9 (12%)	9 (15%)	
Other	13 (18%)	22 (35%)	
Unclassifiable	2 (2.7%)	5 (8.1%)	
Antifibrotic			<0.001
No/not reported	46 (63%)	55 (89%)	
Yes	27 (37%)	7 (11%)	

TABLE 2
Multivariable linear regression modeling follow-up FVC% predicted.

Follow-up interval	362 (324, 404)	364 (314, 417)	>0.9
Baseline FVC%	64 (55, 78)	75 (60, 90)	0.02
Absolute change FVC%	-3 (-9, 2)	1 (-7, 5)	0.03
Change in FVC by clinical diagnosis			
IPF	-2.5 (-10, 3)	7 (-1, 11)	0.01
Non-IPF	-3 (-9, 2)	0 (-8, 4)	0.17

GC = Genomic Classifier
UIP = Usual Interstitial Pneumonia
FVC = Forced Vital Capacity

1. Median (IQR); n (%)
2. Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

FIGURE 1
Box plots of median change in FVC% predicted over one year in GC UIP(-) patients compared to GC UIP(+) patients.

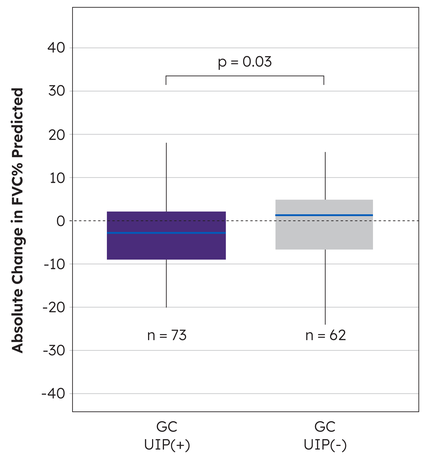
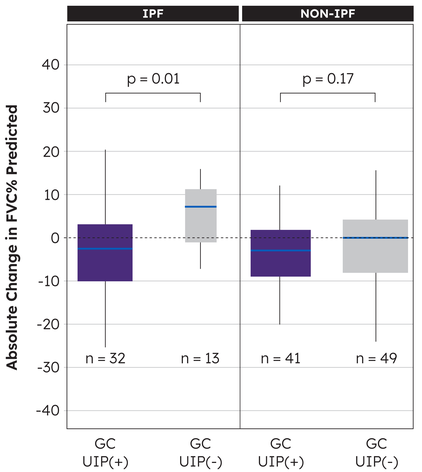


FIGURE 2
Box plots of median change in FVC% predicted over one year in GC UIP(-) patients compared to GC UIP(+) patients grouped by clinical diagnosis.



GC = Genomic Classifier
IPF = Idiopathic Pulmonary Fibrosis
UIP = Usual Interstitial Pneumonia

CONCLUSIONS

- The Genomic Classifier identifies the genomic signature of UIP in patients with fibrotic ILD across a range of clinical diagnoses in patients without definite UIP on HRCT.
- The Genomic Classifier may serve as a biomarker for absolute FVC% decline in patients with ILD across a range of clinical diagnoses. While the observed decline in FVC% is below the threshold of ≥ 5% used to define PPF for an individual patient in the recently updated guidelines, it meets the threshold for minimal clinically important difference for FVC decline in cohorts with fibrotic lung disease.[1,2]

References

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