A positive Envisia Genomic Classifier result may predict clinical progression in fibrotic interstitial lung disease

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PURPOSE

The Envisia Genomic Classifier (EGC) is a molecular diagnostic test that uses gene expression data in tissue samples obtained by transbronchial biopsy to identify a genomic signal of Usual Interstitial Pneumonia (UIP).[1] It was designed to optimize specificity in order to minimize false positive results. A recent systematic review and meta-analysis of the extant literature on EGC reported a pooled specificity of 92% and a sensitivity of 68%.[2] The test is used to aid in the diagnosis of Idiopathic Pulmonary Fibrosis (IPF) and other progressive fibrotic lung diseases with a UIP genomic signature. A positive result can obviate the need for more invasive pathologic sampling that might be considered for patients with suspected IPF or progressive fibrosis who lack a definite UIP pattern on high resolution CT imaging.[3] An EGC result can help inform an ILD multidisciplinary discussion with respect to diagnosis and prognosis and can guide choice of therapy.[4] We hypothesized that patients with an EGC (+) result would show a greater decline in forced vital capacity (FVC) over time compared to EGC (-) patients.

METHODS

Patients in the BRAVE study who underwent pathological evaluation for an undiagnosed ILD, had an EGC result, and had serial Forced Vital Capacity (FVC) testing were identified. Patients were required to have at least one FVC a minimum of six months after their baseline FVC. In patients with FVC measurements at multiple time points, the closest to 1-year follow-up was used for analysis. We performed a retrospective analysis of change in FVC percent predicted (FVC%) in patients with an EGC (+) result compared to those with and EGC (-) (i.e., Envisia non-UIP) result. As the BRAVE study collected pathology for all enrolled patients (surgical lung biopsy, transbronchial cryobiopsy, or transbronchial forceps biopsy), we further evaluated patients subcategorized by pathologic diagnosis (pathologic UIP, pathologic not-UIP, and pathology nondiagnostic) for each EGC result category.

RESULTS

135 patients met all inclusion criteria. The demographics of the cohort grouped by Envisia result are shown in Table 1. 73 of 135 (54%) of patients had an EGC (+) result, and 62 of 135 (46%) of patients had an EGC (-) result. EGC (+) patients were older (66 vs. 61 years, p=0.030); the two groups were otherwise demographically similar. Baseline, follow-up, and absolute change in FVC % predicted are shown in Table 2 and Figure 1. EGC (+) patients had a significantly lower mean baseline FVC compared to EGC (-) patients (66.9% predicted vs. 73.4% predicted, p=0.034) and a significantly lower follow-up FVC (63.2% predicted vs. 73.3% predicted, p=0.002). EGC (+) patients had a greater mean absolute change in FVC compared to EGC (-) patients (-3.7% predicted vs. -0.1% predicted) with borderline statistical significance (p=0.06). Findings were similar independent of pathologic result (Table 3 and Figure 2).

TABLE 1.
Demographics of the subset of patients with an EGC (-) result (n=62) compared to those with an EGC (+) result (n=73)

	Envisia Non-UIP N = 62[1]	Envisia UIP N = 73[1]	p-value[2]
Age	61 (13)	66 (9)	0.030
Sex			0.2
Female	32 (52%)	29 (40%)	
Male	30 (48%)	44 (60%)	
Race			0.4
Asian	1 (1.6%)	0 (0%)	
Black or African American	7 (11%)	4 (5.5%)	
Other	1 (1.6%)	1 (1.4%)	
White	53 (85%)	68 (93%)	
Antifibrotic			<0.001
No/Not Reported	55 (89%)	46 (63%)	
Yes	7 (11%)	27 (37%)	
Deceased	4 (6.5%)	7 (9.6%)	0.5
Received Transplant	0 (0%)	2 (2.7%)	0.5

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

TABLE 2.
Baseline, Follow-up, and Absolute change in FVC % predicted in the subset of patients with an EGC (-) result (n=62) compared to those with an EGC (+) result (n=73)

	Envisia Non-UIP, N = 62[1]	Envisia UIP, N = 73[1]	p-value
	Mean (SD)		Welch two sample t-test
Baseline FVC %	73.4 (18.4)	66.9 (16.4)	0.034
Follow-up FVC %	73.3 (18.9)	63.2 (17.8)	0.002
Absolute Change FVC %	-0.1 (11.2)	-3.7 (10.8)	0.064
	Median (IQR)		Wilcoxon rank sum test
Baseline FVC %	75 (60, 90)	64 (55, 78)	0.022
Follow-up FVC %	74 (60, 86)	61 (50, 73)	0.001
Absolute Change FVC %	1 (-7, 5)	-3 (-9, -2)	0.031

FIGURE 1.
Absolute change in FVC percent predicted in patients with an EGC (-) result (n=62) compared to those with an EGC (+) result (n=73) with data shown as box plot.

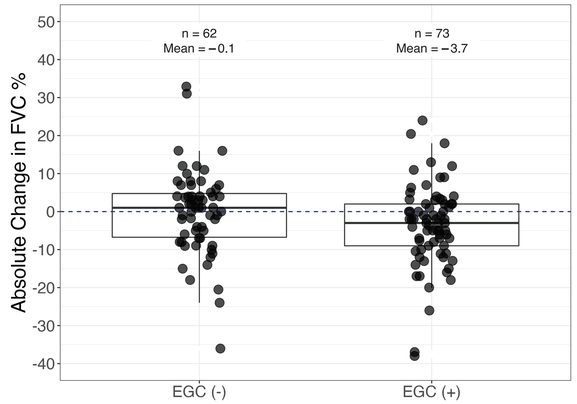


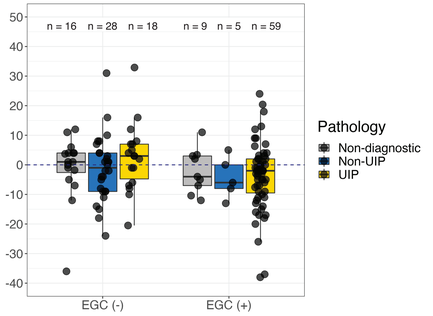
TABLE 3.
Median absolute change in FVC percent predicted in EGC (+) and EGC (-) patients grouped by pathology results.

Pathology = UIP	Envisia Result		
	EGC (+)	EGC (-)	p-value
Median Δ FVC % predicted	-2 (n=59)	3 (n=18)	0.03

Pathology = Non-UIP or Non-diagnostic	Envisia Result		
	EGC (+)	EGC (-)	p-value
Median Δ FVC % predicted	-4.5 (n=14)	0.5 (n=44)	0.4

1. Wilcoxon rank sum test

FIGURE 2.
Absolute change in FVC percent predicted in patients with an EGC (-) result (n=62) compared to those with an EGC (+) result (n=73) subcategorized by pathologic diagnosis.



CONCLUSIONS AND CLINICAL IMPLICATIONS

- An EGC (+) result may serve as a biomarker for FVC decline by identifying the genomic signature of UIP in some patients without definite UIP on CT.
- The finding that the decline in FVC seen in EGC (+) patients was independent of pathology may reflect that the genomic signature is closer to the basic biology of progression in patients with UIP than the histologic manifestations of those diseases.
- **Clinical Implications:** The Envisia Genomic Classifier could have utility in identifying patients with IPF and non-IPF progressive pulmonary fibrosis and underlying UIP earlier in their disease, allowing for aggressive therapy before significant, irreversible FVC loss.

References

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