Progression of interstitial lung disease after the Envisia Genomic Classifier

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Shareable abstract (@ERSpublications)
The Envisia Genomic Classifier, which gives a positive or negative genomic UIP designation based on RNA expression in ILD patients, is found to predict faster progression of interstitial lung disease, potentially greatly enhancing care of patients https://bit.ly/3XPC1Xk

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Abstract

Background Interstitial lung disease (ILD) represents a heterogenous group of diseases that have substantial morbidity and mortality. The Envisia Genomic Classifier (EGC) is a test that analyses RNA derived from transbronchial biopsy (TBBx) samples to make a positive or negative genomic usual interstitial pneumonitis (UIP) designation. Our study assesses the ability for the EGC to predict progression of disease, with a longer duration of follow-up than previous studies.

Methods Patients referred for cryobiopsy for outpatient workup of ILD concurrently had TBBx and EGC testing performed. We performed a retrospective analysis to assess differences in progression of disease between EGC-positive and negative patients, applying Kaplan–Meier survival analysis and log-rank tests. Confidence in ILD diagnosis before and after the EGC result was also noted, and the difference in confidence levels was assessed by a Wilcoxon signed-rank test.

Results 82 patient cases were analysed. EGC-positive patients had a shorter progression-free survival (PFS) than EGC-negative patients, ($p<0.0001$), with 622 *versus* 1487 median PFS days respectively. EGC-positive patients also had worse progression in the subsets of patients with "indeterminate for UIP" computed tomography (CT) ($p=0.0052$), "alternative diagnosis" CT ($p=0.0144$) and non-idiopathic pulmonary fibrosis ILD diagnosis ($p=0.0157$). Additionally, EGC increased the diagnostic confidence level ($p<0.0001$).

Conclusion EGC positivity predicts worse ILD progression over a sustained follow-up period. The ability to predict worse prediction early in the ILD course without the need for surgical biopsy would have significant clinical impact.

Introduction

Interstitial lung disease (ILD) is a heterogenous group of diffuse parenchymal lung diseases characterised by varying degrees of inflammation and fibrosis [1]. Differentiating between idiopathic pulmonary fibrosis (IPF) and non-IPF ILD is the first step in management, as this distinction impacts prognosis and treatment [2, 3]. Guidelines recommend the employment of a multidisciplinary team (MDT) discussion as the gold-standard approach to determining diagnosis and treatment [4]. The role of surgical lung biopsy (SLB) as a data point in MDT discussions is evolving, with fewer being performed due to advancements in imaging diagnosis and known risks associated with the procedure [5, 6], while remaining an important tool, especially in cases where the radiology result is indeterminate [7]. In 2022, updated clinical practice guidelines for the diagnosis of IPF were published and, for the first time, included lung cryobiopsy as a less-invasive alternative to SLB for ILD cases in which tissue biopsy is deemed necessary [8, 9]. It was

also concluded that there was insufficient evidence to make a recommendation for or against routine employment of genomic classification in the management of ILD [8].

Recent advances in the field of transcriptomics and genome sequencing have allowed for the development of a diverse array of next-generation techniques to augment radiographical and histological diagnosis. The Envisia Genomic Classifier (EGC) analyses gene expression from lung transbronchial biopsy (TBBx) samples to detect differential gene expression patterns consistent with usual interstitial pneumonitis (UIP) *versus* non-UIP histopathology. To develop the test, RNA sequencing was performed with TBBx samples from patients from whom SLBs were taken. An algorithm was trained to predict UIP based on the expression levels of 190 genes from the RNA samples [10, 11]. Genes involved in cell adhesion, muscle disease, cell migration, motility and profibrotic signalling were over-represented in the UIP profile, whereas genes involved in immunity were over-represented in the non-UIP profile [11]. The EGC was validated in the prospective multicentre BRAVE study, with a reported 86% agreement between MDT diagnosis incorporating EGC and MDT diagnosis incorporating histopathology [12]. Using the same cohort, Richeldi *et al*. [13] then demonstrated that a positive EGC result in concert with high-resolution CT (HRCT) improves ILD diagnosis without the need for SLB. Kheir *et al*. [14] reported that EGC testing increased diagnostic confidence in MDT cases in which cryobiopsies were performed. Lasky *et al*. [15] found that a positive EGC led to a significant increase in IPF diagnoses, diagnostic confidence and recommendation for antifibrotic therapies.

Two studies have assessed the ability of genomic classifier positivity to predict progression of ILD. Chaudhary *et al*. [16] reported on a multicentre cohort in whom a significant association between positive EGC and ILD progression was not found, with a maximum 18-month follow-up. In two subsets of patients, those with an "alternate diagnosis" HRCT result and those with eventual non-IPF ILD diagnosis, the authors did report worse progression in EGC-positive patients [16]. More recently, Kheir *et al*. [17] also found no significant difference in progression-free survival (PFS) when patients were grouped by EGC result, with a median follow-up between 10 and 20 months. Both studies did demonstrate a trend towards significance in a worse rate of progression for EGC-positive patients.

Here, we report on a large single-centre, quaternary referral ILD programme of the utility of EGC testing in augmenting clinical decision-making and patient outcomes for patients with ILD. We hypothesised not only that EGC classification would improve confidence in MDT diagnosis, but that the UIP transcriptomic profile would be associated with reduced PFS, compared with non-UIP genomic classification, if we had a longer patient follow-up duration than the previous studies.

Methods

Patient cohort

At the University of California, Los Angeles, 85 patients underwent outpatient cryobiopsy with concurrent EGC testing between 2018 and 2023. Three cases without accessible pre-biopsy pulmonary function testing (PFT) results were excluded from the analysis. Patients were referred for the procedures on an outpatient basis and deemed to require tissue as part of usual care of ILD. Institutional review board approval for collection of retrospective patient data was obtained (University of California, Los Angeles, CA, USA, IRB no. 19-000196).

Baseline forced vital capacity (FVC) and diffusion capacity of the lungs for carbon monoxide (D_{LCO}) performed within 6 months of biopsy were assessed. HRCT scans were read by two thoracic radiologists and marked as "probable UIP," "indeterminate for UIP" or "alternate diagnosis," as per the Fleischner Society criteria [18]. Lung cryobiopsy samples were read by a thoracic pathologist as "probable UIP," "indeterminate for UIP" or "alternate diagnosis" as per the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society guidelines [4].

After the MDT diagnosis was established, the ILD-GAP (gender–age–physiology) score (which in addition to the original GAP score components of patients' age, sex, FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) [19], assigns fewer points for non-IPF diagnoses due to their generally more-favourable prognosis [20]), could be calculated.

MDT diagnosis

A multidisciplinary group of physicians specialising in diagnosis and management of ILD, consisted of four pulmonologists, two thoracic radiologists and one thoracic pathologist reviewed the 82 cases to establish MDT diagnoses. The patients' clinical history, HRCT scan and lung cryobiopsy result were considered in establishing a diagnosis while blinded to the EGC result. Additionally, the group's

confidence level in diagnosis was recorded. The EGC result was subsequently unveiled, and the MDT process was repeated, thus establishing a post-EGC ILD diagnosis and level of confidence in diagnosis.

Progression/survival data

PFT and survival data were collected through 31 December 2023. We defined ILD progression as a relative decrease in FVC of 10% from the pre-biopsy baseline, lung transplantation or respiratory-related death. We defined respiratory-related death as a death in which the cause of death in the discharge summary from the patient's hospitalisation was of nonpulmonary aetiology. The earliest progression event was noted as the date of progression, and the number of days between the biopsy and the date of progression was calculated as PFS days. For patients who did not meet criteria for ILD progression as of the last clinical encounter and for patients with a nonrespiratory cause of death without previous FVC decline or lung transplantation, the subject was censored at the date of last clinical encounter.

Statistical analysis

Continuous data are described as median and interquartile range (IQR). Categorical data are described as proportions. To assess test performance, sensitivity, specificity, likelihood ratio, positive predictive value (PPV) and negative predictive value were calculated.

The primary objective of this study was to compare PFS in EGC-positive *versus* EGC-negative patients in the overall cohort of patients in whom EGC testing was performed, utilising Kaplan–Meier survival curves and log-rank test. We also explored PFS in subsets of interest. To assess for differences in PFS adjusted for ILD-GAP stage, we performed Cox proportional hazards regression. To assess the impact of EGC on the confidence of ILD diagnosis, we used the Wilcoxon signed-rank test to compare the confidence levels (low, medium or high) before and after unveiling the EGC result. We utilised Stata/MP (StataCorp, College Station, TX, USA) to perform the statistical analyses.

Results

Patient characteristics

Our cohort consisted of 82 total patients that had baseline PFTs and underwent concurrent cryobiopsy and EGC testing. The earliest EGC test with concurrent cryobiopsy was performed in April 2018, and the most recent EGC test with concurrent cryobiopsy performed was in March 2023, allowing for a potential range in duration of follow-up from 9 months to 5 years and 8 months (through 31 December 2023). The median duration of follow-up from the date of biopsy until the day of censor or progression event for the overall cohort was 690 (IQR 347–1202) days. For EGC-negative patients, the median follow-up was 923 (IQR 484–1284) days. For EGC-positive patients, the median follow-up was 475 (IQR 174–755) days.

75 of the 82 (91%) patients were GAP-ILD stage 1, 6 patients (7%) were GAP-ILD stage 2 and 1 patient (1.2%) was GAP-ILD stage 3 at the time of biopsy (table 1).

MDT diagnoses

Of the 82 total patients who had available EGC testing, 26 had a computed tomography (CT) diagnosis of "indeterminate for UIP," 39 had a CT diagnosis of "alternative diagnosis" and 17 had a CT diagnosis of "probable UIP." 32 had a cryobiopsy result of "indeterminate for UIP," 34 had a cryobiopsy result of "alternate diagnosis," 15 had a cryobiopsy result of "probable UIP" and 1 had a cryobiopsy result of

TABLE 1 Patient characteristics of subjects referred for concurrent cryobiopsy and EGC testing and included in the analysis

Variable	n=82
Age, years	63±10
Family history of ILD	10 (12.2)
Airborne exposure	27 (32.9)
Positive rheumatological serologies	27 (32.9)
Smoking history	28 (34.1)
ILD-GAP stage 1	75 (91.5)
ILD-GAP stage 2	6 (7.3)
ILD-GAP stage 3	1 (1.2)

Data are presented as mean±SD or n (%). EGC: Envisia Genomic Classifier; ILD: interstitial lung disease; GAP: gender–age–physiology.

"UIP." Final MDT diagnoses considering the EGC result were 23 IPF (28.1%), 49 alternate diagnosis (59.8%) and 10 unclassifiable ILD (12.2%). A modified Sankey diagram illustrates the proportions of results for the radiology, pathology, EGC testing and final MDT diagnosis (figure 1).

EGC association with progression-free survival

For the complete cohort of 82 patients, EGC positivity was associated with worse PFS (p<0.0001) compared with EGC negativity (figure 2). EGC-negative patients did not reach a median PFS days at 1487 days, whereas EGC-positive patients had 622 median PFS days. We also substituted all-cause mortality for respiratory death, and EGC remained significantly associated with PFS (p=0.0001) (supplementary figure 1).

We then analysed the impact of EGC on survival in two subsets in which a lung biopsy would typically be considered supportive in determining an ILD diagnosis and hence adjunctive genomic classifier testing may be considered: (1) patients with "indeterminate for UIP" HRCT result (n=26) and (2) patients with an "alternative diagnosis" HRCT result (n=39) (figure 3). For patients with indeterminate HRCT, EGC positivity was associated with worse PFS (p=0.0052), 1629 PFS days for EGC-positive patients, *versus* no median reached for EGC-negative patients. For the subset of patients with alternative diagnosis on HRCT, EGC positivity was also associated with worse PFS (p=0.0144) with 626 median days, whereas EGC-negative patients did not reach the median as of 1487 days.

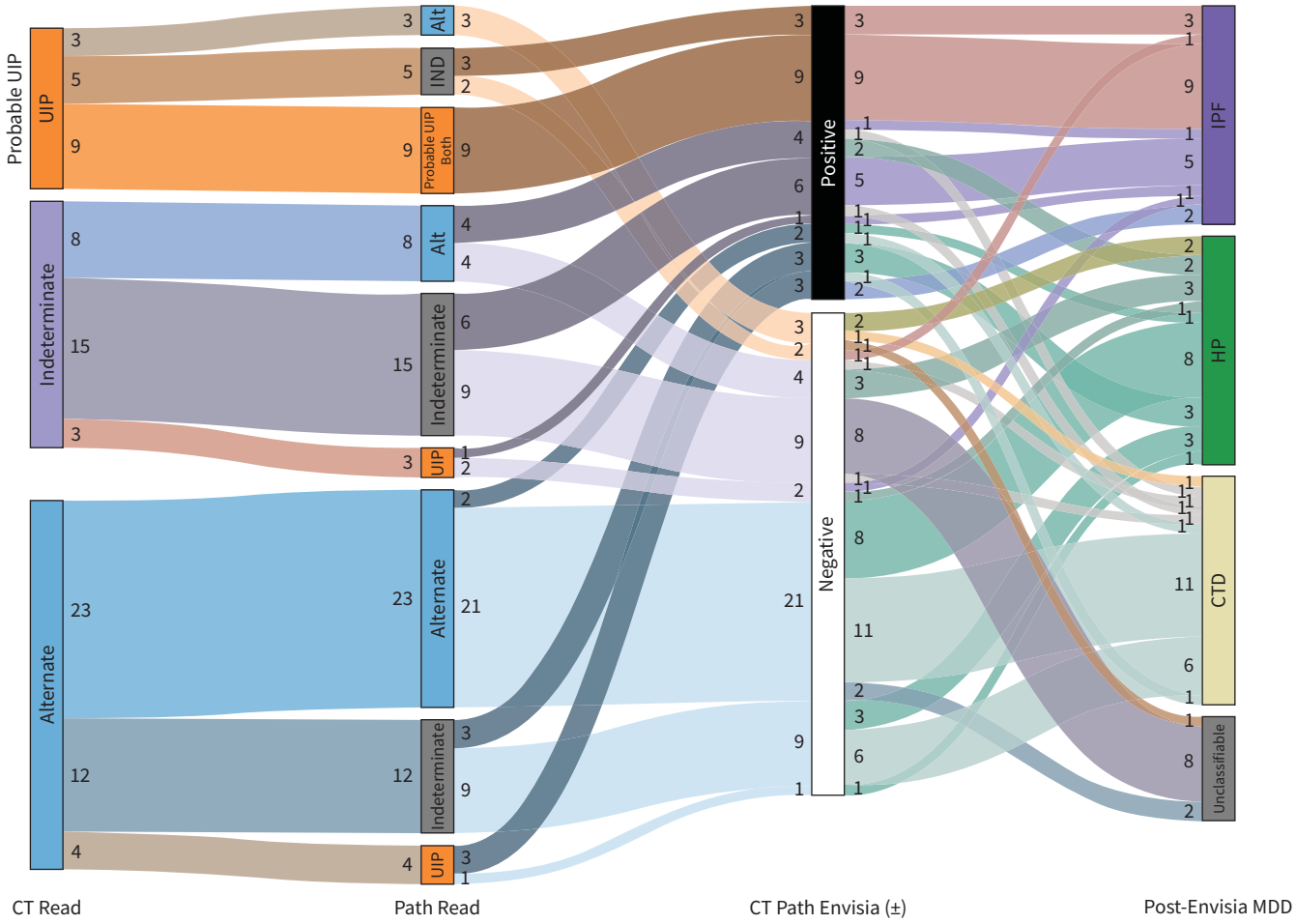

FIGURE 1 Modified Sankey diagram illustrates the numbers of patients with each high-resolution computed tomography (CT) result in the first column, each patient's cryobiopsy result in the second column, then the genomic classifier result, and finally their multidisciplinary team diagnosis. UIP: usual interstitial pneumonitis; Alt: alternate; IND: indeterminate; CTD: connective tissue disease; HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; MDD: multidisciplinary discussion.

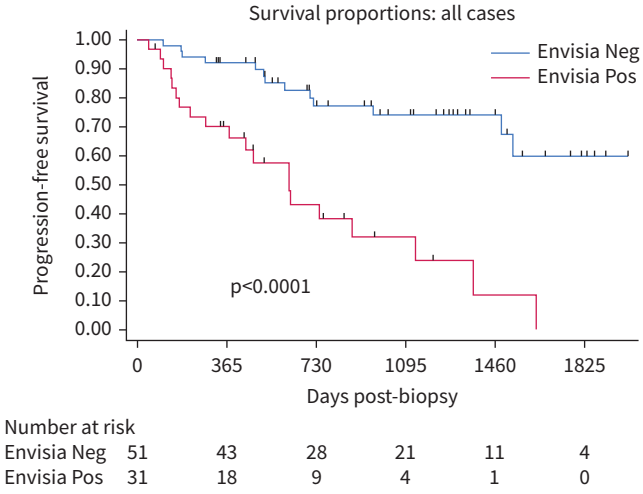

FIGURE 2 For the total cohort of 82 patients, Kaplan–Meier curve demonstrates worse progression-free survival in Envisia Genomic Classifier (EGC)-positive (Pos) patients compared with EGC-negative (Neg) patients. p<0.0001 by log-rank analysis.

We also assessed the effect of EGC result in the subset where final MDT diagnosis was not IPF (figure 4). EGC-positive patients had worse PFS in this subset (p=0.0157), with a median duration of PFS 879 days, whereas the median PFS days was not observed as of 1825 days of follow-up in EGC-negative patients. Finally, for the 23 patients with an MDT diagnosis of hypersensitivity pneumonitis (HP), EGC positivity was associated with worse PFS (p=0.0308), with median PFS 876 days, whereas the EGC-negative patients did not reach the median PFS.

A multivariable Cox regression model showed that after adjustment for ILD-GAP stage, EGC positivity remained a predictor of reduced PFS; in the entire cohort of 82 patients, hazard ratio (HR) for progression was 4.39 (95% confidence interval (CI) 2.09–9.42). In the "alternate diagnosis" by CT subset, EGC positivity predicted worse PFS (HR 3.41, 95% CI 1.20–9.70). In the "indeterminate for UIP" subset, however, HR was non-evaluable, due to no EGC-negative patients demonstrating progression prior to censoring. For patients with a final MDT diagnosis other than IPF, EGC positivity was correlated with worse PFS adjusted for ILD-GAP stage (HR 3.43, 95% CI 1.15–10.21), as well as for the subset of patients with MDT diagnosis of HP (HR 4.17, 95% CI 1.03–16.99) (table 2).

EGC effect on diagnosis and confidence level

In the pre-EGC MDT diagnosis, 17 of the 82 patients (21%) were diagnosed with IPF, based on the clinical history, radiology result and cryobiopsy result. This increased to 23 (28%) following the post-EGC MDT deliberation. One pre-EGC IPF result changed to not IPF, and seven cases initially not thought to be IPF changed to IPF due to EGC positivity. 10 other cases initially not thought to be IPF remained as not IPF despite EGC positivity (supplementary table 1).

In the Wilcoxon signed-rank test of effect of EGC test on the confidence level of diagnosis, the level of confidence in diagnosis increased after the EGC test (p<0.0001). The confidence level increased in 38% of cases and decreased in only 7%, whereas the confidence level remained unchanged in 55% of cases (figure 5).

Of 26 patients with an indeterminate HRCT, 13 patients had a pre-EGC result of unclassifiable ILD. Five of those patients were given a specific MDT diagnosis when the EGC result was unveiled. Similarly, of 32 patients with an indeterminate cryobiopsy result, 13 patients were labelled as unclassifiable ILD by MDT, and 4 of those patients were given specific ILD diagnoses when the EGC result was considered.

Progression of disease in patients in whom the EGC changed the diagnosis

65 patients were labelled with non-IPF diagnoses by MDT prior to unveiling the EGC result. In the group of seven cases in which EGC helped to change the diagnosis from alternative to IPF, worse PFS was seen than the group of 58 patients in whom the diagnosis remained not IPF after EGC result (p=0.0352)

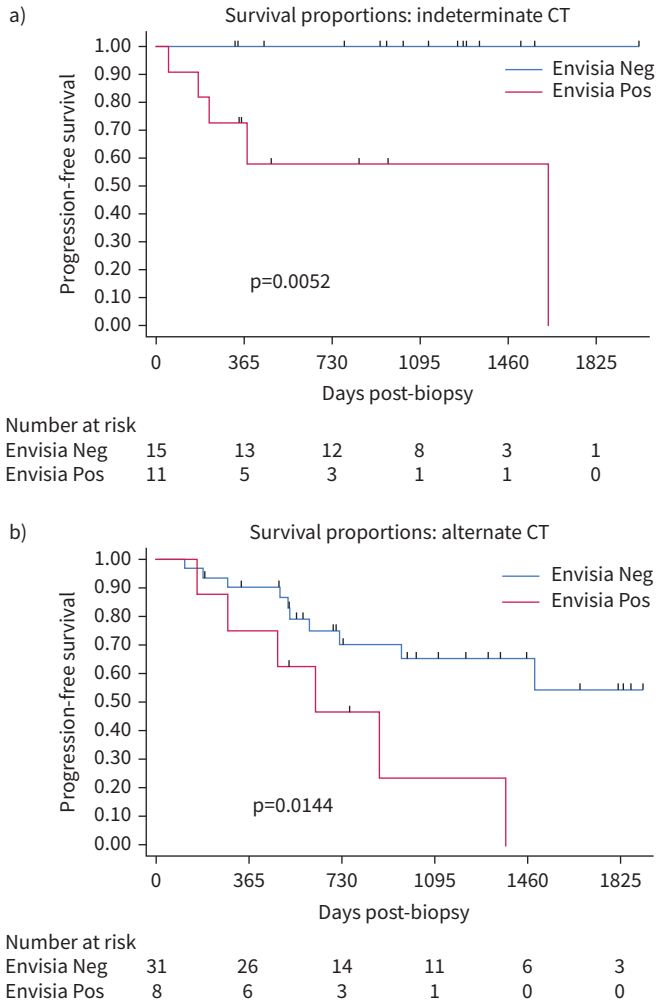

FIGURE 3 a) In the cohort of 28 patients with "indeterminate for usual interstitial pneumonitis" computed tomography (CT) result, Kaplan–Meier analysis demonstrates worse progression-free survival for Envisia Genomic Classifier (EGC)-positive patients (p=0.0052). b) In the cohort of patients with "alternate diagnosis" CT result, EGC-positive (Pos) patients have faster progression of interstitial lung disease than EGC-negative (Neg) patients (p=0.0144).

(figure 6), with a median PFS of 1629 days, whereas the cases in which diagnosis was unchanged did not reach the median. Corrected for GAP score, the HR was 3.06 (95% CI 0.68–13.65).

Test characteristics of EGC for the diagnosis of IPF

We also assessed the test characteristics of EGC result in isolation as a test for IPF diagnosis, using a reference standard of pre-EGC MDT deliberation, including clinical history, CT result and cryobiopsy. This resulted in a sensitivity of EGC as a test for IPF of 0.82 and a specificity of 0.74. The positive likelihood ratio of EGC as a test for IPF was 3.15 and the negative likelihood ratio was 0.24.

With consideration of pre-EGC MDT diagnosis as the reference standard, the prevalence of IPF in our cohort was 21%. The PPV for EGC positivity was 0.54 and the negative predictive value was 0.94.

Discussion

Our study is the first to demonstrate a correlation between EGC positivity and risk of progression of disease in ILD. ILD is a challenging clinic entity due in part to its heterogeneity and variable disease progression, making timely and accurate diagnosis critical [21]. We hypothesise that previous analyses were not able to detect this correlation due to the relatively limited duration of follow-up. Chaudhary *et al.* [16] collected patient data up to 18 months following biopsy, and while Kheir *et al.*'s [17] retrospective

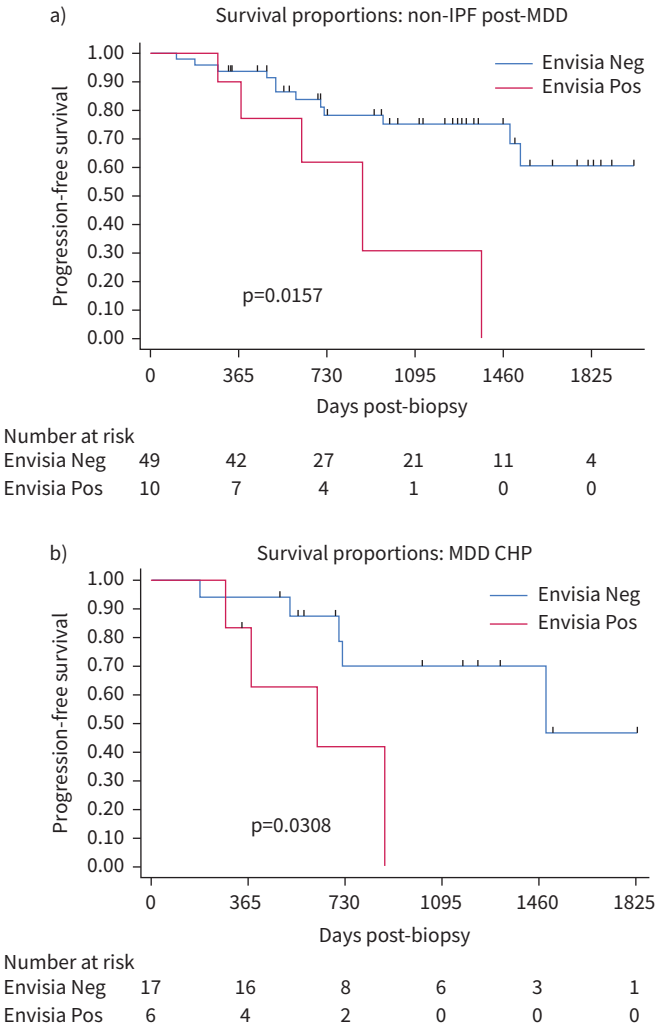

FIGURE 4 a) In our cohort of 59 patients with a final multidisciplinary team diagnosis that was not idiopathic pulmonary fibrosis (IPF), Kaplan–Meier curve demonstrates worse progression-free survival (PFS) in Envisia Genomic Classifier (EGC)-negative patients compared with EGC-positive patients (p=0.0157). b) In patients with hypersensitivity pneumonitis, which was the most common non-IPF diagnosis, Kaplan–Meier curve demonstrates worse PFS in EGC-negative patients in this subset (p=0.0308). CHP: chronic hypersensitivity pneumonitis; MDD: multidisciplinary discussion.

TABLE 2 Multivariable Cox regression model demonstrates increased risk of ILD progression for EGC-positive patients when adjusted for ILD-GAP stage

Subset	Hazard ratio ± SE positive *versus* negative	95% CI
All (n=82)	4.44 ± 1.70	(2.00–9.42)
Indeterminate for UIP CT (n=28)	Not evaluable	
Alternate CT (n=39)	3.41 ± 1.82	(1.20–9.70)
MDT non-IPF (n=59)	3.43 ± 1.91	(1.15–10.21)
HP (n=23)	4.17 ± 2.99	(1.03–16.99)

ILD: interstitial lung disease; EGC: Envisia Genomic Classifier; GAP: gender–age–physiology; UIP: usual interstitial pneumonitis; CT: computed tomography; MDT: multidisciplinary team; IPF: idiopathic pulmonary fibrosis; HP: hypersensitivity pneumonitis.

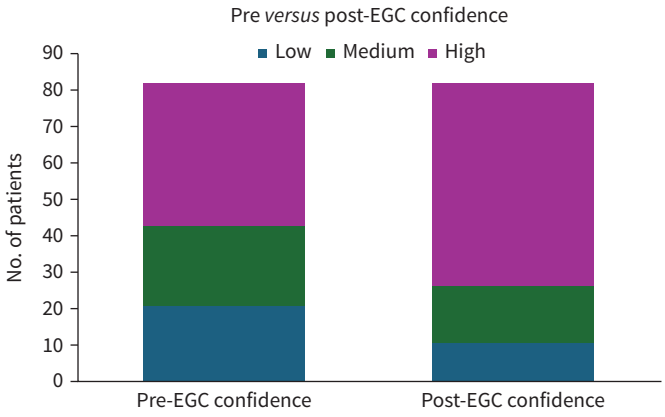

FIGURE 5 Illustration of effect of Envisia Genomic Classifier (EGC) on confidence level of interstitial lung disease diagnosis, showing the numbers of cases in which the multidisciplinary team had low, medium and high confidence in diagnosis before and after unveiling the EGC result.

review included follow-up up to 50 months for three patients, the median follow-up for their overall cohort appeared to be about 12 months, considerably shorter than our median 690 (IQR 247–1202) follow-up days. The extended duration of days lapsed since biopsy in our study allowed enough EGC-positive patients to progress, while also allowing for longer follow-up in the EGC-negative non-progressors, so that a difference could be detected.

As a test for IPF diagnosis, EGC performed strongly compared with the reference standard of pre-EGC MDT diagnosis. We found a sensitivity of 0.82 and specificity of 0.74 compared with Richeldi *et al.*'s [13] report of sensitivity and specificity of 0.62 and 0.92, respectively, as well as Raghu *et al.*'s [12] report of 0.76 and 0.88. Of note, we chose not to use a reference standard of post-EGC MDT diagnosis to calculate sensitivity and specificity, given that it would be a circuitous exercise. Despite the strong test characteristics, the EGC is limited as a single arbiter of IPF diagnosis in a low-IPF-prevalence (28% in our cohort) environment, evidenced by our reported PPV of 0.54. Lung biopsies are now performed in fewer patients and are somewhat enriched for patients with non-IPF ILD, as patients with "probable UIP" CTs are less frequently biopsied [22, 23]. Nevertheless, we found EGC to be additive to MDT deliberations and with significant clinical impact, as seven patients had their diagnosis changed from alternative to IPF with the EGC as the determining factor, and they went on progress more quickly than the rest of the patients in whom the diagnosis did not change.

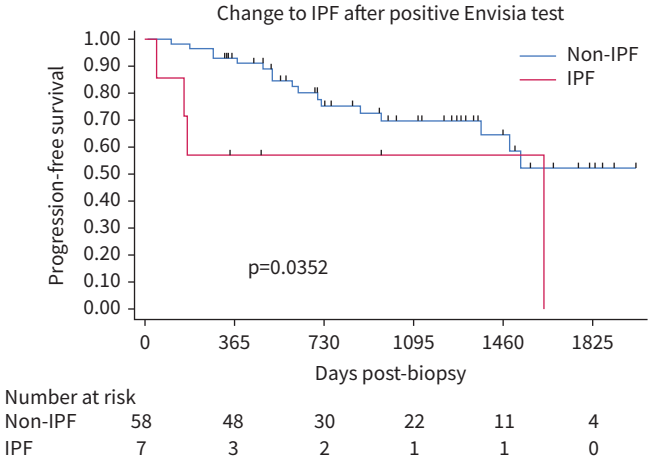

FIGURE 6 In the subset of 65 patients in whom the pre-Envisia Genomic Classifier (EGC) multidisciplinary team diagnosis was not idiopathic pulmonary fibrosis (IPF), the subset of seven patients in whom the diagnosis was changed to IPF following unveiling of the EGC had worse progression-free survival than the remaining 59 patients in whom the diagnosis remained not IPF (p=0.0352).

Our study has potential limitations to the generalisability of our findings. Our overall cohort size of 82 is small, leading to even smaller subsets in which the confidence intervals for HR, while not crossing 1.0, were nonetheless wide. With regard to patient selection, the referral patterns for cryobiopsy vary widely [24], depending on local technical expertise and experience interpreting cryobiopsy histology. A prospective study design not limited to patients who were referred for cryobiopsy, would more directly answer whether EGC predicts progression in the general population of ILD patients. A multicentre effort would minimise the potential bias of referral and practice patterns of a single centre. In another note on study population characteristics, 91% of the patients in our cohort were GAP-ILD stage 1, reflecting a shift in clinical practice, in which ILD providers eschew tissue biopsy in more-advanced disease for concern of complications from biopsy [25]. Consequently, we do not have sufficient data to posit that EGC positivity portends a worse prognosis in patients with advanced disease.

We surmise that our finding might be reproducible in other centres, provided that the duration of follow-up is sufficient. With just 23 patients with HP, we were able to detect a difference between EGC-positive and negative patients. And the group of patients in whom diagnosis was changed from alternative to IPF due to EGC had only seven patients, but we saw worse progression when compared with the rest of the cohort in whom the diagnosis remained not IPF. The ability to detect these differences with relatively small numbers, as well as the trends towards significance reported by Chaudhary *et al.* [16] and Kheir *et al.* [17], suggest that our finding of predictiveness would be corroborated by other cohorts with extended follow-up.

In conclusion, we show for the first time that the EGC result is correlated with progression of ILD. If corroborated in a multicentre study, the test would be of significant research and clinical interest. The regularity with which patients with clear non-IPF diagnoses, as well as patients with alternative or indeterminate diagnoses on HRCT, had genomic UIP as defined by the EGC, together with the predictiveness for PFS, demonstrate that a fibrotic transcriptomic signature may be more indicative of future progression than what can be seen on HRCT at the time of biopsy. The EGC could benefit patient care by indicating which patients merit more-aggressive treatment or earlier consideration for lung transplant. In current clinical practice, when a patient is diagnosed with non-IPF ILD, treating physicians may elect for observation and wait for evidence of progression before initiating therapy if the extent of disease is mild; EGC positivity may tip the scales towards earlier treatment in such cases, which would diminish the worsening that otherwise would have occurred. The EGC could also help enrich clinical trials with patients more likely to progress, allowing for easier detection of treatment effect. Although there are other promising biomarkers of disease progression at a research stage, none is currently available in practice [26, 27]. The EGC, if validated by other studies, may be such a biomarker.

Provenance: Submitted article, peer reviewed.

Ethics statement: We collected retrospective patient data that were anonymised and stored on a secure drive, after obtaining local institutional review board approval. We evaluated patient cases in which referrals had been made for a lung cryobiopsy and concurrent genomic classifier testing as part of usual care of ILD patients. Therefore, as this research study was a retrospective review, it did not influence any clinical decisions on the part of the clinicians.

Conflict of interest: A. Chung reports consultancy fees from US Food and Drug Administration Orphan Products Division and MEDACorp, and an internal speaking fee for Veracyte. S. Oh reports a position on an advisory board for Veracyte. G. Kim reports grant support from Boehringer Ingelheim. S.S. Weigt reports speaker bureau fees from Boehringer Ingelheim and consulting fees from Fibrogen. A. Oh, C. Durant, R. Watson, J. Channick, G. Fishbein, L. Pourzand, S. Kim and R. Ronaghi report no conflicts of interest.

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