Genomic classifier: biomarker for progression in interstitial lung disease

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Genomic classifier might serve as a biomarker for disease progression in fibrotic interstitial lung disease https://bit.ly/3YuGjoF

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Fibrotic interstitial lung disease (ILD) is a heterogeneous group of diseases, the most common of which is idiopathic pulmonary fibrosis (IPF), a disease characterised by the histologic features of usual interstitial pneumonia (UIP) [1]. Although some ILDs share overlapping radiographic and histopathologic features, prognosis and treatment response vary across the ILD spectrum. Delays in diagnosis can lead to missed opportunities to intervene early and potentially slow progression.

Antifibrotics remain the main treatment for IPF and are largely supported by evidence [1]. However, other fibrotic lung diseases can display pathologic UIP, and this is typically associated with progressive disease [1]. Although antifibrotic therapy may also benefit those with progressive non-IPF ILD the ability to predict a progressive phenotype early in the disease course in order to influence outcome remains questionable [2, 3]. Recent development of novel diagnostic techniques is causing a paradigm shift toward increased precision, targeted therapeutics and potentially improved patient outcomes.

A genomic classifier (GC) has recently been introduced for clinical use [4]. It was developed using machine learning analysis of next generation RNA sequencing based on genomic data from surgical lung biopsies and quantifies 190 exons to identify a profile predictive of UIP in lung tissue obtained by transbronchial forceps biopsy (minimum of three samples from lower or upper lobes). The classifier distinguishes UIP from non-UIP histopathology, helping clinicians and multidisciplinary teams (MDTs) predict histologic UIP in patients without a definite UIP pattern at chest imaging with a specificity of 92% and a sensitivity of 68% [5]. Unlike descriptive pathology reports, the genomic classifier report is binary and reported as positive or negative for UIP.

A prospective randomised decision impact survey found pulmonologists were more likely to diagnose UIP and start antifibrotic treatment when provided with a positive genomic classifier result [6]. There was a 36% increase in antifibrotic recommendation in the pre-/post-genomic classifier cohort when information was given in a staged fashion and an 11% increase in antifibrotic recommendation in an independent cohort when all information was given simultaneously [6]. Furthermore, GC has shown a significant increase in confidence levels of IPF diagnosis in MDT discussion when the classifier was added to cryobiopsy in patients where high-resolution computed tomography (HRCT) scanning indicated probable UIP with confounding clinical factors or was indeterminate for UIP [7].

Two recent studies evaluated the ability of GC to predict progression and impact on management strategy [8, 9]. Chaudhary *et al.* [8] compared progression-free survival defined as composite outcomes (time to death, lung transplant or forced vital capacity decline ⩾10% up to 18 months) in a retrospective, multicentre, US-based cohort study comparing patients that were GC positive and GC negative for UIP. Overall, this study did not show a statistically significant association between disease progression and a positive classifier pattern. However, there was significant evidence of progression in patients with an

alternative pattern on HRCT as well as MDT diagnosis of non-IPF-ILD. This study was limited by a small sample size (n=60), relatively short-term follow-up (18 months) and possible slower progression in patients on antifibrotics which affected the overall progression between GC positive and negative cohorts.

Another study evaluated whether combined GC and cryobiopsy were associated with a change of treatment strategy and evaluated the disease progression in patients with positive GC as compared with patients who had negative GC [9]. Combined GC and histopathologic data were associated with change of therapeutic strategy in 59.5% of patients, and this increased to 76.2% when the genomic classifier was positive for UIP and cryobiopsy was indeterminate. This 16.7% increase in initiation of antifibrotics could potentially increase appropriate antifibrotic prescriptions and mitigate the risk of immunosuppressive therapies in such a patient population. There was no statistically significant difference in disease progression in patients that had positive genomic classifier as compared with UIP negative. However, there was a trend toward statistical significance among patients who were positive for UIP by genomic classifier and not treated with antifibrotics compared to patients with genomic classifier-negative results (hazard ratio 1.8, 95% CI 0.99–3.4, p=0.053). [9] This study was limited by a relatively short term follow-up (12 months).

In this issue of *ERJ Open Research*, Chung *et al.* [10] conducted a single centre retrospective study to evaluate whether GC might serve as a biomarker for disease progression in patients with ILD where biopsy was deemed necessary by MDT. Eligible patients underwent concurrent cryobiopsy and GC with a median follow up of ∼23 months (690 days). The majority of patients (91%) had stage I ILD according to the GAP (gender-age-physiology) index. The HRCT pattern was labelled as alternative and indeterminate for UIP in 48% and 32% of patients respectively. Overall, a GC positive for UIP was associated with a disease progression hazard ratio of 4.39 (95% CI 2.09–9.42). In patients with an "alternate diagnosis" from HRCT, MDT diagnosis other than IPF as well as MDT diagnosis of hypersensitivity pneumonitis that was GC

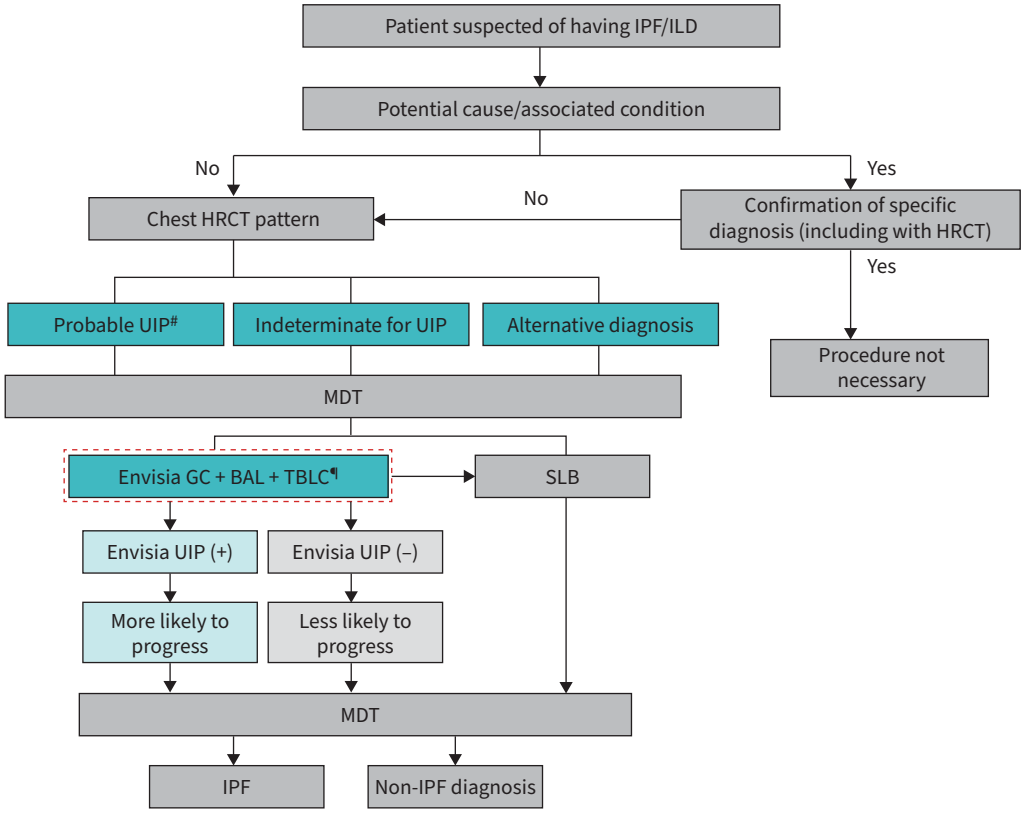

FIGURE 1 Integrating the Envisia genomic classifier into clinical practice. IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; MDT: multidisciplinary team; GC: genomic classifier; BAL: bronchoalveolar lavage; TBLC: transbronchial lung cryobiopsy; SLB: surgical lung biopsy. #: the Envisia genomic classifier can be used in probable UIP patients if the clinical context is not clear; ¶: transbronchial lung cryobiopsy is preferrable over SLB.

positive for UIP was associated with disease progression. Furthermore, four out of 13 patients (31%) who were deemed unclassifiable by MDT after cryobiopsy were given specific ILD diagnosis following GC results. In addition, seven patients from 65(10.8%) had their diagnosis changed from an alternative to IPF based solely on GC and progressed more quickly as compared to patients in which the diagnosis did not change.

The use of a GC to evaluate disease progression is an attractive concept. There has been a paradigm shift by some experts proposing that UIP can represent a single diagnostic entity, whether due to primary (IPF) or secondary (non-IPF) aetiology. This is due to similarities in disease behaviour, pathogenic profile, progression and possible treatment response to antifibrotic therapy [11]. This could represent diagnostic simplification where UIP identified at cryobiopsy, or GC could facilitate earlier treatment with currently approved antifibrotics or antifibrotic trials for specific secondary UIP or trials of novel agents. This current study, as well as previous studies by Chaudhary *et al.* [8] and Kheir *et al.* [9], suggest the following: 1) GC can serve as complementary diagnostic test to cryobiopsy in patients where biopsy is needed per the MDT; 2) GC may detect molecular UIP in a cohort where the HRCT pattern suggests alternative diagnosis or MDT diagnosis was as labelled as non-IPF-ILD; and 3) GC may serve as a disease biomarker for progression regardless of underlying clinical diagnosis. This will likely impact patient management, leading clinicians to initiate antifibrotics early in the disease, or sometimes to close monitoring for patients with molecular UIP regardless of underlying clinical diagnosis, to alter patient prognosis.

With the concept of progressive pulmonary fibrosis, which clinicians often face in practice, either as first presentation or occurring despite management, it is important to individualise treatment approach. Whether intensifying immunosuppressants, adding antifibrotics or starting antifibrotics as monotherapy in patients with non-IPF, fibrotic ILD treatment can be better informed with the use of a GC to identify molecular UIP patterns that might not be apparent on radiographic imaging alone.

A few barriers exist to the widespread use of GCs. First, it is not available outside the United States. Second, a GC requires a biopsy in ILD patients who are able to tolerate bronchoscopy. Third, it has a binary outcome and cannot differentiate ILD subtypes. Last of all, it is still mainly used to increase confidence in diagnosis and not as biomarker of progression in clinical practice.

As current guidelines recommend a MDT to review radiographical and tissue data to reach a consensus in the diagnosis of ILD, GC may be a beneficial addition to this multidisciplinary discussion process (figure 1). It is useful to the diagnostic armamentarium in patients with unclassifiable ILD who need further testing for a confident diagnosis and may serve as a biomarker for disease progression. The GC is an example of how molecular data can be integrated into the clinical, radiological, and pathological framework for patients with ILD leading to a confident diagnosis, targeted therapeutics and prediction of disease course.

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