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The Genomic Classifier and Our Quest for Diagnostic Certainty in Interstitial Lung Disease

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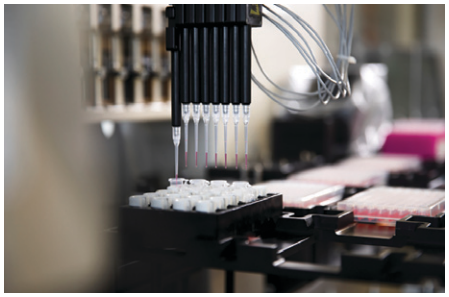

Interstitial lung diseases (ILDs) are a collection of complex and heterogeneous diseases that can be challenging to diagnose. Multidisciplinary discussions (MDDs) involve the dynamic exchange of information between chest radiologists, ILD clinicians, and lung pathologists and are currently the gold standard for ILD diagnosis (1). In particular, the addition of histopathologic data increases the diagnostic confidence of clinical radiologic diagnoses (2). Surgical lung biopsies (SLB) have traditionally been the preferred method to obtain tissue as they provide larger samples to better assess morphology; however, the associated risks may preclude patients from undergoing the procedure (3–5). As a result, a patient may be left with a low-confidence ILD diagnosis (i.e., unclassifiable ILD). Such a scenario is not uncommon, with 10–24% of ILD cases being unclassifiable (6, 7).

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive ILD with a poor prognosis comparable to aggressive cancers (8). An accurate diagnosis of IPF is important as it has therapeutic implications (e.g., early initiation of an antifibrotic) and informs discussions around prognosis. IPF can be diagnosed without a biopsy when there is high clinical suspicion and a definite or probable usual interstitial pneumonia (UIP) pattern on high-resolution computed tomographic (HRCT) imaging. Otherwise, a biopsy may be required to determine histopathological features to either support or refute an IPF diagnosis.

The Envisia Genomic Classifier (GC) was developed with the intent to identify a UIP pattern on transbronchial forceps biopsies (TBBx) and thus potentially avoid the need for more invasive procedures such as SLB for ILD diagnosis (9). Using machine learning, an algorithm based on genomic data from SLBs was used to identify a molecular signature for a UIP pattern (9). The RNA sequence of lung tissue obtained by TBBx is first determined, and then, using the classifier, its pattern of gene expression is classified as UIP or not UIP.

In this issue of *AnnalsATS*, Kheir and colleagues (pp. 827–832) conducted a systematic review on the use of GC testing in ILD diagnosis that will be used to inform updates to the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society clinical practice guideline for IPF (10). Studies were eligible if they included patients with an undiagnosed ILD, evaluated the use of the GC, and reported diagnostic test characteristics, agreement, and/or diagnostic confidence. There were four studies included that evaluated diagnostic test characteristics with a sensitivity of 68% and specificity of 92% based on pooled estimates. There were only two studies included that assessed diagnostic agreement, with moderate kappas (0.64 and 0.75) when comparing GC results to reference standards (MDD or histopathology alone). Both studies demonstrated improved diagnostic confidence when the GC was integrated into MDD review, although agreement between the GC and MDD diagnosis was more likely for cases with a probable HRCT pattern than indeterminate.

The use of a GC to aid accurate ILD diagnosis is an attractive concept. In theory, a GC decreases the subjectivity and interobserver variability of histopathology interpretation and increases the yield of less invasive testing. However, barriers to its widespread use remain. It likely best serves specific clinical scenarios (e.g., patients with a probable UIP pattern on imaging and/or those without access to an ILD center). It is unable to determine the specific ILD subtype

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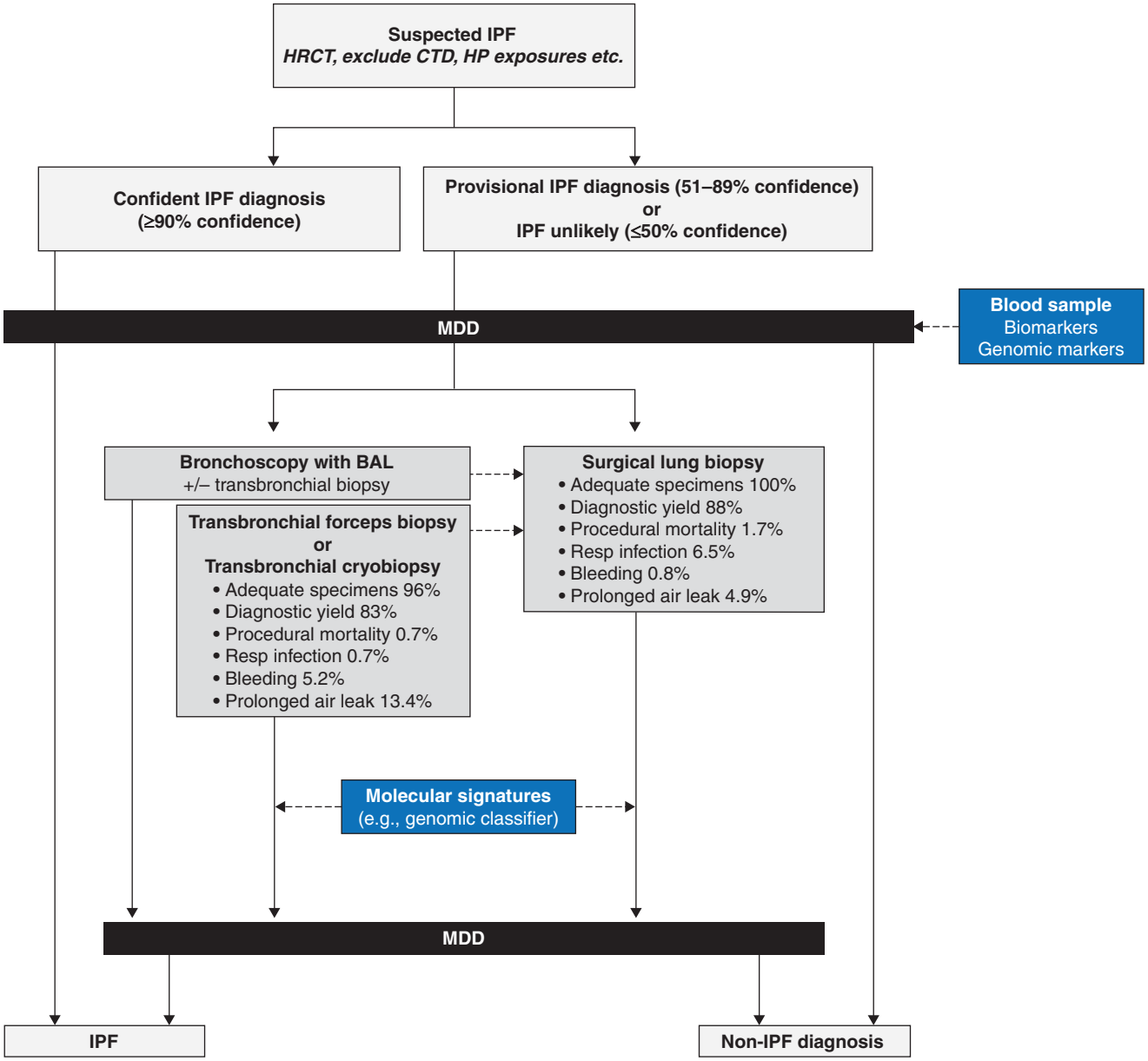

Figure 1. Approach to IPF diagnosis with current and potential future diagnostic tools. Current tests used to diagnose suspected IPF are shown in dark gray. Additional diagnostic tools that theoretically could support interstitial lung disease diagnosis in the future are shown in blue. The percentages of adequate specimens refer to the percentage of patients for whom adequate samples were obtained, and the diagnostic yield refers to the percentage of adequate samples that led to a specific diagnosis (1, 17). BAL = bronchoalveolar lavage; CTD = connective tissue disease; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; MDD = multidisciplinary discussion; Resp = respiratory.

associated with the UIP pattern (e.g., a UIP pattern in rheumatoid arthritis-associated ILD vs. IPF). It is not widely available, and the interpretation of the results from this systematic review is limited by the small number of studies, difference in reference standards between the studies (e.g., MDD vs. histopathology), sponsorship bias, and confirmation bias (i.e., the same clinicians who developed the GC were involved in MDD reviews using the GC).

All ILD diagnoses are initially established on the foundation of clinical and radiological data. However, what should clinicians do when these domains are exhausted and a confident ILD diagnosis cannot be made? Herein lies the Achilles' heel of ILD diagnosis. Our armamentarium in this scenario is limited, with most options centered around histopathologic evaluation. The procedures to obtain lung tissue are not without risk. Surgical lung biopsies are associated with an in-hospital and 90-day mortality ranging between 1.0–2.8% for elective procedures (4, 5). Cryobiopsies have lower associated risks, but this advanced bronchoscopic procedure is not readily available (11, 12). Despite its limitations, the GC can be applied to TBBx obtained by conventional bronchoscopy and offers objective data without the need for a specialist to interpret the results. Previous studies have shown that diagnostic

confidence increases as more information is provided to an MDD (2). This was similarly seen when the GC was added to MDD reviews. The GC also demonstrates how machine learning and molecular data can be integrated into clinical practice, a foreshadow of how ILD diagnosis will likely evolve over time (Figure 1). Genetic mutations and telomere abnormalities have been implicated in ILD (13, 14), and the ability to add genetic and biomarker data into the current clinical, radiological, and pathological framework would allow for comprehensive and precision-based ILD phenotyping that informs diagnosis, targeted therapies, treatment response, and disease trajectory.

With the concept of progressive fibrosing ILD (PF-ILD) emerging over the last few years and evidence supporting the use of antifibrotic therapy in these patients (15, 16), some may argue that it is unnecessary to make the distinction of UIP on histopathology. However, it is important to note that PF-ILD is not a diagnosis, but rather describes a phenotype of patients with a fibrotic ILD that is progressive based on change in clinical status, physiology, and/or imaging. The distinction of a UIP pattern remains important when trying to determine the underlying ILD. ILD diagnosis has implications for other important aspects of management (e.g., antigen identification and avoidance or monitoring/management of extrapulmonary involvement in connective tissue diseases). It is also unknown whether patients with a non-IPF PF-ILD should be treated with antifibrotics or immunosuppression first, or even simultaneously. Furthermore, patients with a UIP pattern may be more responsive to antifibrotic therapy than immunosuppression (15).

The systematic review by Kheir and colleagues points to the exciting potential of genetic and molecular data in ILD diagnosis and a precision-based approach to our patients. The GC is currently approved in the United States; however, more studies will likely be needed before there is broader uptake. Several questions remain on how the GC would best be used in the current diagnostic pathway. Should SLB or cryobiopsy remain first-line to obtain tissue when possible? Does the GC increase accurate diagnoses when used by centers without access to ILD MDD? Is it a cost-effective technology? In the meantime, a significant proportion of patients continue to have a low-confidence ILD diagnosis, and the quest for tools that increase diagnostic confidence with minimal risk to patients continues with great fervor. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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