Genomic Classifiers in Diagnosing Interstitial Lung Disease: Finding the Right Place at the Right Time

Gillian C. Goobie, M.D., F.R.C.P.C.[1,2], and Daniel J. Kass, M.D.[2,3]

[1]Department of Human Genetics, Graduate School of Public Health, [2]Simmons Center for Interstitial Lung Disease, Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, and [3]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

ORCID IDs: 0000-0001-7982-5635 (G.C.G.); 0000-0001-6597-7830 (D.J.K.).

Idiopathic pulmonary fibrosis (IPF) is a fibrotic interstitial lung disease (fILD) characterized by dyspnea, progressive lung scarring, and high mortality (1). Despite substantial advances in our understanding of the risk factors and pathophysiologic mechanisms underlying IPF development and progression, clinicians still struggle to make a confident diagnosis of this condition. Patients undergoing evaluation for fILD often experience delays, multiple procedures, occasional misdiagnoses, and dissatisfaction (2, 3). This is of particular concern for patients whose high-resolution computed tomography (HRCT) imaging is classified as "probable" or "indeterminate" for usual interstitial pneumonia (UIP) (1, 4).

In patients without a typical UIP pattern, current guidelines conditionally recommend a surgical lung biopsy (SLB) (1, 4). Despite improvements in selection of patients for SLB, this procedure is still associated with significant morbidity and mortality (5). In contrast to SLB, transbronchial biopsies (TBBx) have a low complication rate (<10% of procedures) and minimal mortality risk but are not a cornerstone of fILD diagnostic workups because of low sensitivity in diagnosing fILD subtypes (6). Transbronchial lung cryobiopsies have increased diagnostic yield; however, they remain limited in their application because of increased complication rate compared with TBBx, specialized implementation requirements, and interrater reliability issues (7).

Recent studies have demonstrated how a genomic classifier (GC) may be incorporated into the diagnostic evaluation of patients with fILD to increase diagnostic confidence without having to resort to SLB. In this issue of *AnnalsATS*, Lasky and colleagues (pp. 916–924) report using a GC consisting of 190 genes previously identified through machine learning analysis of whole-transcriptome mRNA sequencing of TBBx specimens in patients with fILD (8, 9). In the BRAVE (Bronchial Sample Collection for a Novel Genomic Test) study of patients undergoing diagnostic evaluation for fILD, this classifier had a sensitivity of 70% and specificity of 88% for the identification of UIP in comparison to SLB histopathology (10). The present study sought to evaluate how this GC would modify U.S.-based pulmonologist decision-making in cases of multidisciplinary discussion (MDD) expert consensus–diagnosed IPF without a typical UIP pattern on HRCT (8).

The authors isolated 11 cases of patients with fILD from the BRAVE study without a typical UIP HRCT pattern whose eventual MDD diagnosis was IPF. Subsequently, 103 U.S.-based pulmonologists performed 605 case reviews of the cases without knowledge of their final MDD diagnosis. The study evaluated both a pre- and post-GC cohort to evaluate the performance of the GC when implemented in a staged fashion. The investigators also used a second independent cohort to evaluate the GC's performance when clinicians were provided the GC concurrently with all other clinical and radiographic information. In the pre/post cohort, IPF was listed as the diagnosis 30% of the time pre-GC, which increased to 69% post-GC. The surge in IPF diagnoses was accompanied by recommendations for antifibrotics, which increased from 10% pre-GC to 46% post-GC. Interestingly, when the GC was evaluated in independent cohorts, the effect size was substantially smaller. Physicians in the independent cohort, where clinical, radiographic, and GC data were all provided simultaneously, made a diagnosis if IPF 13% more often and recommended antifibrotics 11% more often than did physicians in the independent cohort who never received GC data.

The intended implementation timing for this GC is after initial evaluation of standard clinical and radiographic data, when more information is required to make a confident diagnosis. As such, the authors argue that the 36% increase in IPF diagnoses in the pre-/post-GC cohort is most representative of the clinical application of this tool. However, the differences in the rate of IPF diagnoses

Supported in part by AR060780, HL133232, UL1 TR001857, AR076024 National Institutes of Health (NIH) grants, Boehringer-Ingelheim grants, and receives collaborative research funding from Regeneron Pharmaceuticals, outside of the submitted work (D.J.K.).

DOI: 10.1513/AnnalsATS.202112-1353ED

between the pre-/post-GC cohort and the independent cohorts highlights the potential for cognitive biases to influence clinician diagnostic decision-making. These factors need to be thoroughly considered as this tool is integrated into our ILD diagnostic armamentarium.

Cognitive biases are likely to act in both directions, amplifying the impact in the pre-/post-GC cohort while simultaneously decreasing the magnitude of effect in the independent cohorts. Previous studies indicate that supporting information has a stronger impact on decision makers when presented sequentially, rather than simultaneously, thus constituting a form of confirmation bias that may increase the proportion of respondents diagnosing IPF in the post-GC cohort (11). Furthermore, the "representativeness heuristic," where people make judgements on the basis of preexisting mental frameworks, could contribute to an overestimation of the likelihood of a true diagnosis of IPF. If a clinician is given additional information that is consistent with their preconceived notion of IPF (i.e., a UIP-positive pattern on a GC) they are more likely to identify IPF as the diagnosis regardless of the baseline rate of IPF in the population in question (12). In the context of this manuscript, the baseline rate of "true IPF" was 100%, but this is not the case in real-world applications, where the base rate of a true IPF diagnosis in any context is variable, depending on multiple clinical and radiographic parameters. Although typically applied to monetary purchases, bundling bias, where a bundle of items is perceived as less valuable than the items individually (13), may act to lessen the impact of the GC in the independent cohorts. In this context, clinicians may fail to fully recognize the added value of the GC when it is presented with all other clinical and radiographic data. People have a limited capacity to process each piece of information immediately when receiving a large quantity of data simultaneously, so provision of the results of a GC may not be appropriately considered in this context (14). Based on this knowledge, we would argue that the true impact of the GC on IPF diagnoses is likely somewhere between the 36% and 13% reported in the pre-/post-GC and independent cohorts, respectively.

Lasky and colleagues should be commended for the design of this study, given that it provides an evaluation of not only the clinical performance of this GC but also how the implementation timing influences clinician decision-making (8). This study also provides insight into the real-world utility of this test, highlighting diagnostic differences between general U.S.-based pulmonologists and specialized ILD MDDs. But despite its many strengths, several questions warrant further study. Of 237 patients undergoing investigation for ILD, only 11 patients had a HRCT pattern not classified as typical UIP and a final MDD diagnosis of IPF. This sample size is quite small, reflecting the low frequency of this exact clinical scenario in which the GC may provide the greatest utility. Furthermore, all the patients who did meet these criteria were White, which limits the generalizability of these findings to more diverse cohorts of patients with fILD.

Last, one must raise the question of whether defining the diagnosis of IPF is necessary in these ambiguous cases, especially given recent studies demonstrating benefit of antifibrotic therapy in multiple subgroups of patients with fILD (15). As the authors argue, making a diagnosis of IPF may reduce the risk of initiation of harmful immunosuppressive therapies or may increase appropriate antifibrotic prescriptions in these patients (8). The next most important step in defining the GC's role in the ILD clinician's toolkit may be to evaluate the association between a UIP-positive result and clinical response to antifibrotics. Since the very first transcriptomic analyses of IPF lungs (16), the arrival of the GC may presage an era of precision diagnostics in patients with fILD. ■

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

References

1 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al.*; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198:e44–e68.

2 Cosgrove GP, Bianchi P, Danese S, Lederer DJ. Barriers to timely diagnosis of interstitial lung disease in the real world: the INTENSITY survey. *BMC Pulm Med* 2018;18:9.

3 Lancaster L, Bonella F, Inoue Y, Cottin V, Siddall J, Small M *et al.*, Idiopathic pulmonary fibrosis: physician and patient perspectives on the pathway to care from symptom recognition to diagnosis and disease burden. *Respirology* [online ahead of print] 5 Oct 2021; DOI: 10.1111/resp.14154.

4 Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, *et al.* Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med* 2018;6:138–153.

5 Aussedat PH, Chebib N, Ahmad K, Glerant JC, Drevet G, Grima R, *et al.* Impact of lung biopsy on lung function in idiopathic pulmonary fibrosis. *Respiration* 2020;99:1101–1108.

6 Poletti V, Ravaglia C, Gurioli C, Piciucchi S, Dubini A, Cavazza A, *et al.* Invasive diagnostic techniques in idiopathic interstitial pneumonias. *Respirology* 2016;21:44–50.

7 Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, *et al.* Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the Cryobiopsy Working Group on Safety and Utility and a call for standardization of the procedure. *Respiration* 2018;95:188–200.

8 Lasky JA, Case A, Unterman A, Kreuter M, Scholand MB, Chaudhary S, *et al.* The impact of the Envisia Genomic Classifier in the diagnosis and management of patients with idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2022;19:916–924.

9 Kim SY, Diggans J, Pankratz D, Huang J, Pagan M, Sindy N, *et al.* Classification of usual interstitial pneumonia in patients with interstitial lung disease: assessment of a machine learning approach using high-dimensional transcriptional data. *Lancet Respir Med* 2015;3:473–482.

10 Raghu G, Flaherty KR, Lederer DJ, Lynch DA, Colby TV, Myers JL, *et al.* Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study. *Lancet Respir Med* 2019;7:487–496.

11 Jonas E, Schulz-Hardt S, Frey D, Thelen N. Confirmation bias in sequential information search after preliminary decisions: an expansion of dissonance theoretical research on selective exposure to information. *J Pers Soc Psychol* 2001;80:557–571.

12 Klein JG. Five pitfalls in decisions about diagnosis and prescribing. *BMJ* 2005;330:781–783.

13 The Decision Lab. Why do we value items purchased in a bundle less than those purchased individually? The bundling bias, explained. 2021 [accessed 2021 Dec 1]. Available from: https://thedecisionlab.com/biases/bundling-bias/.
14 Forstmann BU, Ratcliff R, Wagenmakers EJ. Sequential sampling models in cognitive neuroscience: Advantages, applications, and extensions. *Annu Rev Psychol* 2016;67:641–666.
15 Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, *et al.*; INBUILD trial investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* 2020;8:453–460.
16 Zuo F, Kaminski N, Eugui E, Allard J, Yakhini Z, Ben-Dor A, *et al.* Gene expression analysis reveals matrilysin as a key regulator of pulmonary fibrosis in mice and humans. *Proc Natl Acad Sci USA* 2002;99:6292–6297.

Comorbid Chronic Obstructive Pulmonary Disease and Heart Failure: Shared Risk Factors and Opportunities to Improve Outcomes

Sadiya S. Khan, M.D., M.S.[1,2], and Ravi Kalhan, M.D., M.S.[2,3]

[1]Division of Cardiology, Department of Medicine, [2]Department of Preventive Medicine, and [3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

ORCID IDs: 0000-0003-0643-1859 (S.S.K.); 0000-0003-2443-0876 (R.K.).

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are highly prevalent conditions, commonly cooccur, and risk for both increases with aging. COPD and HF are associated with significant morbidity and mortality, with poorer outcomes in the setting of comorbid disease. In fact, cardiovascular disease accounts for more than half of all deaths in patients with COPD (1). In a recent analysis of the Clinical Practice Research Datalink, incident HF in patients with COPD was associated with a threefold higher 1-year mortality than patients with COPD without HF (2). Although symptomatic COPD and HF often coexist in older adults, clinical presentations and outcomes remain poorly defined. Without an improved understanding of the heterogeneous patterns of healthcare utilization and treatment in these high-risk patients, improving health-related quality of life, quality of care, and survival will not be possible.

In this issue of *AnnalsATS*, Gulea and colleagues (pp. 971–980) report on a retrospective cohort study of insured patients in the United States with COPD and HF between 2008 and 2018 (3). The analysis examines differences among HF subtypes based on ejection fraction (EF): *1*) HF with preserved EF (HFpEF, ⩾50%); *2*) HF with mildly reduced EF (HFmrEF, 40–49%); and *3*) HF with reduced EF (HFrEF, <40%). Of the included sample of 5,419 adults, median age was 74 years. The leading subtype of HF was HFpEF (70%), followed by HFrEF (20%) and HFmrEF (10%). Regardless of the HF subtype, there was a high prevalence of comorbidities (e.g., atrial fibrillation [49%], diabetes [47%], hypertension [97%]). Overall, 38% of patients died in follow-up, with similar crude mortality rates observed among patients with HFrEF, HFmrEF, and HFpEF. Nearly half of patients were hospitalized within 1 year, with similar hospitalization rates among each HF subtype. Overall, the leading cause for hospitalization was acute exacerbation of COPD (36%). However, the causes for hospitalization differed when examined by HF subtype, with the highest rate of HF-specific hospitalization in patients with COPD and HFrEF (20%) compared with COPD and HFpEF (16%). In contrast, acute exacerbation of COPD was more likely among those with HFpEF (38%) than HFrEF (29%). The amount of guideline-based medical therapy was low in patients with COPD and HFrEF, with 49% on β-blockers and 75% on either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In all patients with COPD, only 43% were receiving either a short-acting bronchodilator, long-acting bronchodilator, or inhaled corticosteroid regimen at baseline.

The study by Gulea and colleagues is an important contribution to the growing body of literature examining the complex interplay between lung and heart phenotypes. Strengths of the analysis include a relatively large sample of insured adults from the Optum Labs Data Warehouse, which links administrative claims with electronic healthcare records (including data on EF from echocardiography). Although the study focused on patients with COPD and comorbid HF, approximately 40% of all the patients identified with HF in cohort development had concomitant COPD, suggesting that this high-risk subset captures a large proportion of patients with HF. This may be related to the pathophysiologic sequelae of pulmonary vascular abnormalities and hypoxia present in patients with COPD, which may drive right

Supported by National Heart, Lung, and Blood Institute grant 1R01HL159250.

DOI: 10.1513/AnnalsATS.202202-152ED