oxygenation in patients with severe respiratory failure from COVID-19. *Intensive Care Med* 2021;47:208–221.
6. Urner M, Barnett AG, Bassi GL, Brodie D, Dalton HJ, Ferguson ND, *et al.*; COVID-19 Critical Care Consortium Investigators. Venovenous extracorporeal membrane oxygenation in patients with acute covid-19 associated respiratory failure: comparative effectiveness study. *BMJ* 2022;377:e068723.
7. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, *et al.* Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009;111: 826–835.
8. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, *et al.* Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med* 2013;39:847–856.
9. Combes A, Fanelli V, Pham T, Ranieri VM; European Society of Intensive Care Medicine Trials Group and the "Strategy of Ultra-Protective lung ventilation with Extracorporeal CO_2 Removal for New-Onset moderate to severe ARDS" (SUPERNOVA) investigators. Feasibility and safety of extracorporeal CO_2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med* 2019;45:592–600.
10. Brusatori S, Zinnato C, Busana M, Romitti F, Gattarello S, Palumbo MM, *et al.* High vs. low flow extracorporeal respiratory support in experimental hypoxemic acute lung injury. *Am J Respir Crit Care Med* 2023;207:1183–1193.
11. Combes A, Tonetti T, Fanelli V, Pham T, Pesenti A, Mancebo J, *et al.* Efficacy and safety of lower versus higher CO_2 extraction devices to allow ultraprotective ventilation: secondary analysis of the SUPERNOVA study. *Thorax* 2019;74:1179–1181.
12. Abrams D, Agerstrand C, Beitler JR, Karagiannidis C, Madahar P, Yip NH, *et al.* Risks and benefits of ultra-lung-protective invasive mechanical ventilation strategies with a focus on extracorporeal support. *Am J Respir Crit Care Med* 2022;205:873–882.
13. McNamee JJ, Gillies MA, Barrett NA, Perkins GD, Tunnicliffe W, Young D, *et al.*; REST Investigators. Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. *JAMA* 2021;326:1013–1023.
14. Goligher EC, Costa ELV, Yarnell CJ, Brochard LJ, Stewart TE, Tomlinson G, *et al.* Effect of lowering Vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance. *Am J Respir Crit Care Med* 2021;203:1378–1385.
15. Dianti J, McNamee JJ, Slutsky AS, Fan E, Ferguson ND, McAuley DF, *et al.* Determinants of effect of extracorporeal CO2 removal in hypoxemic respiratory failure. *NEJM Evid* (In press)

Defining the Genetic Landscape of Idiopathic Pulmonary Fibrosis: Role of Common and Rare Variants

Idiopathic pulmonary fibrosis (IPF) is a disease with complex pathophysiology, in which genetic and environmental factors play significant roles; however, their relative contributions remain undefined (1). Understanding the genetic basis of IPF can help define its heritability, risk, pathogenic mechanisms, and therapeutic targets. Evidence for genetic risk stems from observations that 5–20% of patients with IPF have relatives with fibrotic interstitial lung disease and that genetic variants identified in familial forms of pulmonary fibrosis (FPF) are present in nonfamilial, or "sporadic," IPF (2). As genetic determinants could significantly contribute to disease, investigators have sought to identify the full scope of genetic variants that account for IPF risk.

Increasingly powerful methodologies have elucidated the genetic landscape of IPF, including candidate gene screens, genome-wide association studies, whole exome sequencing (WES), and most recently whole genome sequencing (WGS). These methods have identified both common (typically with minor allele frequency [MAF] $\geq$ 0.05) and rare variants (RVs) (variably defined as MAF $\leq$ 0.0001–0.01). Common variants are more likely to be found in healthy individuals, whereas RVs tend to cosegregate with affected families and more clearly contribute to disease pathogenicity (3). To date, at least 25 genetic loci have been associated with IPF (4, 5). The most prevalent is the MUC5B risk allele, which accounts for up to 30% of IPF risk and is also present in 10–20% of the general population (6, 7). IPF RVs have been identified in the telomere-related genes (TRGs) *TERT*, *RTEL1*, and *PARN* (8–12); surfactant-related genes (13–15); and the mitotic spindle gene *KIF15* (4, 16). Of note, non-TRGs have not been consistently replicated across studies and methodologies (7, 10, 12, 16–18).

In this issue of the *Journal* (pp. 1194–1202), Peljto and colleagues (19) further define the scope of RVs in IPF by using WGS from the Trans-omics for Precision Medicine (TOPMed) program. Compared with prior methods, WGS provides a more unbiased analysis of both coding and noncoding regions. Peljto and colleagues included 2,180 IPF cases and 2,457 control subjects (without interstitial lung disease), split into discovery and validation cohorts. Cases of IPF were defined using diagnostic criteria from international society guidelines (20). The primary analysis focused on putative loss-of-function RVs (MAF $\leq$ 0.01). Five RVs were significantly associated with IPF in the discovery cohort, but only *RTEL1* remained significant in the validation cohort. A prespecified secondary analysis included missense variants and identified only *TERT* as significant. However, *SPDL1*, a gene involved in cell division checkpoint regulation, was modestly associated with IPF, as previously reported (4, 21, 22). Notably, the authors used the Rare Variant Filtering Tool to determine that a single variant in each of *RTEL1*, *TERT*, and *SPDL1* genes accounted for most of the increased risk for IPF for that RV. Patients with FPF were more likely to carry the influential variant in

Originally Published in Press as DOI: 10.1164/rccm.202301-0177ED on February 16, 2023

TERT but not in *RTEL1* and *SPDL1*. Two potentially novel common variants were also identified (in *MCL1* and ENSG00000260803) that require further validation.

Peljto and colleagues were among the first to use WGS to examine genomic noncoding regions for RVs in IPF and have affirmed previous findings that TRGs represent the most significant RVs in IPF. The authors used well-defined and prespecified preliminary, primary, secondary, and meta-analyses, which limits potential biases. Use of the Rare Variant Filtering Tool provides potentially useful information by highlighting individual RVs in genes with the strongest influence on IPF risk. This may be important in prioritizing variants for prognostication and personalizing care for patients with IPF and their families. These results are further supported by a contemporary WGS study of exonic variants that identified *TERT* and *RTEL1* as the only significant RVs contributing to risk (23).

Major contributions of this study are determining that the genetic heritability of IPF is 32% and providing additional evidence that most heritability is determined by common variants. Hence, we agree with the conclusion that the overall SNP contribution to IPF heritability may only modestly change as larger and more diverse population genomes are studied. However, efforts to identify additional RVs should continue, as their discovery will provide novel insights into IPF pathogenesis. For example, the discovery of *KIF15* (16), a mitotic spindle–related gene, could uncover novel disease mechanisms and contribute to drug discovery. As the cost of sequencing decreases and more patients undergo genetic testing, it will be important to continue defining pathogenic RVs using larger studies in diverse populations with refinement of statistical methodologies.

There are several limitations to the study. First, the analysis of Peljto and colleagues was restricted to IPF cases of European ancestry, which potentially reduces the pool of RVs. For example, *KIF15* was identified in WES and WGS studies when non-European individuals were included (4, 24). Second, MAF cutoffs have been inconsistent across studies. In a large cohort WES study, the MAF was 0.005 (10), which is lower than that used by Peljto and colleagues. Third, because RVs are, by definition, rare, splitting the sample into a discovery and validation cohort may have resulted in loss of significance of RVs in the validation cohort that were significant in the discovery cohort. Together, these limitations may explain why only two RVs (three if significance limitations are less stringent) were associated with IPF, whereas previous studies identified additional non-TRG RVs, such as *SFTPC* (13) and *KIF15* (16). Last, in the bulk of the analysis, familial and sporadic IPF were grouped together. As FPF is more strongly associated with pathogenic RVs, it may be useful to investigate genetic risk solely in sporadic IPF.

We believe that this study represents an important contribution to further refine the genetic landscape of IPF; however, it may be difficult to estimate the risk of acquiring IPF by genetic studies alone, as myriad gene–gene and gene–environment interactions are likely to contribute to the phenotypic penetrance of individual genetic variants. To fully determine the genetic and environmental contribution to IPF risk, more studies are needed on the "exposome," which integrates the entirety of an individual's exposure starting from conception, including genomic, metabolic, and other -omics approaches (25). Continued efforts at understanding factors that contribute to IPF risk will ultimately allow better prognostication and therapies for patients and their families. ■

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

Benjamin J. Moss, M.D., Ph.D.
Ivan O. Rosas, M.D.
Department of Medicine, Pulmonary, Critical Care, and Sleep Medicine
Baylor College of Medicine
Houston, Texas

References

1. Moss BJ, Ryter SW, Rosas IO. Pathogenic mechanisms underlying idiopathic pulmonary fibrosis. *Annu Rev Pathol* 2022;17:515–546.
2. Zhang D, Newton CA. Familial pulmonary fibrosis: genetic features and clinical implications. *Chest* 2021;160:1764–1773.
3. Newton CA, Oldham JM, Applegate C, Carmichael N, Powell K, Dilling D, *et al.*; Pulmonary Fibrosis Foundation Genetic Testing Work Group. The role of genetic testing in pulmonary fibrosis: a perspective from the Pulmonary Fibrosis Foundation Genetic Testing Work Group. *Chest* 2022;162:394–405.
4. Partanen JJ, Häppölä P, Zhou W, Lehisto AA, Ainola M, Sutinen E, *et al.*; International IPF Genetics Consortium; Global Biobank Meta-Analysis Initiative (GBMI). Leveraging global multi-ancestry meta-analysis in the study of idiopathic pulmonary fibrosis genetics. *Cell Genom* 2022;2: 100181.
5. Wang JY, Young LR. Insights into the pathogenesis of pulmonary fibrosis from genetic diseases. *Am J Respir Cell Mol Biol* 2022;67:20–35.
6. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, *et al.* A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med* 2011;364:1503–1512.
7. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, *et al.* Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet* 2013;45:613–620.
8. Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, *et al.* Short telomeres are a risk factor for idiopathic pulmonary fibrosis. *Proc Natl Acad Sci USA* 2008;105:13051–13056.
9. Mushiroda T, Wattanapokayakit S, Takahashi A, Nukiwa T, Kudoh S, Ogura T, *et al.*; Pirfenidone Clinical Study Group. A genome-wide association study identifies an association of a common variant in TERT with susceptibility to idiopathic pulmonary fibrosis. *J Med Genet* 2008; 45:654–656.
10. Petrovski S, Todd JL, Durheim MT, Wang Q, Chien JW, Kelly FL, *et al.* An exome sequencing study to assess the role of rare genetic variation in pulmonary fibrosis. *Am J Respir Crit Care Med* 2017;196:82–93.
11. Moore C, Blumhagen RZ, Yang IV, Walts A, Powers J, Walker T, *et al.* Resequencing study confirms that host defense and cell senescence gene variants contribute to the risk of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;200:199–208.
12. Allen RJ, Guillen-Guio B, Oldham JM, Ma SF, Dressen A, Paynton ML, *et al.* Genome-wide association study of susceptibility to idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2020; 201:564–574.
13. Lawson WE, Grant SW, Ambrosini V, Womble KE, Dawson EP, Lane KB, *et al.* Genetic mutations in surfactant protein C are a rare cause of sporadic cases of IPF. *Thorax* 2004;59:977–980.
14. Wang Y, Kuan PJ, Xing C, Cronkhite JT, Torres F, Rosenblatt RL, *et al.* Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. *Am J Hum Genet* 2009;84:52–59.
15. Sutton RM, Bittar HT, Sullivan DI, Silva AG, Bahudhanapati H, Parikh AH, *et al.* Rare surfactant-related variants in familial and sporadic pulmonary fibrosis. *Hum Mutat* 2022;43:2091–2101.
16. Zhang D, Povysil G, Kobeissy PH, Li Q, Wang B, Amelotte M, *et al.* Rare and common variants in *KIF15* contribute to genetic risk of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2022;206:56–69.
17. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, *et al.* Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and

mortality: a genome-wide association study. *Lancet Respir Med* 2013; 1:309–317.
18. Zhang D, Newton CA, Wang B, Povysil G, Noth I, Martinez FJ, *et al.* Utility of whole genome sequencing in assessing risk and clinically relevant outcomes for pulmonary fibrosis. *Eur Respir J* 2022;60: 2200577.
19. Peljto AL, Blumhagen RZ, Walts AD, Cardwell J, Powers J, Corte TJ, *et al.*; NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium. Idiopathic pulmonary fibrosis is associated with common genetic variants and limited rare variants. *Am J Respir Crit Care Med* 2023;207:1194–1202.
20. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022;205:e18–e47.
21. Zhou W, Kanai M, Wu K-HH, Rasheed H, Tsuo K, Hirbo JB, *et al.*; Biobank of the Americas; Biobank Japan Project; BioMe; BioVU; CanPath - Ontario Health Study; China Kadoorie Biobank Collaborative Group; Colorado Center for Personalized Medicine; deCODE Genetics; Estonian Biobank; FinnGen; Generation Scotland; Genes & Health Research Team; LifeLines; Mass General Brigham Biobank; Michigan Genomics Initiative; National Biobank of Korea; Penn Medicine BioBank; Qatar Biobank; QSkin Sun and Health Study; Taiwan Biobank; HUNT Study; UCLA ATLAS Community Health Initiative; Uganda Genome Resource; UK Biobank. Global Biobank Meta-analysis Initiative: powering genetic discovery across human disease. *Cell Genom* 2022;2:100192.
22. Koskela JT, Häppölä P, Liu A, Partanen J, Genovese G, Artomov M, *et al.* Genetic variant in SPDL1 reveals novel mechanism linking pulmonary fibrosis risk and cancer protection [preprint]. medRxiv; 2021 [accessed 20 Jan 2023]. Available from: https://www.medrxiv.org/content/10.1101/2021.05.07.21255988v1.
23. Donoghue LJ, Stockwell AD, Neighbors M, Sheng RX, Prabhakaran R, Wolters PJ, *et al.* Identification of a genetic susceptibility locus for idiopathic pulmonary fibrosis in the 16p subtelomere using whole genome sequencing. *Am J Respir Crit Care Med* 2023;206: 941–944.
24. Zhang D, Povysil G, Newton CA, Maher TM, Molyneaux PL, Noth I, *et al.* Genome-wide enrichment of *TERT* rare variants in idiopathic pulmonary fibrosis patients of Latino ancestry *Am J Respir Crit Care Med* 2022; 206:903–905.
25. Wheelock CE, Rappaport SM. The role of gene-environment interactions in lung disease: the urgent need for the exposome. *Eur Respir J* 2020; 55:1902064.

Could DNA Fragments Be the Key to Early Detection of Lung Cancer?

In the United States, lung cancer remains the leading cause of cancer-related mortality, accounting for an estimated 136,000 deaths in 2023 (1). The survival of patients with lung cancer at 5 years after diagnosis has improved to 23%, although it remains considerably lower than survival rates observed for other common cancers such as breast, colon, and prostate cancer. Multiple clinical trials have now confirmed the efficacy of annual low-dose computed tomographic (LDCT) screening in reducing lung cancer mortality (2–4); however, the implementation of LDCT screening at the population level has proven difficult because of challenges in eligibility determination and concerns regarding potential harm from false-positive imaging results, radiation exposure, and morbidity from invasive diagnostic procedures (5). Internationally, lung cancer screening implementation remains limited; although there has been more rapid uptake in some countries in Asia, the inclusion of low-risk individuals may influence population-level outcomes (6, 7). Thus, in the short run, the use of LDCT is likely to have only a limited impact on the global disease burden of lung cancer. Advocates of alternative noninvasive approaches to lung cancer screening have suggested that accurate blood-based assays have the potential to overcome many of the limitations observed with LDCT.

The ability to noninvasively interrogate genomic and epigenomic changes in circulating cfDNA may transform the landscape of early lung cancer detection. Plasma cell-free DNA (cfDNA) arises from chromatin fragmentation that occurs during cell death; it is shed into circulation and can be isolated from plasma obtained through a routine blood draw (8). Plasma cfDNA contains circulating tumor DNA (ctDNA), which is DNA specifically shed from tumor cells and represents only a small fraction of the total cfDNA molecules. ctDNA can be detected by utilizing highly sensitive sequencing assays to identify tumor-specific genetic alterations. The use of ctDNA, often termed "liquid biopsy," is already an integral part of routine clinical practice for noninvasive tumor genotyping in advanced non–small cell lung cancer as well as other malignancies; however, its use remains limited for the detection of early-stage disease. Although advancements in sequencing methodologies and computational biology have improved the yield of rare ctDNA somatic variant detection, the scarce amount of ctDNA shed into circulation by small tumors, typically $<0.1\%$ of the total cfDNA concentration, is often below the limit of detection of current sequencing assays (9). In addition, most cancer-derived DNA fragments are unmutated and are thus not detected by mutation-based technologies. Several tumor genotype–naive cfDNA-sequencing strategies have emerged to help mitigate this limitation for early cancer detection that assess epigenetic features such as methylation and fragmentation patterns. Whole-genome sequencing analyses have shown that cfDNA fragment sizes are more variable in cancer patients, compared with those in healthy individuals (10–13), and that tumor-derived cfDNA fragments tend to have shorter size distributions compared with

Supported by National Institute of Environmental Health Sciences grant P30-ES013508 (A.V.) and National Cancer Institute grant 5UM1CA221939 (A.V.) and K08 CA234335 (J.C.T.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Originally Published in Press as DOI: 10.1164/rccm.202303-0387ED on March 8, 2023