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Three Steps to Cure Pulmonary Fibrosis

Step 1: The Runaway Train or Groundhog Day?

If idiopathic pulmonary fibrosis (IPF) is to be cured, then it is likely that the "fibrosis" will need to be identified before it has led to widespread architectural destruction of the parenchyma. Unfortunately, by the time IPF is diagnosed, most patients have suffered symptoms for a number of years (1) and have considerable physiological abnormality, with reduced FVC and gas transfer (D_{LCO}) and irreversible loss of lung function (2).

Therefore, step one on the path to cure IPF requires that early precursor lesions must be identified in presymptomatic individuals at a point at which the natural history can be positively altered. We've all seen the movie: the runaway train barreling down the tracks but somehow the hero manages to divert the course.

In the last decade, a number of studies assessing radiological changes in longitudinal cohorts of people without obvious IPF-identified parenchymal changes, referred to as interstitial lung abnormalities (ILAs), have demonstrated an increase in both all-cause mortality and mortality from pulmonary fibrosis (3, 4), raising the prospect that ILAs may be the precursor lesions for IPF. Furthermore, there is overlap in the genetic architecture of IPF and ILA (5), and, indeed, serum biomarkers associated with pulmonary fibrosis are associated with ILA (6). This raises two fundamental questions: *1*) are ILAs a precursor lesion for IPF and, if so, *2*) should at-risk populations be screened for them?

I started to write this editorial on Groundhog Day (February 2, 2020), and folklore suggests that the groundhog's shadow can lead to its prediction of the duration of winter; however, the phrase has come to epitomize the futility of trying to change the future even when you know what is going to happen. This could be an even greater concern when the future is less than certain. The prevalence of ILA is high, between 7% and 9% of screened populations (4), which would suggest that if ILAs were indeed precursor lesions, the incidence of IPF should be much higher than currently reported (7, 8). Will identification of ILAs offer us the chance to save the runaway train or will it just lead to a Groundhog Day of recurrent harm associated with lead-time bias–related anxiety or adverse effects associated with overdiagnosis?

In this issue of the *Journal*, studies by Salisbury and colleagues (pp. 1230–1239) and Hunninghake and colleagues (pp. 1240–1248) provide data that help inform the answers to these two crucial questions (9, 10). Both these studies use computed tomography scanning to "screen" unaffected first-degree relatives of patients with familial pulmonary fibrosis (FPF), and the study by Hunninghake and colleagues also screens first-degree relatives of patients with sporadic IPF. Both studies used a similar definition of ILA, and the rates of observed ILA in relatives of patients with FPF were similar across the cohorts (23% of the Vanderbilt cohort and 26% in the Brigham Cohort). The presence of the minor allele of the *MUC5B* promoter polymorphism rs35705950 and shorter telomeres were associated with ILAs in both cohorts. These data are similar to findings by Mathai and colleagues (11). Although Mathai and colleagues used a different definition of ILA, which they termed preclinical pulmonary fibrosis, they found 18% of first-degree relatives had an ILA, with 15.6% being described as fibrotic and, by the authors definition, preclinical pulmonary fibrosis. They also found an association between the *MUC5B* promoter variant and ILA but not the common variant of *TERT*, although they did not measure telomere length. All three studies showed an association between increasing age and ILAs, with the age of those with an ILA being a mean of 59 years (9), a median of 61 years (10), and a mean of 66 years (11) compared

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with a mean of 52 years (9), a median of 58 years (10), and a mean of 56 years (11), respectively, in those without ILA. A remarkable finding by Hunninghake and colleagues was that there were, if anything, more people with ILAs in those screened who were related to patients with sporadic IPF (10). If ILAs really are precursor lesions for IPF, then it would appear that there is more heritable disease than currently recognized. Overall, these data support the hypothesis that ILAs are precursor lesions of IPF, the latter presenting late in 60th decade or early in the 70th decade (2), but are also associated with the *MUC5B* polymorphism and short telomeres (12, 13). However, it is a little premature to describe even fibrotic ILAs as preclinical pulmonary fibrosis because the natural history of these lesions is still not known and there do appear to be some key differences that need to be clarified.

In contrast with IPF, the majority of patients with ILAs in all three cohorts were female, although this is similar to the observations in FPF. This may indicate a difference between males and females in their fibrogenic exposures; disease progression; or, indeed, physician gender bias when making a diagnosis of sporadic IPF as opposed to FPF. Furthermore, demographic differences were observed in relation to ever-smoking with lower rates in ILA than would be expected in IPF, with less than 50% of those with observed with ILA describing themselves as ever-smokers. However, the risk of having ILA compared with no ILA was only lower in male ever-smokers in one study (9). Therefore, it might be possible that ILAs are precursor lesions in those with additional risk factors such as male sex, ever-smoking history, *MUC5B* polymorphism, and short telomeres. However, for this to be confirmed, it is crucial to know the natural history of ILA because the defining feature of IPF is its remorselessly progressive nature (2). Unfortunately, only one study directly addressed this, and then only in 129 patients. However, after five years of follow-up, almost 20% had developed study-defined interstitial lung disease (ILD). Most of these were in patients with an ILA at enrollment, although six relatives without an ILA at enrollment went on to develop an ILD (9). These rates of progression are substantially lower than observed in AGES (Age Gene/Environment Susceptibility)-Reykjavik study in which 73% of 327 patients progressed radiologically over five years (14).

Another concern is that these studies are just revealing undiagnosed pulmonary fibrosis. It is well-recognized that patients present after years of increasing symptoms (1). However, it seems unlikely that the study by Salisbury and colleagues was revealing undiagnosed disease because only 4% had extensive ILA and there was little functional difference between patients with or without ILA, with near-normal lung function in the small number of patients with available data (9). However, in contrast, 18% of people in the study by Hunninghake and colleagues had changes sufficiently extensive to merit the label of an ILD even though they had a fairly well-preserved FVC, although a substantially reduced D_{LCO}, and a number required treatment with an antifibrotic (10).

Should we screen people for ILA? The two major risks for any screening intervention are lead-time bias and harm due to overdiagnosis. Given the nature of antifibrotic therapy, it would seem that lead-time bias should not be a major concern, at least in health care settings outside of the United Kingdom. However, in the United Kingdom, lead-time bias would be a major problem because, perversely, patients would still need to progress until their FVC dropped to 80% predicted before they would be eligible for treatment to slow progression. The risk of overdiagnosis is, however, a considerable risk. Antifibrotic therapies have considerable adverse effects (15, 16) and their long-term adverse effects are uncertain, especially for nintedanib, and so it would be difficult to recommend therapy for an ILA if it was not certain to progress to progressive fibrotic lung disease. Furthermore, the economic effects of treating 10% of the population over the age of 55 years with antifibrotics would not be trivial in any health care setting.

Therefore, the ILD community urgently needs to determine which patients have ILAs that will progress and which have ILAs that will not. This will require carefully performed longitudinal studies with appropriately conducted and validated risk prediction models. This is step two to curing IPF! It is frustrating that the three studies investigating screening of first-degree relatives published in the last 12 months used different definitions of ILA (9–11), and did not collect standardized lung function, symptom, or follow-up data. Definitely more Groundhog Day than runaway train.

It is crucial, given the small number of people with ILAs in such studies, that definitions are standardized to both maximize the potential for meta-analysis and also to develop appropriate management protocols. More importantly, given the risk of overdiagnosis, there urgently needs to be agreement on how to distinguish an ILA from an ILD and define when treatment should be initiated. For example, should a 55-year-old female with no symptoms and normal FVC and D_{LCO} but with evidence of honeycombing and traction change on high-resolution computed tomographic imaging be labeled as having an ILA or a fibrotic ILD in need of antifibrotic therapy? Would the label change in the presence of an appropriate exposure history, genetic architecture, or biomarker profile? These are urgent questions that need answering and, once again, I find myself calling for collaboration between groups to address these time-pressured questions. Groundhog Day again?!

These studies highlight the enormous potential that screening people for ILAs holds and how crucial it will be to cure IPF. However, who to screen; when to screen; how often to screen; and, most importantly, what to do when an ILA is discovered remain to be determined. I have little doubt that if the community can work together and build on the fascinating results presented in these two important studies, we will all be the heroes as we prevent the runaway train of progressive fibrosis and find a way to cure patients with IPF. ■

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The Wnt Signaling Pathway and the Development of Bronchopulmonary Dysplasia

Extremely premature neonates born at the canalicular to saccular stage of lung development (22–28 wk of gestation) are at very high risk of developing bronchopulmonary dysplasia (BPD). The premature lung, now having to complete lung development in the extrauterine environment, is subjected to many adverse exposures, including hyperoxia, that promote the development of BPD. Many developmental pathways are precisely orchestrated for optimal lung maturation. Decreased or sustained activation of these pathways may contribute to the pathogenesis of this disease or may impair recovery of the lung from injury. Identification of these novel pathways and their mediators is crucial for the establishment of mechanisms leading to BPD and the development of novel therapeutic strategies.

The Wnt signaling pathway is critical both during embryonic development and in lung diseases throughout the lifespan (1). The Wnt family of proteins includes a large number of members that control a variety of developmental processes, including cell fate, proliferation, polarity, and migration. Wnt signaling consists of canonical, β-catenin–dependent signaling and two noncanonical pathways, including planar cell polarity and calcium-calmodulin–dependent protein kinase II/protein kinase C signaling. The canonical signaling pathway involves a number of proteins, including the transmembrane receptor Frizzled, coreceptors, and a variety of proteins that make up a "destruction complex" that control degradation versus nuclear translocation of β-catenin. On translocation to the nucleus, β-catenin activates several Wnt target genes (1). In distal lung development, Wnts provide spatiotemporal cues to coordinate an intricate crosstalk between the lung epithelium and mesenchymal cells (2). Frank and colleagues showed that Wnt signaling is reactivated during alveologenesis and leads to proliferation of type 2 alveolar epithelial cells (AECs), whereas inhibition of Wnt signaling decreased proliferation and promoted transdifferentiation of type 2 AECs to type 1 AECs (3). Increased Wnt/β-catenin activity occurs in patients with BPD, whereas inhibition of WNT/β-catenin signaling attenuates hyperoxia-induced lung injury in neonatal rodent models (4–6).

In this issue of the *Journal*, studies by Sucre and colleagues (pp. 1249–1262) focus on the role of Wnt5a, a noncanonical Wnt that is required for normal distal lung morphogenesis (7). The authors chose to study Wnt5a because of previously published reports of its role in lung diseases such as idiopathic pulmonary

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