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Interstitial lung abnormalities: erecting fences in the path towards advanced pulmonary fibrosis

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ABSTRACT

Interstitial lung abnormalities, when present in members of undiagnosed family members recruited on the basis of familial interstitial pneumonia, or in undiagnosed research participants, have been associated with a syndrome that includes distinct sets of imaging abnormalities, restrictive physiological and exercise impairments, and an increased prevalence of histopathological findings, and genetic predictors, that have been noted in patients with idiopathic pulmonary fibrosis. Recent longitudinal studies have demonstrated that qualitative and quantitative assessments of interstitial abnormalities are associated with accelerated lung function decline, an increased rate of clinical diagnoses of interstitial lung disease and an increased rate of mortality. In this perspective, in addition to reviewing the prior information, four major efforts that could help the field of early pulmonary fibrosis detection move forward are discussed. These efforts include: (1) developing standards for characterising and reporting imaging findings from patients with existing CTs; (2) developing consensus statements on when undiagnosed and asymptomatic imaging abnormalities should be considered a disease; (3) identifying populations for which screening efforts might be beneficial; and (4) considering approaches to developing effective secondary prevention trials.

INTRODUCTION

> *If people are falling over the edge of a cliff and sustaining injuries, the problem could be dealt with by stationing ambulances at the bottom or erecting a fence at the top. Unfortunately, we put far too much effort into the provision of ambulances and far too little into the simple approach of erecting fences.* — Denis Burkitt, in a paraphrase[1] of the ideas in a poem 'The Ambulance Down in the Valley' (1895) by Joseph Malins

While Denis Burkitt, an Irish paediatric surgeon, is best known for his description of, and work to cure, a common childhood cancer which now bears his name (Burkitt's lymphoma), he is also remembered for his efforts to increase the emphasis on prevention in medicine. This quotation, which alludes to his frustration at the low priority preventive efforts for common malignancies were given in medical education,[2] is also an apt description of the current focus of medical care in pulmonary fibrosis. To be fair, the process of erecting effective fences in the path to advanced pulmonary fibrosis will not be simple and will require more investigation and thoughtful planning.

How can we begin the process of stopping, or slowing, our patient's progress towards the cliff whose precipice often begins with the development of respiratory symptoms? The answer to this question is not entirely straightforward; however, a rational approach is beginning to take shape. To explore this topic, let us confront the controversial issues in the field of early pulmonary fibrosis detection and consider approaches that may help address the most important challenges.

In this perspective I will briefly discuss background information with an emphasis on discussing longitudinal outcome data, much of which have been published since prior reviews. Given the scope of the problem of undiagnosed early stages of pulmonary fibrosis I will discuss a logical set of approaches that begin to address those with existing chest CTs, groups where research on further screening may be warranted and future secondary prevention trials.

BACKGROUND

While the concept of early disease detection in those at risk for pulmonary fibrosis is not new,[3] accelerating interest in this topic likely stems from clinical trial results demonstrating that the rate of decline in pulmonary function in patients with idiopathic pulmonary fibrosis (IPF), the most severe form of pulmonary fibrosis,[4] can be slowed with antifibrotic medical therapy,[5 6] even when started in patients with less severe disease.[7 8] If durable benefits like these extend to those in the earliest stages of their disease process it is rational to conclude that major reductions in the morbidity and mortality associated with a delay in the development of more advanced stages of pulmonary fibrosis are achievable.

What defines an early stage of pulmonary fibrosis? We don't have answer to this question yet. However, replicable findings are accumulating that should be helpful in providing a core body of evidence on which consensus definitions could be based. Much of the recent evidence emanates from a starting point that begins with chest CT assessments of undiagnosed family members of patients with Familial Interstitial Pneumonia (FIP)[9–11] and undiagnosed participants in epidemiological studies initiated to address other medical concerns.[12–14]

Although the definition varies slightly by study, a common definition of FIP includes the presence of more than one first-degree relative in a family with a diagnosis of an idiopathic interstitial pneumonia.[15] Standardised methods of declaring early pulmonary fibrosis in undiagnosed relatives of patients with FIP (or determining that FIP is present an additional family member who has not been clinically diagnosed) have not been clearly

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defined. In undiagnosed research participants, the term interstitial lung abnormalities (ILA) is often used to characterise the chest CT scan image when abnormalities are present that are similar to those noted in patients with an interstitial lung disease (ILD).[13 14 16 17] In some studies, the research participant with an abnormal chest CT is referred to as having subclinical ILD.[18–20] Definitions for ILA and subclinical ILD (also referred to by other names including 'dirty-lung',[21] or preclinical ILD)[22] vary more widely by study. Definitions for ILA include qualitative assessments of individual chest CTs in studies with unique recruitment criteria by single[23] or multiple[24] imaging readers with differing imaging characterisation criteria.[13 16 18 23] Definitions of quantitative assessments of interstitial features include those that result from densitometric[12] and algorithmically trained local histogram measures.[25] Quantitative metrics of interstitial abnormalities have been termed high attenuation areas when referring to densitometric assessments,[12] and interstitial features when referring to local histogram measures.[25] Standardised methods of declaring early pulmonary fibrosis in an undiagnosed research participant have also not been clearly defined. Some effort to develop these standards among the various research groups should be undertaken so that readers can adequately compare findings across populations.

LONGITUDINAL OUTCOMES AND ILA

Prior reviews[26–28] have covered some of the evidence that demonstrates common imaging, physiological and genetic links between research participants with ILA, or subclinical ILD, and patients with a known diagnosis of ILD, or IPF. This information will not be represented here in detail. Briefly, insights from this work include the fact that although ILA is more prevalent (2%–10% in adults)[12 13 16] than IPF is reported to be (~0.5% of the population >age 65),[29–31] research participants with ILA can have a similar syndrome that includes overlapping imaging findings,[32] restrictive physiological and exercise impairments,[13 14 33–35] and an increased prevalence of histopathological findings,[9 36] genetic predictors[9 14 32 37] and profibrotic biomarkers,[19 38 39] which have been noted in patients with IPF.

Although this information is compelling and suggests important connections between undiagnosed research participants with ILA and patients with clinically identified pulmonary fibrosis, the argument to pursue clinical screening efforts would be much less convincing if evidence did not suggest that those with ILA could progress and experience adverse longitudinal outcomes. This has not been the case. As reviewed in table 1, numerous groups have demonstrated data on the rates of imaging progression[16 18 23 40 41]

Table 1 Comparisons of longitudinal outcome measures in research participants with interstitial lung abnormalities (ILA) or subclinical interstitial lung disease (ILD) by cohort

	Per cent or median/means where appropriate and noted								
Variable	**MESA†**	**Nagano, Japan‡**	**COPDGene§**	**MILD¶**	**FHS****	**ECLIPSE††**	**NLST‡‡**	**AGES-Reykjavik§§**	**BWH RoCI¶¶**
Baseline prevalence of ILA (%)	11	3	8	4	7	9	10	7	8
Radiological progression									
Overall progression, follow-up time	–	46%, 4 years	–	25%, 3 years	43%, 6 years	–	20%, 2 years	–	–
Morbidity									
FVC annual rate of decline (compared with general pop)	–	–	–	–	~2 times greater (for those with imaging progression)	–	–	–	–
Development of ARDS	–	–	–	–	–	–	–	–	OR 4.2 (among those presenting to the ICU with SIRS or sepsis)
Development of clinical ILD/PF diagnoses	Increased ILD diagnoses in those with elevated measures of HAA	–	–	–	–	–	Some cases identified on death certificates	Some cases identified on death certificates	Some cases identified on autopsy
Mortality									
Risk of death	Increased mortality in those with elevated measures of HAA	–	RR 1.6* (also increased in those with increased quantitative interstitial changes)	–	RR 2.2*	RR 1.4*	RR>4.0*	RR 1.3	RR 2.1
Absolute mortality	–	–	10% ~5 years	–	7% ~4 years	11% ~3 years	97% ~12 years	56% ~9 years	37% ~28 days

†MESA: The Multi-Ethnic Study of Atherosclerosis—lung study. Data in the MESA column refer to Lederer *et al*,[12] Podolanczuk *et al*[19] and Podolanczuk *et al*.[41] The range of values noted in the column refers to the differences in expected prevalence depending on the threshold of high attenuation areas used to define ILA.
‡Nagano, Japan: Subjects participating in a health screening programme from Nagano Prefecture, Japan. Data refer to Tsushima *et al*.[23]
§COPDGene: Data in the COPDGene column refer to Washko *et al*,[13] Putman *et al*[42] and Ash *et al*.[34]
¶MILD: The Multicentric Italian Lung Detection trial. Data in the MILD column refer to Sverzellati *et al*.[18] Estimates of prevalence, frequency and median values refer to those with interstitial abnormalities but limited to either a usual interstitial pneumonia or another chronic interstitial pneumonia pattern on chest CT.
**FHS: Framingham Heart Study. Data in the FHS column refer to Hunninghake *et al*,[14] Putman *et al*[42] and Araki *et al*.[40]
††ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints. Data in the ECLIPSE column refer to Putman *et al*.[42]
‡‡ NLST: National Lung Screening Trial. Data in the NLST column refer to Jin *et al*[16] and Pompe *et al*.[44]
§§AGES-Reykjavik: Age Gene/Environment Susceptibility-Reykjavik study. Data in the AGES-Reykjavik column refer to Putman *et al*.[42]
¶¶ BWH RoCI: Brigham and Women's Hospital Registry of Critical Illness cohort. Data in the BWH RoCI column refer to Putman *et al*.[43]
ARDS, acute respiratory distress syndrome; HAA, high attenuation areas (of the lung); ICU, intensive care unit; PF, pulmonary fibrosis; SIRS, systemic inflammatory response syndrome.

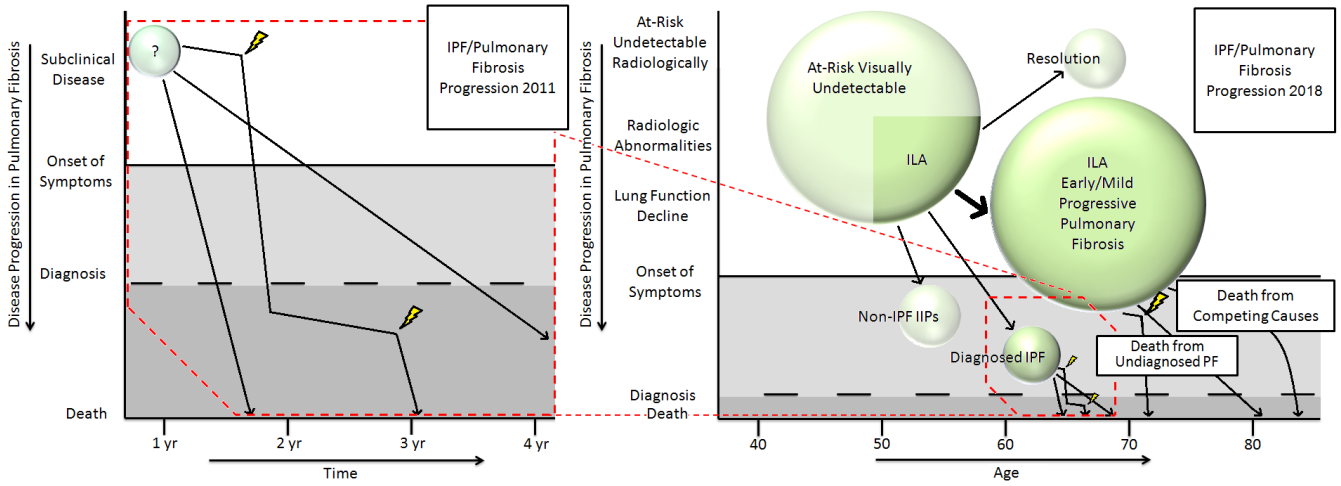

Figure 1 The figure (adapted from Ley *et al* (2011)[56]) includes a speculative representation of how idiopathic pulmonary fibrosis (IPF) progression might occur from those with an early stage of pulmonary fibrosis (PF) or subclinical disease (left panel). An updated and expanded representation of current knowledge (right panel) which highlights the under-recognised burden of early PF, the risk for accelerated lung function decline and early death[40 42] even among those not diagnosed with IPF. IIP, idiopathic interstitial pneumonia; ILA, interstitial lung abnormalities.

(including an interval development of fibrosis in general, and imaging patterns consistent with usual interstitial pneumonia (UIP) in particular)[40 41] experienced by research participants with ILA. Additionally, while ILA progression has been associated with an accelerated lung function decline and an increased rate of mortality,[40] ILA in general (as well as quantitative metrics suggestive of ILA) have been associated with increased rates of clinical ILD/pulmonary fibrosis development,[41–43] and an increased risk for death (including elevated respiratory-related mortality rates from pulmonary fibrosis and acute respiratory distress syndrome).[19 34 42–45] In total these findings suggest a paradigm shift in our thinking about the early undiagnosed phase of pulmonary fibrosis is warranted (see figure 1).

These consistent and replicable findings show us that the development of fibrotic imaging findings and accelerated lung function decline frequently occur before the development of respiratory symptoms leads to a diagnosis of clinical ILD. While there is no current evidence that early interventions will lead to improved outcomes in those with ILA the case for indifference is becoming harder to support. In the remainder of this perspective I will discuss steps that should help lay the foundation on which fences attempting to obstruct the path towards advanced pulmonary fibrosis could be built (summarised in table 2).

STANDARDISING RADIOLOGICAL REPORTING OF ILA

The first step in this process includes developing a consensus on reporting ILA in patients with existing chest CTs obtained when an underlying clinical ILD, or early stage of pulmonary fibrosis, was not initially suspected. Much has been written on

Table 2 Key findings in interstitial lung abnormalities, important missing information and action items

Key findings	Goal	Missing information	Action items
Interstitial lung abnormalities (a diverse set of chest CT imaging findings suggestive of an underlying interstitial lung disease) are relatively common in older adults and are associated with adverse outcomes.	To develop radiological standards on reporting interstitial abnormalities.	Do specific imaging findings help predict progression and adverse outcomes in those with interstitial abnormalities?	Studies should focus on trying to identify if specific radiological features and patterns help predict adverse outcomes in those with interstitial abnormalities.
Studies of physiological and histopathological data suggest that some people with interstitial abnormalities have an early stage of pulmonary fibrosis.	To develop consensus statements on when an imaging abnormality constitutes a disease in an undiagnosed and asymptomatic person.	Can consensus on updated disease definitions be achieved?	Committees should be developed so that evidence-based consensus guidelines and position statements from major societies could be generated and updated when appropriate.
Some groups appear to be at an increased risk to develop interstitial abnormalities.	To develop effective screening programmes in high-risk groups.	What are the results of early pulmonary fibrosis screening studies? What groups are interested in participating in these types of studies?	In addition to encouraging publication from studies actively participating in screening efforts, funding agencies should consider encouraging these efforts so that populations for secondary prevention trials can be developed.
Antifibrotic therapy slows lung function decline in patients with IPF, even among those more preserved measures of pulmonary function.	To conduct secondary prevention trials in patients with early stages of pulmonary fibrosis.	What groups with interstitial abnormalities would benefit the most from early therapeutic intervention? Are there secondary endpoints that help predict longer term outcomes in those with interstitial abnormalities?	Early discussions should be undertaken to consider how to define reasonable endpoints and how to appropriately power trials in those with early stages of pulmonary fibrosis.

IPF, idiopathic pulmonary fibrosis.

methods for reporting imaging patterns,[46] and the importance of,[47] a chest CT in the evaluation of a patient suspected of having IPF. Efforts have also been made to standardise the reporting of imaging features found in patients suspected to have an ILD in general.[48] Despite this body of work, our findings demonstrate that radiological reports of these imaging features and patterns can be quite variable in the clinical setting when the chest CT scan is performed for another reason.[36 43 49] For example, when an oncologist orders a chest CT scan to exclude recurrent malignancy and the radiologist's report of interstitial features is limited to the statement 'bilateral subpleural reticulation is present' it could be argued that this report does not seem designed to raise an appropriate level of clinical concern.[36 43 49] As a contrast, the radiologist's report could include the statement, 'Bilateral subpleural reticulation is present. These findings may represent an early stage of an ILD or pulmonary fibrosis. In the right clinical context, a referral to a pulmonologist for further evaluation is recommended.'

As first suggested by Wells and Kokosi,[49] a consensus position paper on recommendations for radiological reporting of ILA, and ILA subgroups, similar to those that exist for patients with clinically suspected IPF,[46] is warranted. However, for standardised radiological reporting of ILA to be effective, it would be important to determine if different imaging features and patterns of ILA confer variable outcomes. Based on the diversity of ILA phenotypes[32] and ILDs in general,[50] current definitions of ILA[24] almost certainly include a spectrum of diverse forms of ILD (as well as some cases of other conditions masquerading as ILD). While there are data to suggest that different imaging patterns in undiagnosed research participants with ILA are associated with different degrees of relative lung volume reduction[13] and exercise limitation,[51] it will be critical to determine if different imaging features and patterns (or the quantity of these imaging features and patterns) confer variable longitudinal outcomes. For example, it would be helpful to determine if the increased rate of mortality noted in research participants with ILA is different in those whose ILA is defined by the presence of centrilobular ground glass nodules versus those whose ILA is defined by the presence of traction bronchiectasis. These imaging findings are often present in distinct forms of ILD and are felt to confer different prognoses when identified in the clinical setting.[52] Attempts should be also made to develop consensus recommendations on further evaluation and clinical referral.

FROM ABNORMALITY TO DISEASE

If agreement can be reached on standardised methods of reporting chest CT imaging in the clinical setting, we should be prepared to address the question of what set of findings constitutes merely an imaging abnormality and what set of findings constitutes a disease. To what extent should reduced, or declining, lung volume or gas exchange measures be included in these definitions? When should a lung biopsy be recommended for a diagnosis to be made? Should we consider separating some diseases into clinical stages (eg, would there be a value to defining an early and/or mild stage of IPF)? These distinctions are important for multiple reasons.

The most recent guidelines from the American Thoracic, European Respiratory, and Japanese Respiratory Societies, and Latin American Thoracic Association, on IPF diagnosis provide guidelines on the diagnostic criteria in symptomatic, *and asymptomatic,* patients suspected of having clinical IPF.[53] We may be able to agree as an ILD community that a chest CT demonstrating a UIP pattern, even in an asymptomatic older patient (without clinical or serological evidence for an alternate diagnosis), can be sufficient to diagnose IPF as a disease. The label 'disease' is important as this would qualify the patient for antifibrotic[5 6] therapy. However, given the relatively high prevalence of ILA in the general population[14] (much of which could be described as having an indeterminate for UIP pattern[32 53]) it is easy to see how these guidelines could lead to overdiagnosis of 'disease' and the institution of medical therapy in groups who would not have made entry criteria into the studies of antifibrotic therapy.[5 6] If we do use the term 'disease' perhaps creating clinical subsets (eg, early and/or mild IPF) would allow us to define subgroups for whom we should acknowledge that the benefit of medical therapy is currently less clear.

IDENTIFYING POPULATIONS FOR SCREENING

Although general chest CT screening efforts for pulmonary fibrosis are not warranted due to small, but measurable, increases in the rate of malignancy that are conferred by accumulating radiation exposure,[54] there are groups at a higher risk for subclinical ILD for whom the benefits of screening may one day be realised. Given the potential scope of the problem, groups have become interested in, and the National Institutes of Health (NIH) is funding, screening efforts in undiagnosed patients with rheumatoid arthritis (NIH grant numbers K23HL119558 and K23HL138131) and in undiagnosed first-degree relatives of patients with FIP specifically (NIH grant numbers P01HL092870) and with an idiopathic interstitial pneumonia with pulmonary fibrosis more generally (NIH grant numbers R01HL130974 and R01HL103676). There may be other groups for whom screening efforts might be of value. In addition to discovering shared and novel pathophysiological mechanisms,[9] hopefully these studies will also address other important questions. Are there important, and easily measured, factors (beyond chest CT imaging) that help predict underlying pulmonary fibrosis in populations screened? How commonly do those screened for an early and/or mild stage of pulmonary fibrosis progress (and over what period of time)? How do individuals respond to receiving information about the presence of an early and/or mild stage of pulmonary fibrosis? What are the perceived benefits and negative consequences of receiving this type of information? These questions are critical to address before investments in prevention, and clinical trials, in screened populations are considered.

PREVENTION, CLINICAL TRIALS AND PRIMARY OUTCOMES

While the ultimate goal of this work is to consider if interventions targeted to those with early and/or mild stages of pulmonary fibrosis would mitigate or prevent the progression to more advanced stages of disease, this topic should be approached with some caution. It is not known what percentage of people diagnosed with an early and/or mild stage of pulmonary fibrosis would want to participate in an interventional study. Interventional studies should consider the possibility that primary preventive efforts (eg, smoking cessation) could be of value. The tolerance of drug side effects is likely to be much lower in asymptomatic people who may need to be on therapy for longer periods of time. Interventional studies hoping to achieve more global patient-oriented benefits should carefully consider other competing risks such as lung function decline from COPD or mortality from coronary artery disease (particularly in older populations). Although imaging progression of ILA has been associated with an accelerated decline in measures of FVC,[40] the annual rates of FVC decline in those with ILA are substantially less than

the declines noted in clinical studies of patients with IPF.[55] This suggests that future clinical trials of those with early and/or mild stages of pulmonary fibrosis may need to enroll larger numbers, follow patients for longer periods of time, or consider alternate surrogate enpoints. In addition, some effort should be given to enriching trials with those experiencing greater degrees of physiologic decline so that they can be sufficiently powered to detect important differences.

SUMMARY AND FUTURE DIRECTIONS

As the process of early disease detection for pulmonary fibrosis moves closer to becoming a reality it is important to stop to review the information that has led to this point. In this perspective, I reviewed the background and longitudinal outcome data that suggest the scope of the problem of early and/or mild pulmonary fibrosis. Deficiencies in our knowledge in this field were highlighted. In order to make progress to mitigate, or prevent, the advancement towards pulmonary fibrosis a set of steps was described. These steps include standardising chest CT image reporting and considering the role redefining disease definitions. Current efforts and goals of screening efforts for pulmonary fibrosis in unique populations were described. This perspective concludes with some thoughts on what issues might be important to address before future interventional trials are considered.

Hopefully we will continue to make progress, and continue to invest in, the processes of erecting effective fences that may one day help keep more people included on the grassy fields of good health. Walls to exclude people are rarely effective.

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