Patterns of progression in non-IPF fibrotic interstitial lung disease

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Purpose of review
To characterize patterns of disease progression in the designation of progressive pulmonary fibrosis (PPF), including their relative prevalence and subsequent prognostic significance, in patients with fibrotic interstitial lung disease (ILD), including key patient sub-groups.

Recent findings
In recent large clinical cohorts, PPF criteria suited to early PPF identification, based on their prevalence and short time to progression, include a relative forced vital capacity (FVC) decline exceeding 10% and various combinations of lower thresholds for FVC decline, symptomatic worsening and serial progression of fibrosis on imaging. Amongst numerous candidate PPF criteria, these progression patterns may have the greatest prognostic significance based on subsequent mortality, although there are conflicting data based on subsequent FVC progression. The prevalence of patterns of progression is similar across major diagnostic sub-groups with the striking exception of patients with underlying inflammatory myopathy.

Summary
Based on prevalence and the prognostic significance of PPF criteria, and the need for early identification of disease progression, recent published data in large clinical cohorts provide support for the use of the INBUILD PPF criteria. The patterns of disease progression used to designate PPF in a recent multinational guideline are mostly not based on data in previous and subsequent real-world cohorts.

Keywords
criteria for progressive pulmonary fibrosis, evidence-based guidelines, prevalence, prognostic significance

INTRODUCTION

In patients with fibrotic lung diseases other than idiopathic pulmonary fibrosis (IPF), an important subset progresses despite initial management. This phenotype has been variously termed 'the progressive fibrotic phenotype', 'progressive fibrosing interstitial lung disease' and, in a recent guideline statement, 'progressive pulmonary fibrosis' (PPF), the term adopted in this review [1,2,3▪▪]. PPF has a high morbidity and mortality. The majority of patients in large cohorts exploring PPF have had multidisciplinary diagnoses of fibrotic hypersensitivity pneumonitis (fHP), interstitial lung disease associated with connective tissue disease (CTD-ILD) or idiopathic interstitial pneumonias (IIP) other than idiopathic pulmonary fibrosis (IPF), including fibrotic nonspecific interstitial pneumonia (fNSIP) and unclassifiable interstitial lung disease (U-ILD) [2,4,5,6▪▪]. The proportion of patients with PPF occurring within 24 months in non-IPF fibrotic ILD, excluding fibrotic sarcoidosis, was initially believed to approximate 30%, based on retrospective series [7]. However, the prevalence of PPF varies according to the pattern of progression, variably defined using INBUILD criteria, stand-alone serial measures and various other multidimensional combinations. In this review, the prevalence of patterns of progression in large cohorts is examined. The prognostic significance of individual PPF criteria, and the prevalence of progression in key diagnostic sub-groups, before and after the designation of PPF, are explored.

PATTERNS OF PROGRESSION IN THE DESIGNATION OF PROGRESSIVE PULMONARY FIBROSIS AND THEIR PREVALENCE

In the pivotal INBUILD trial of nintedanib in PPF, enrolment required satisfaction of progression

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KEY POINTS

- Patterns of disease progression used to identify PPF in the INBUILD study appear to be suited to the early identification of PPF.
- The prognostic significance of patterns of disease progression that define INBUILD PPF criteria has been broadly validated against subsequent mortality and appears to be more accurate against mortality than alternative candidate PPF criteria.
- Based on serial data in large cohorts, future PPF criteria may need to be nuanced in CTD-ILD, and especially in patients with underlying inflammatory myopathy.
- These conclusions are strictly provisional and need to be explored in future prospective studies, with an additional focus on alternative PPF criteria, including guideline criteria.

criteria in the previous 24 months, defined as a relative decline of forced vital capacity (FVC) at least 10%, or two of any of an at least 5% to less than 10% relative decline in FVC, symptomatic worsening or progression of fibrosis on computed tomography (CT) [2]. These criteria were chosen in order to integrate serial variables routinely used in clinical practice and were broader than those used to define PPF in other antifibrotic trials [8,9]. The proportion of INBUILD patterns of disease progression in large cohorts is shown in Table 1. In the INBUILD cohort, PPF most frequently manifested as a relative decline in FVC at least 10% (332 of 663 patients, 50.1%).

Criteria used to define PPF were the subject of reviews in which modifications of the INBUILD were proposed [3▪▪,10,11]. Importantly, the definitions of PPF in antifibrotic trials and in subsequent expert group statements, including a recent guideline statement, were not evidence-based but were constructed based on expert perceptions of real-world practice and the routine accessibility of monitoring variables. Separate definitions of PPF in trials and expert group statements, with the exception of guideline recommendations, are not discussed further in this review, as it can be argued that future definitions of PPF should be based on actual data in large real-world cohorts and data likely to emerge in the near future.

Hambly *et al*. [6▪▪] explored the real-world prevalence and characteristics of disease progression, defined by the satisfaction of INBUILD enrolment criteria within 24 months of diagnosis, in a prospective registry of patients with fibrotic ILD of all subtypes. In the whole cohort (including IPF patients),

Table 1. Prevalence of patterns of progression in non-IPF fibrotic ILD

	Maher [14▪]	Nasser [4]	Torrisi [5]	Oldham [12▪▪]	Hambly [6▪▪]
Nature of cohort	Pharmaceutical	Retrospective real world	Retrospective real world	Retrospective real world	Prospective real world
ILD diagnoses	Non-IPF fibrotic ILD $n=663$	Non-IPF fibrotic ILD $n=165$	Non-IPF fibrotic ILD $n=566$	fHP, CTD-ILD, or non-IPF IIP $n=1,227$	Fibrotic ILD including IPF $n=2746$
Duration of monitoring	24 months	24 months	24 months	Not time limited	24 months
Prevalence of progression, defined using INBUILD criteria***	663, 100%	165, 100%	274, 48.4%	Not quantified*	1376, 50.1% (46.8%, in non-IPF patients)
Rel. FVC decline ≥10%	332, 50.1%	109, 66.1%	189, 33.4%	689, 56.2%	675, 24.6%
Rel. FVC decline ≥5% - <10%, symptomatic decline	20, 31.2%	41, 24.8%	175, 31.2%	205/795** 25.8%	166, 6.0%
Rel FVC decline ≥5% - <10% Increasing fibrosis on CT			152, 26.9%	151/648** 23.3%	113, 4.1%
Worsening symptoms, increasing fibrosis on CT	124, 18.7%	15, 9.1%	40, 7.0%	353/1013** 34.8%	352, 12.8%
Absolute FVC decline ≥5%	Not quantified	Not quantified	106, 18.7% (within 6 months)	754, 61.5%	Not quantified

*Grouped INBUILD criteria not evaluated.
**Patient sub-groups for individual PPF criteria selected according to the performance of serial CT and the existence of retrospective statements on serial respiratory symptoms.
***Prevalence of first INBUILD criterion met within the 24 month time interval from diagnosis.
The prevalence of patterns of progression in non-IPF fibrotic ILD, defined using INBUILD PPF grouped criteria, individual INBUILD PPF criteria and an absolute decline in FVC ≥5% (a progression criterion in a recent multinational PPF guideline). CTD-ILD, interstitial lung disease associated with connective tissue disease; fHP, fibrotic hypersensitivity pneumonitis; IIP, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; CT, computed tomography; FVC, forced vital capacity.

progression occurred in 1376 of 2746 patients (50.1%). The frequency of PPF in major non-IPF disease sub-groups was 58% (125/216) in fHP, 51% (281/550) in U-ILD, 45% (402/902) in CTD-ILD and 39% (140/360) in other diseases. Excluding patients with sarcoidosis, the prevalence of PPF was 47.5% (919/1936), compared with a prevalence of progression within 24 months of 59.5% in 718 IPF patients. In the whole cohort, including IPF patients, the criterion of a relative FVC decline greater than 10% was satisfied in 675 of 1376 patients (49.1%) with PPF or IPF progression. Time to progression was similar across major disease sub-groups and virtually identical in IPF and fHP. Importantly, time to progression was a continuum across 24 months: there were minimal differences in the prevalence of progression, comparing 0–12 months with 12–24 months, in all major diagnostic sub-groups.

Several important conclusions come from this large, prospective study. The prevalence of PPF (approximating 50% at 2 years with censoring of follow-up) appears to be higher than previously estimated from small, early retrospective series [7], although similar to that in a larger retrospective cohort [4]. The study validates earlier reports that amongst INBUILD PPF criteria, a relative FVC decline at least 10% is the most frequent pattern of progression. Importantly, based on the continuous distribution of progression events in major diagnostic sub-groups, it is difficult to argue that progression within 12 months should be viewed separately from progression occurring 12–24 months after diagnosis in non-IPF fibrotic ILD.

In a retrospective study, Oldham *et al.* [12▪▪] explored patterns of progression in 1227 patients with fHP, CTD-ILD or non-IPF IIP, with a test cohort of 754 patients from three USA centres and a UK validation cohort of 473 patients. Candidate PPF criteria, including INBUILD criteria, their component parts (i.e. stand-alone serial measures) and other potential criteria were identified during prolonged follow-up of up to 10 years. The prevalence of individual PPF criteria was broadly similar in the test and validation cohorts. Amongst all candidate PPF criteria, the most frequent was a standalone relative FVC decline at least 5%, observed in 69.7% of subjects in the combined cohorts, with median times to progression of 10.6 and 12.9 months, in the test and validation cohorts respectively. A relative FVC decline of at least 5% to less than 10% was more frequently associated with a relative carbon monoxide diffusion capacity (DLco) decline of at least 15% than with progression of fibrosis on CT or worsening respiratory symptoms. The median time to progression was shortest for at least 5% relative decline and longest for progression of fibrosis on CT (24.5 and 30.2 months in the test and validation cohorts). Importantly, amongst INBUILD PPF criteria, a relative decline in FVC at least 10% was observed in 56.2% of patients in the combined cohorts, with median times to progression of 15.3 months in the test cohort and 24 months in the validation cohort. Key outcome analyses and patient sub-group data in this study are covered in later sections of this review.

This is the only large cohort containing sophisticated analyses of a number of stand-alone progression variables. Importantly, the relative prevalence of patterns of progression in the designation of PPF is influenced, in part, by the selective performance of serial CT and also, in this and other retrospective series, missing data on the presence or absence of change in respiratory symptoms. By contrast, lung function follow-up was obtained in all patients in all studies and overall, it appears that the single most prevalent pattern of progression is a relative FVC decline of more than 5%, alone or in combination with other serial variables.

In the only other large cohort in which a number of selected stand-alone variables were explored, the prevalence of an isolated relative decline in FVC at least 5% was not quantified [5]. However, patient sub-groups with FVC declines of at least 5% to less than 10% associated with worsening respiratory symptoms and worsening of fibrosis on CT totalled 58.1%, compared with the 33.4% prevalence of a relative FVC decline at least 10% (although it is likely that a significant proportion of patients satisfied both composite criteria).

Thus, across series, amongst the widely used INBUILD criteria, a relative FVC decline greater than 10% has consistently been the single most prevalent pattern of progression. The higher prevalence of a relative FVC decline greater than 5%, either as a stand-alone measure or in combination with other variables, allows the earlier identification of progression. However, the prognostic significance of candidate PPF criteria is also an important consideration, especially when low thresholds for FVC decline are considered.

THE PROGNOSTIC SIGNIFICANCE OF PROGRESSIVE PULMONARY FIBROSIS CRITERIA

In the INBUILD cohort, the rate of decline in FVC in the placebo arm did not differ significantly from that in the placebo arms of the INPULSIS IPF trials [13]. However, the rate of FVC progression in the INBUILD placebo arm was linked to criteria used to define PPF at enrolment. FVC decline was

substantially greater in patients enrolled with a relative FVC decline at least 10% (241.9 ml) than in those with a decline in FVC at least 5% to less than 10%, associated with worsening respiratory symptoms and/or increased extent of fibrosis on HRCT (133.1 ml), and in those with worsening respiratory symptoms and increased extent of fibrosis on HRCT (115.3 ml) [14▪].

In some series, outcomes have been examined from baseline and have included the time to progression as well as time intervals following progression [4,5]. However, in the Oldham *et al.* [12▪▪] cohort, linkages between the satisfaction of individual PPF criteria and subsequent FVC progression were evaluated. Amongst nine proposed PPF criteria, progression of fibrosis on CT, alone or in combination with other serial measures, was associated with larger subsequent FVC decline over the next 12 months, in both the test and validation cohorts (122.7 and 155.5 ml). This was followed by an at least 5% to less than 10% FVC decline associated with worsening respiratory symptoms or a relative decline in DLco at least 15% (86.3, 92.3 ml). By contrast, PPF criteria that consisted of FVC and DLco thresholds in isolation, including a relative FVC decline at least 10%, were all associated with considerably lower subsequent FVC decline. Thus, the prognostic significance of PPF criteria was greater with the use of multidimensional criteria in this study.

In an expansion of the Oldham cohort, Pugashetti *et al.* [15▪▪] undertook a validation of potential PPF criteria against transplant-free survival (TFS) in a retrospective real-world cohort of 1341 patients with fHP, CTD-ILD or non-IPF IIP. TFS was most strongly predicted by a relative FVC decline greater than 10%, irrespective of cohorts, ILD subtypes and treatment groups. Ten additional PPF criteria were predictive of reduced TFS in the test cohort, with six being reproduced in the validation cohort: PPF criteria consisting of combinations of symptomatic, lung function and radiologic worsening were generally more strongly associated with TFS than their stand-alone components but identified PPF less frequently.

Taken together, the above series provide conflicting results. In two studies, a relative decline in FVC at least 10% was the PPF criterion most strongly associated with greater subsequent FVC decline [9] or mortality [15▪▪]. However, this threshold was poorly predictive of subsequent FVC decline in the study of Oldham *et al.* [12▪▪]. It is difficult to interpret the strong prognostic value of progression on CT in that study as serial CT was not performed in all cases and the median times to CT progression were 25.9 and 32.6 months in the test and validation cohorts, respectively. Despite discrepancies between studies, the findings suggest that patterns providing optimal prognostic value should include both a relative FVC decline at least 10% and a multidimensional approach. However, all current data in this area have come from a pharmaceutical trial and a retrospective cohort: it appears essential that future PPF criteria be based, in part, on their prognostic significance in prospective real-world cohorts.

PATTERNS OF PROGRESSION IN KEY PATIENT SUB-GROUPS

In the two largest real-world cohorts, the prevalence of progression from the time of diagnosis was compared between individual ILD diagnoses. As discussed earlier, in the Canadian registry, time to progression, defined using INBUILD progression criteria, was shortest in fHP (and similar to IPF) but was significantly longer in U-ILD and CTD-ILD [6▪▪]. By contrast, in the cohort of Oldham, time to progression (i.e. the satisfaction of individual PPF criteria) was broadly similar across the three defined diagnostic ILD sub-groups [12▪▪]. The reasons for this discrepancy are unclear: one possible explanation is that the expert centres participating in the Oldham study may have referral practices that are more focused on overtly progressive ILD.

More importantly, there are conflicting data regarding the prognostic significance of PPF criteria when ILD diagnoses are compared. In the INBUILD cohort, there were only minor differences in the rate of FVC progression comparing diagnostic sub-groups in the placebo arm [14▪,16]. However, in the study of Oldham, FVC progression after PPF designation exhibited considerable heterogeneity mostly driven by the CTD-ILD diagnostic sub-group [12▪▪]. In the CTD-ILD cohort, median FVC change at 12 months, varying according to individual PPF criteria, ranged from +48.8 to −84.5 ml. The corresponding ranges for fHP and non-IPF IIP were −55.3 to −222.3 ml and −62.1 to −188.6 ml, respectively. Within the CTD-ILD sub-group, strikingly lower FVC decline after PPF designation in patients with underlying inflammatory myopathy (poorly represented in the INBUILD cohort) made a major contribution to differences in FVC progression between CTD-ILD and the other two diagnostic sub-groups.

Across a variety of individual non-IPF diagnoses, a UIP pattern, whether present at biopsy or on CT, has been associated with substantially worse outcomes including lung function progression and mortality [17]. The prognostic significance of an underlying UIP pattern, once PPF criteria have been met, has been less studied. In the placebo arm of the INBUILD cohort, patients with a UIP-like pattern on CT had the same FVC progression at 1 year as

patients in the placebo arms of the INPULSIS IPF trials, whereas FVC decline in INBUILD patients with other fibrotic patterns on CT had a significantly lesser rate of FVC progression [13]. Similarly, in the cohort of Oldham, greater FVC decline at 1 year after satisfaction of PPF criteria in patients with UIP was seen for five of the nine PPF criteria [12▪▪].

CAVEATS WITH REGARD TO RECENT PROGRESSIVE PULMONARY FIBROSIS GUIDELINE CRITERIA

As emphasized earlier, recent guideline criteria for the designation of PPF are not based on cohort data in previous and subsequent real-world cohorts, leading some to argue that the guideline designation of PPF criteria is premature [18,19]. Two immediate caveats relate to a designated progression pattern based on serial DLco trends and the requirement that PPF designation should be limited to a time interval of 12 months.

A progression pattern consisting of the combination of an absolute decline in DLco of at least 10% and worsening of respiratory symptoms specifically addresses the scenario in which lung function trends in an individual patient do not include an FVC decline threshold: in essence, an isolated decline in DLco associated with symptomatic worsening. An absolute decline in DLco at least 10% is a very high threshold in many patients with severe reduction in DLco at presentation and may risk promulgation of the view that lesser declines in DLco can be disregarded. A large decline in DLco, not associated with FVC change, is a classic manifestation of progressive pulmonary vasculopathy, and is likely to be associated with loss of exercise tolerance in individual patients. This criterion risks serious misclassification of PPF in some cases, especially in patients with CTD-ILD who have pulmonary vasculopathic processes not linked to parenchymal lung disease. The guideline authors advise clinicians to evaluate serial CT change in this scenario but this presupposes that an initial CT scan has been performed immediately before an adverse DLco trend and does not take into account the scenario of minor ILD progression as judged by CT and a separate progressive pulmonary vasculopathy of much greater clinical significance. Importantly, the accuracy of this threshold of DLco decline has never been validated, either in studies published before guideline designation or in the recent work reviewed above.

Equally controversial is a definition of PPF requiring disease progression within a 12-month time-interval as a basis for PPF designation and the use of antifibrotic therapy in non-IPF ILD. This stipulation is not based on recent evidence: in peer reviewed data covered in this review, PPF was designated either within a 24 month period [2,4,5,6▪▪] or was explored over longer time periods [12▪▪,15▪▪]. It is important to stress that patterns of progression in non-IPF fibrotic lung disease vary greatly between patients in their rapidity. There is no consensus on patterns of 'slow' and 'rapid' progression or, indeed, reason to view the rapidity of disease progression as anything other than the temporal continuum clearly demonstrated in recent large cohorts [6▪▪,12▪▪]. Progression occurring over 12–24 months or longer may have vital clinical significance in patients with moderate-to-severe disease. By excluding these patients from access to recommended PPF treatments, the current guideline criteria do not address their unmet needs [20].

It is important to acknowledge the possibility that future research will validate the nonevidence-based guideline PPF criteria and to prioritize research studies that either confirm or refute these 'eminence-based' criteria.

CONCLUSION

Ideally, patterns of progression that define PPF should facilitate the early identification of disease progression (based on their prevalence and time to progression) and should also provide optimal prognostic significance against subsequent mortality and lung function decline. Published large real-world cohorts have variability in the duration of monitoring, the timing of follow-up from time of diagnosis, the selective use of serial CT, and the retrospective identification of serial changes in symptoms. However, these constraints aside, the INBUILD PPF criteria have largely met the above goals. Alternative progression criteria are less studied and may, in future, be integrated in revised PPF criteria derived from prospective cohorts. PPF criteria may need to be nuanced in selected diagnostic sub-groups. Some of the current guideline PPF criteria are not derived from published data, lack a robust evidential basis and require prospective validation.

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Conflicts of interest

A.U.W. has received consultancy fees and/or speaking honoraria from Boehringer Ingelheim, Roche and Veracyte.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

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Guideline recommendations add value by providing a uniform framework based on published data when there is prevailing uncertainty. This guideline is likely to be highly consequential in clinical practice, including access to antifibrotic therapy in non-IPF patients with disease progression despite initial management. However, some PPF progression patterns designated in this guideline statement have little or no evidential basis and are discrepant with PPF criteria explored in previous and subsequent cohorts. Key issues requiring urgent validation include the selection of FVC thresholds, the limitation of PPF to a time interval of 12 months and the optimal integration of DLco trends.

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The rapid development of a large prospective fibrotic ILD registry was an immense achievement that attests to collegiality across Canadian respiratory centres. This cohort allowed confirmation of observations in earlier retrospective studies and establishes that previous data in retrospective studies and much smaller cohorts, had understated the prevalence of PPF in non-IPF fibrotic ILD. Importantly, the distribution of progression events across 24 months was a linear continuum in the whole cohort, and also in individual major non-IPF sub-groups, and in IPF patients. This undermines the guideline stipulation that PPF is, by definition, confined to progression within a time interval of 12 months.

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A very large retrospective cohort, with large test and validation sub-cohorts. The analyses are complex but provide extremely important messages. This was the first, very large, real-world cohort to examine the prevalence and rapidity of a large number of candidate PPF criteria and also to define the prognostic value of individual patterns of progression, as judged by subsequent FVC decline. Importantly, initial progression occurred significantly less rapidly in patients with CTD-ILD. After initial progression, there was lower subsequent FVC decline in CTD-ILD than in other major diagnostic sub-groups and this was especially the case in patients with inflammatory myopathy.

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In the pivotal INBUILD cohort, the PPF patterns of progression at enrolment were examined against FVC decline in the placebo arm during the 12-month study. All PPF criteria were associated with subsequent mean FVC decline greater than 100 ml over 52 weeks: decline was substantially higher (241.9 ml) following a relative FVC decline at least 10%. These data can be viewed as a validation of INBUILD PPF criteria.

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A very important study in which the prognostic significance of a number of candidate PPF criteria was defined against mortality (rather than FVC decline as a surrogate for mortality). The findings validate PPF criteria consisting of either a relative decline in FVC at least 10% or multidimensional criteria with various combinations of lesser FVC decline thresholds, symptomatic worsening and progression on CT.

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