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The role of precision medicine in interstitial lung disease

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Take-home message Precision medicine holds great promise in ILD management, with advances in computational biology and biomarker research giving rise to robust diagnostic technologies and emerging applications for staging, prognosis, and assessment of treatment response.

ABSTRACT The management of interstitial lung disease (ILD) may benefit from a conceptual shift. Increased understanding of this complex and heterogeneous group of disorders over the past 20 years has highlighted the need for individualised treatment strategies that encompass diagnostic classification and disease behaviour. Biomarker-based approaches to precision medicine hold the greatest promise. Robust, large-scale biomarker-based technologies supporting ILD diagnosis have been developed, and future applications relating to staging, prognosis and assessment of treatment response are emerging. Artificial intelligence may redefine our ability to base prognostic evaluation on both diagnosis and underlying disease processes, sharpening individualised treatment algorithms to a level not previously achieved. Compared with therapeutic areas such as oncology, precision medicine in ILD is still in its infancy. However, the heterogeneous nature of ILD suggests that many relevant molecular, environmental and behavioural targets may serve as useful biomarkers if we are willing to invest in their identification and validation.

Introduction: A conceptual shift

A conceptual shift towards precision medicine is a key aspiration for the management of interstitial lung disease (ILD), which constitutes a complex, heterogeneous group of conditions [1]. Although the traditional goal of management has been to determine treatment according to an initial diagnosis, the advent of treatments and disease pathways that span multiple types of ILD suggests there is a need to move toward strategies based on more than diagnosis alone. Precision medicine offers approaches tailored to individual patients, primarily based on biomarkers [2]. It has the potential to add objectivity to management decisions that have traditionally been subjective, and flexibility to treatment pathways that have tended towards rigidity.

We propose that accurate and effective precision medicine has three broad requirements (figure 1): 1) selection of the appropriate strategy; 2) selection of appropriate tactics; and 3) evaluation of the accuracy of the individualised regimen. We define "strategies" as overall approaches that, in ILD, are a choice between observation in non-progressive disease, or intervention based on inflammatory/fibrotic and/or epithelial/fibrotic (idiopathic pulmonary fibrosis [IPF]-like) pathways. "Tactics" are defined as the selection of individual therapies to meet strategic goals. Ideally, all three of these requirements are addressed using biomarkers, with the accuracy of the individualised regimens evaluated by assessing short-term changes in biomarker signal after initial treatment. Ultimately, using precision medicine, our aim is to identify patients with progressive disease before progression occurs, and enable the course of treatment to be changed or fine-tuned in response to ongoing evaluation.

This vision for precision medicine in ILD has technological prerequisites. We believe that recent rapid developments in artificial intelligence (AI) and other technologies such as multi-omics, along with increasing understanding of ILD biomarkers, mean that a shift towards precision medicine is achievable. In this article, we chart the evolution of precision medicine in ILDs, from the categorisation of disease behaviour to the use of machine learning in diagnosis, and the 5-year outlook for identifying progressive phenotypes at presentation and individualising treatment strategies and tactics accordingly.

Foundations of precision medicine in ILD: The need for individualisation beyond diagnosis

The first landmark event for precision medicine in ILD came in 2001, with the development of an international standard classification of idiopathic interstitial pneumonias (IIPs) by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [3]. The 2001 ATS/ERS consensus classification provided uniform terminology, definitions and descriptions for use in routine clinical practice and research [3].

In 2011, evidence-based guidelines on the diagnosis and management of IPF from the ATS, ERS, Japanese Respiratory Society and Latin American Thoracic Association introduced criteria defining usual interstitial pneumonia (UIP) patterns based on high-resolution computed tomography (HRCT) imaging [4]. The ATS/ERS consensus classification was updated in 2013, introducing an additional classification of IIP according to patterns of disease behaviour. Disease behaviour classification can be particularly useful in unclassifiable forms of IIP and in IIPs that are associated with multiple different behaviours, such as non-specific interstitial pneumonia (NSIP) [5].

Five disease behaviours were defined in the ATS/ERS 2013 consensus, formally endorsed in unclassifiable ILD, but applicable in principle, with the exception of category 1, to the whole spectrum of fibrotic ILD [5]: 1) reversible and self-limited (*e.g.* many cases of respiratory bronchiolitis–interstitial pneumonia); 2) reversible disease with risk of progression (*e.g.* organising pneumonia/NSIP and desquamative interstitial pneumonia); 3) stable with residual disease (*e.g.* some fibrotic NSIP); 4) progressive, irreversible disease with potential for stabilisation (*e.g.* some fibrotic NSIP); and 4) progressive, irreversible disease despite therapy (*e.g.* IPF).

Then came the INBUILD and RELIEF trials, in which the possibility that ILD disorders with a progressive phenotype could all respond to similar treatment was investigated [6, 7]. Previously, large multicentre ILD trials took a more rigid approach, whereby the efficacy of each treatment had to be demonstrated for each individual ILD. In the INBUILD and RELIEF trials, inclusion was focused more on disease behaviour (progressive fibrotic phenotype) than specific diagnosis (non-IPF ILD) on the basis that there may be similarities between the pathobiological mechanisms of different ILDs that lend themselves to convergence in treatment strategies [6, 7]. Indeed, as reviewed in detail elsewhere [8], progressive fibrotic ILDs share many cellular, molecular and structural mechanisms that may contribute to the development of this aggressive phenotype. “Splitting” and “lumping” are both valid approaches depending on the disease stage and, rather than being mutually exclusive, may be considered a stepwise process that facilitates a more sophisticated classification of ILD [9]. At early presentation, it is common practice to split by defined diagnosis; however, in the major subgroup of patients in whom disease-specific approaches fail to prevent progression and fibrosis has advanced, we tend to move to lumping, whereby treatment focuses on disease mechanism rather than disease aetiology.

Although the positive data from INBUILD and RELIEF point toward the value of considering IPF alongside other forms of progressive fibrosing lung disease, they may also result in a tendency to “over-lump”. The need to balance between splitting and lumping is therefore critical. While the results of the INBUILD trial support the

concept that there are similar pathobiological mechanisms underlying the development of progressive fibrosing ILD, this phenotype may or may not be mediated by common molecular drivers which, even if universal, are yet to be defined. Addressing the possibility that progression is mediated by different molecular drivers is central to establishing a "precision medicine" approach to ILDs. Additionally, it is important to consider that the optimal approach to personalised medicine depends on the prevailing treatment landscape. Further research into this therapy area may lead to better identification of individual ILDs and, potentially, the emergence of new treatments that favour one diagnosis over another, thus supporting truer individualisation in ILD management based on diagnosis.

The challenge now is how to objectively identify an individual's disease classification and disease behaviour and choose treatment strategies and tactics accordingly. Here, splitting and lumping appear to be complementary approaches; indeed, biomarkers identified as specific to certain diagnoses (*e.g.* IPF) should be investigated for their value in all patients with non-IPF fibrosing lung disease. Ultimately, reconciling splitting and lumping requires "smart splitting" and "smart lumping". While a lumping approach with existing therapies is currently applied after conventional diagnostic splitting has failed, we advocate an alternative form of splitting based on a broad separation between inflammatory/fibrotic and epithelial/fibrotic pathways (driven by individualised pathway biomarkers) that can be applied at presentation and might inform initial management. In some cases, these pathways may co-exist, and a combination precision approach employing both disease-specific and pathway-specific treatments would become appropriate, much as personalised treatment approaches in oncology are often combined with other treatments that act more broadly.

Biomarkers and technologies: Diagnostic, prognostic and precision medicine

The concept of precision medicine relies on the identification and implementation of biomarkers that can be used to inform diagnosis, prognosis, and treatment stratification. Ideally, biomarkers that are used for these purposes, as well as for monitoring treatment responses, should be obtained via non-invasive methods, with potential sources including peripheral blood, urine, and exhaled breath condensate; however, peripheral samples and clinical evaluations such as pulmonary function tests may not accurately reflect pathobiological processes in the lung [10, 11]. On the other hand, obtaining biomarkers directly from the airway or lung parenchyma requires potentially invasive techniques such as bronchoalveolar lavage or surgical lung biopsy, which may limit their routine use. Likewise, the risks associated with radiation exposure with techniques such as HRCT present a challenge to serial acquisition of radiologic biomarkers [11].

Various blood- or airway-based protein biomarkers, as well as mutations identified through genetic testing, can help to distinguish ILD from healthy controls and, in some cases, between ILD subtypes, and/or may be useful for predicting ILD prognosis and monitoring treatment responses. Current evidence suggests that biomarkers for IPF fall into three mechanistic categories [10-12]: epithelial cell dysfunction and senescence (*e.g.* CA125 [13], SP-A, SP-D, *MUC5B*, KL-6, telomerase reverse transcriptase); aberrant innate and adaptive immunity (*e.g.* CCL18, HSP-70, T-cell pathways); and abnormal lung remodelling (*e.g.* MMP-7, LOXL2, integrin, collagen synthesis, degradation biomarkers [14, 15]). Examples of candidate biomarkers that relate to these mechanistic pathways are summarised in Table 1. Among these, the association of short telomeres and/or telomere-related mutations with rapid disease progression and a poorer prognosis is well established, and there are several commercially available tests for measuring telomere length [16, 17]. In addition to these markers, disease severity and response to treatment are often monitored in the clinic using pulmonary function tests such as forced expiratory volume (FEV_1), forced vital capacity (FVC) and/or diffusing capacity of the lung for carbon monoxide (DL_{CO}). For example, the GAP index and staging system uses (G)ender, (A)ge and two lung (P)hysiological parameters (percentage predicted FVC and percentage predicted DL_{CO}) to help predict ILD prognosis, while the composite physiologic index is a prognostic tool that reconciles the morphological extent of pulmonary fibrosis with lung function parameters, including FEV_1, FVC, and DL_{CO}. [18, 19].

Technologies such as high-throughput microarrays and bioinformatics analysis have played an important role in elucidating the pathogenesis, molecular diagnosis and prognosis of diseases [20], and in identifying biomarkers that can be used in disease diagnosis, staging, prognosis and monitoring treatment response [21]. However, for ILDs, applications of precision medicine relating to staging, prognosis and treatment are aspirational at present.

High-throughput bioinformatics analysis of genomic or transcriptomic data permits the rapid identification of differentially expressed genes in disease. In IPF, analysis of genomic microarray datasets from IPF and control lung tissue samples has revealed over 250 differentially expressed genes that may play important roles in the occurrence and development of IPF, and act as biomarkers for the diagnosis of IPF [20]. Similarly, bioinformatics analysis of multiple transcriptomic datasets has identified over 350 upregulated, differentially expressed genes that may be diagnostic biomarkers [22]. Proteomics has also been used to compare the protein expression profiles of individuals with IPF with healthy controls, utilising data obtained with high-definition mass spectrometry to identify and confirm candidate biomarkers of IPF [23]. Although informative, the studies have focused on analysis of biomarkers in IIP/IPF versus normal tissue, whereas, ideally, such studies should be performed in ways that help to distinguish one ILD and/or one ILD behaviour from another.

AI is particularly important here because it allows diagnosis to be refined. AI algorithms may redefine our current ability to base prognostic evaluation both on diagnosis and on separations of the underlying disease process. Within the broad category of AI, machine learning, which comprises mathematical algorithms that learn a task through experience without human instruction, is of specific interest for ILD research. At a more advanced stage this becomes "deep learning", incorporating multiple layers of learning architecture. A deep learning system improves autonomously, creating increasingly complex schema that deviate from the general machine learning task-specific algorithm [24].

Because ILDs have multiple, overlapping pathophysiological pathways, the use of large-scale sequencing platforms that incorporate numerous biomarkers is an attractive approach. For example, the Envisia Genomic Classifier (Veracyte, San Francisco, CA, USA), which utilises a 190-gene expression signature to differentiate between UIP and non-UIP, has been demonstrated to significantly improve the diagnostic confidence of multidisciplinary teams in the management of patients with probable UIP [25-29]. An essential component of the validation of genomic classifiers is that their prognostic value is shown to be superior to routine baseline tests.

Deep learning has also been applied to HRCT imaging with promising results [30, 31]. Walsh *et al.* trialled a deep learning algorithm trained using respiratory society guidelines to classify HRCT scans with fibrotic lung disease, comparing the results with classifications from 91 thoracic radiologists [30]. Median accuracy was 73.3% for the algorithm and 70.7% for the radiologists [30]. The algorithm provided equally prognostic discrimination between UIP and non-UIP diagnoses (hazard ratio [HR] 2.88, 95% CI 1.79–4.61, $p<0.0001$) compared with the majority opinion of the thoracic radiologists (HR 2.74, 95% CI 1.67–4.48, $p<0.0001$). A more recent HRCT machine learning study also incorporated histopathology as a reference standard. Shaish *et al.* used a deep learning convolutional neural network to assess HRCT scans from patients who also had diagnostic histopathology [31]. Sensitivity and specificity were 74% and 58%, respectively. Convolutional neural network–predicted UIP was associated with an increased risk of death or lung transplantation (HR 1.5; 95% CI 1.1–2.2; $p=0.03$). The results of the study suggest that the convolutional neural network could use HRCT images to predict histopathologic UIP pattern and transplant-free survival.

Vision for the next 5 years: Prognostic precision and robust treatment algorithm

The 2013 ATS/ERS consensus classification advises that several factors should be considered to formulate a prognosis for future disease behaviour, including observed past disease behaviour [5]. However, although broad

likelihoods of future disease behaviour are provided by the classification, the prediction of future progression remains insufficiently precise at presentation to guide management strategies. Clinicians must therefore base initial management on standard approaches for individual ILDs and adopt a lumping approach, using anti-fibrotic therapies, only when disease progression has already occurred despite management. Our aspirational vision of precision medicine in ILD is to be able to: 1) accurately classify a patient's disease behaviour group and hence the overall strategy at baseline; 2) predict the tempo of disease progression; 3) develop a robust tactical treatment algorithm; and 4) identify key points along the course of the illness where precision medicine techniques would be valuable. Specifically, the aspiration is to differentiate between disease pathways predominantly driven by inflammation, and those in which inflammation-driven treatments fail to inform the tactical selection of individual therapies.

Several precision medicine technologies that are already in use in ILD, or have been applied to different therapy areas, may play a role in achieving this vision. Multi-omics analyses examine the roles, relationships and actions of various types of molecules in the cells of an organism, and can incorporate genomics, transcriptomics, epigenomics, proteomics, metabolomics and other -omics areas [32], such as radiomics, a quantitative approach to medical imaging that aims at enhancing the existing imaging data available to clinicians using advanced mathematical analysis [33]. However, there is often little overlap between different -omics datasets, and measures obtained from one -omics approach often do not correlate well with data obtained by other methods. Analysis of such complex datasets can be challenging, meaning that truly integrated multi-omics analyses have not yet been widely utilised, and new approaches may be needed in the future [32].

Computational biology and bioinformatics, including machine learning, are already in use or under investigation for use in ILD, and their use is expected to continue and increase in the coming years. Mathematical modelling and simulation have an established role in drug development [34], and researchers are aiming to use these techniques to inform precision dosing, particularly in oncology [34, 35]. There may also be the potential for using *in silico* modelling to help drive clinical decision-making [36].

Although we expect the discovery and validation of biomarkers for ILDs to continue, it is crucial that potential biomarkers are thoroughly validated according to standardised guidelines, so that they gain regulatory approval and insurance coverage before subsequently transitioning to use in clinical practice [37]. Biomarkers themselves need to be separated into strategic biomarkers to inform the overall management approach, tactical biomarkers that pinpoint the specific agents to be used, and evaluative biomarkers to confirm that the individualised

management approach is indeed accurate. Candidates for such biomarkers are under investigation. N-acetylcysteine therapy, for example, has been shown to be associated with a significant reduction in composite endpoint risk in patients with IPF with the homozygous genotype for the single nucleotide polymorphism rs3750920 in the *TOLLIP* gene [38]. With a prospective trial now underway (RCT04300920), this may represent the first genomics theragnostic biomarker to be assessed in a randomised, controlled IPF trial.

Challenges of and approaches to realising the full potential of precision medicine in ILD

Oncology provides the benchmark for what is currently possible in precision medicine, with an increasing number of approved therapies targeting specific molecular phenotypes [39]. Similarly, in asthma, endotype-specific biological therapies have been approved for specific patient subgroups [12, 40]. By contrast, precision medicine in ILD is in its relative infancy. Its implementation has been restricted by several factors, including the lack of appropriate prospective cohort studies, the paucity of robust biomarkers, a lack of consensus regarding the best tissues for analysis, limited research funding and, until recently, a lack of treatments to provide a relevance and impetus for endotyping.

Transcriptomic studies have led to the identification of novel genes and pathways involved in IPF as well as insights into developmental pathways and epithelial and fibroblast phenotypes. However, to date, transcriptomic studies have only analysed bulk lung tissue, and not considered the cellular and spatial heterogeneity of the IPF lung. To take advantage of emerging technologies that can address this heterogeneity (*e.g.* single-cell RNAseq, microenvironment analysis), we may need new approaches to sampling that consider all microenvironments and cells in the lung [41]. Furthermore, innovations can only have an impact as part of precision medicine if they reach clinical practice. We need to ensure that new and innovative technologies, applications, and techniques are cost-effective and suitable to be implemented beyond specialist units in academic medical centres. The application of precision medicine approaches has been outpaced by our capacity to generate large-scale molecular data. Data analysis and interpretation and its subsequent translation into clinically actionable information has been challenging, and we need to further develop methods for extracting useful information to help guide clinical practice from these complex datasets [32]. Although precision medicine has the potential to reduce costs incurred through inappropriate use of expensive pharmacological treatments, and hospitalisations for severe toxicity, the implementation of biomarkers and technologies may require substantial financial investment, for example, in laboratory testing facilities and IT infrastructure [42, 43]. An important prerequisite to the advancement of personalised care is in demonstrating the economic value of precision medicine to

decision-makers who are responsible for recommending new health care technologies. However, previous economic evaluations of precision medicine in indications other than ILD have identified various challenges and uncertainties in estimating cost effectiveness; for example, the exact costs of novel biomarker tests may be unknown, and differences may exist in the permutations of multiple tests or in the implementation of testing by clinicians [42, 43]. Some of these challenges may be overcome by considering the requirements for economic evaluations at an earlier stage during research and development, thus ensuring that sufficient evidence is generated for later-stage decision making [43].

Although we have two approved therapies for IPF, pirfenidone and nintedanib, which block multiple disease pathways, results for more targeted therapies such as interferon gamma, endothelin antagonists, anti-IL13 antibodies and CCL2 antagonists have been disappointing in general IPF populations when assessed according to standard IPF endpoints such as FVC decline and mortality, despite promising preclinical evidence [44-50]. Randomised controlled trials remain the gold standard approach for investigating the efficacy and safety of potential therapeutic agents; however, they have disadvantages in terms of cost, inefficiency, and limited scope of the research questions. As a result, future research into precision medicine in ILD may need to implement novel trial designs such as adaptive clinical trials, in which multiple therapeutic interventions can be studied in an ongoing manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm [51]. Regulatory bodies may, in turn, require new models for decision-making for ILD drug approvals.

Despite these challenges, precision medicine has the potential to make a significant positive impact in the management of ILD. The clinical heterogeneity of this group of diseases suggests there may be a wide variety of relevant genetic/molecular, environmental and behavioural factors that could be potential targets for precision medicine [12]. Firstly, we need tools to correctly stratify patients into the four strategy groups illustrated in figure 1. For each therapy, the risk–benefit balance needs to be addressed, which requires well-designed prospective studies of patients with specific subtypes of ILD to discover and validate candidate biomarkers, and the analysis of large scale -omic data derived from disease-specific biological samples [50]. In this regard, several large prospective, longitudinal studies have completed or are ongoing. PROFILE was one such study that identified SP-D and CA125 as biomarkers that predict disease progression and death in IPF [13]. Likewise, results from the ongoing PFBIO cohort showed that longitudinal levels of type I and III collagen turnover were associated with progressive disease [52].

The success of precision medicine in ILD must be demonstrated in appropriately designed randomised controlled trials of unselected patients with ILD stratified by rational biomarkers (such as those indicative of a progressive fibrosing phenotype), and/or of a population made up of patients with defined disease endotypes [50]. The results of the INBUILD trial, for example, which specifically enrolled patients with a progressive fibrotic phenotype other than IPF, led to the subsequent approval of nintedanib for the treatment of chronic fibrosing ILDs with a progressive phenotype [53]. Ideally, identification of the patient subgroups most likely to respond to treatment should occur prior to registrational clinical trials. However, personalised treatment strategies may also be developed post-approval. For such trials to be undertaken in IPF, there is an urgent requirement for efficacy endpoints that enable evaluation in smaller and shorter clinical studies [50].

Technological advances, such as improved machine learning and higher sample throughput capabilities, are always welcome; however, the primary focus will be on maximising the capabilities of current technologies to meet the requirements of precision medicine in ILD. Simply identifying more biomarkers will not benefit patients unless clinicians use them. In other indications, as well as in ILD, potentially useful tests have not been widely adopted in clinical practice, partly due to a lack of common standards for assessing the utility of biomarker tests for selecting targeted treatments and improving patient outcomes. Indeed, an Institute of Medicine committee that assembled to discuss how to advance the appropriate use of biomarker tests for molecularly targeted therapies identified this as a key goal, noting that common evidentiary standards would inform regulatory, insurance coverage and reimbursement decisions [54]. Other recommendations included integration of electronic health records and laboratory information systems to enhance sustainable implementation and evaluation of biomarker tests, and ensuring equal access to biomarker testing and targeted therapies through patient and provider education, better labelling, and supportive reimbursement. Achievement of these goals may be facilitated by establishing interdisciplinary collaboration initiatives involving clinicians and laboratory scientists, as well as experts in informatics, who could continuously collect and annotate data on biomarkers and targeted therapies and share these with regulators, health care providers, payers, and patients [54].

The goal is to achieve widespread, cost-effective, clinic-ready precision medicine. Much as introduction and adoption of new therapies into the clinic depends on demonstration of cost/benefit (i.e., the pharmaco-economic model), a similar process is expected to apply to the application of new biomarkers and technologies. However, as outlined in figure 2, this requires a solid foundation (a conceptual framework) upon which acquisition of high-quality, convincing research (bench-to-bedside) and demonstration of clinical utility (i.e., improved real-

world healthcare outcomes in cost-effective manner) rests. Only then can the process for adoption into routine clinical practice begin. The framework that we propose is one of smart splitting and smart lumping. In essence, we are advocating a new approach to splitting at initial presentation, based on a separation between inflammatory/fibrotic and epithelial/fibrotic pathways and informed by rational biomarkers. It is hoped that this framework will maximise the likelihood of data derived from research being sufficiently informative to drive adoption in the clinic.

Conclusions

Although there are still many challenges to overcome, the recent breakthrough of precision medicine technologies from the research arena into clinical practice represents an exciting translational leap forward. The beginnings of precision medicine in ILD arose with the development of a standard classification of IIPs, eventually to incorporate disease behaviour, and the development of criteria for defining UIP patterns based on HRCT imaging. The INBUILD and RELIEF trials then demonstrated the need for individualisation beyond diagnosis. Technologies such as large-scale sequencing platforms and bioinformatics analysis have now brought precision medicine into ILD diagnosis in clinical practice, and deep learning has been applied to HRCT imaging with promising results. We anticipate that these achievements will be augmented by advances in computational biology and the discovery and validation of relevant strategic, tactical and evaluative ILD biomarkers, allowing for potentially transformative changes in the management of ILD over the next 5 years.

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References

1 Cottin V, Hirani NA, Hotchkin DL, *et al*. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27: 180076.

2 Newton CA, Herzog EL. Molecular markers and the promise of precision medicine for interstitial lung disease. *Clin Chest Med* 2021; 42: 357–364.

3 American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002; 165: 277–304.

4 Raghu G, Collard HR, Egan JJ, *et al*; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.

5 Travis WD, Costabel U, Hansell DM, *et al*; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.

6 Flaherty KR, Wells AU, Cottin V, *et al*; INBUILD Trial Investigators. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.

7 Behr J, Prasse A, Kreuter M, *et al*; RELIEF Investigators. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021; 9: 476–486.

8 Selman M, Pardo A. When things go wrong: exploring possible mechanisms driving the progressive fibrosis phenotype in interstitial lung diseases. *Eur Respir J* 2021; 58.

9 Ryerson CJ. Lumpers versus splitters: What to do with suspected idiopathic pulmonary fibrosis? *Respirology* 2019; 24: 300-301.

10 Ley B, Brown KK, Collard HR. Molecular biomarkers in idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2014; 307: L681–L691.

11 Bowman WS, Echt GA, Oldham JM. Biomarkers in Progressive Fibrosing Interstitial Lung Disease: Optimizing Diagnosis, Prognosis, and Treatment Response. *Front Med (Lausanne)* 2021; 8: 680997.

12 Brownell R, Kaminski N, Woodruff PG, *et al*. Precision medicine: the new frontier in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016; 193: 1213–1218.

13 Maher TM, Oballa E, Simpson JK, *et al*. An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. *Lancet Respir Med* 2017; 5: 946–955.

14 Organ LA, Duggan AR, Oballa E, *et al*. Biomarkers of collagen synthesis predict progression in the PROFILE idiopathic pulmonary fibrosis cohort. *Respir Res* 2019; 20: 148.

15 Jenkins RG, Simpson JK, Saini G, *et al*. Longitudinal change in collagen degradation biomarkers in idiopathic pulmonary fibrosis: an analysis from the prospective, multicentre PROFILE study. *Lancet Respir Med* 2015; 3: 462–472.

16 Courtwright AM, El-Chemaly S. Telomeres in Interstitial Lung Disease: The Short and the Long of It. *Ann Am Thorac Soc* 2019; 16: 175-181.

17 Stock CJW, Renzoni EA. Telomeres in Interstitial Lung Disease. *J Clin Med* 2021; 10.

18 Ley B, Ryerson CJ, Vittinghoff E, *et al*. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med* 2012; 156: 684-691.

19 Wells AU, Desai SR, Rubens MB, *et al*. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med* 2003; 167: 962-969.

20 Xu Z, Mo L, Feng X, *et al*. Using bioinformatics approach identifies key genes and pathways in idiopathic pulmonary fibrosis. *Medicine (Baltimore)* 2020; 99: e22099.

21 Laterza OF, Hendrickson RC, Wagner JA. Molecular biomarkers. *Drug Inf J* 2007; 41: 573–585.

22 Li D, Liu Y, Wang B. Identification of transcriptomic markers for developing idiopathic pulmonary fibrosis: an integrative analysis of gene expression profiles. *Int J Clin Exp Pathol* 2020; 13: 1698–1706.

23 Saraswat M, Joenvaara S, Tohmola T, *et al*. Label-free plasma proteomics identifies haptoglobin-related protein as candidate marker of idiopathic pulmonary fibrosis and dysregulation of complement and oxidative pathways. *Sci Rep* 2020; 10: 7787.

24 Trusculescu AA, Manolescu D, Tudorache E, *et al*. Deep learning in interstitial lung disease-how long until daily practice. *Eur Radiol* 2020; 30: 6285–6292.

25 Choi Y, Lu J, Hu Z, *et al*. Analytical performance of Envisia: a genomic classifier for usual interstitial pneumonia. *BMC Pulm Med* 2017; 17: 141.

26 Choi Y, Liu TT, Pankratz DG, *et al*. Identification of usual interstitial pneumonia pattern using RNA-Seq and machine learning: challenges and solutions. *BMC Genomics* 2018; 19: Suppl. 2, 101.

27 Raghu G, Flaherty KR, Lederer DJ, *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.

28 Richeldi L, Scholand MB, Lynch DA, *et al*. Utility of a molecular classifier as a complement to HRCT to identify usual interstitial pneumonia. *Am J Respir Crit Care Med* 2021; 203: 211–220.

29 Kheir F, Alkhatib A, Berry GJ, *et al*. Using bronchoscopic lung cryobiopsy and a genomic classifier in the multidisciplinary diagnosis of diffuse interstitial lung diseases. *Chest* 2020; 158: 2015–2025.

30 Walsh SLF, Calandriello L, Silva M, *et al*. Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study. *Lancet Respir Med* 2018; 6: 837–845.

31 Shaish H, Ahmed FS, Lederer D, *et al*. Deep learning of computed tomography virtual wedge resection for prediction of histologic usual interstitial pneumonitis. *Ann Am Thorac Soc* 2020; 18: 51–59.

32 Olivier M, Asmis R, Hawkins GA, *et al*. The need for multi-omics biomarker signatures in precision medicine. *Int J Mol Sci* 2019; 20: 4781.

33 van Timmeren JE, Cester D, Tanadini-Lang S, *et al*. Radiomics in medical imaging-"how-to" guide and critical reflection. *Insights Imaging* 2020; 11: 91.

34 Chaturvedula A, Palasik BN, Cho HJ, *et al*. Broader implications of modeling and simulation (M&S) tools in pharmacotherapeutic decisions: a cautionary optimism. *Front Pharmacol* 2020; 11: 571.

35 Darwich AS, Ogungbenro K, Harley OJ, *et al*. Role of pharmacokinetic modeling and simulation in precision dosing of anticancer drugs. *Transl Cancer Res* 2017; 6: Suppl. 10, S1512–S1529.

36 Zikos D, DeLellis N. CDSS-RM: a clinical decision support system reference model. *BMC Med Res Methodol* 2018; 18: 137.

37 Inoue Y, Kaner RJ, Guiot J, *et al*. Diagnostic and prognostic biomarkers for chronic fibrosing interstitial lung diseases with a progressive phenotype. *Chest* 2020; 158: 646–659.

38 Oldham JM, Ma SF, Martinez FJ, *et al*; IPFnet Investigators. TOLLIP, MUC5B, and the response to N-Acetylcysteine among individuals with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2015; 192: 1475–1482.

39 Schmidt KT, Chau CH, Price DK, *et al*. Precision oncology medicine: the clinical relevance of patient-specific biomarkers used to optimize cancer treatment. *J Clin Pharmacol* 2016; 56: 1484–1499.

40 Hetherington KJ, Heaney LG. Drug therapies in severe asthma - the era of stratified medicine. *Clin Med (Lond)* 2015; 15: 452–456.

41 Vukmirovic M, Kaminski N. Impact of transcriptomics on our understanding of pulmonary fibrosis. *Front Med (Lausanne)* 2018; 5: 87.

42 Berm EJ, Looff M, Wilffert B, *et al*. Economic Evaluations of Pharmacogenetic and Pharmacogenomic Screening Tests: A Systematic Review. Second Update of the Literature. *PLoS One* 2016; 11: e0146262.

43 Gavan SP, Thompson AJ, Payne K. The economic case for precision medicine. *Expert Rev Precis Med Drug Dev* 2018; 3: 1-9.

44 King TE, Jr., Brown KK, Raghu G, *et al*. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 92-99.

45 Raghu G, Million-Rousseau R, Morganti A, *et al*. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *Eur Respir J* 2013; 42: 1622-1632.

46 Raghu G, Richeldi L, Crestani B, *et al*. SAR156597 in idiopathic pulmonary fibrosis: a phase 2 placebo-controlled study (DRI11772). *Eur Respir J* 2018; 52.

47 Maher TM, Costabel U, Glassberg MK, *et al*. Phase 2 trial to assess lebrikizumab in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2021; 57.

48 Parker JM, Glaspole IN, Lancaster LH, *et al*. A Phase 2 Randomized Controlled Study of Tralokinumab in Subjects with Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2018; 197: 94-103.

49 Raghu G, Martinez FJ, Brown KK, *et al*. CC-chemokine ligand 2 inhibition in idiopathic pulmonary fibrosis: a phase 2 trial of carlumab. *Eur Respir J* 2015; 46: 1740-1750.

50 Maher TM. Precision medicine in idiopathic pulmonary fibrosis. *QJM* 2016; 109: 585–587.

51 Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov* 2019; 18: 797–807.

52 Jessen H, Hoyer N, Prior TS, *et al*. Turnover of type I and III collagen predicts progression of idiopathic pulmonary fibrosis. *Respir Res* 2021; 22: 205.

53 Food & Drug Administration (FDA). OFEV® (nintedanib). US Prescribing Information. 2020 [cited 2021 Nov 30]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205832s013lbl.pdf

54 Lyman GH, Moses HL. Biomarker Tests for Molecularly Targeted Therapies--The Key to Unlocking Precision Medicine. *N Engl J Med* 2016; 375: 4-6.

55 Kreuter M, Lee JS, Tzouvelekis A, *et al*. Monocyte Count as a Prognostic Biomarker in Patients with Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2021; 204: 74-81.

56 Maher TM, Simpson JK, Porter JC, *et al*. A positron emission tomography imaging study to confirm target engagement in the lungs of patients with idiopathic pulmonary fibrosis following a single dose of a novel inhaled alphavbeta6 integrin inhibitor. *Respir Res* 2020; 21: 75.

57 Mukae H, Iiboshi H, Nakazato M, *et al*. Raised plasma concentrations of alpha-defensins in patients with idiopathic pulmonary fibrosis. *Thorax* 2002; 57: 623-628.

TABLE 1 Mechanistic categories of candidate biomarkers for IPF [10-15, 55-57]

Core mechanism	**Biomarkers**	**Potential biomarker use**[a]
Epithelial cell dysfunction and senescence	*SP-C*, *SPA-2* mutations SP-A, SP-D protein levels	Diagnostic, prognostic
	Short telomeres *TERT*/*TERC*/*PARN*/*RTEL* mutations	Diagnostic, prognostic
	MUC5B polymorphisms	Prognostic
	CA125 protein levels	Diagnostic, prognostic
	KL6/MUC1 protein levels	Diagnostic, prognostic
	cCK18 protein levels	Diagnostic, prognostic, treatment response
Aberrant immunity	α-defensin protein levels	Prognostic
	YKL40 protein levels	Diagnostic, prognostic
	CCL18 protein levels	Diagnostic, prognostic
	T-cell subsets	Prognostic
	HSP70 anti-HSP70 IgG positivity	Prognostic
	CXCL13 protein levels	Diagnostic, prognostic
Abnormal lung remodelling	MMP-1, MMP-7 protein levels	Diagnostic, prognostic, treatment response
	LOXL2	Prognostic
	Integrin αvb6	Prognostic, treatment response (target engagement)
	OPN/SPP1	Diagnostic, prognostic
	Periostin	Diagnostic, prognostic, treatment response
	Circulating fibrocytes	Diagnostic, prognostic
	Collagen synthesis/degradation biomarkers	Diagnostic, prognostic, treatment response

[a] "Diagnostic" refers to biomarkers that can potentially be used to distinguish ILD from healthy controls and/or to distinguish IPF from other ILD subtypes.

cCK18: cleaved cytokeratin 18; CCL18: circulating chemokine ligand 18; CKCL13: C-X-C motif chemokine 13; KL6/MUC1: Krebs von den Lungen-6/mucin 1; LOXL2: lysyl oxidase-like 2; MMP: matrix metalloproteinase; MUC5B: mucin 5B; OPN: osteopontin; *PARN*: poly[A]-specific RNase; *RTEL*: regulator of telomere elongation helicase; SP-A: surfactant protein A; *SPA-2*: surfactant protein A2 gene; *SP-C*: surfactant protein C gene; SP-D: surfactant protein D; SPP1: secreted phosphoprotein 1; *TERC*: telomerase RNA component; *TERT*: telomerase reverse transcriptase.

Figure legends

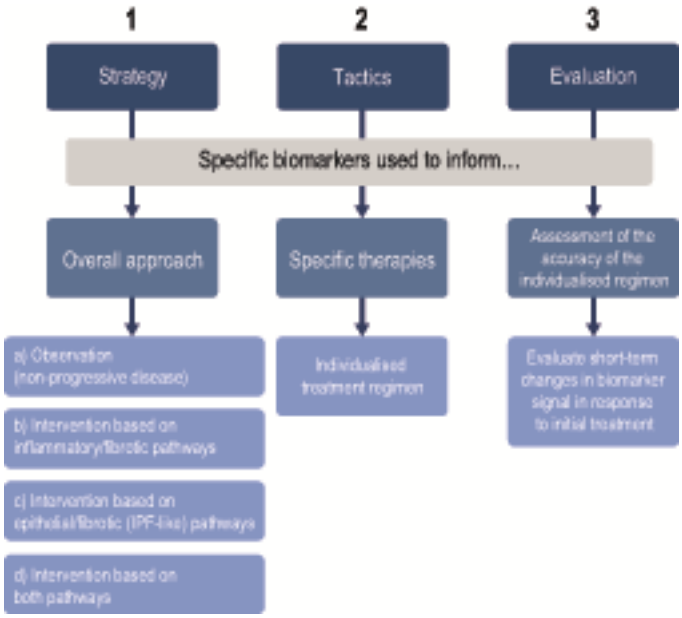

FIGURE 1 Three requirements for accurate and effective precision medicine in ILD. ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

FIGURE 2 Three-tiered approach to the advancement of precision medicine in ILD. ILD: interstitial lung disease.