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Walking the path of treatable traits in interstitial lung diseases

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Abstract

Interstitial lung diseases (ILDs) are complex and heterogeneous diseases. The use of traditional diagnostic classification in ILD can lead to suboptimal management, which is worsened by not considering the molecular pathways, biological complexity, and disease phenotypes. The identification of specific "treatable traits" in ILDs, which are clinically relevant and modifiable disease characteristics, may improve patient's outcomes. Treatable traits in ILDs may be classified into four different domains (pulmonary, aetiological, comorbidities, and lifestyle), which will facilitate identification of related assessment tools, treatment options, and expected benefits. A multidisciplinary care team model is a potential way to implement a "treatable traits" strategy into clinical practice with the aim of improving patients' outcomes. Multidisciplinary models of care, international registries, and the use of artificial intelligence may facilitate the implementation of the "treatable traits" approach into clinical practice. Prospective studies are needed to test potential therapies for a variety of treatable traits to further advance care of patients with ILD.

Keywords Treatable traits, Biomarkers, Endotype, Phenotype, Interstitial lung diseases, Personalized medicine, Artificial intelligence

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Introduction

ILDs include more than 200 entities of either known or unknown etiology [1]. The "Oslerian paradigm" has represented with unquestionable merit the traditional approach to ILDs management in the last decades. This paradigm classifies the diseases by linking the principal organ system in which symptoms and signs manifest with anatomic and histopathology findings [2–4]. Traditionally, diagnostic classification of diseases is given based on a set of clinical features, and patients are treated accordingly [5, 6]. According to the "Oslerian paradigm", the traditional goal of ILD management has been to determine the right treatment according to the initial and accurate diagnosis. However, this approach has become somewhat outdated with advances in technology allowing recognition of disease endotypes and phenotypes that can be treated with targeted interventions. Moreover, recent data have highlighted variability in disease pathogenesis

across ILD subtypes resulting in unpredictable natural history and heterogeneous treatment response [7–10]. This evidence points towards the existence of "treatable traits", specific disease characteristics that are clinically relevant and modifiable through pharmacological or non-pharmacological interventions [11]. "Treatable traits" approaches have been successfully implemented over the past decade in other chronic respiratory diseases, including bronchiectasis, asthma, and chronic obstructive pulmonary disease (COPD) [12, 13]. A number of treatable traits have also been identified in ILDs, such as progressive fibrosis or inflammation, either eosinophilic or neutrophilic [14–17]. The majority of these are phenotype-driven, while several studies are underway to stratify ILD patients according to clinically relevant endotypes [15–17]. Moving from a "disease-centered" to a "personalized" management approach that is based on specific treatable traits is a priority for the field, with the aim of identifying new targets to customize treatment and improve patients' outcomes [8]. In this perspective, we describe the future potential of using treatable traits in the management of ILDs.

The "splitting" approach in ILDs

ILDs are a heterogeneous group of conditions with overlapping clinical features, radiological and histological findings, as well as pathobiological underpinnings. This heterogeneity represents a substantial barrier in understanding disease mechanisms and developing efficacious and personalized treatments. The diagnosis and treatment of ILD has challenged physicians since the middle of the last century [18]. The first milestone in ILD diagnosis was the clinical-radiological-pathologic description by Louis Hamman and Arnold Rich in 1944 of four patients who died of progressive respiratory failure within 6 months of symptoms' onset at the Johns Hopkins Hospital in the United States [18] (Fig. 1).

The term Hamman-Rich syndrome became a synonym for an acute interstitial pneumonia of unknown cause that rapidly progressed to pulmonary fibrosis and almost invariably resulted in death. In 1957, Rubin and Lubliner reviewed 48 cases of the Hamman-Rich syndrome and added 15 cases of their own [19]. It soon became evident that the course of this new entity was not always acute, progressive, or fatal. In 1964, thanks to Sheridan and colleagues, the concept of idiopathic interstitial pneumonia evolved from the acute (or subacute) and fulminant disease described by Hamman and Rich [20]. Subsequently, at the Brompton Chest Hospital in London, Scadding and Hinson coined the term "cryptogenic fibrosing alveolitis" to describe the inflammatory and fibrotic changes that occurred in the lung parenchyma of patients with pulmonary fibrosis of unknown origin.

Open lung biopsy rapidly emerged as the gold standard for diagnosing ILDs [21]. In 1975, according to his own clinical and pathologic data, Averill Liebow classified interstitial pneumonitis into five different histologic categories: usual interstitial pneumonitis (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans interstitial pneumonia (BIP), lymphoid interstitial pneumonia (LIP), and giant cell interstitial pneumonia (GIP) [22]. In 1982, a key step towards the diagnosis and classification of ILDs was the implementation in clinical

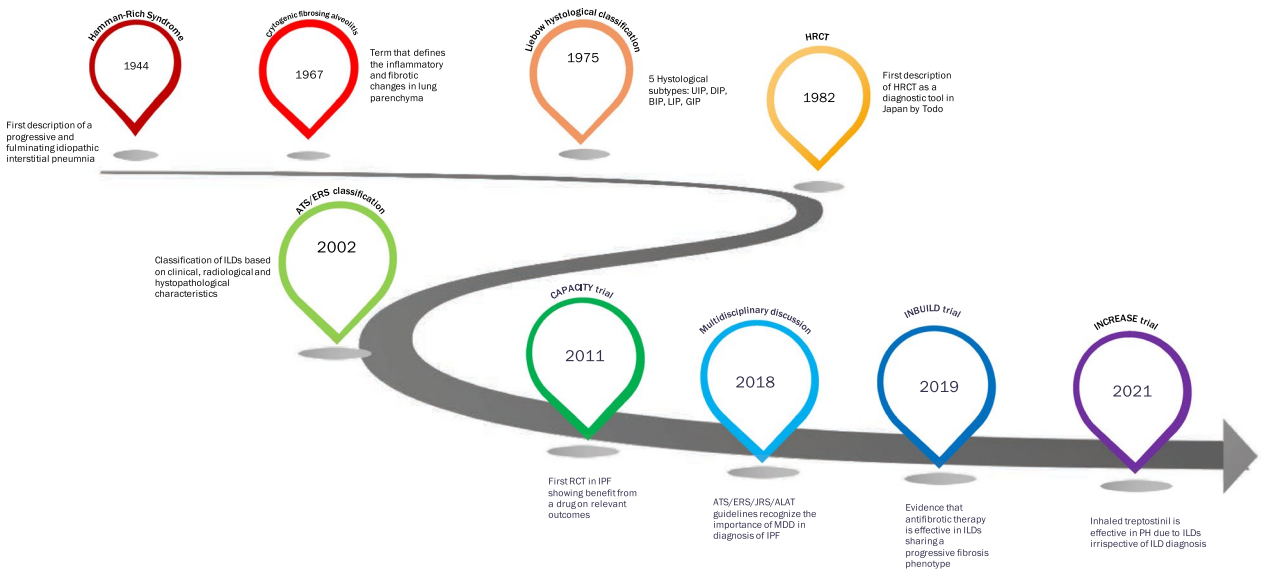

Fig. 1 Milestones in history of ILD

practice of the high-resolution computed tomography (HRCT) of the chest by Todo and coworkers [23], which substantially improved the ability to classify ILD subtypes through noninvasive means. Consequently, clinical, radiological, and, when available, histopathological data were integrated to improve diagnostic accuracy and implement classification of ILDs through the so-called "splitting" approach [24]. This approach allowed the design and conduct of randomized controlled trials (RCT)s for common ILDs, namely idiopathic pulmonary fibrosis (IPF) and systemic sclerosis-associated (SSc) ILD [25–29]. While this approach has resulted in the approval of several therapies to slow IPF and SSc-ILD, it left many other ILDs understudied, and it is limited by several factors. Firstly, ILD patients sharing the same diagnosis might respond differently to the same pharmacological treatment. Irrespective of ILD diagnosis, individuals with reduced telomere length endotype and/or known telomere-related mutations have more rapid disease progression and shorter lung transplant-free survival [30]. IPF patients who carry a specific polymorphism within the Toll-interacting protein (TOLLIP) gene might benefit from *N*-acetylcysteine (NAC), despite being ineffective for patients lacking this polymorphism and when studied in all-comers with IPF [31]. A European, multicenter, retrospective study demonstrated that IPF patients carrying mutations within Telomerase Reverse Transcriptase (TERT) or Telomerase RNA Component (TERC) gene may not benefit from pirfenidone in terms of reduction of lung function decline, although this drug is recommended for IPF [32]. Moreover, in a post-hoc analysis of two trials, IPF patients carrying rare variants within one telomere-related gene (TRG) showed a more rapid decline in forced vital capacity (FVC) than non-carriers [33]. Finally, a strong correlation has been reported between the presence of reduced telomere and the harmful effect of immunosuppressive medication in ILD patients [34]. Taken together, these findings suggest a more nuanced approach may be needed to effectively treat diverse ILDs.

Secondly, multiple comorbidities are common in ILD and have a detrimental effect on survival, especially if untreated [35–37]. Although clinicians should have a low threshold for suspecting comorbidities in patients with ILD, recent data show that treatment of relevant comorbidities is suboptimal, and often lacking altogether [35, 36].

Thirdly, data from both registries and multicenter studies show low-quality standards with regards to the management of ILD, including adherence to pharmacological treatment and referral to lung transplant centers, when indicated [37, 38].

A "treatable traits" strategy: lessons learned from other chronic respiratory diseases

Chronic respiratory diseases are often complex and heterogeneous conditions that require individualized assessment and treatment. Precision medicine is defined as "treatments targeting the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from others with similar clinical presentations" [39, 40]. The precision medicine strategy relies on the systematic evaluation of "treatable traits", as originally reported for chronic airway diseases by Agusti et al. in 2015 [12]. According to this approach, patients are individually assessed for a specific set of treatable problems. The identification of treatable traits has led to the adoption of different and specific therapeutic strategies, thus going beyond the "Oslerian paradigm". In the field of airway diseases, the Oslerian diagnostic classification might lead to sub-optimal management because specific molecular pathways and disease phenotypes are not taken into account [3, 4, 41]. Indeed, phenotypic and endotypic features of chronic airway diseases (e.g.: treatable traits) are variable, show non-linear dynamic interactions, and differentially regulate patterns and burden of the disease as well as response to treatment [42, 43]. Different trials using a "treatable traits" strategy have been conducted both in asthma and COPD [44, 45]. These studies have shown that a "holistic" approach based on the identification of treatable traits might improve outcomes if compared to a "guideline-based" approach. This represents an important step forward in the management of chronic airway diseases [44, 45].

A "treatable traits" strategy in ILDs: integrating "lumping" and "splitting" approaches

We recently propose and summarize a "treatable traits" strategy for patients with ILDs [14] (Table 1). Treatable traits have been classified into four different domains (pulmonary, etiological, comorbidities, and lifestyle) along with the identification of related assessment tools, potential treatment options, and expected benefits.

From a pulmonary perspective, patients with a progressive pulmonary fibrosis (PPF) phenotype represents one of the most promising treatable traits [16, 46–50]. PPF refers to a spectrum of ILDs that share a phenotype characterized by an increasing extent of fibrosis on HRCT, decline in lung function, and worsening symptoms, resulting in decreased quality of life, and early death [51]. It has been hypothesized that ILDs with this phenotype may also share pathobiological mechanisms regardless of their underlying cause and thus may also

Table 1 Treatable traits in interstitial lung diseases according to pulmonary, aetiological, comorbidities and lifestyle domains

Treatable trait	Assessment tool	(Potential) treatment option	Expected benefits of treatment*
Aetiological			
CTDs/Vasculitis	Clinical features Serum antibodies	Refer to rheumatologist Screening for extra-respiratory involvement Immunosuppressive drugs	Prevent or reduce lung damage Reduce mortality
Drugs	Drug history	Assess risk–benefit of stopping potentially harmful drug	Reduce lung damage Improve lung function
Exposure-related (organic and inorganic)	Environmental/ work/ domestic history of exposure Serum precipitins	Prevent or stop exposure	Prevent or reduce lung damage Improve outcomes Reduce mortality
Genetic	Family history Age of onset DNA genetic testing	Refer to geneticist Family screening Targeted therapy	Improve outcomes
Lifestyle			
Smoking	Patient reported Urine cotinine levels	Tobacco cessation support Nicotine replacement Antidepressant drug	Improve quality of life Improve lung function Prevent or reduce lung damage
Adherence to treatment	Patient and relatives feedback	Education Written instructions Self-management Family and social support	Improve outcomes
Exposure to air pollution	PM10 and NO2 concentrations	Reduce exposure	Reduce disease progression Reduce exacerbation
Lack of exercise/ Deconditioning of skeletal muscle	Cardiopulmonary exercise testing 6MWT	Prescribed exercise programs Pulmonary rehabilitation	Improve quality of life Improve lung function Improve exercise capacity
Diet	Patient reported	Diet instructions	Improve quality of life
Pulmonary			
Progressive fibrosis	Patient reported symptoms Pulmonary function tests HRCT	Optimization of therapy Consider antifibrotics Referral to lung transplant center	Slow lung function decline Reduce mortality Prevent exacerbation
Eosinophilic inflammation	HRCT BAL CBC	Steroid therapy Adjust immunosuppression	Prevent or reduce lung damage Improve quality of life
Neutrophilic inflammation	HRCT BAL CBC	Azithromycin	Reduce lung damage Improve quality of life
Acute exacerbation	HRCT BAL	Antifibrotic therapy Systemic glucocorticoids	Improve survival
Acute infection	Patient reported symptoms Sputum cultures BAL	Airway clearance Antibiotic therapy Prophylaxis with influenza and pneumococcal vaccination Adjust immunosuppression	Prevent exacerbation Reduce mortality Reduce hospitalization
Chronic infection or recurrent infection	Patient reported symptoms Sputum cultures BAL	Airway clearance Adjust immunosuppression Consider prophylactic antibiotics	Prevent exacerbation Improve quality of life Slow lung function decline
Chronic respiratory failure	Patient reported symptoms ABG 6MWT Polysomnography	Long term oxygen therapy Non-invasive ventilation Referral to lung transplant center Pulmonary rehabilitation Palliative care	Improve quality of life Improve survival
Intractable chronic cough	Patient reported symptoms Scores (LCQ, VAS, CQLQ)	Antitussive Thalidomide Gabapentin	Improve quality of life
Emphysema / Obstructive ventilatory defects	Pulmonary function tests HRCT	Bronchodilator therapy	Improve quality of life Slow lung function decline

Table 1 (continued)

Treatable trait	Assessment tool	(Potential) treatment option	Expected benefits of treatment*
Comorbidities			
GERD	Symptoms Oesophageal pH monitoring Manometry Upper Endoscopy	Diet instructions PPIs, H2-receptor antagonists, pro-kinetics Fundoplication	Improve outcomes Reduce lung damage
Pulmonary hypertension	Echocardiography Consider RHC	Referral to lung transplant center Trial with PH targeted therapies in selected patients (e.g.: Treprostinil) Oxygen/Non-invasive ventilation	Improve quality of life Improve outcomes Reduce mortality
Congestive heart failure	NT-proBNP Echocardiography	Targeted pharmacological treatment ICD implantation	Improve quality of life Reduce mortality
OSA	Sleep study	Diet instructions CPAP treatment	Improve quality of life Reduce mortality
Lung cancer	HRCT PET- CT Biopsy	Surgical resection Radiotherapy Chemotherapy	Reduce mortality
Diabetes	Fasting glucose persistently above 125 mg/dl Random glucose levels above 200 mg/dl occurring in the context of high-dose glucocorticoid therapy	Diet instructions Lifestyle instructions Insulin Oral hypoglycemics	Improve quality of life Reduce systemic complication of diabetes Reduce mortality
Osteoporosis/Osteopenia	Bone densitometry	Diet instructions Lifestyle instructions Pharmacological therapy	Improve quality of life Reduce risk of fractures Reduce mortality
Pulmonary embolism	CT pulmonary angiogram	Anticoagulants	Reduce mortality
Obesity	BMI	Diet instructions Pulmonary rehabilitation Bariatric surgery	Improve quality of life Improve exercise tolerance
Cachexia/Malnutrition	BMI	Nutritional support Pulmonary rehabilitation	Improve quality of life
Frailty	FFP binary score Frailty Index	Nutritional supportive Pulmonary rehabilitation Physical activity programs	Improve quality of life Reduce mortality
Anxiety/Depression	Patient reported scores (K-BILD; SGRQ-IPF)	Counseling/cognitive behavioural therapy Antidepressant/Anxiolytics Pulmonary rehabilitation	Improve quality of life Improve adherence to treatment

CTD connective tissue disease, *PM10* particulate matter 10, *NO2* nitrogen dioxide, *6MWT* six-minute walk test, *HR-CT* high-resolution computed tomography, *BAL* bronchoalveolar lavage, *CBC* complete blood count, *ABG* arterial blood gas, *LCQ* leicester cough questionnaire, *VAS* visual analogue scale, *CQLQ* cough-specific quality of life questionnaire, *GERD* gastro-esophageal reflux disease, *PPI* proton pump inhibitor, *RHC* right heart catheterization, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *ICD* implantable cardioverter defibrillator, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure, *PET-CT* Positron emission tomography computed tomography, *BMI* body mass index, *FFP* Fried's frailty phenotype, *K-BILD* King's brief interstitial lung disease, *SGRQ-IPF* St George's respiratory questionnaire idiopathic pulmonary fibrosis

* Most of benefits are speculative. Most of them are based on case report/case series or benefits coming from evidences in other diseases

respond to similar treatments. Indeed, in patients with PPF, nintedanib, an intracellular tyrosine kinase inhibitor with antifibrotic properties, reduces the rate of disease progression irrespective of the underlying ILD diagnosis [52–54]. Interestingly, molecular pathways targeted by nintedanib are augmented to a similar magnitude in lung tissue from several PPF, regardless of etiology [15, 54]. Pirfenidone, a compound with antifibrotic, anti-oxidant, and anti-inflammatory properties, might also represent an effective treatment for patients with PPF ILDs [55–57]. Taken together, these data suggest that the PPF phenotype of ILD is a clinically relevant and modifiable trait.

From an etiological perspective, the elimination of the inciting agent is an essential intervention in patients with exposure-related ILDs. A recent study showed that a standardized interview is able to reveal relevant inhalational exposures in most patients across all types of ILDs [38]. Exposures were markedly different based on demographics and were associated with worse transplant-free survival [38]. A thorough professional cleaning of the

domestic or working environment needs to be undertaken if the patient remains within that environment [58, 59].

From a comorbidity perspective, the majority of ILD patients share additional complexity related to aging, concomitant conditions and extra-respiratory involvement [60–62]. These traits are often underestimated, leading to a vicious cycle that results in an accelerated clinical deterioration and worse prognosis [17, 60, 61, 63, 64]. A specific trait might be a major determinant of disease progression and may further influence other disease traits. This is the case of cachexia, frailty, and pulmonary hypertension (PH) among others. As an example, ILD patients frequently suffer from cachexia that often correlates with rapid clinical deterioration and early death [65–67]. Targeting cachexia in patients considered for lung transplant could have a substantial impact not only on body weight, but also on exercise tolerance, skeletal muscle strength, anxiety, and depression, thus potentially impacting the final decision on whether to proceed with transplantation [66, 68, 69]. Similarly, frailty is common in patients with ILDs and is strongly associated with dyspnea and clinical outcomes, including hospitalizations and mortality [69–71]. Frail patients generally have several comorbidities that are common causes of exclusion from clinical trials. In patients with ILD, physical frailty is an important determinant of prognosis and may represent a modifiable target for intervention [72, 73]. PH secondary to ILDs is associated with worse outcomes such as dyspnea, quality of life, and short-term mortality [74]. No therapies are currently approved for PH in ILD [74, 75]. However, inhaled treprostinil has been shown to improve exercise capacity, as assessed by 6-min walk test, compared with placebo in patients with PH due to ILD [76].

From a lifestyle/behavioral perspective, there are multiple studies showing the association of ILDs with air pollution, although the mechanisms through which air pollution leads to the development and worsening of ILD remain speculative [77–81]. Air pollution, as demonstrated by the PM_{10} concentration, is associated with an increasing rate of pulmonary function decline in IPF, as well as with higher risk of disease exacerbations [77, 81]. Thus, it is important to integrate markers of air pollution in the clinical evaluation of ILD patients irrespective of the underlying diagnosis.

The multidisciplinary team as a tool to implement the "treatable trait" strategy in ILD

Multidisciplinary team (MDT) has become the diagnostic gold standard for ILD, particularly IPF [82–84]. The "treatable traits" approach requires the MDT be actively involved non only in disease diagnosis but also in the identification and management of pulmonary, aetiological, comorbidities, and lifestyle-related treatable traits with the aim of improving patients' outcomes (Table 2) [82, 83]. This is the case, for example, of radiologists in the example of radiological progression of pulmonary fibrosis, cardiologists in the case of coexisting PH, or geriatricians for patients with frailty, or rheumatologist for possible connective tissue disease-ILD.

"Treatable traits" strategy in ILD: challenges and opportunities

Definitions and prevalence of treatable traits

Data on definition and prevalence of treatable traits in ILD are limited and mostly derived from monocentric observational studies [15, 46–48, 63]. The heterogeneity in prevalence of each trait depends on the intensity and type of the diagnostic workup, the threshold used to describe the trait as clinically relevant, and the setting where the trait has been identified (e.g.: primary, secondary or tertiary-care). For example, the prevalence of gastro-esophageal reflux disease (GERD) as a comorbidity varies substantially depending on the methods used to ascertain its presence or absence (e.g., medical records versus sensitive oesophageal pH-monitoring) [63, 85, 86]. Accordingly, the prevalence of GERD in IPF ranges from 0 to 94% [63]. Multicentre, prospective studies as well as international registries shared across different settings and countries are needed to improve the accuracy of estimates for both prevalence and characteristics of each single treatable trait [87–89].

Lack of endotypes in ILDs and related biomarkers

Recent RCTs in asthma and COPD have successfully tested that a biomarker-guided therapy directed to a specific treatable trait is superior to a symptom-guided therapy [90–92]. Specific biomarkers are already used in clinical practice to identify several endotypes in chronic respiratory diseases (e.g.: blood eosinophilia and the T2-high endotype in patients with asthma) [90]. However, there are few reliable biomarkers available for use in ILD. Biomarker discovery and identification of endotypes in ILDs represent a growing field of research owing to their potential clinical relevance. The pathophysiology of ILD is multifactorial, involving a complex interaction between host and environmental factors that results in the activation of multiple overlapping profibrotic pathways [93]. As a result, IPF and other ILDs may be indistinguishable from each other and have similarly variable and unpredictable clinical course, despite different underlying etiologies [94–96]. In addition, IPF and non-IPF PF-ILD patients share similar rates of functional decline, disease progression, and response to treatment [54].

Table 2 Specialist competencies within the ILD multidisciplinary care team

Specialist	Competencies	Treatable trait areas of focus
Chest physician (coordination of the multidisciplinary team)	✓ Diagnosis confirmation and investigation of etiology ✓ Performance and evaluation of PFTs ✓ Bronchoscopy ✓ Medication review (side effects of treatment and polypharmacy review) ✓ Ensure patient's adherence to treatment ✓ Management of respiratory failure, LTOT, NIV ✓ Identification of patients who are candidates for lung transplant ✓ Identification and management of acute exacerbations ✓ Identification of patients eligible for RCTs ✓ Monitoring of disease severity and potential complications ✓ End-of-life care	✓ Etiological ✓ Lifestyle ✓ Pulmonary ✓ Comorbidities
Rheumatologist	✓ CTD suspicion and diagnosis ✓ Identification of extra-respiratory involvement ✓ Co-management and prescription of immunosuppressive and antifibrotic drugs	✓ Etiological ✓ Comorbidities
Physiotherapist and/or respiratory therapist	✓ Airway clearance ✓ Pulmonary rehabilitation ✓ Inhaled therapy management	✓ Lifestyle ✓ Pulmonary
Nurse	✓ Coordinate input of other healthcare professionals ✓ Support patients and their families to recognize symptoms so as to avoid complications ✓ Ensure patient's adherence to treatment	✓ Lifestyle
Pathologist	✓ Support etiological diagnosis ✓ Identification of progressive fibrosis ✓ Identification of complications	✓ Etiological ✓ Comorbidities
Radiologist	✓ Support etiological diagnosis ✓ Identification of progressive fibrosis ✓ Identification of AE ✓ Identification of complications	✓ Etiological ✓ Comorbidities
Gastroenterologist	✓ Diagnosis and management of GERD ✓ Management of gastrointestinal side effects of treatment (e.g.: antifibrotics) ✓ Evaluation and management of extra-respiratory involvement	✓ Comorbidities
Geneticist	✓ Diagnosis of genetic disorders ✓ Genetic counseling for patient and relatives	✓ Lifestyle ✓ Etiological
Infectious disease specialist	✓ Advice on potential prophylaxis in patients treated with immunosuppressive drugs ✓ Treatment of acute and chronic infection	✓ Multisystem
Cardiologist	✓ Diagnosis and management of RHF ✓ Evaluate heart involvement in some ILDs (e.g.: sarcoidosis or scleroderma)	✓ Comorbidities
Psychologist	✓ Management of anxiety and depression ✓ Family support ✓ End-of-life care	✓ Lifestyle
Endocrinologist	✓ Diagnosis and management of osteoporosis and diabetes in patients treated with chronic steroid therapy	✓ Comorbidities
Nutritionist	✓ Diet instruction	✓ Lifestyle ✓ Comorbidities
Geriatrician	✓ Identification of frail patients ✓ Medication review ✓ Familial and social support	✓ Lifestyle ✓ Comorbidities
Pharmacologist	✓ Medication review (side effects of treatment and polypharmacy review) ✓ End-of-life care	✓ Pulmonary
Thoracic Surgeon	✓ Surgical biopsy ✓ Co -management of lung cancer ✓ Lung transplant	✓ Etiological ✓ Comorbidities
General practitioner	✓ Medication review (side effects of treatment and polypharmacy review) ✓ Ensure patient's adherence to treatment ✓ Support patients and their families to recognize symptoms so as to avoid complications ✓ End-of-life care	✓ Lifestyle ✓ Pulmonary ✓ Comorbidities

PFTs pulmonary function tests, *LTOT* long-term oxygen therapy, *NIV* non-invasive ventilation, *RCTs* randomized controlled trials, *CTD* connective tissue disease, *ILD* interstitial lung disease, *GERD* gastro-esophageal reflux disease, *RHF* right heart failure

Thus identify, develop, and validate molecular endotypes in ILD through the use of specific biomarkers is of paramount importance in order to evaluate disease activity and guide decision-making. Molecular biomarkers identified so far in ILDs, along with their clinical implications, are summarized in Table 3. However, most of these have been investigated in observational and retrospective studies without assay validation or replication in an external cohort. Issues related to reproducibility and inter-individual variability has also been highlighted for circulating biomarkers [128]. Thus, baseline and longitudinal measurement of specific and sensitive biomarkers in large and prospectively collected cohorts is of paramount importance for improving disease management. Machine learning and artificial intelligence (AI) might offer the opportunity to identify combinatorial

Table 3 Molecular biomarkers identified in ILDs that are associated with relevant outcomes

Biomarker	Matrix	Disease*	Field of action	Prognostic relevance	Potential treatment
Short telomere length [34, 30, 97–101]	Peripheral blood leucocytes	IPF HP Unclassifiable ILD IPAF CTD-ILD	Dysfunctional alveolar repair	Higher post-transplant morbidity Significantly increased risk of harm in patients receiving immunomodulatory treatment	Placenta derived mesenchymal stromal cells
TOLLIP gene variant [31, 102]	Peripheral blood leucocytes	IPF	Immune dysregulation	Lung function decline Mortality	NAC
MUC5B promoter polymorphism [97–99, 103]	Peripheral blood leucocytes	IPF	Dysfunctional alveolar repair	Mortality	Unknown
KL-6 [104–113]	Serum BAL	CTD-ILD NSIP PAP CHP IPF	Dysfunctional alveolar repair	Severity of disease Risk of progression Risk of exacerbation Radiological scores	Unknown
Surfactant protein D [104–109, 112, 113]	Serum	IPF	Dysfunctional alveolar repair	Risk of progression	Unknown
MMP-7 [105, 106, 110, 114]	Serum	IPF CHP	Extracellular matrix turnover and remodeling	Lung function decline Mortality	Unknown
YKL-40 [104, 115, 119, 120]	Serum BAL	IPF CHP CTD-ILD Sarcoidosis	Extracellular matrix turnover and remodeling	Risk of progression Risk of exacerbation Mortality	Unknown
CCL-18 [104, 111, 116]	Serum	IPF	Immune dysregulation	Lung function decline Mortality	Unknown
IL-6 [117, 118]	Serum	CTD-ILD	Immune dysregulation	Lung function decline Mortality	Tocilizumab
PRO-C3 and PRO-C6 [121, 122]	Serum	IPF	Extracellular matrix turnover and remodeling	Risk of progression	Unknown
CRPM [123]	Serum	IPF	Extracellular matrix turnover and remodeling	Lung function decline	Unknown
Periostin [124]	Serum	IPF CHP	Extracellular matrix turnover and remodeling	Lung function decline Mortality Risk of exacerbation	Unknown
VCAM-1 [125, 126]	Serum	CTD-ILD IPF Unclassifiable ILD CHP	Immune dysregulation	Lung function decline Mortality	Unknown
CXCL 13 [126, 127]	Serum	CTD-ILD CHP IPF Unclassifiable ILD	Immune dysregulation	Lung function decline Mortality	Unknown

IPF idiopathic pulmonary fibrosis, *HP* hypersensitivity pneumonitis, *IPAF* interstitial pneumonia with autoimmune features, *CTD-ILD* connective tissue disease-interstitial lung disease, *TOLLIP* toll interacting protein, *NAC* N-acetyl cysteine, *MUC5B* Mucin 5B, *KL-6* Krebs von den Lungen 6, *BAL* bronchoalveolar lavage, *NSIP* non-specific interstitial pneumonia, *PAP* pulmonary alveolar proteinosis, *MMP-7* matrix metallopreinase 7, *YKL-40* chitinase-3-like protein 1, *CCL-18* C–C Motif Chemokine Ligand 18, *IL-6* Interlukin-6, *CRPM* serum matrix metalloproteinase-degraded C-reactive protein, *VCAM-1* vascular cell adhesion protein 1, *CXCL 13* C-X-C motif chemokine 13

* Disease(s) in which the biomarker has been identified

biomarkers, which, in turn, may be more informative than markers used in isolation [129, 130].

Information technology and artificial intelligence

Information technology (IT) and AI are increasingly integrated in clinical practice [90]. Deep learning-based HRCT image algorithms has the potential to improve diagnostic accuracy and predict disease behavior in ILD [131–134]. Similarly, machine learning and genomic analysis have been employed for the categorization of ILD morphology in the setting of computational pathology [130, 135, 136]. Several other traits might be suitable targets of AI. In this context, one of the most interesting and promising traits is represented by air pollution and its role in the pathogenesis and progression of ILDs [77, 80, 81]. Although air pollution is quantifiable, predicting air quality is a complex task due to the dynamic nature, and high variability in space and time of pollutants and particulates. AI and deep learning algorithms might provide useful information on these dynamic changes. Thus, data-driven decision-making in ILDs can be leveraged by incorporating deep learning algorithms into clinical practice. However, large datasets for adequate training of deep learning algorithms are needed to make effective this approach. Open science research and collaboration between academia and industry should be encouraged to identify and standardize treatable traits through deep learning analysis and algorithms.

Managing treatable traits

The management of treatable traits in ILD remains a matter of debate, with no clear guidance for (1) the prioritization of treatable traits for management; (2) the timing of treatable trait intervention and (3) the integration of patient preferences and values into this approach. Evidence from other chronic pulmonary diseases has demonstrated improved outcomes when patients are included at all stages in the decision-making process [137].

How to identify and interpret treatable traits over time

ILD may evolve within weeks, months, or years. The evaluation of treatable traits should thus be assessed repeatedly throughout the disease course. Dynamic biomarker change may reflect an evolving treatable trait, prompting a change in management strategy. One example is the regression of ground glass opacities (a "radiological biomarker") in the context of local inflammation (the "trait") following steroid treatment, which might lead physicians to re-define their management strategy and address other disease traits. An additional example is the development of overt autoimmune disease in a patient initially diagnosed with "idiopathic" nonspecific interstitial pneumonia (NSIP) [138, 139]. For such patients, a regular clinical review of new treatable traits related to the autoimmune disease will be critical for the appropriate management of the extra-respiratory autoimmune manifestations.

How to make the "treatable traits" approach feasible across different healthcare systems

While a "treatable traits" approach in ILD may be feasible in high-income countries with well-resourced hospitals and strong multidisciplinary networks, this can be challenging in under-resourced countries. For example, the implementation of deep learning technologies within the MDT is strictly dependent on local resources and varies across countries [140]. However, although this approach is initially highly resource-consuming, it would likely become cost-saving over time. The presence of a multidisciplinary discussion (MDD) can optimize patients' flow and avoid unnecessary delays in pharmacological and non-pharmacological interventions [141]. Beyond establishment of an ILD diagnosis and initial management plan, additional multidisciplinary input from a variety of healthcare professionals can also have a prominent role in identifying and managing treatable traits. For example, the role of a nutritionist in the management of ILD patients with obesity can potentially have a positive impact not only on the lifestyle domain but also on other traits, such as GERD, obstructive sleep apnea (OSA), or chronic cough. However, several questions remain unanswered, especially with regard to the optimal structure of such a multidisciplinary care team and which patients would benefit most from such intervention.

How to implement a "treatable traits" approach into the current landscape of ILD research

The use of traditional disease diagnosis has resulted in a large proportion of patients with ILDs being excluded from RCTs [25, 142, 143]. Using an "Oslerian paradigm", 10–20% of ILD patients remain "unclassifiable" despite an intensive diagnostic work-up [82, 144]. Patients with unclassifiable ILD have a heterogeneous clinical course and are generally excluded from RCTs, although a recent phase 2 trial has investigated the efficacy and safety of pirfenidone in this patient subset [56]. Moreover, the benefit of pharmacological and non-pharmacological treatments is frequently limited by their effect on a single disease pathway, partially explaining the modest impact of these treatments on clinically relevant outcomes [25, 142, 143]. Trials in COPD and asthma showed that the implementation of a "treatable traits" strategy improves patients' outcomes [44, 45]. The continued identification and implementation of molecular signature-based approaches to treatable traits may overcome these relevant limitations [134, 135, 145].

Conclusion

ILDs comprise a group of complex and heterogeneous diseases that remain a challenge for treating physicians. The strategy described in this perspective focusses on key clinical treatable traits and underscores the importance of biomarkers for identifying clinically relevant treatable traits in patients with ILD, with the goal of using this approach in the daily management of ILD to improve outcomes. Compared to traditional ILD management, the treatable traits strategy is based on a "proactive" rather than "reactive" approach. This subtle distinction implies a relevant meaning that shift toward increasingly patient-centered medicine, moving beyond the "one size fits all" view. This is in line with an evolving healthcare system that is predictive, preventive, personalized and participatory, the so called "P4 medicine" [146, 147]. From a preventive point of view, Interstitial lung abnormalities (ILAs) are increasingly recognized on chest CTs [148]. Although the clinical relevance of ILA remains to be clarified, increased mortality as well as reduced pulmonary function have been reported [149, 150]. Thus, identification of biomarkers able to predict disease progression in ILA are of paramount importance. Finally, a SWOT analysis of the "treatable traits" proposal is provided in Fig. 2. Importantly, the identification and management of treatable traits should not be restricted to the pulmonary domain. In fact, the detection of extra-pulmonary comorbidities as well as lifestyle and behavioral traits, although not strictly biologically related to ILDs, might impact quality of life and clinical outcomes. Multidisciplinary models of care, international registries, and the use of AI may facilitate the implementation of the "treatable traits" approach into clinical practice. This perspective aims to foster collaboration among the respiratory community, regulatory agencies and pharmaceutical industries. The "treatable traits" approach is a clinical and research priority, with properly designed cohorts and RCTs needed to test potential therapies for a variety of treatable traits to further advance care of patients with ILD.

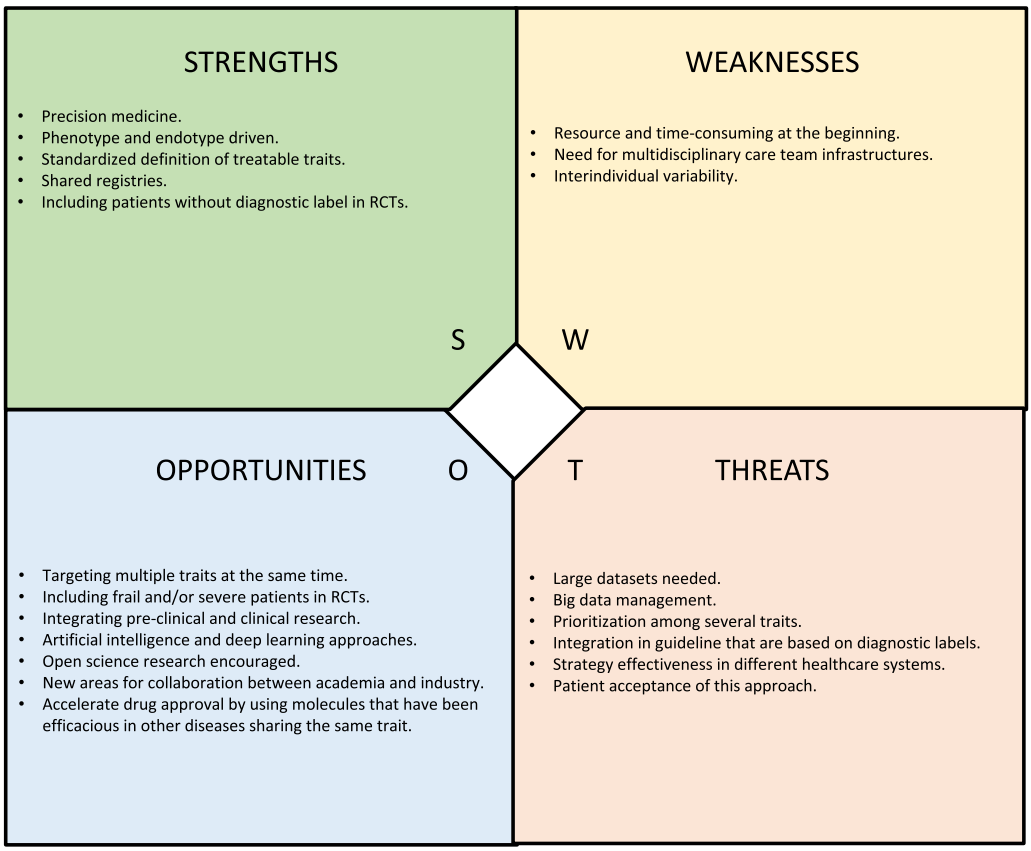

Fig. 2 SWOT analysis of the treatable trait strategy in ILD. SWOT is an acronym that identifies the four elements of the analysis: strengths (S), weakness (W), opportunities (O), and threats (T). A SWOT analysis allows to critically explore advantages and disadvantages resulting from internal and external factors

Abbreviations

ILD	Interstitial lung disease
COPD	Chronic obstructive pulmonary disease
UIP	Usual interstitial pneumonitis
DIP	Desquamative interstitial pneumonia
BIP	Bronchiolitis obliterans interstitial pneumonia
LIP	Lymphoid interstitial pneumonia
GIP	Giant cell interstitial pneumonia
HRCT	High-resolution computed tomography
RCT	Randomized controlled trial
IPF	Idiopathic pulmonary fibrosis
SSc	Systemic sclerosis
TOLLIP	Toll-interacting protein
TERT	Telomerase reverse transcriptase
TERC	Telomerase RNA component
NAC	*N*-Acetylcysteine
TRG	Telomere-related gene
FVC	Forced vital capacity
PPF	Progressive pulmonary fibrosis
PH	Pulmonary hypertension
MDT	Multidisciplinary team
GERD	Gastro-esophageal reflux disease
AI	Artificial intelligence
IT	Information technology
NSIP	Nonspecific interstitial pneumonia
MDD	Multi-disciplinary discussion
OSA	Obstructive sleep apnea
ILAs	Interstitial lung abnormalities

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F.A. and S.A. conceived the original idea and developed the theory. F.A. wrote the manuscript with support from S.A., P.S, J.O., CJR. S.A. supervised the project. All authors provided critical feedback and give final approval of the manuscript.

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