

# Idiopathic pulmonary fibrosis

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**Abstract** | Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease characterized by progressive lung scarring and the histological picture of usual interstitial pneumonia (UIP). It is associated with increasing cough and dyspnoea and impaired quality of life. IPF affects ~3 million people worldwide, with incidence increasing dramatically with age. The diagnostic approach includes the exclusion of other interstitial lung diseases or overlapping conditions and depends on the identification of the UIP pattern, usually with high-resolution CT; lung biopsy might be required in some patients. The UIP pattern is predominantly bilateral, peripheral and with a basal distribution of reticular changes associated with traction bronchiectasis and clusters of subpleural cystic airspaces. The biological processes underlying IPF are thought to reflect an aberrant reparative response to repetitive alveolar epithelial injury in a genetically susceptible ageing individual, although many questions remain on how to define susceptibility. Substantial progress has been made in the understanding of the clinical management of IPF, with the availability of two pharmacotherapeutic agents, pirfenidone and nintedanib, that decrease physiological progression and likely improve progression-free survival. Current efforts are directed at identifying IPF early, potentially relying on combinations of biomarkers that include circulating factors, demographics and imaging data.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease (ILD; BOX 1) in which progressive lung scarring occurs in the supporting framework (interstitium) of the lungs<sup>1</sup> (FIG. 1). IPF is defined on the basis of the presence of a radiographic and/or histopathological pattern of usual interstitial pneumonia (UIP) in the absence of an alternate aetiology for this pattern. UIP usually presents as ‘honeycombing’ (subpleural cystic airspaces with well-defined walls), traction bronchiectasis (dilatation of the bronchi) and peripheral alveolar septal thickening. IPF is thought to begin at the base and periphery (edge) of the lungs, gradually progressing to involve all lung tissue. The disease, which can present as sporadic or familial forms, is associated with increasing cough and dyspnoea (shortness of breath), with a devastating effect on a patient’s quality of life (QOL)<sup>2</sup>. Improved diagnostic methods are of increasing importance to enable the institution of effective therapies. Recent years have witnessed radical improvements in therapeutic options and their availability, translating into an opportunity to preserve lung function<sup>3</sup>.

For many years, IPF was considered a principally inflammatory disease, given the increase in inflammatory cells in the lungs. However, a growing body of evidence indicates that IPF is an epithelial-driven disease whereby an aberrantly activated lung epithelium

produces mediators of fibroblast migration, proliferation and differentiation into active myofibroblasts. These myofibroblasts secrete exaggerated amounts of extracellular matrix (ECM) that subsequently remodel the lung architecture<sup>4</sup>. This Primer provides a comprehensive view of IPF epidemiology, the biological basis of pathogenesis, the current diagnostic approaches and the effects on patient QOL. A detailed description of current and evolving therapeutic approaches is also provided.

## Epidemiology

IPF treatment guidelines published in 2011 highlighted a lack of adequate epidemiological evidence<sup>1</sup>. Over the past 5 years, numerous publications from Europe, North America and East Asia have improved the evidence base<sup>5–12</sup>. The interpretation of these data is difficult owing to fundamental differences in data sources and case definitions used<sup>13,14</sup>. Most importantly, the code-based methodologies used to identify patients with IPF in most of these studies have been shown to be highly inaccurate owing to inappropriate assignment<sup>6</sup>. Accordingly, a real need remains for epidemiological studies using large-scale, representative data sets with patient-level data for case validation.

Despite these limitations, systematic reviews of the available epidemiological studies have provided insight into the incidence and prevalence of IPF<sup>15</sup>. For example,

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studies using less-restrictive criteria to define IPF suggest an incidence ranging from 2–30 cases per 100,000 person-years and prevalence ranging from 10–60 cases per 100,000 people<sup>5–12</sup>. These figures roughly translate to a population prevalence of 130,000 in the United States, 300,000 in Europe, 640,000 in East Asia and ~3 million people worldwide. There is a paucity of data from other continents.

In patients >65 years, the estimated prevalence of IPF is as high as 400 cases per 100,000 people<sup>16</sup>. Most studies report a slight male predominance; whether this finding reflects a biological predilection or results from behavioural and environmental factors is unclear. On the basis that incidence and prevalence of IPF increases dramatically with age, the pathobiological paradigm of IPF as a disease of age-related alveolar epithelial cell dysfunction has emerged<sup>17</sup>. Indeed, age has accordingly been incorporated into clinically useful diagnostic algorithms<sup>18,19</sup>. Alongside age, dyspnoea or cough in older individuals should be viewed as risk factors for IPF given its frequency in this population.

The prognosis for patients with IPF is quite poor, with some studies suggesting that IPF survival is worse than many cancers that affect people with similar demographics<sup>20</sup>. Importantly, survival is quite variable from patient to patient<sup>2</sup>, with a median survival of 3–5 years if untreated<sup>1</sup>. In general, older age, male sex, worse dyspnoea and greater physiological abnormality have been associated with impaired prognosis<sup>2</sup>. A multidimensional index including sex, age and physiological abnormality has been shown to be strongly associated with mortality<sup>21</sup>.

**Mechanisms/pathophysiology**

The lungs are constantly exposed to many injuries but display a remarkable ability to repair and recover through a cascade of finely synchronized biological processes. However, repetitive alveolar epithelial injury

in a genetically susceptible ageing individual could lead to stochastic pro-fibrotic epigenetic reprogramming, premature and persistent epithelial cell senescence, excessive production of pro-fibrotic mediators and ongoing activation of mesenchymal cells, leading to a maladaptive response and eventual development of IPF.

Several risk factors have been implicated in the pathogenesis of IPF, including environmental exposures, smoking, chronic viral infections and certain comorbidities. Of these, the genetic risks are the most compelling<sup>22</sup>; genetic variants are estimated to explain up to one-third of the inherent individual risk of disease<sup>23</sup>. Age is the strongest demographic risk factor for IPF, suggesting that ‘accelerated’ lung ageing is a driving force for its development<sup>17</sup>. Indeed, almost all of the cellular and molecular hallmarks of ageing are exaggerated or occur prematurely in IPF. Alveolar epithelial cells, mainly alveolar epithelial type 2 cells (AEC2s), are primarily affected. AEC2s have critical secretory (surfactant), metabolic and immunological functions and are progenitor cells for alveolar epithelial type 1 cells (AEC1s), which maintain alveolar epithelial turnover. In IPF, AEC2s demonstrate genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence and altered intercellular communication<sup>24</sup>. Indeed, IPF is a complex disorder resulting from interactions between these risk factors whereby the relative contribution of each factor probably differs between individuals<sup>25</sup> (FIG. 2). The complexity of IPF is also determined by innumerate multidirectional interactions between epithelial cells, mesenchymal cells and the ECM. However, the exact mechanisms of how these factors interact to cause disease remain unclear; currently, all patients diagnosed with IPF — regardless of their risk factors — are considered mechanistically similar.

**Genetics**

Studies regarding the genetic architecture of sporadic IPF and the currently known mutations involved in its familial form highlight the role of the lung epithelium in the development of the disease. Several rare variants of the genes *TERT* (encoding telomerase reverse transcriptase) and *TERC* (encoding telomerase RNA component) as well as of other genes related with telomere maintenance, such as *TINF2*, *DKC1*, *RTEL1*, *PARN* and *NAF1*, have been identified in ~25% of patients with familial pulmonary fibrosis<sup>26–31</sup>. These mutations result in abnormally short telomeres that specifically affect AEC2s in the lungs. Shortened telomeres are also observed in a number of patients with sporadic IPF<sup>32</sup>. Similarly, mutations in genes encoding surfactant proteins — primarily the gene encoding surfactant protein C (*SFTPC*), which is exclusively expressed by AEC2s — cause dysfunctional folding and processing of surfactant, dysregulated proteostasis and endoplasmic reticulum stress and might promote epithelial dedifferentiation (that is, epithelial–mesenchymal transition)<sup>33</sup>.

The variant rs35705950 of the promoter of the gene encoding mucin 5B (*MUC5B*) is the most common polymorphism that markedly increases the risk of both

sporadic and familial IPF<sup>34,35</sup>. *MUC5B* plays an important part in mucociliary clearance and host defence, but the mechanisms by which it promotes IPF remain unclear. However, this *MUC5B* promoter variant is not universally observed; it is rare in Asian populations but is a strong risk factor in white and Mexican populations<sup>34–37</sup>. Paradoxically, patients with this promoter variant have improved survival compared with those without this variant<sup>38</sup>.

Variants in *TOLLIP* (which encodes an inhibitor of the transforming growth factor- $\beta$  (TGF $\beta$ ) pathway and critical regulator of Toll-like receptor-mediated innate immune responses) and *OBFC1* (encoding oligonucleotide/oligosaccharide-binding fold-containing 1; also known as STN1) as well as *TERC* and *TERT* have also been implicated in sporadic IPF. Patients with IPF who harbour the protective minor allele rs5743890\_G of *TOLLIP*, which decreases the risk of developing the disease, have increased mortality<sup>35</sup>. Additionally, variants in *DSP* and *DPP9*, which are involved in cell–cell interactions and epithelial integrity, have been implicated<sup>34,35</sup>. Testing for these genetic variants is now recommended in selected patients with idiopathic interstitial pneumonias<sup>39</sup>.

### Environmental factors

Several environmental exposures that target the lung epithelium increase the risk of IPF, with the most consistent evidence being for cigarette smoking in both sporadic and familial disease<sup>40,41</sup>. An increased risk has also been linked to occupational exposures such as agriculture and farming, livestock, wood dust, metal dust, stone dust and silica<sup>40</sup>.

Several studies have also suggested that viruses might play a part in the pathogenesis of IPF; Epstein–Barr virus (EBV) has primarily been detected in the alveolar epithelia of patients with IPF<sup>42,43</sup>. Moreover, in AEC2s, latent human herpesviruses (such as EBV, cytomegalovirus and Kaposi sarcoma-associated herpesvirus) colocalize with markers of endoplasmic reticulum stress and the unfolded protein response, which is a process that has been associated with the pathogenesis of IPF<sup>44</sup>.

Studies assessing the role of bacteria in IPF pathogenesis are in their infancy. The lungs of patients with IPF have higher bacterial loads and substantial differences in the composition and diversity of their microbiota compared with control subjects, including increases in several potentially pathogenic bacteria such as *Staphylococcus* spp. and *Streptococcus* spp.<sup>45–47</sup>. Importantly, these alterations in the lung microbiota have been associated with clinical markers of disease progression<sup>46,47</sup> and with evidence of circulating and lung measures of host immune response<sup>48,49</sup>. In the past decade, microaspirations of gastric content have been suggested as another potential cause of injury to the lung epithelium in IPF. In support of this notion, the prevalence of gastro-oesophageal reflux is elevated in those with IPF<sup>50</sup>. Although all these risk factors could contribute to epithelial injury, in general, further evidence is required to support a causal link between any risk factor and the pathogenesis or progression of the disease.

### Epigenetic reprogramming

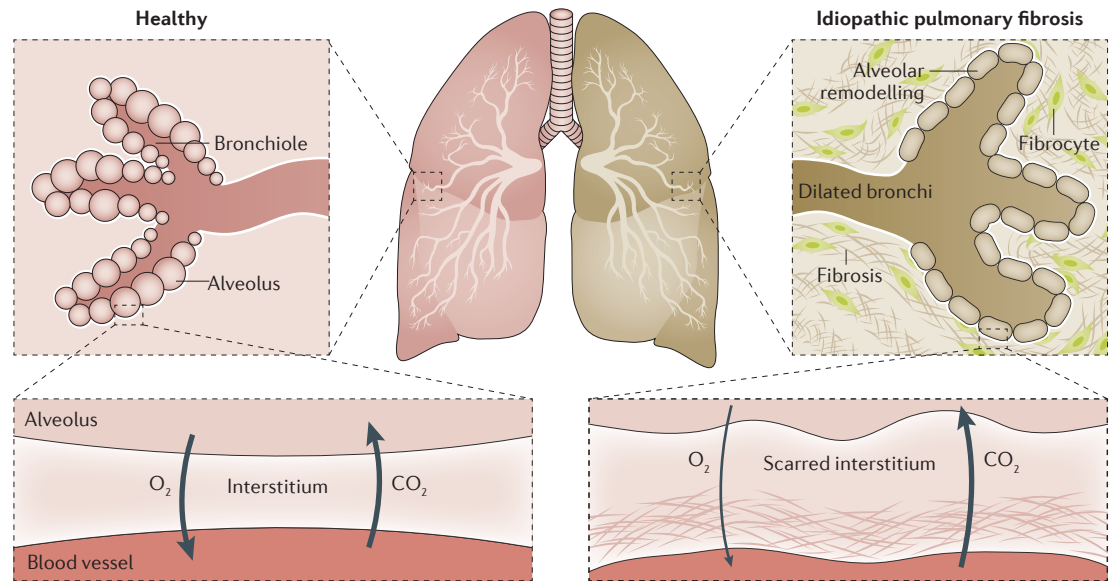
During ageing, many epigenetic changes — including loss of histones, deregulation of microRNAs (miRNAs) and a DNA methylation drift (characterized in part by non-directional stochastic changes of the methylome) — are evident<sup>51,52</sup>. These changes lead to unpredictable differences in the methylomes between individuals; the stochastic nature of the changes is thought to have a major role in the pathogenetic processes leading to IPF<sup>53</sup>.

In a 2014 study, 2,130 genome-wide differentially methylated regions were identified in patients with IPF compared with healthy controls<sup>54</sup>. The analyses revealed that several regulators of lung development, such as WNT- $\beta$ -catenin signalling, were upregulated. Some *trans*-regulatory methylation marks were found near transcription factors, suggesting a complex deregulation of downstream genes<sup>54</sup>. Other studies in patients with IPF have also identified significant modifications in miRNAs with potential pathogenetic roles<sup>55</sup>. For example, the miRNA Let-7 is significantly downregulated in epithelial cells from IPF lungs and might contribute to epithelial–mesenchymal transition<sup>56</sup>. Similarly, miR-21 is highly upregulated in IPF lungs as well as in the lungs of mice with bleomycin-induced fibrosis, and it promotes TGF $\beta$ -induced fibrogenic activation by targeting SMAD7, which is a negative regulator of TGF $\beta$ <sup>57</sup>. These miRNAs affect AEC2s and fibroblasts and, in general, result in activation of the TGF $\beta$  signalling pathways, pro-fibrotic processes and some developmental signalling pathways<sup>25,55</sup>.

Few studies have examined the role of structural changes of chromatin in IPF. One report showed that almost all class I and II histone deacetylases are upregulated in IPF, mainly in myofibroblasts and in abnormal bronchiolar basal cells<sup>58</sup>. However, their exact targets and effects in the setting of IPF are currently unknown. Studies examining histone modifications have identified that several important anti-fibrotic genes are silenced, including *CAV1* (encoding caveolin 1), which is a regulator of TGF $\beta$ 1 signalling; *PTGS2*, which encodes prostaglandin G/H synthase 2 (also known as *COX2* and cyclooxygenase 2, respectively) is also silenced, resulting in the loss of prostaglandin E2, an important anti-fibrotic mediator. Additionally, *FAS*, which encodes

#### Box 1 | Interstitial lung disease

The interstitium of the lung is a lace-like network of tissue that extends throughout the lungs and provides support to the air sacs (alveoli). Tiny blood vessels traverse the interstitium and facilitate gas exchange between the blood and air. Interstitial lung disease is a category of disorders that includes many different conditions, all of which affect the interstitium in various ways, including with increased inflammation, oedema and/or fibrosis. These disorders — which include idiopathic pulmonary fibrosis, other interstitial pneumonia and hypersensitivity pneumonitis — generally cause thickening of the interstitium and impair gas exchange. The conditions generally present with cough and/or breathlessness on exertion. Some interstitial lung diseases are acute, whereas others are chronic, progressive and irreversible.



**Figure 1 | Alveolar damage in idiopathic pulmonary fibrosis.** Idiopathic pulmonary fibrosis results in traction bronchiectasis (dilatation of the bronchi), alveolar remodelling and parenchymal fibrosis, which impair gas exchange (particularly oxygenation).

tumour necrosis factor (TNF) receptor superfamily member 6, is silenced, contributing to increased apoptotic resistance of fibroblasts in IPF<sup>59</sup>. Finally, histone modifications have been described in IPF as causing the silencing of the gene encoding the anti-fibrotic receptor Thy1 membrane glycoprotein (*THY1*), the activation of NADPH oxidase 4 (which produces reactive oxygen species) and the decrease in miR-29c, a potent regulator of collagen expression<sup>59–64</sup>.

#### The role of epithelial cells

The IPF lung is characterized by concurrent epithelial cell proliferation, apoptosis, senescence (see below) and partial epithelial–mesenchymal transition, which is likely linked to a migratory programme. For example, several studies have demonstrated the presence of AEC2s undergoing apoptosis, usually in areas of active fibrogenesis; this apoptosis might be one of the initial events in response to epithelial damage<sup>65,66</sup>. Additionally, areas of hyperplastic proliferation of the epithelium have been identified (using Ki67 antigen and proliferating cell nuclear antigen (PCNA) assays of cell proliferation) in some areas of IPF lungs<sup>67,68</sup>. The origin and timing of this diversity are uncertain.

Although repetitive alveolar epithelial damage by exogenous injuries might be a critical factor leading to dysregulated repair and regeneration in IPF, emerging evidence challenges this paradigm, instead suggesting that epithelial disintegration without exogenous injury triggers the initiation of the lung fibrotic response<sup>69,70</sup>. For example, mice lacking CD151, an essential tetraspanin for normal function of alveolar epithelial cells, spontaneously exhibit age-related lung fibrosis<sup>71</sup>. Similarly, telomere dysfunction in AEC2s in mice provoked by deletion of the shelterin protein telomere repeat binding factor 1 (*Trf1*) led to spontaneous age-associated lung remodelling and fibrosis<sup>72</sup>. Telomere dysfunction

restricted to AEC2s also impairs stem cell function, severely affects the regenerative potential of parenchymal epithelial stem cells and might lead to alveolar stem cell exhaustion or failure<sup>29</sup>. However, these data cannot rule out the notion that loss of integrity of the alveolar epithelium and exhaustion of alveolar stem cells predisposes the individual to IPF following external stressors.

Migration and proliferation of bronchiolar basal cells and AEC2s, and the increase or emergence of epithelial progenitor cell populations, might participate in re-epithelialization as a response to injury<sup>73</sup>. For example, the analysis of the RNA profiles of single epithelial cells from normal and IPF lungs revealed that markers of alveolar epithelial cells and conducting airways are co-expressed in IPF, suggesting that epithelial cells of the IPF distal lung acquire atypical mixed differentiation states<sup>74</sup>. Moreover, markers of ciliated, basal and goblet cells have also been identified in close proximity to AEC2s, and the epithelium of IPF cysts has been shown to contain p63-positive basal cells located in close proximity to cuboidal AEC2s — indicating a loss of regional specification and epithelial cell gene expression<sup>74</sup>.

**Secreted factors.** Importantly, most of the epithelial cells in the IPF lungs are aberrantly activated and produce virtually all the mediators that contribute to the expansion of the fibroblast and myofibroblast populations and to the remodelling of the ECM<sup>4,24</sup>. These mediators include TGF $\beta$ , platelet-derived growth factor, connective-tissue growth factor (CTGF), TNF, osteopontin, angiotensinogen, several matrix metalloproteinases (including MMP1, MMP7, MMP19, membrane-type MMP1 and membrane-type MMP2) and a number of chemokines (including CC motif chemokine 2 (CCL2; also known as monocyte chemoattractant protein 1) and stromal cell-derived factor 1 (also known as CXC motif chemokine 12, CXCL12)).



Epithelial cells also secrete factors that are involved in coagulation and that have been implicated in fibrogenesis, such as tissue factor, factor VIIa, factor X and plasminogen activator inhibitor-1<sup>24</sup>. Remarkably, abnormally activated epithelial cells are responsible for the persistent reactivation of embryological pathways through the expression of WNT-pathway components and Sonic Hedgehog, which crosstalk with TGF $\beta$  and activate a pro-fibrotic feedback loop<sup>25</sup>. Thus, strong evidence demonstrates that the cocktail of mediators that drives the fibrotic response is produced by the epithelium.

**Cell senescence.** Highly regulated cell senescence has a beneficial role during embryonic patterning and organogenesis, tumour suppression and tissue repair (adaptive response). However, chronic accumulation of senescent cells, as occurs in IPF, leads to detrimental consequences and is considered a maladaptive response in a variety of human pathologies<sup>75</sup>. In this context, accelerated — and probably persistent — AEC2 senescence, at least partially related to telomere attrition, has been consistently observed in IPF lungs<sup>25,32,76,77</sup>.

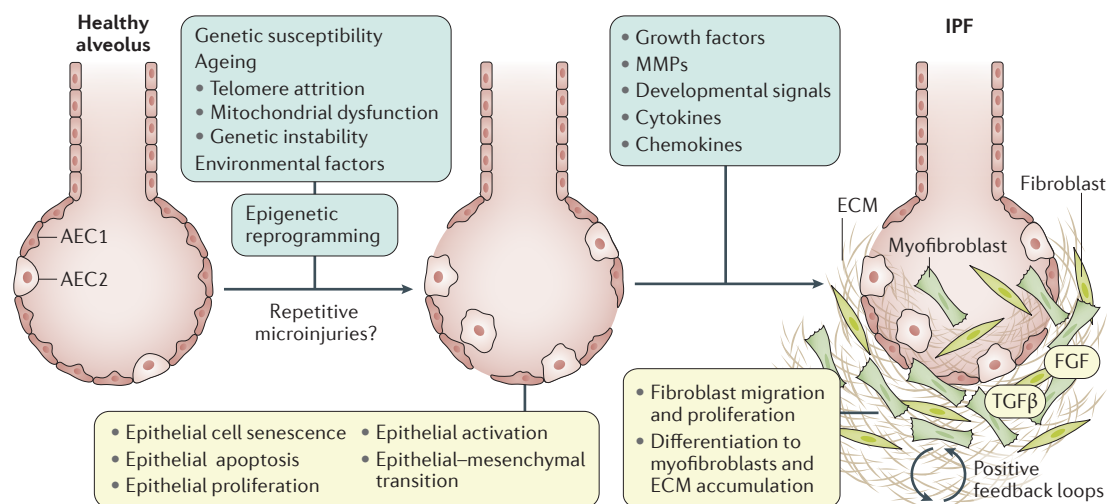
Senescence is characterized by a plethora of secreted cytokines, growth factors, matrix-degrading enzymes and development-related molecules that mediate cell–cell communication and strongly modify the micro-environment. The senescence-associated ‘secretome’ varies according to the stimulus that induces senescence and to the features of cellular microenvironment. In this context, a two-phase model of senescence was proposed<sup>78</sup>. In both fibroblasts and epithelial cells, it was shown that in the first stage, a pro-senescent, pro-fibrotic

NOTCH1-driven TGF $\beta$  programme is activated, which negatively regulates the expression of pro-inflammatory cytokines and matrix metalloproteinases. In the second phase, a pro-inflammatory, matrix-degrading and senescence-clearing programme — driven by the activity of the transcription factors of the C/EBP $\beta$  family — takes place, resulting in elimination of the deposited ECM and the progressive clearance of senescent cells by immune cells. Interestingly, although the secretome changed in a dynamic and reciprocal fashion over time, cell growth arrest remained unaffected<sup>78</sup>. This model might explain the diverse functional consequences of senescence and suggests that, if the second phase is corrupted, a persistent pro-fibrotic (maladaptive) programme could run rampant. However, whether this altered programme occurs in IPF is currently unknown.

Additionally, in influenza-injured mice, persistent Notch signalling after injury results in the formation of parenchymal microscopic honeycombing, which is indicative of failed regeneration<sup>79</sup>; Notch activity was also observed in honeycomb cysts in IPF lungs. Thus, persistent Notch signalling prevented alveolar differentiation, whereas removal of this signal promoted maturation towards AEC2s<sup>79</sup>. However, whether these findings are associated with senescence is unknown. Notch might also induce epithelial–myofibroblast transition via TGF $\beta$  signalling<sup>80</sup>.

### The role of myofibroblasts

In general, a characteristic of maladaptive repair is the exaggerated expansion of the fibroblast population and its differentiation to myofibroblasts. Myofibroblasts



**Figure 2 | A proposed pathogenetic model of idiopathic pulmonary fibrosis.** The convergence of three elements — a genetic architecture affecting epithelial cell integrity, environmental factors and accelerated ageing-associated changes — results in a complex epigenetic reprogramming that promotes aberrant epithelial cell activation in idiopathic pulmonary fibrosis (IPF), which might or might not be exacerbated by injury. The activated epithelium secretes a plethora of mediators that induce migration, proliferation and activation of fibroblasts and myofibroblasts, which are resistant to apoptosis and persistently secrete extracellular matrix (ECM) components. The ECM is also a reservoir of growth factors that can be released as soluble ligands upon degradation. Rather than being linear, the sequence is characterized by a number of positive feedback loops, such as between matrix stiffness and fibroblast activation. Additionally, signalling crosstalk (for example, fibroblast growth factor (FGF) and transforming growth factor- $\beta$  (TGF $\beta$ ) signalling) adds to the complexity and likely leads to the inexorable progression of the disease. AEC1, alveolar epithelial type 1 cell; MMP, matrix metalloproteinase.

also induce epithelial cell apoptosis through the secretion of angiotensin peptides and oxidants that affect re-epithelialization<sup>81,82</sup>. As discussed, many of the mediators secreted by epithelial cells participate in myofibroblast recruitment. However, the source of myofibroblasts in IPF, and their contributions to the disease, remain unclear. Candidates include resident cells (local fibroblasts, pericytes and mesenchymal progenitor cells) or circulating bone marrow-derived progenitor cells (fibrocytes); epithelial, mesothelial or endothelial cells transitioning to mesenchymal cells are also plausible candidates<sup>4</sup>.

Once in the damaged areas, highly contractile myofibroblasts become resistant to apoptosis, a feature that translates into accumulation of ECM components in the lung interstitium — predominantly fibrillar collagens, fibronectin, tenascin and proteoglycans<sup>83</sup>. Indeed, the ECM is a highly organized structure that provides a physical framework to cells and has a dynamic role in signalling; it is also a reservoir of growth factors that can be released as soluble ligands upon ECM degradation. Additionally, some proteoglycans are critical for certain growth factor signalling pathways; for example, fibroblast growth factor (FGF) requires heparin sulfate binding to engage its cognate receptor, and TGF $\beta$  first binds to membrane-anchored non-signalling receptors such as endoglin or TGF $\beta$ -receptor type 3 (also known as  $\beta$ -glycan)<sup>84</sup>.

The mechanical characteristics of the matrix (its stiffness and deformability) have also been recognized to contribute to cell behaviour<sup>85</sup>; the ECM itself might be an active player in the pathogenesis of IPF, ascribed in part to its elasticity and stiffness<sup>86</sup>. Mechanical properties (namely, measurement of the Young modulus, which describes the tensile elasticity of a material) of the lung matrix analysed by atomic force microscopy have revealed considerable matrix stiffening in IPF lungs compared with normal lungs<sup>86</sup>. The influence of ECM stiffness on lung fibroblasts has been documented by numerous experimental approaches<sup>87,88</sup>. Thus, lung fibroblasts cultured under pathologically 'stiff' conditions differentiate to myofibroblasts and display increased contractility, proliferation, collagen production and active TGF $\beta$ . Additionally, IPF extracellular matrix also induces alterations in the transcriptional regulation of lung fibroblasts but, more so, influences the translation of proteins enriched in the IPF proteome ECM, such as COL1A1, COL1A2, COL3A1, COL5A2, COL4A2, MMP2, MMP3, MMP10 and TIMP2 (REF. 9). Interestingly, the genes encoding these proteins are targets for miR-29, which seems to be downregulated in fibroblasts grown on IPF-derived ECM. This finding suggests a positive feedback loop between fibroblasts and aberrant ECM in which the fibrotic ECM is both a cause and a consequence of fibroblast activation<sup>89</sup>.

Other studies have identified a key role for myofibroblast  $\alpha$ -integrins in the regulation of fibrosis through the activation of TGF $\beta$ . For example, integrin  $\alpha 6$  contributes as a mechanosensing integrin subunit that mediates matrix stiffness-regulated myofibroblast invasion<sup>90,91</sup>. Fibroblasts and/or myofibroblasts might also play a part in blood clotting and angiogenesis,

and produce paracrine signals (such as insulin-like growth factor binding proteins 3 and 5), CTGF, various chemokines and reactive oxygen species that further enhance the fibrotic response. However, whether these functions participate in IPF remodelling *in vivo* is currently unclear<sup>92</sup>.

### The role of the immune system

Several alterations in the number and activity of diverse subpopulations of T cells have been described in IPF. However, whether immune response dysfunction contributes to the pathogenesis or to the progression of the disease, represents a frustrated defence mechanism or occurs because of viral and bacterial infections is currently unclear. Moreover, most studies have been performed in peripheral blood or in inflammation-driven mouse models of fibrosis; accordingly, the precise implication of T cells in the IPF lung parenchyma remains uncertain. Furthermore, contradictory results have been reported for some important subsets of lymphocytes; for example, CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> regulatory T cells have been shown to be either significantly increased or decreased in patients with IPF<sup>93,94</sup>.

Thus, although some progress has been made to understand the innate and adaptive immune response in IPF, the effects of the diverse immune dysfunctions in the lung revealed so far are still elusive, and they may have both negative and positive roles. Indeed, some subsets of T cells in the lung might be protective, whereas others accelerate disease progression<sup>95</sup>. In this context, cytokine receptor-like factor 1, which is a selective stimulus of AEC2s, might drive an anti-fibrotic response that enhances T helper 1 and regulatory T cell inflammatory responses in the lung<sup>96</sup>. In general, most studies suggest that changes in the proportion or activation of some T cell and B cell subsets as well as the presence of some autoantibodies will influence disease progression and accelerate the decline of lung function<sup>97–100</sup>.

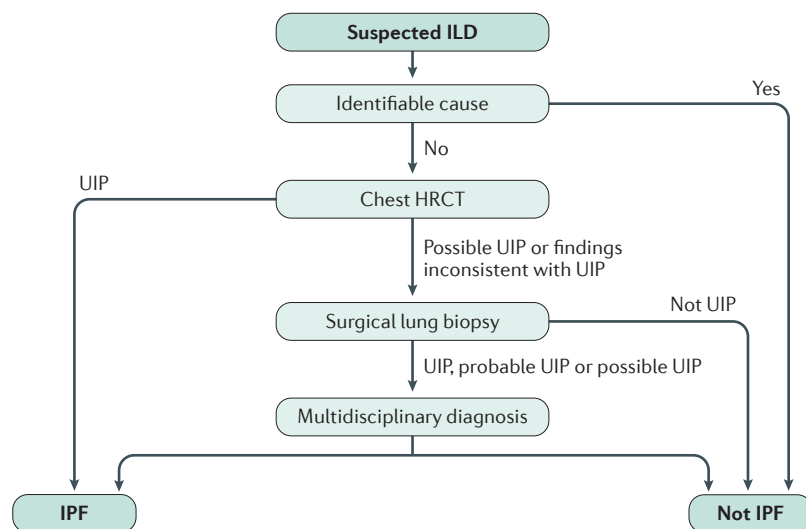
Importantly, some reports suggest that immunosuppressive forces influence and shift the phenotype and function of immune cells in IPF. Indeed, the downregulation of relevant immune-response pathways has been associated with changes in the abundance of specific microorganisms<sup>48</sup>. Specifically, abundant microorganisms of low diversity drive decreased expression of several immune pathways in IPF lungs and in peripheral blood mononuclear cells; these features are associated with poor progression-free survival<sup>48</sup>. Similarly, myeloid-derived suppressor cells, which are a heterogeneous population of immature myeloid cells with potent T cell-suppressive capabilities, are increased in the blood and lungs of patients with IPF — a result that inversely correlates with lung function<sup>101</sup>. Taken together, these data indicate that an immunosuppressive environment is operating in the peripheral blood and lungs of patients with IPF, which influences disease progression. Indeed, the putative downregulation of protective immune pathways could at least partially explain the failure of the PANTHER clinical trial, in which patients who received a combination of immunosuppressive agents had worse outcomes than those in the placebo group<sup>102,103</sup>.

## Diagnosis, screening and prevention

### Diagnosis

The diagnosis of IPF starts from a clinical suspicion of ILD (BOX 1). Without sufficient awareness and adequate knowledge of this group of respiratory diseases by clinicians, both early diagnosis and prevention remain elusive. Typically, patients with IPF present with the nonspecific symptom of exertional dyspnoea (difficulty breathing when active), with or without dry cough. Some patients will present with digital clubbing. However, these initial symptoms are usually attributed to ageing, deconditioning or other comorbidities, such as pulmonary emphysema or cardiovascular disease. Indeed, the lack of specific symptoms and the coexistence of other disorders delay diagnosis, which has a negative consequence on the survival of patients<sup>104</sup>. Occasionally patients present acutely, with days to weeks of respiratory worsening, often accompanied by fever and flu-like symptoms; some of these dramatic presentations represent acute exacerbations of IPF<sup>105</sup>.

To establish a diagnosis and rule out other ILDs or overlapping conditions, clinical features, chest imaging and, potentially, lung histopathology are needed (FIG. 3). A diagnosis of IPF is usually achieved through an iterative discussion within a multidisciplinary team, a practice<sup>106</sup> endorsed by international guidelines<sup>1,107</sup>.



**Figure 3 | Suggested approach for the diagnosis of IPF.** A diagnosis of interstitial lung disease (ILD) includes an initial comprehensive history, physical examination, physiological testing and the use of selective laboratory studies. An ILD that is not idiopathic pulmonary fibrosis (IPF) might be identified, such as occupational lung disease, hypersensitivity pneumonitis or connective tissue-associated lung disease. A high-resolution CT (HRCT) is a key diagnostic test, as it provides important imaging insight into the pattern of lung injury; it is particularly useful to identify the pattern of usual interstitial pneumonia (UIP). In the setting of idiopathic disease, UIP establishes a diagnosis of IPF. Surgical lung biopsy is currently recommended in patients with an HRCT pattern of possible UIP or inconsistent with UIP in an appropriate clinical setting. Multidisciplinary diagnosis is recommended as a key feature of the diagnostic pathway. Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. Raghu, G. *et al.* (2011) An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am. J. Respir. Crit. Care Med.* **183**, 788–824. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

The multidisciplinary team comprises clinicians, radiologists and pathologists who work together to increase diagnostic confidence. Recent work has identified that agreement between multidisciplinary teams in academic institutions more frequently achieves a diagnosis of IPF than clinicians or radiologists independently, and with higher confidence<sup>108,109</sup>. Importantly, an IPF diagnosis by the multidisciplinary team has higher prognostic significance than an IPF diagnosis rendered by clinicians or radiologists in isolation<sup>108</sup>. However, limited evidence is available on how the multidisciplinary team approach has been implemented in routine clinical care, and whether this affects diagnostic accuracy and treatment decisions. Accordingly, the approach suggested in FIG. 3 must be adapted to an individual patient on the basis of local expertise and the availability of diagnostic testing.

**Exclusion of other ILDs.** A major challenge to clinicians remains the exclusion of other known causes of ILD, such as domestic and occupational exposures, connective tissue disease<sup>110</sup> and drug toxicity<sup>111</sup>. Many patients have histories of environmental exposures, medications and symptoms that require clinicians to make a judgement regarding their aetiological significance. Careful attention to signs is essential to rule out ILD associated with connective tissue disease, one of the main differential diagnoses with IPF<sup>111</sup>. Little objective evidence supports a role for routine serological screening in patients with suspected IPF, but most experts believe that testing these patients for occult connective tissue disease is useful<sup>1</sup>. Chronic hypersensitivity pneumonitis (CHP) — an inflammatory disease of the lungs caused by hypersensitivity to inhaled antigens — should always be considered in the differential diagnosis of patients suspected of having IPF. Unfortunately, the diagnostic pathway for CHP has not been standardized<sup>112</sup>, but it might include identification of IgG to known antigens, culture of specimens from the patient's environment, bronchoalveolar lavage cellular analyses and bronchoprovocation testing (in which lung function is measured after exposure to common triggers of CHP)<sup>113–116</sup>. The diagnosis of CHP is highly dependent on a high index of suspicion based on clinical presentation<sup>112,113</sup>.

**Physical examination.** Physical examination of the chest is the only point-of-care test able to refine the clinical suspicion of IPF<sup>117</sup>. Fine, high-pitched bibasilar inspiratory crackles (the so-called velcro-like sounds) are generally heard and are the most specific among the chest physical signs at initial presentation ([Supplementary information S1](#) (audio)). Other physical findings are generally used in excluding alternate disorders, particularly connective tissue diseases<sup>110,118</sup>.

**Physiology.** Pulmonary function tests typically identify restrictive disease (reduced total lung capacity) and abnormal gas exchange (reduced diffusion capacity for carbon monoxide)<sup>1</sup>. Early-stage disease (or, in some cases, disease coexisting with emphysema, which pseudo-normalizes lung volumes) can demonstrate



normal spirometry (which measures volume of expired air) and plethysmography (which measures total lung volume and its components), with only an isolated reduction in diffusion noted<sup>119</sup>.

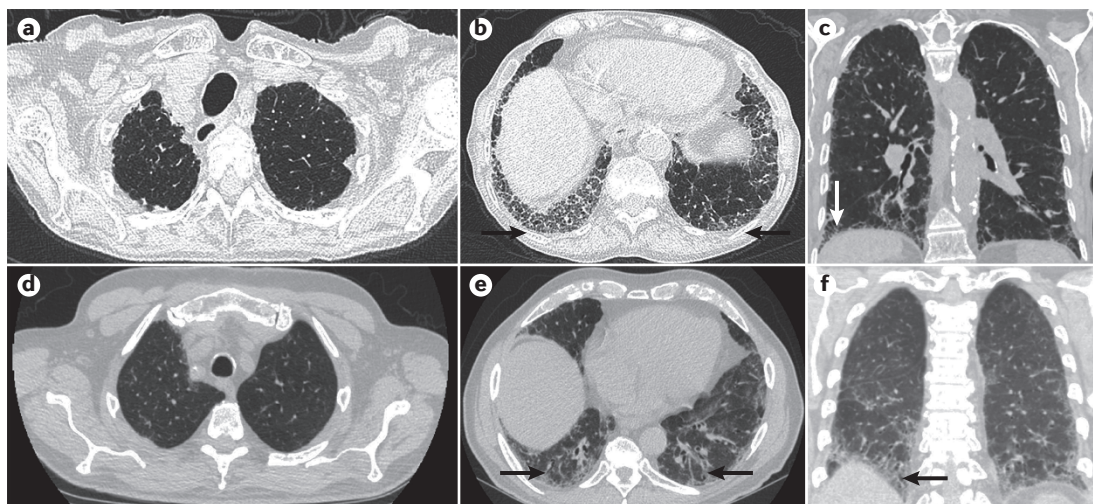
**Imaging.** The current diagnostic approach for IPF depends on identification of the UIP pattern, one approach for which is high-resolution CT (HRCT)<sup>1,107</sup>. Chest HRCT can reveal reticular changes associated with traction bronchiectasis and honeycombing. A predominantly bilateral, peripheral and basal distribution is typical of the UIP pattern and can be used to diagnose IPF in a compatible clinical context (FIG. 4). On the other hand, features such as mosaic attenuation (a patchwork of regions with low density on CT), ground glass opacities (an area of increased attenuation, appearing white and hazy on CT) and profuse nodules suggest an alternative diagnosis, such as CHP or nonspecific interstitial pneumonia<sup>1,120</sup>.

Although the presence of honeycombing is required for a definite radiological diagnosis of IPF, recent phase III clinical trials have not uniformly applied this criterion, instead diagnosing IPF radiologically if either honeycombing or traction bronchiectasis and a reticular abnormality consistent with fibrosis were present in a basal and peripheral predominance<sup>121</sup> (FIG. 4). Predefined analyses of these subgroups identified the rate of functional decline to be identical in both groups, supporting a broadening of the HRCT criteria for a confident identification of the UIP pattern in the appropriate clinical setting<sup>122</sup>. Clinical features, particularly patient age<sup>18</sup>, and additional imaging features increase the pre-test likelihood of UIP and further enhance the diagnostic

value of these 'expanded' HRCT criteria<sup>19</sup>. This latter approach has not yet been adopted by evidence-based international guidelines on IPF diagnosis, which are due to be updated soon.

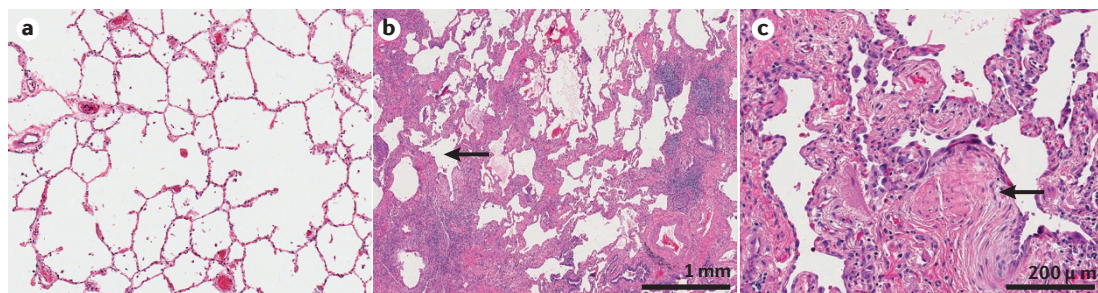
**Histology.** If HRCT features do not enable a confident diagnosis of the UIP pattern, guidelines indicate that surgical lung biopsy is needed to achieve a conclusive diagnosis<sup>1</sup>. As for any other surgical procedure, surgical lung biopsy has a risk of mortality and major complications. Aggregate data from multiple studies show that the in-hospital mortality after elective surgical lung biopsy in patients <65 years of age and with limited comorbidities is very low (<2%); nonetheless, every patient requires careful consideration as to whether the risks of lung biopsy outweigh the diagnostic information to be gained<sup>123</sup>. In older patients, those with comorbidities or significant physiological impairment, or those who are hospitalized for their disease, the risk is substantial, and any invasive procedure should be carefully considered. In the individual patient, surgical lung biopsy should be considered only when the histopathological pattern is expected to meaningfully alter treatment decisions and outcome prediction. The decision to proceed should be discussed in the context of the physician and patient's desire for a definitive diagnosis and a clear understanding of and tolerance for the risks related to the surgical procedure<sup>124</sup>.

The histopathological UIP pattern is characterized by interstitial fibrosis showing spatial heterogeneity with patchy involvement of the lung parenchyma, areas of marked fibrosis, architectural distortion and microscopic honeycombing<sup>1</sup> (FIG. 5). At the interface between



**Figure 4 | HRCT images from two patients with IPF.** High-resolution CT (HRCT) images collected from a woman with progressive cough and dyspnoea, showing her upper lung zones (panel a), lower lung zones (panel b) and the sagittal plane of the lungs (panel c). These images show lower lobe-predominant peripheral honeycomb change (panels b and c, arrows), which is typical of the usual interstitial pneumonia (UIP) pattern. In this patient, who had no systemic disease or exposures that would exclude idiopathic disease, the diagnosis of idiopathic pulmonary fibrosis (IPF) is certain. By contrast, the second patient — a woman with progressive breathlessness — could be diagnosed with 'expanded' HRCT criteria for IPF<sup>121</sup>, which is an emerging definition that has not yet been adopted by international guidelines. Here, the upper lung zones (panel d), lower lung zones (panel e) and sagittal image of the lungs (panel f) demonstrated peripheral, basilar-predominant, reticular densities with traction bronchiectasis (panels e and f, arrows) consistent with fibrosis. Surgical lung biopsy confirmed a typical UIP pattern.





**Figure 5 | Honeycombing typical in UIP.** Honeycombing is the feature of subpleural cystic airspaces with well-defined walls that is characteristic of the usual interstitial pneumonia (UIP) pattern. **a** | Normal lung histology of a terminal bronchiole, respiratory bronchiole, alveolar duct and alveoli. Magnification  $\times 10$ . **b** | Low-power haematoxylin and eosin (H&E)-stained section obtained from surgical lung biopsy in a patient with UIP, revealing the micro-honeycombing pattern (arrow). **c** | High-power H&E-stained section obtained from the same lung biopsy as in panel **b**, confirming fibroblastic foci (arrow), which are aggregates of proliferating fibroblasts and myofibroblasts that are thought to represent areas of active IPF disease.

fibrotic and normal-appearing lung tissue are aggregates of proliferating fibroblasts and myofibroblasts within a myxoid-appearing matrix (so-called fibroblast foci); these foci are a key histopathological feature of the UIP pattern and are thought to represent areas of active disease, and their absence excludes a definite histopathological diagnosis of UIP<sup>107</sup>. In two dimensions, these foci have been considered small, distinct lesions; however, in three dimensions, the foci have been shown to form heterogeneous structures with large variations in shape and volume<sup>125</sup>, although the implications of this finding are unclear. As HRCT interpretation has become increasingly important in the diagnosis of IPF, a minority of patients now undergo surgical lung biopsy.

### Prognostication

Patients with IPF invariably experience progressive disease. Although some patients experience gradual, steady deterioration over the course of the disease, others have periods of stability that can last for months to years<sup>2</sup>. Some patients experience acute deteriorations in their disease, which are unpredictable and often fatal. Many of these events are considered to be acute exacerbations of IPF and are thought to represent an abnormal response to an acute stressor in the lung (such as infection)<sup>105</sup>. As IPF progresses, patients experience increasing dyspnoea and hypoxaemia, which leads to reduced exercise tolerance and QOL. Patients with advanced-stage disease are at increased risk of complications such as pulmonary hypertension and acute exacerbation, and they eventually require supplemental oxygen and palliative management of symptoms.

Predicting prognosis is an important part of IPF management, but it remains difficult in individual patients. Several models for predicting mortality risk have been developed that incorporate demographic, clinical, radiological and biological parameters<sup>21,126–130</sup>. A simple-to-use predictive model called the GAP model incorporates the patient's sex, age and lung physiology variables and can be used to classify patients into three disease stages with distinct mortality risk over 1–3 years<sup>21</sup>. The use of prognostic models such as the GAP model at

the time of diagnosis and subsequent follow-up might aid the clinician to refine prognostic discussions with patients, help to guide management decisions such as the timing of lung transplantation and enable appropriate end-of-life planning.

### Screening and prevention

As our biological understanding of and knowledge of risk factors for IPF improves, some investigators have advocated the primary prevention of ILDs, in particular IPF<sup>131</sup>. Numerous cohorts of at-risk patients have been assessed to define imaging changes that precede the development of clinically significant ILD. For example, HRCT can be used to detect interstitial lung abnormalities (ILAs) or increased CT lung attenuation; novel techniques have been reported that can quantify structurally abnormal areas<sup>132,133</sup>, but conclusions of their usefulness cannot yet be drawn. Any system that evaluates the risk of ILD must also include the known risk factors of advanced age, male sex, gastro-oesophageal reflux disease<sup>50</sup> and diabetes mellitus<sup>134</sup>, as well as occupational exposures<sup>40,135</sup> and cigarette smoking<sup>41</sup>. In those with familial forms of ILDs, a high frequency of imaging abnormalities and abnormalities in biopsy samples has been identified<sup>136</sup>; however, the optimal approach to radiological screening in individuals with familial interstitial pneumonias remains unclear<sup>39</sup>. These individuals would probably benefit the most from primary prevention efforts<sup>131</sup>.

### Management

As with other chronic lung disorders, management of patients with IPF focuses on amelioration of symptoms, improving health status, preserving lung function, minimizing adverse effects of therapy and, ideally, improving survival.

### Pharmacotherapy

Substantial progress in the understanding of the clinical management of IPF, based on evidence acquired since the 2011 guidelines<sup>1</sup>, led to the update of treatment guidelines for IPF in 2015 (REF. 137). The 2015 American Thoracic Society, European Respiratory Society,

**Box 2 | The 2015 ATS/ERS/JRS/ALAT guidelines****Conditional recommendation for use**

- Pirfenidone
- Nintedanib
- Antacid therapy

**Conditional recommendation against use**

- Dual endothelin receptor antagonists (macitentan and bosentan)
- Phosphodiesterase-5 inhibitor (sildenafil)
- *N*-Acetylcysteine monotherapy

**Strong recommendation against use**

- Anticoagulation (warfarin)
- Combination prednisone, azathioprine and *N*-acetylcysteine
- Selective endothelin receptor antagonist (ambrisentan)
- Imatinib

The named drugs are those reviewed in the guideline<sup>137</sup>. ALAT, Latin American Thoracic Association; ATS, American Thoracic Society; ERS, European Respiratory Society; JRS, Japanese Respiratory Society.

Japanese Respiratory Society and Latin American Thoracic Association (ATS/ERS/JRS/ALAT) international IPF therapy guidelines made strong and conditional recommendations for and against certain treatments (BOX 2). The treatment recommendations in the 2015 guidelines focused entirely on pharmacotherapy.

Importantly, combination treatment with prednisone (a corticosteroid), azathioprine (an immunosuppressive) and *N*-acetyl cysteine (NAC; a mucolytic), which had been used as a conventional standard of care for patients with IPF worldwide, is now strongly not recommended owing to its association with harmful and adverse clinical outcomes<sup>102</sup>. NAC use alone might only be beneficial in patients with specific genotypes<sup>35,103</sup>, requiring pharmacogenomics analysis before use<sup>138</sup>; accordingly, the guidelines recommended conditionally against its use. Similarly, the results from large, well-conducted studies led to the abandonment of anticoagulation with warfarin<sup>139</sup> and the endothelin receptor antagonist ambrisentan<sup>140</sup>. The availability of two effective agents — nintedanib and pirfenidone — provides patients and their clinicians with flexible therapeutic options that enable the personalization of therapy<sup>141</sup>. However, the timing of therapy initiation remains unclear<sup>142</sup> and requires a discussion with the patient regarding potential benefits and risks of early intervention.

**Pirfenidone and nintedanib.** The 2015 ATS/ERS/JRS/ALAT guideline update was revolutionary in conditionally recommending treatment with several pharmacotherapies on the basis of safety and efficacy in clinical trials. Pirfenidone has been studied in several randomized controlled trials<sup>143–146</sup>. The data support a beneficial effect of pirfenidone on physiological deterioration, progression-free survival and, potentially, other clinical outcomes<sup>147</sup>. Although considered

an anti-fibrotic agent, its exact mechanism of action is unknown. Adverse effects include upper gastrointestinal symptoms, photosensitivity, skin rash, anorexia and liver toxicity; these effects were well tolerated in patients participating in clinical trials, especially when the dose was decreased. Monitoring of liver function before and periodically during treatment is suggested.

The multi-target tyrosine kinase inhibitor nintedanib reduced forced vital capacity (FVC; the total amount of air exhaled during a forced expiratory volume test, which measures how much air a person can exhale during a forced breath) decline and acute exacerbations in patients with physiologically mild to moderate IPF in an initial phase II clinical trial<sup>148</sup>. The physiological benefits were replicated in two subsequent phase III randomized controlled trials; however, the effect on acute exacerbations was inconsistent between the two studies<sup>149</sup>. Adverse effects include diarrhoea, weight loss, liver toxicity and potential bleeding risks<sup>150</sup>; despite these effects, nintedanib was generally well tolerated in the clinical trials. The clinical benefits of nintedanib have been noted in a broad range of patient subgroups<sup>122,151</sup>. As with pirfenidone, monitoring of liver function before and periodically during treatment is suggested. Arterial thromboembolic events occurred in numerically more nintedanib-treated patients than placebo-treated patients; myocardial infarction was the most common event. Caution has been advised in patients with known coronary artery disease and myocardial ischaemia.

Owing to the quality of evidence from the randomized controlled trials and the internal consistency between physiological surrogates and other disease progression markers, the US FDA approved the use of pirfenidone and nintedanib in patients with IPF<sup>152</sup>. Similarly, the 2015 ATS/ERS/JRS/ALAT guideline recommended the potential use of both nintedanib and pirfenidone. Extension of the pivotal studies and prospective registry data has suggested a similar tolerability profile for pirfenidone, with predominantly gastrointestinal and skin adverse events<sup>153,154</sup>. Importantly, adjusting dose on the basis of tolerability has been associated with improved compliance<sup>153</sup>. In addition, substantial intra-subject heterogeneity in longitudinal outcomes has been reported, which limits therapeutic response assessment in individual patients<sup>155,156</sup>.

Unfortunately, no head-to-head comparisons have been performed to compare pirfenidone and nintedanib. Accordingly, one agent cannot be recommended over the other. Two complex network analyses have contrasted results of clinical trials testing multiple agents; both these analyses suggest that pirfenidone and nintedanib give similar results<sup>157,158</sup>. Although nintedanib and pirfenidone have offered hope for patients and clinicians confronted with the management of IPF, several questions need to be resolved<sup>159</sup>. For example, whether the drugs can be used in sequence or in combination is still unclear. Similarly, if these agents are effective in patients with lung function impairments and comorbid conditions beyond those included in the clinical trials remains unclear.

**Antacid therapy.** Gastro-oesophageal reflux has been suggested as an inciting factor in IPF development and worsening<sup>160</sup>. However, the quality of evidence supporting the conditional recommendation of treatment with antacids for IPF is low<sup>137</sup>. Potential adverse effects of long-term use of proton pump inhibitors include infection, cognitive functional problems and myocardial infarction<sup>161–164</sup>. In patients with IPF without evidence of gastro-oesophageal reflux, these risks must be weighed against the potential benefits of suggested decreased rate of progression of disease in observational studies<sup>165</sup>. Although the potential of proton-pump inhibitors as anti-fibrotic agents has been described<sup>166</sup>, prospective trials to address antacid and antireflux therapy are warranted<sup>137</sup>.

### Non-pharmacotherapy

The management of IPF requires an orderly approach, with regular evaluations and implementation of both pharmacotherapy and non-pharmacotherapy.

**Pulmonary rehabilitation.** Exercise limitation, exercised-induced hypoxia and pulmonary hypertension are related to altered respiratory mechanics, impaired gas exchange and circulatory limitation and are common in patients with IPF. Peripheral muscle dysfunction such as quadriceps weakness is also an important contributor to exercise limitation<sup>167</sup>. Accordingly, physical conditioning probably exerts a similar beneficial effect in IPF as in patients with other chronic respiratory diseases.

Pulmonary rehabilitation is a comprehensive intervention designed to improve the physical and psychological condition of the patient and also promote the long-term adherence to health-enhancing behaviours<sup>168</sup>. Results in patients with IPF suggest that pulmonary rehabilitation provides benefits similar to those seen in chronic obstructive pulmonary disease (COPD)<sup>168</sup>. Indeed, the results of a meta-analysis of randomized clinical trials of pulmonary rehabilitation in IPF demonstrated an improvement in walk distance and QOL<sup>169</sup>. However, although most patients participated in a 12-week programme and improvements were observed shortly after completion, whether the improvements can be sustained for longer durations is unclear<sup>169</sup>. Another randomized trial in patients with ILDs confirmed improved walk distance and health status with 8 weeks of rehabilitation; the beneficial effect was particularly evident in those with IPF<sup>170</sup>. However, after 6 months of follow-up, exercise capacity had fallen to baseline<sup>170</sup>. The ATS/ERS/JRS/ALAT 2011 IPF guidelines made a weak positive recommendation for pulmonary rehabilitation, stating that although the majority of individuals with IPF should be treated with pulmonary rehabilitation, it might not be feasible in all<sup>1</sup>.

**Long-term oxygen therapy.** No data directly address the use of long-term supplemental oxygen therapy in patients with IPF. The 2011 ATS/ERS/JRS/ALAT IPF guidelines recommended that patients with resting

hypoxaemia should be treated with long-term oxygen therapy (strong recommendation, very low-quality evidence)<sup>1</sup>. Many people with IPF are normoxic at rest but rapidly desaturate on exertion, which can limit exercise capacity and worsen dyspnoea. The use of ambulatory or short-burst oxygen supplementation when mobilizing or during other activities might improve exercise capacity and relieve dyspnoea in these patients<sup>171,172</sup>. In patients with COPD, oxygen therapy upon exertional desaturation has only been shown not to influence hospitalization-free survival or health status<sup>173</sup>. However, the evidence base in IPF is weak, and further research is needed to examine the role of this treatment. A study to evaluate the need for increased delivery of supplemental oxygen during pulmonary rehabilitation in patients with IPF is ongoing<sup>174</sup>.

**Lung transplantation.** Given the progressive and incurable nature of IPF, lung transplantation is commonly considered for patients with moderate to severe disease<sup>1</sup>. The ideal timing for referral and listing for lung transplantation remains challenging owing to the wide variability in clinical course and life expectancy as well as the rapid and often catastrophic clinical deterioration associated with acute exacerbations<sup>105</sup>. For these reasons, early referral and close longitudinal follow-up for potential lung transplant candidates are favoured<sup>175,176</sup>. Whether bilateral lung transplantation is superior to single-lung transplantation in patients with IPF is unclear. Analysis of observational studies and available databases suggests improved outcomes with bilateral transplantation, but the quality of the data are poor and potentially suffer inherent bias<sup>176</sup>.

**Mechanical ventilation.** The 2011 ATS/ERS/JRS/ALAT guideline suggested that mechanical ventilation — in which an artificial airway (endotracheal tube or tracheostomy tube) is used — might only be a reasonable intervention in a minority of patients (weak recommendation, low-quality evidence)<sup>1</sup>. The guideline stated that mechanical ventilation use requires “a value-laden decision that is best made by the patient, clinician, and family ahead of time” based on a firm understanding of the patient’s goals of care. A systematic review of patients with IPF and respiratory failure reported a poor hospital mortality with mechanical ventilation<sup>177</sup>. Mechanical ventilation alone<sup>178</sup> or with extracorporeal lung assist<sup>179</sup> has been successfully used as a bridge to lung transplantation.

A retrospective cohort study using data from the US Nationwide Inpatient Sample reported higher mortality and longer hospital stays in those undergoing mechanical ventilation compared to those receiving non-invasive mechanical ventilation, which does not use an artificial airway<sup>180</sup>. Indeed, non-invasive mechanical ventilation might be appropriate in some patients, especially in those with acute exacerbation<sup>181</sup>. Contemporary management approaches to respiratory failure and acute lung injury (such as low tidal volume ventilation) are probably improving in-hospital survival; this area of care requires careful research<sup>105</sup>.



**Comorbid conditions.** Pulmonary and extrapulmonary comorbid conditions are increasingly being recognized as important in patients with IPF<sup>182</sup>. A systematic review confirmed a high frequency of pulmonary comorbidities, including pulmonary hypertension, COPD and lung cancer; systemic comorbidities including obstructive sleep apnoea, ischaemic heart disease and gastro-oesophageal reflux were also quite common<sup>183</sup>. One single-centre study demonstrated that 12% of patients with IPF had no comorbid illness, 58% of patients had 1–3 comorbidities and 30% had 4–7 comorbid conditions<sup>184</sup>.

Of the pulmonary comorbid conditions, pulmonary hypertension is the best characterized; its prevalence varies but tends to be noted in 30–50% of patients<sup>182</sup>. In general, the presence of pulmonary hypertension has been associated with impaired survival, even when the elevation in pulmonary pressures is mild<sup>185</sup>. Unfortunately, therapeutic trials to date have been unsuccessful and the current recommendation states that vasodilator therapy should be reserved for those enrolled in therapeutic trials or managed at expert centres<sup>182</sup>.

Another important comorbid condition is combined pulmonary fibrosis and emphysema (CPFE)<sup>186</sup>, the diagnosis of which is generally established with HRCT (FIG. 6). Although the implications of therapy have not been explicitly studied, the presence of significant emphysema in a patient with IPF decreases the rate of FVC decline<sup>187,188</sup>. The survival implication of CPFE remains controversial with some suggesting worsened survival compared with IPF and others noting no difference<sup>189,190</sup>. Additionally, lung cancer and IPF frequently associate epidemiologically even after adjustment of common and shared risk factors<sup>191</sup>. Lung cancer development is more common in lower lung zones (FIG. 7) and is often of the squamous cell carcinoma subtype<sup>191</sup>. In general, survival is particularly impaired in the setting of IPF and lung cancer.

Numerous extrapulmonary comorbid conditions, including gastro-oesophageal reflux as discussed earlier, have clinical relevance. Cohort and population-based studies have suggested an increased risk of arrhythmias, congestive heart failure and ischaemic heart disease<sup>182</sup>. Similarly, reports have suggested an increased

incidence of venous thromboembolism<sup>182</sup>. Sleep-disordered breathing is increasingly evident in patients with IPF<sup>192</sup>, which might be associated with impaired health status<sup>182</sup>.

### Monitoring response and adverse events

With evolved knowledge of the management of IPF, the standard of care for patients with IPF has clearly improved<sup>193</sup>. Monitoring a patient's disease course should include pulmonary function testing and assurance of adequate oxygenation measured routinely at 3–4-month intervals or sooner based on clinical need<sup>1</sup>. Acute deteriorations should prompt investigation of complications or worsening comorbid conditions, including the development of an acute exacerbation of IPF<sup>105</sup>, for appropriate therapeutic interventions and timely referral for lung transplantation, if appropriate. Patients should be monitored and treated for known adverse effects of the available agents.

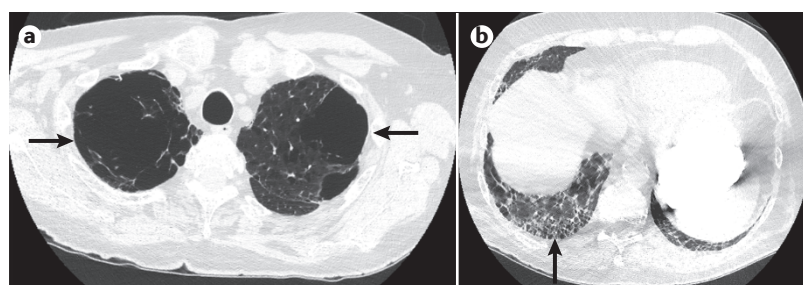
### Palliative care

The goals of palliative care are to provide symptom management, prevent and relieve suffering, and support the best possible QOL, regardless of stage of the disease<sup>194</sup>. For patients with IPF who are not approved for lung transplantation, the emerging consensus is that palliative care should be provided early following diagnosis, considering the lack of effective medical interventions (especially for patients in the terminal stage). The majority of patients with IPF die in a hospital setting, with only a minority receiving a formal palliative care referral<sup>194</sup>. Advanced directives and end-of-life care issues should be addressed in the ambulatory setting in all patients with IPF, particularly those with advanced-stage disease or comorbidity.

Cough and dyspnoea — common symptoms in patients with IPF — have proven difficult to treat. Limited data suggest that corticosteroids and thalidomide might be beneficial in managing cough, although they have not been shown to alter IPF progression<sup>195,196</sup>; some studies have shown that systemic morphine administration provided significant improvement in dyspnoea without observation of severe adverse effects<sup>197</sup>.

### Quality of life

QOL refers to the extent to which a person is satisfied with whether their wants and needs are being met. It is inherently a personal judgement and, by definition, self-reported. Some might argue that, to date, QOL has never been truly measured in any IPF study or trial. Doing so would require assessment of wants and needs across 16 life dimensions (only one of which is physical health)<sup>198,199</sup> or, at a minimum, asking respondents to answer the direct question, “How is your quality of life?” Given their focus on patients' symptoms and physical functioning, and to a lesser extent their emotional well-being, what investigators have measured in IPF studies is health status (physical and mental). This argument notwithstanding, impairments in the physical and/or mental health of patients with IPF clearly adversely affect their QOL<sup>200</sup>.



**Figure 6 | Idiopathic pulmonary fibrosis and emphysema.** High-resolution CT supine inspiratory images from a 78-year-old previous smoker with idiopathic pulmonary fibrosis (IPF). **a** | Apical, large, thin-walled cystic spaces (arrows) are visible and are consistent with emphysema. **b** | Smaller, well-circumscribed, subpleural, basilar cystic spaces (arrow) are visible consistent with a pattern of usual interstitial pneumonia.



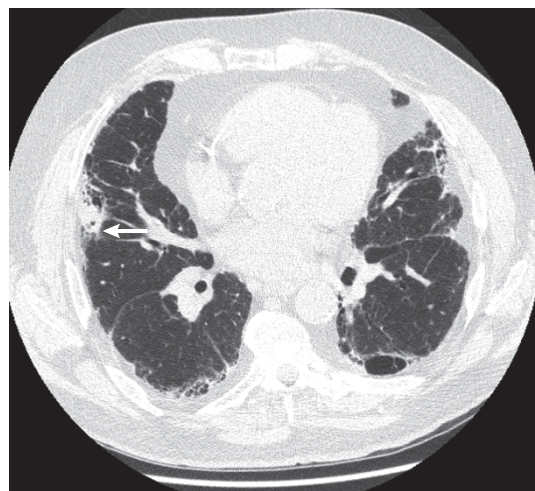
Symptoms, including cough, fatigue and, in particular, exertional dyspnoea (and their downstream effects) drive much of the QOL impairment. Mental anguish and dependence on others generated by living with a progressive, incurable disease contribute as well<sup>201,202</sup>. Among patients, there are myriad 'QOL phenotypes': cough, fatigue and emotional well-being inevitably burden some patients more than others. However, the inability to perform certain physical activities is central to QOL impairment. Scores from the two most commonly used instruments in IPF research — the St. George's Respiratory Questionnaire (SGRQ) and Short-Form 36-item Instrument (SF-36) — confirm domains that assess physical health and functioning are repeatedly the most profoundly impaired<sup>203</sup>. Additionally, supplemental oxygen impairs QOL as well: it is cumbersome and detracts from patients' ability to live carefree<sup>200,201</sup>. Patients with the most severe disease experience the greatest impairments in QOL. Although most patients adapt to the challenges of IPF reasonably well, they need to re-adapt and formulate new coping strategies as the disease progresses.

No medicinal therapies definitively improve QOL in patients with IPF. In the STEP-IPF trial, sildenafil was associated with improved dyspnoea and QOL (measured by the SGRQ) compared with placebo<sup>204</sup>. However, these seemingly positive results never gained much traction for several reasons, including that the primary end point of the trial (change in 6-minute walk distance) was not met, QOL was a secondary end point, effects were not consistent across all QOL measures and, arguably, between-group QOL score differences did not meet minimal importance. Additionally, no data strongly suggest that nintedanib or pirfenidone has beneficial effects on QOL<sup>205,206</sup>. Pulmonary rehabilitation is the one intervention that has been repeatedly shown to improve QOL in patients with IPF<sup>170,207–209</sup>. However, these gains are lost after 6 months unless patients continue to exercise<sup>207</sup>. Accordingly, therapeutic modalities aimed at improving this important outcome are needed.

## Outlook

### Diagnosis

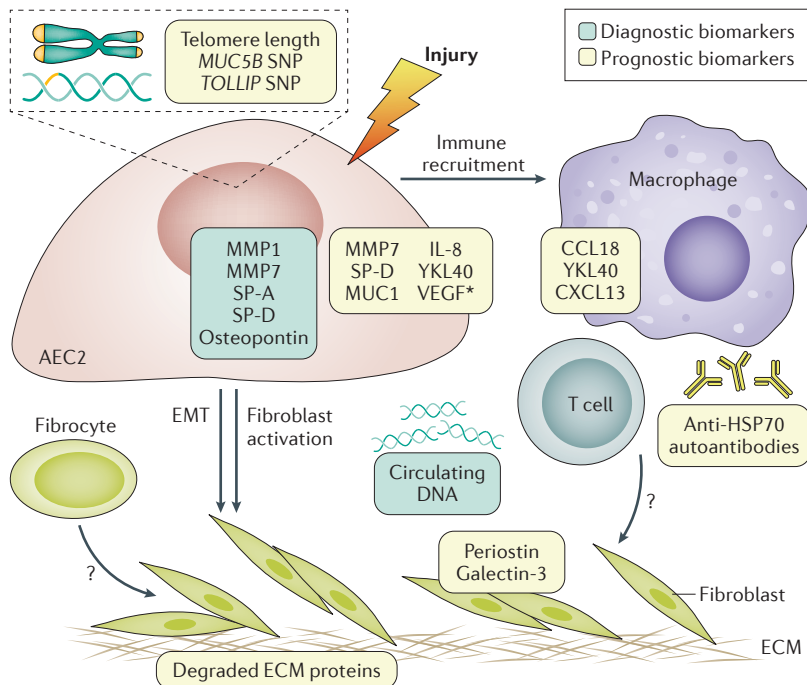
In terms of the clinical evaluation of IPF, the most important developments in the near future are likely to centre on the development of more inclusive diagnostic criteria. The ATS/ERS/JRS/ALAT guideline diagnostic criteria<sup>1</sup> enable the formulation of an accurate and highly confident diagnosis of IPF, but this comes at the price of under-diagnosis in a large patient subgroup with non-classic HRCT findings and broadly grouped as having 'possible UIP'. The guideline recommendation that these patients require a diagnostic surgical lung biopsy, with no acceptable alternative non-invasive diagnostic algorithm, has not stood the test of time; growing unease surrounds routine surgical lung biopsy given its associated short-term mortality and other complications<sup>123</sup>. The large number of patients with probable IPF, with no approved means of making a final diagnosis of IPF, has been highlighted in several studies<sup>145,149,210</sup>, with the most informative data emerging from subgroup analyses in the INPULSIS placebo-controlled nintedanib trials<sup>122</sup>.



**Figure 7 | Idiopathic pulmonary fibrosis and lung cancer.** A high-resolution CT supine inspiratory image showing a solid opacity (arrow) in the right middle lobe. Transbronchial biopsy of this lesion confirmed fibroblastic foci and honeycomb change suggestive of usual interstitial pneumonia and co-occurring squamous cell carcinoma.

**Diagnostic criteria.** The process of diagnosis increasingly uses interactive multidisciplinary team discussion of non-standardized clinical information (that is, information providing suggestive diagnostic information in some but not all patients), including the observed natural history and treated course of disease when these data exist. Given the many permutations and combinations of non-standardized data in individual patients, it is unlikely that new rigid diagnostic criteria will replace the multidisciplinary process. Thus, a probable future multidisciplinary model will consist of restructured formal diagnostic criteria supplemented by clinical reasoning based on non-standardized information. In this setting, the emerging technique of transbronchial lung cryobiopsy (TBLC) might have an important role<sup>211,212</sup>.

**Diagnostic techniques.** TBLC using a flexible bronchoscope is an alternative method for sampling lung parenchyma proposed to have lower complication rates and mortality<sup>212,213</sup>. In skilled hands, TBLC has a diagnostic yield of 80%, whether in the definition of a histological pattern or in the formulation of a multidisciplinary diagnosis<sup>212</sup>. As a direct comparison to the gold-standard (surgical lung biopsy) has not been completed, robust conclusions on TBLC diagnostic accuracy cannot yet be reached<sup>213</sup>. The documentation of a lower mortality than that associated with surgical biopsy could, in principle, lead to an increased biopsy rate in patients with moderately severe disease, with the potential that tissue acquired at TBLC might provide diagnostic biomarker information. However, TBLC is associated with a learning curve, with less-experienced centres noting higher initial risk to the patient<sup>214</sup>. TBLC will not become a routine diagnostic tool until the yield and risk profile has been shown to be acceptable in the hands of less-experienced practitioners.



**Figure 8 | Emerging biomarkers in IPF.** Several biomarkers have been identified that have diagnostic or prognostic potential in idiopathic pulmonary fibrosis (IPF). Diagnostic and prognostic biomarkers are listed in blue and yellow boxes, respectively, alongside their putative sources, which are the key components involved in the pathogenesis of IPF (namely, alveolar epithelial type 2 cells (AEC2s), immune cells and fibroblasts). In addition to those shown, fibrocytes, galectin-3 and epithelial-derived intercellular adhesion molecule 1 (ICAM1) might be markers of acute exacerbations. Furthermore, panels of biomarkers might be useful; for example, matrix metalloproteinase 7 (MMP7), ICAM1 and IL-8 might have prognostic value, whereas a combination of pulmonary surfactant-associated protein D (SP-D), MMP7 and osteopontin has diagnostic value. Vascular endothelial growth factor (VEGF) from epithelial cells and endothelial cells might have prognostic value, but this remains unclear; similarly, platelet-derived growth factor and fibroblast growth factor have unknown value. \*The prognostic power is unclear. CCL18, CC motif chemokine 18; CXCL13, CXC motif chemokine 13; ECM, extracellular matrix; EMT, endothelial-mesenchymal transition; HSP70, heat shock protein 70; MUC1, mucin-1; SNP, single nucleotide polymorphism; YKL40, chitinase-3-like protein 1.

**Biomarkers.** The investigation of subclinical interstitial lung abnormalities (ILAs) might provide crucial insights to enable early diagnosis of IPF. ILAs and IPF share a number of characteristics. For example, both become more prevalent with advancing age<sup>215–218</sup> and in smokers<sup>216,218–221</sup>. ILAs are associated with the *MUC5B* promoter polymorphism in individuals >50 years of age<sup>217</sup> and with increased mortality<sup>218</sup> and are characterized by reductions in exercise capacity<sup>222</sup> and in resting pulmonary function<sup>218,219</sup>. In the Framingham Heart Study cohort, >80% of ILAs were reticular and subpleural. Importantly, serial progression of ILAs was associated with greater FVC decline and a four-fold increase in subsequent mortality<sup>223</sup>. Despite these similarities, the identification of individuals in whom ILAs are early manifestations of IPF is complicated by the high prevalence of ILAs (6–8%) in general population cohorts<sup>218,223</sup> compared with the prevalence of IPF. A combination of biomarker data<sup>224</sup>, careful HRCT morphological definition of ILA subgroups and a focus on ILA progression using serial HRCT observation

will probably be required<sup>225</sup>. The evolution of ILAs to the clinical entity of IPF might have a long lead time; if so, the required time and resources to map early IPF progression will be justified by the potential for transformative pathogenetic insights.

Additionally, numerous groups have focused on lung-specific sampling or circulating molecular markers to improve the diagnosis of IPF<sup>226</sup> (FIG. 8). These biomarkers include ECM-modifying enzymes, such as MMPs<sup>136,227</sup> and MMP-degraded proteins<sup>228,229</sup>. The combination of pulmonary surfactant-associated protein D, MMP7 and osteopontin has proven useful in segregating patients with IPF from those with other interstitial pneumonias<sup>230</sup>. Serum miRNAs<sup>231</sup>, a peripheral blood transcriptomic signature<sup>232</sup> and circulating inflammatory proteins<sup>233</sup> have also been suggested to have potential diagnostic value. Numerous groups have examined lung inflammatory proteins<sup>233,234</sup> and lung gene expression as diagnostic markers<sup>235,236</sup>, which includes a machine learning approach applied to surgical lung biopsy samples<sup>237</sup> and extended to trans-bronchial lung biopsy samples<sup>238</sup>. How these techniques, which provide accurate insight into the genomic signature of a UIP pattern, will contribute to clinical diagnosis requires additional investigation.

Also unclear is how biomarker approaches will segregate various clinical diagnoses, how the heterogeneity in tissue abnormality will be accounted for or how the unwieldy data sets will be simplified for use in clinical practice. Well-designed, large, prospective studies are urgently needed to measure the effects of different diagnostic approaches, which will hopefully enable clinicians to use molecular biomarkers in combination with other clinical, physiological or imaging features to precisely identify patients who will benefit from specific therapeutic approaches<sup>111</sup>.

### Emerging treatments

The partial efficacy of highly pleiotropic anti-fibrotic agents in slowing chronic progression in IPF<sup>146,149</sup> has fuelled intense debate on paradigms of IPF drug development. On the basis of the large number of co-activated pathways and the complex pathogenetic interactions discussed earlier, it can be argued that combinations of pleiotropic therapies hold the key to further therapeutic advances<sup>239</sup>. This view is supported by the fact that routine practice is shaped by emerging trial data. As placebo arms are no longer ethically acceptable in phase III studies in IPF, future trial design will largely consist of comparisons between an existing monotherapy and a combination of that therapy with a novel agent<sup>3,239</sup>.

Against this background is the increasing conviction that the future of IPF therapy lies in the selection of agents tailored to individual environmental triggers or genetic and biomarker profiles<sup>240</sup>. Indeed, the growing allure of precision medicine as ‘the great desideratum’ in IPF management is mostly based on precedence in other chronic respiratory diseases, including asthma and lung cancer, in which targeted therapies have proven efficacious<sup>241</sup>. To date, the most compelling therapeutic data in IPF in support of this paradigm are the differential

treatment effects observed with NAC monotherapy in relation to patients harbouring certain *TOLLIP* polymorphisms in what was, admittedly, a single, underpowered study<sup>103</sup>. The difficulty in selecting personalized therapies lies in the large number of ways of subgrouping patients: on the basis of genetic data, biomarker data, immunological information and clinical phenotype (such as rapidity of disease progression)<sup>242</sup>, microbiome status<sup>46,47</sup> and the existence of microaspiration due to gastro-oesophageal regurgitation<sup>166</sup>. For example, as mentioned, the lung microbiota might influence host immune response; these features may identify viable biomarkers that can be used to guide future therapy. In this regard, two ongoing clinical trials — CleanUP-IPF (NCT02759120) and EME-TIPAC (EudraCT 2014-004058-32) — are assessing whether antimicrobial therapy can augment usual IPF treatment.

Mesenchymal stem cells (MSCs) are non-haematopoietic, multipotent stromal cells that have the ability to differentiate into tissue derived from a single germ layer<sup>243</sup>; these cells have been demonstrated to have anti-inflammatory effects, migratory properties and immunoprivilege<sup>244</sup>. Several animal models have suggested that MSCs can ameliorate inflammation and reduce the degree of fibrosis<sup>243</sup>. Indeed, MSCs have been

identified in patients with IPF and noted to vary in functional status in relation to disease activity<sup>245</sup>. One phase I study demonstrated the safety of placenta-derived MSC administration in eight patients with IPF<sup>246</sup>. A subsequent phase I study confirmed that administration of bone marrow-derived MSCs in nine patients with IPF was associated with no toxicity >60 weeks after administration<sup>247</sup>, whereas a separate phase Ib study confirmed the safety of endobronchial administration of adipose-derived stromal cells (a type of MSC)<sup>248</sup>. The ATS has noted the need for careful evaluation of safety and efficacy of such therapy before the widespread therapeutic use of MSC in chronic lung disease<sup>249</sup>.

The aspiration of monotherapy in IPF based on the use of highly specific agents, selected from highly individualized patient data, is perhaps unrealistic in the short-term. However, personalized combination therapy might be developed using existing highly pleiotropic agents and novel targeted therapies<sup>250,251</sup>, an approach that would satisfy the current requirements of trial design. The missing piece of the jigsaw is the definition of pivotal pathways or triggers that are operant early in the course of disease, ideally preceding and leading to multiple pathway co-activation and playing an ongoing part in driving disease progression.

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#### Author contributions

Introduction (F.J.M.); Epidemiology (H.R.C.); Mechanisms/pathophysiology (A.P. and M.S.); Diagnosis, screening and prevention (L.R. and F.J.M.); Management (G.R., H.T. and F.J.M.); Quality of life (J.J.S.); Outlook (A.U.W.); Overview of the Primer (F.J.M.).

#### Competing interests statement

F.J.M. has received personal fees from the American College of Chest Physicians, American Thoracic Society, AstraZeneca, Boehringer Ingelheim, Genentech/Roche, GlaxoSmithKline, Novartis, Patara and Pearl; he has made continuing medical education presentations to AstraZeneca, Boehringer Ingelheim, Miller Communications, the National Association for Continuing Education, Prime, the University of Alabama at Birmingham and UpToDate; he has served on steering committees for studies supported by Afferent, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead and GlaxoSmithKline; and he has served on the data and safety monitoring board for studies supported by Biogen, Boehringer Ingelheim, Genentech and GlaxoSmithKline. H.R.C. has received personal fees from aTyr Pharmaceuticals, Bayer, Blood Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Genoa, ImmuneWorks, Moerae Matrix, Navitor, Parexel, Patara, PharmAkea, Prometic, Takeda and Toray. G.R. has received personal fees and other fees from Boehringer Ingelheim, Bristol-Myers Squibb, FibroGen, Gilead, Patara, Promedior, Roche/Genentech, Sanofi, United Therapeutics, UCB and Veracyte outside the submitted work. L.R. has received grants and personal fees from InterMune, and he has received personal fees from Asahi Kasei, Bayer, Biogen, Boehringer

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