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REVIEW

Diagnosis of interstitial lung diseases: from Averill A. Liebow to artificial intelligence

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Histopathologic criteria of usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF) were defined over the years and endorsed by leading organizations decades after Dr. Averill A. Liebow first coined the term UIP in the 1960s as a distinct pathologic pattern of fibrotic interstitial lung disease. Novel technology and recent research on interstitial lung diseases with genetic component shed light on molecular pathogenesis of UIP/IPF. Two antifibrotic agents introduced in the mid-2010s opened a new era of therapeutic approaches to UIP/IPF, albeit contentious issues regarding their efficacy, side effects, and costs. Recently, the concept of progressive pulmonary fibrosis was introduced to acknowledge additional types of progressive fibrosing interstitial lung diseases with the clinical and pathologic phenotypes comparable to those of UIP/IPF. Likewise, some authors have proposed a paradigm shift by considering UIP as a stand-alone diagnostic entity to encompass other fibrosing interstitial lung diseases that manifest a relentless progression as in IPF. These trends signal a pendulum moving toward the tendency of lumping diagnoses, which poses a risk of obscuring potentially important information crucial to both clinical and research purposes. Recent advances in whole slide imaging for digital pathology and artificial intelligence technology could offer an unprecedented opportunity to enhance histopathologic evaluation of interstitial lung diseases. However, current clinical practice trends of moving away from surgical lung biopsies in interstitial lung disease patients may become a limiting factor in this endeavor as it would be difficult to build a large histopathologic database with correlative clinical data required for artificial intelligence models.

Key Words: Usual interstitial pneumonia; Idiopathic pulmonary fibrosis; Progressive pulmonary fibrosis; Familial pulmonary fibrosis; Digital pathology; Artificial intelligence

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Liebow and Carrington [1] introduced the diagnosis of usual interstitial pneumonia (UIP) over 50 years ago as a type of interstitial pneumonias. The word "usual" in UIP was used because it was the most common and usual type among interstitial pneumonias. In addition to UIP, desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with interstitial pneumonia (BIP), lymphoid interstitial pneumonia (LIP), and giant cell interstitial pneumonia (GIP) were included in their classification of interstitial pneumonias [1]. While UIP, DIP, and LIP are still acknowledged in the current classification of interstitial pneumonias, BIP and GIP have been excluded; a subset of BIP might correspond to organizing pneumonia (OP) and GIP is now regarded as hard metal pneumoconiosis. Characteristic histopathologic features of various types of interstitial lung diseases (ILDs) are illustrated in Fig. 1A–D. Nearly three decades after the term UIP was first introduced, Katzenstein and Myers [2] clarified cardinal histologic features of UIP that became the current histopathologic criteria for diagnosing UIP.

The 2002 American Thoracic Society (ATS)/European Respiratory Society (ERS) statement summarized the consensus from the first international meeting on the diagnosis and treatment of idiopathic interstitial pneumonias (IIPs) [3,4]. This statement established a basic framework of the contemporary classification scheme of IIPs: UIP, nonspecific interstitial pneumonia (NSIP), DIP, OP, acute interstitial pneumonia (AIP), and LIP [4]. This nomenclature for IIP became applicable to other ILDs as patterns,

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which facilitated a clearer communication in the non-idiopathic ILDs with underlying conditions or identifiable causes (such as connective tissue disease [CTD] and hypersensitivity pneumonitis [HP] or other exposure–related conditions, etc.). Some significant modifications have been made over the ensuing years in a few subsequent consensus statements by ATS and other international organizations [5-7]. Novel technologies including omics at different levels (genetic, epigenetic, transcriptional, translational, and metabolic, etc.) advanced the deep understanding in pathogenesis of ILDs and expedited the development of several effective antifibrotic medications that have been U.S. Food and Drug Administration–approved or on active clinical trials.

Pathologic examination has been the gold standard to classify ILDs until high-resolution computed tomography (HRCT) became an acceptable method after the second ATS/ERS statement in 2013, which led to a significant decrease in the frequency of lung biopsies for diagnosing ILDs [5]. Currently, most cases characteristic for UIP on chest HRCT no longer undergo lung biopsies (Fig. 2). Only atypical and complex ones are subject to lung biopsies, posing great challenges to pathologists. Surgical lung biopsy has been the main approach but transbronchial lung cryobiopsy was accepted in the 2022 practice guidelines by ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) as a conditional alternative in the centers with appropriate expertise [7]. Genetic profiling of transbronchial biopsy specimens has been introduced to classify ILDs and it completely bypasses morphologic evaluation [8,9]. No recommendation was made in 2022 guidelines either for or against this

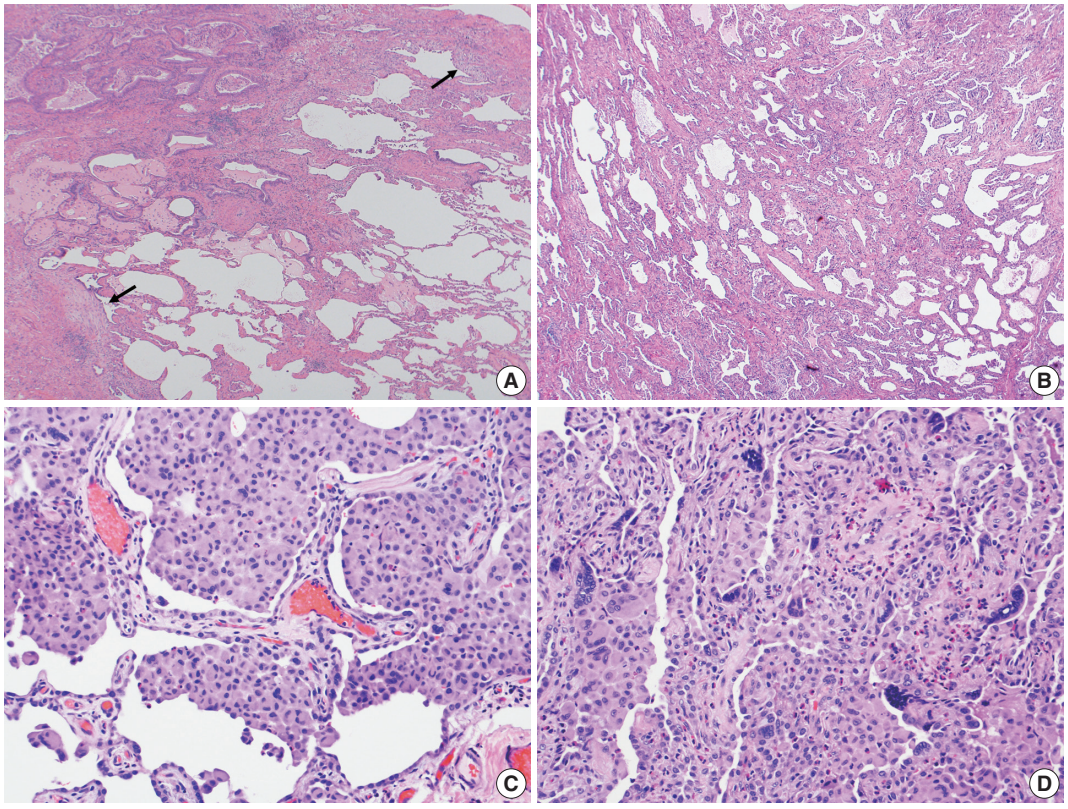

Fig. 1. (A) Usual interstitial pneumonia (UIP), the prototype of interstitial lung disease, showing patchy interstitial fibrosis with subpleural accentuation, marked architectural distortion of alveolar architecture with scarring and microscopic honeycomb changes, and temporal heterogeneity of fibrosis evidenced by scattered fibroblastic foci with dome-shaped myofibroblastic/fibroblastic proliferation over scarred areas (arrows), which likely implies an ongoing acute lung injury in already scarred lung tissue causing progressive clinical course. (B) Nonspecific interstitial pneumonia (NSIP) shows diffuse and uniform fibrous interstitial thickening. In contrast to UIP, NSIP shows relatively well-preserved alveolar architecture without honeycomb changes or fibroblastic foci, which likely explains a more favorable prognosis of NSIP than UIP. (C) Desquamative interstitial pneumonia (DIP) characterized by diffuse collection of pigmented macrophages in the alveolar spaces with mild to moderate interstitial fibrosis. DIP in the original classification by Dr. Liebow is included in the current American Thoracic Society classification. (D) Giant cell interstitial pneumonia (GIP) showing many scattered multinucleated giant cells in the alveolar spaces or septa. GIP was included in the Dr. Liebow's original classification of interstitial lung diseases but dropped in the current idiopathic interstitial pneumonia classification as GIP is now primarily regarded as a hard metal pneumoconiosis (e.g., cobalt).

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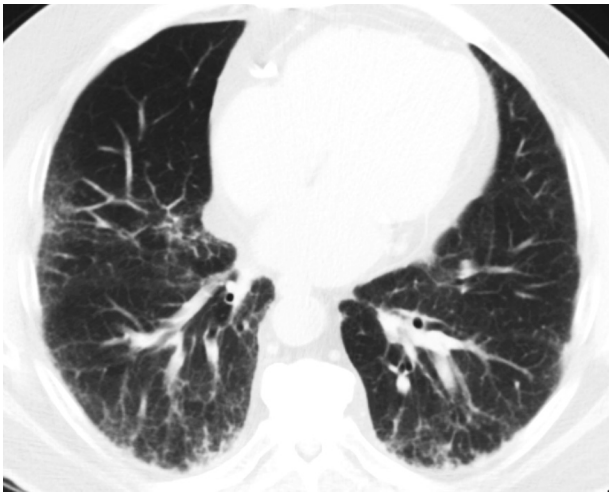

Fig. 2. An axial view of high-resolution computed tomography demonstrates a portion of lower lung fields with classific findings of usual interstitial pneumonia characterized by peripherally accentuated reticular densities and honeycomb changes.

genomic classifier testing, due to the lack of consensus among the committee members [7].

Recent advances in whole slide imaging (WSI) and artificial intelligence (AI) technology, such as deep learning (DL)–based image processing, have opened the door to quantitatively evaluate histopathologic findings. However, relative paucity of database, as compared to radiologic counterpart, is a limiting factor for widespread investigation and advancement to a higher level of interpretation beyond quantitative analysis, thus far.

Several topics that represent milestones in the field of ILD diagnosis are reviewed with emphasis on significant recent changes in concepts and trends relevant to practicing pathologists and pulmonologists.

SELECTED TOPICS

Usual interstitial pneumonia

Evolution of histopathologic criteria for UIP

The histologic classification of interstitial pneumonias evolved in a time when surgical lung biopsies were infrequently performed owing to significant morbidity associated with the surgical techniques of the day. As a result, histologic findings did not inform clinical decision-making in most patients with interstitial pneumonia. Clinicians were left to diagnose and manage patients with ILD primarily based on clinical and radiologic features; clinical concepts did not evolve in concert with the histologic classification. In this background, idiopathic pulmonary fibrosis (IPF) originated as a clinical diagnosis without established histopathologic correlates.

The original histologic description of UIP contained a wide spectrum of findings including acute lung injury in the form of what today would be considered diffuse alveolar damage, as well as chronic fibrosis and end-stage lung [2]. Although the histologic findings considered diagnostic of UIP were refined over time, established diagnostic criteria were still lacking into the 1990s with many investigators simply requiring the presence of inflammation and fibrosis in various proportions as diagnostic of UIP [3]. Many also considered even DIP to represent an early "cellular stage" of UIP [2].

In 1998, Katzenstein and Myers [2] described the crucial histologic features that were reflected in the ATS/ERS international consensus statement and established as the current histopathologic criteria of UIP [2,4]. The most recent 2022 ATS/ERS/JRS/ALAT clinical practice guideline used the same criteria including (1) patchy, dense fibrosis with architectural distortion causing destructive scarring and/or honeycombing, (2) predominantly subpleural and/or paraseptal distribution of fibrosis, (3) temporal heterogeneity of fibrosis characterized by fibroblast foci over scarred lung tissue, and (4) absence of features suggesting an alternate diagnosis (including prominent airway-centered changes, significant degree of OP, granulomas, hyaline membranes, dense lymphoid infiltrates, and marked chronic pleuritis, etc.) [4]. Different levels of confidence such as diagnostic of UIP (meeting all criteria) and probable UIP (having only some of these features) were proposed for pathologic diagnosis categories as in radiologic counterparts. This type of categorization may be useful in the clinical trial setting to recruit patients although it has not been widely applied in routine pathology practice.

In the 2013 ATS/ERS statement, the major IIPs were subdivided into three categories: chronic fibrosing interstitial pneumonias (IPF and NSIP), smoking-related interstitial pneumonias (respiratory bronchiolitis-ILD and DIP), and acute/subacute interstitial pneumonias (cryptogenic OP and AIP) [5]. The classification also includes rare IIPs (idiopathic LIP and idiopathic pleuroparenchymal fibroelastosis) and unclassifiable IIP. Each of the IIPs has an associated radiologic and/or pathologic-morphologic pattern (e.g., UIP for IPF) and is considered a "clinical-radiologic-pathologic diagnosis," emphasizing the multidisciplinary approach to diagnosis.

Recent trends of decreasing lung biopsy use

The role of surgical lung biopsy in the diagnosis of IPF has changed over time. With the original ATS statement on IPF,

surgical lung biopsy was recommended in most patients to establish the diagnosis, especially in those with atypical clinical or radiologic features for IPF [4]. The 2002 ATS/ERS IIP guidelines stated that biopsy was required for a confident diagnosis of UIP/IPF, but also noted that in more than 50% of cases of suspected IPF, the presence of typical clinical and HRCT features of UIP was sufficiently characteristic to allow a confident diagnosis without the need for surgical lung biopsy [4]. In the 2011 ATS statement of IPF, radiologic and pathologic criteria were developed to establish confidence categories for UIP (i.e. UIP pattern, probable UIP pattern, possible UIP pattern); thus, surgical lung biopsy was no longer required for histopathologic confirmation in patients with HRCT showing typical UIP pattern [6]. The only change regarding sampling since that time was the adoption of transbronchial lung cryobiopsy as an acceptable alternative to surgical lung biopsy in patients with ILD of undetermined type based on evidence that there was often diagnostic agreement between transbronchial cryobiopsy and surgical lung biopsy samples [7].

Antifibrotic therapy for patients with IPF and those with UIP due to underlying cause

Patients with IPF undergo a progressive decline in pulmonary function with eventual death from either respiratory failure or a complicating comorbidity, with a median survival of 2 to 3 years from the time of diagnosis [6]. Acute exacerbation may occur with histologic manifestions of diffuse alveolar damage or OP, though less common [10]. Based on the hypothesis that inflammation might be the underlying cause of lung injury and fibrosis, corticosteroids and other immunosuppressive agents have been tried without success. No effective pharmacologic therapy for IPF was available until the early 2010s, when two promising antifibrotic agents emerged. Randomized trials showed in disease progression and rate of forced vital capacity decline in IPF patients treated with nintedanib, a tyrosine kinase inhibitor, or pirfenidone, an inhibitor of transforming growth factor β–associated collagen synthesis [11-14]. These two medications were recommended for use in IPF patients as of the 2015 treatment guidelines [15]. Data from more recent clinical trials led to an expansion of antifibrotic therapy to other types of fibrosing ILD if they show evidence of clinical, physiologic, or radiologic progression [4].

As such, diagnostic paradigm seems to have shifted to categorize the ILDs into two groups: cases to be treated vs. not to be treated with antifibrotics, a transition from the previous paradigm: to give or not to give corticosteroids (or other immunosuppressants). The recent proposal advocating UIP as a stand-alone diagnostic entity regardless of underlying causes is at least partly based on this therapeutic paradigm. However, such a lumping of various fibrosing ILDs might not be entirely justified, given the limited efficacy, significant side effects, and high cost of currently available antifibrotics as well as the risk of losing potentially useful diagnostic granularity. This proposal is reviewed in the section below. Similarly, the recent concept of progressive pulmonary fibrosis (PPF) published in the 2022 ATS guidelines would be in keeping with such a trend of lumping ILD diagnoses (see Concept of PPF: green light for lumping fibrosing ILD diagnoses, as exactly shown in the manuscript).

Recent proposal of UIP as stand-alone entity

UIP is generally regarded as the correlate of IPF. Accordingly, the cases with histopathologic features of other diseases such as fibrotic HP and CTD-related ILD are considered not consistent with UIP [16]. It is not uncommon, however, to have some minor changes associated with HP, CTD-related ILD, or other diseases (e.g., a few poorly formed granulomas, interstitial chronic inflammatory infiltrates, lymphoid hyperplasia, and airway-centered fibrosis, etc.) in the cases otherwise acceptable for UIP. Pathologists are often in a difficult position to determine whether the presence of these minor changes would disqualify the diagnosis of UIP or not. There have been widely differing opinions and approaches in this regard even among expert pulmonary pathologists.

In this backdrop of diagnostic conundrum, a bold concept was proposed to consider UIP as a stand-alone diagnostic entity, encompassing not only IPF but also other secondary processes, based on the presence of radiologic or histopathologic features of UIP [17]. It was argued that UIP pattern of fibrosis in other ILDs (especially fibrotic HP and CTD-associated ILD) as well as in IPF is associated with unfavorable clinical outcomes [18]. In addition, acute exacerbation may occur in rheumatoid arthritis–associated ILD and fibrotic HP with similarly dismal outcome to that seen in IPF [19,20]. The significant similarities between IPF and other secondary conditions with UIP features in clinical behavior, pathogenic pathways, and the efficacy of anti-fibrotic therapy were cited as the justification for a lumping approach in this proposal. A radiologic study reported that the presence of honeycomb change alone predicted an IPF-like mortality in patients with other conditions (fibrotic HP, CTD-ILD, and unclassifiable ILD), which could support this notion [21].

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Concept of PPF: green light for lumping fibrosing ILD diagnoses

There are many types of idiopathic and secondary fibrosing ILDs, in which IPF is considered as the prototype [22]. Non-IPF fibrosing ILDs include other IIPs (e.g., fibrotic NSIP, DIP, and AIP, etc.), autoimmune ILDs (e.g. rheumatoid arthritis-associated ILD), exposure-related ILDs (e.g. HP, occupational exposures, medications), pulmonary Langerhans cell histiocytosis and sarcoidosis, among others [7]. Recently, fibrosing ILDs have been studied as a group, given their clinical, radiological, and histopathological overlap. In this approach, a subset of non-IPF fibrosing ILDs was found to show a very similar clinical phenotype to that of IPF, characterized by progressive worsening of respiratory symptoms, declining lung function, developing acute exacerbation, and resistance to conventional therapy, ultimately resulting in high mortality [23-26]. In 2017, a term "progressive fibrosing ILDs" was first coined to this group of cases but an alternative term "progressive pulmonary fibrosis" (PPF) was endorsed in the 2022 ATS/ERS/JRS/ALAT clinical practice guideline [7,26]. In this 2022 statement, PPF was officially defined as an ILD of known or unknown etiology, other than IPF, with radiologic evidence of pulmonary fibrosis as well as meeting the set of specific clinical/radiological criteria including worsening respiratory symptoms and a certain degree of progression in pulmonary function abnormalities and/or radiological evidence of disease progression, occurring within the past year [7]. In this guideline, PPF is clearly stated as an entity of prognostic significance but not a specific diagnosis per se. The conceptual evolution to PPF over time is illustrated in Fig. 3.

Clinical trials have evaluated the efficacy of antifibrotics approved for IPF in the non-IPF patients who underwent progressive fibrosis, regardless of the type of underlying ILDs. Nintedanib therapy in the INBUILD trial resulted in a significant reduction in the annual decline of FVC in patients with PPF [27]. Pirfenidone therapy in two randomized control trials also showed a reduced FVC decline in some PPF patients [28,29]. Based on the results of these trials, the 2022 ATS clinical practice guidelines gave a conditional recommendation for nintedanib for the treatment of PPF in patients who have failed standard management, but not for pirfenidone given the lack of sufficient evidence [7].

This novel approach to treat ILD based on the disease behavior (i.e., PPF) without consideration of the specific underlying diagnosis will have a broader, potentially deleterious, influence in many aspects of ILD. The ATS guideline on PPF explicitly stated that this new concept of PPF should not discourage clinicians from their rigorous effort to identify the underlying type of ILD before antifibrotic therapy. In reality, however, it is most likely that the incentive of establishing a definitive diagnosis of

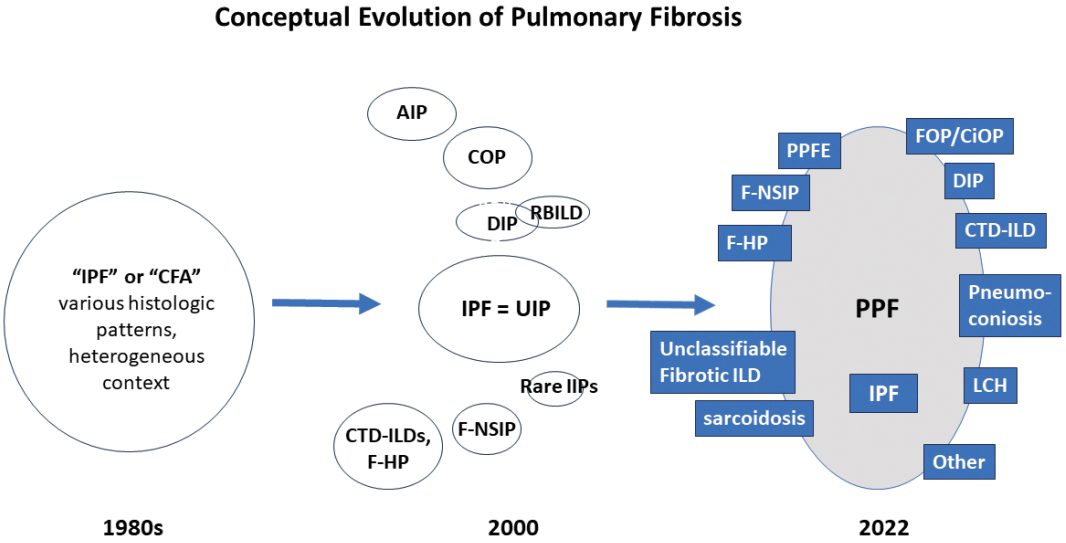

Fig. 3. The idiopathic interstitial pneumonia (IIP) classification established in 2000s is evolved from the less well-defined idiopathic pulmonary fibrosis (IPF) that encompassed various histologic patterns. Progressive pulmonary fibrosis in the current official practice guideline by American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) can be the manifestion by many fibrotic lung diseases other than IPF. AIP, acute interstitial pneumonia; CFA, cryptogenic fibrosing alveolitis; CiOP, cicatricial organizing pneumonia; COP, cryptogenic organizing pneumonia; CTD-ILD, connective tissue disease–associated interstitial lung disease; DIP, desquamative interstitial pneumonia; F-HP, fibrotic hypersensitivity pneumonitis; F-NSIP, fibrotic nonspecific interstitial pneumonia; FOP, fibrotic organizing pneumonia; LCH, Langerhans cell histiocytosis; PPFE, pleuroparenchymal fibroelastosis; RBILD, respiratory bronchiolitis interstitial lung disease; UIP, usual interstitial pneumonia.

the underlying ILD would be markedly reduced if not completely vanished. A few studies attempted to analyze the clinical trials data based on specific ILD subgroups within PPF but did not have enough power to provide evidence of benefit in different subgroups [30,31]. The criteria of PPF do not include pathologic findings, but it may be helpful to evaluate any histopathologic findings that correlate with progressive fibrosis. While UIP histopathologic pattern is an obvious leading candidate given its well-known compelling evidence, characterization of other histologic features that could predict the PPF phenotype has yet to be established [17].

Familial pulmonary fibrosis: a clue to decode molecular pathogenesis of fibrosing ILD

Familial cases of ILDs were reported in 1907, which suggested a possibility of genetic factors in ILDs [32]. The concept of familial IPF was first introduced in the 2000 ATS statement with the following definition: at least two members of a primary biological family (parent, child, sibling) with clinical features of IPF and histologic confirmation [3]. Though not explicitly recommended in later ATS statements, the histology requirement in the criteria was eventually dropped in practice, which is in keeping with the trends of bypassing the biopsies and making IPF diagnosis based on HRCT at least in more classic cases of IPF on clinical ground. Familial clustering of non-IPF fibrosing ILDs have also been observed. Other names have been used for this group of diseases, including familial/inherited interstitial lung disease, familial interstitial pneumonia, familial pulmonary fibrosis, and familial IIP, if limited to idiopathic cases. The plethora of terminology has clouded the literature and hampered clearer communication. In this review, the term familial pulmonary fibrosis (FPF) will be used that encompasses all types of pulmonary fibrosis including IPF.

The frequency of FPF may be as high as 20% of patients with pulmonary fibrosis according to the previous studies reported in the literature [33-38]. Among the subtypes of fibrotic ILD, IPF most frequently had a family history of pulmonary fibrosis (20%–25%), followed by chronic HP (14%–17%), and CTD-related ILD (3%–8%) [38-41]. Of note, relatives in the same family may show different subtypes of fibrotic ILD [42,43]. Radiographic screening studies revealed some radiological abnormalities in 15 to 31% of the asymptomatic relatives of patients with known pulmonary fibrosis, suggesting even higher prevalence of FPF than suspected [44-46].

The remarkable advances in molecular technology led to several large-scale, population-based studies on pulmonary fibrosis to identify genetic risk variants that could be associated with crucial pathogenetic mechanisms in pulmonary fibrosis. Two broad categories of the variants associated with pulmonary fibrosis have been recognized based on their frequency in the population: common and rare genetic variants. Common genetic variants typically represent single nucleotide polymorphisms (SNPs) and confer a smaller effect than rare variants as the impact on disease risk tends to be inversely proportional to the frequency of a variant within the population [47]. It has been well accepted that SNPs may contribute to overall risk but not entirely sufficient to cause disease on their own. On the other hand, rare variants often demonstrate cosegregation in FPF kindreds, suggesting a causal relationship.

Linkage analysis and genome-wide association studies have identified numerous common genetic variants associated with IPF. Gain-of-function promoter variant rs35705950 in the promoter region of the *MUC5B* gene is most widely recognized in association with pulmonary fibrosis. A study reported that this genetic variant is identified in 34% of the subjects with familial IIP, 38% of those with sporadic IPF, and 9% of the control subjects [48].

Rare genetic variants in pulmonary fibrosis were mainly implicated in dysfunctional surfactant metabolism and telomere maintenance. Genes involved in abnormal surfactant metabolism include *SFTPC*, *SFTPA1/2*, and *ABCA3* [40]. The pattern of inheritance is autosomal dominant for *SFTPC* and *SFTPA1/2* and autosomal recessive for *ABCA3* [49]. Disease onset has a wide range from infancy to late adulthood in families with a rare surfactant-related gene variant; histologic and radiologic features of ILD are also diverse with the features of UIP, NSIP, and DIP [50-52]. No extrapulmonary manifestations are present in these patients as surfactant production is limited to the lung. The rare genetic variants associated with deranged telomere maintenance account for approximately 25% of FPF kindreds and involve *TERT*, *TERC*, and numerous other genes [53,54]. Unlike the gene variants associated with surfactant dysfunction, these variants of telomere-related genes often cause extrapulmonary systemic manifestations (known as short telomere syndrome or other related terms) [55]. Dyskeratosis congenita (DC) is one of the best known telomeropathy due to homozygous telomere-related gene mutations resulting in extreme telomere shortening. DC causes pulmonary fibrosis (20%) as well as life-threatening bone marrow failure (80%) at pediatric age or in very early adulthood. DC often shows various cutaneous or mucosal manifestations including nail dystrophy, abnormal skin pigmentation, and oral leukoplakia [55,56].

The patients with heterozygous telemere–related gene muta-

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tions also often develop pulmonary fibrosis including IPF (50%), fibrotic HP (7%–12%) connective tissue disease–associated ILD (2%–3%), or other IIPs (14%–18%) with similar extrapulmonary manifestations of DC but at an older age than in DC [43,57,58]. Interestingly, about 10% of adult-onset sporadic IPF, chronic HP, and rheumatoid arthritis-related ILD patients have rare telomere-related gene variants [59-62]. Short telomere length is often seen in FPF cases and a frequent finding in sporadic cases of pulmonary fibrosis as compared to control subjects, suggesting a possibility that short telomere length might be a potential cause of pulmonary fibrosis [63].

Despite a remarkable progress in identifying key genetic features associated with FPF (and some sporadic fibrosing ILD cases), characterization of the matching pathologic features in FPF seemed to have lagged behind. Steele et al published a study in 2005 with histopathologic assessment in some of their cases from families with IIPs and found significant heterogeneity within a given family, showing more than one histopathologic subtype of IIP in 45% of family pedigrees [42]. A comprehensive histopathologic study by Leslie et al compiled the findings to differentiate familial and sporadic IIP cases in an effort to characterize the features of familial IIP, primarily focusing on familial IPF [64]. Although most of their patients had some histopathologic features associated with UIP, up to 60% of them did not qualify as UIP, mainly due to lack of the temporal heterogeneity of fibrosis, one of the most important histologic criteria for UIP [64]. Most of these cases ended up in the unclassifiable fibrotic ILD category [64]. Prevailing notion in the past has been that familial and sporadic IPF cases do not have distinguishable clinical or histological features other than earlier onset in familial IPF [6]. However, this 2012 study by Leslie et al. [64] suggested that there may be some histopathologic features differentiating sporadic and familial fibrotic lung diseases. Based on this observation, they concluded that unclassifiable pattern of lung fibrosis should raise a possibility of FPF or familial IPF [64]. They also suggested that less than classic histopathologic features of UIP could still be compatible with familial IPF in an appropriate clinical context [64].

AI in diagnosis of interstitial lung diseases

The application of AI tools on radiologic images for characterization of indeterminate lung nodules, fibrotic lung diseases, and lung cancer risk stratification has been well studied and documented in the literature. As compared to radiology arena, digital pathology (DP) by WSI started more recently and most AI approach has been applied to cancers and biomarker arena of other organs (such as breast and prostate). In the lungs, AI tools have also been more widely applied to cancers than to ILDs, partly due to the current tendency of relying on high-resolution CT and bypassing surgical lung biopsies for diagnosis of ILDs, especially after the 2013 ATS/ERS guidelines.

As there are many clinically as well as morphologically ambiguous cases of ILD, AI-assisted diagnosis may offer a crucial contribution by detecting some features that are not discernable by traditional diagnostic methods. Moreover, AI apporach may resolve some interobserver variability in diagnosing ILDs that has been well-recognized even among the expert pulmonary pathologists. It is inherently subjective to interpret the basic histopathologic parameters for ILD diagnosis (such as architectural distortion or scarring, honeycomb change, traction bronchiectasis, distribution of fibrosis, degree of inflammation, fibroblast foci, presence of granulomas, to name a few). Thus, more objective interpretation and quantitation of these parameters would be ideal by appropriate training and development of AI algorithm. Once AI-assisted diagnostic tool becomes widely available, it may mitigate the challenges encountered by many hospitals without direct access to experienced pathologists who are well versed in ILD diagnoses. Finally, some advanced AI technology (e.g. DL-based AI via unsupervised feature learning) might offer new insights into ILDs by elucidating previously unknown histopathologic features associated with progressive clinical behavior as in PPF cases. Such an approach, however, requires a large number of surgical lung biopsy cases with clinical annotation, which became scarce these days due to the changing practices as elaborated in the earlier sections. Multi-institutional collaboration might be needed to form a consortium for securing sufficient database to develop appropriate AI model.

A complete coverage of AI tools in DP is beyond the scope of the present review and only a brief introduction of basic concepts in the AI approach will be provided, followed by summary of several original studies in the literature on predicting pathologic diagnosis and prognosis of ILDs, or evaluation of histopathologic biomarkers in IPF with AI technology (Table 1).

AI is a broad discipline with multiple approaches to construct a model for a particular task. There are two common ways to extract feature representation for building an AI model: (1) DL-based unsupervised feature learning, (2) hand-crafted approach [65]. Convolutional neural network (CNN) is a type of DL approach suited for low-level tasks such as detecting, identifying, and classification of images. DL-based unsupervised feature learning is favored in low-level tasks such as cell and lung tumor detection and classification. This is useful since visual confirmation of the result is sufficient and does not require interpretation

Table 1. Published original research on interstitial lung diseases with AI-based methods

Study	Purpose of study	Method	Country	No. of cases	Main finding
Makela et al. (2021) [66]	Quantitation of histologic parameters for survival analysis in IPF	Deep CNN	Finland	71 IPF	Increased FF is associated with poor prognosis—interstitial mononuclear infiltrate & intra-alveolar macrophage with longer survival
Uegami et al. (2022) [67]	Prediction of UIP diagnosis	MIXTURE	Japan	231 (UIP+non-UIP) cases; 715 WSI	A model approach to differentiate diseases by AI with collaboration with humans based on expert pathologists' input
Testa et al. (2021) [68]	Pilot study to quantitate fibrosis in HPSPF & IPF	Automated quantitation of fibrosis with "dedicated software"	USA	3 HPSPF & 9 IPF	Their automated image analysis offered accurate, reader-independent pulmonary fibrosis quantitation in HPSPF and IPF groups

AI, artificial intelligence; CNN, convoluted neural network; IPF, idiopathic pulmonary fibrosis; FF, fibroblastic foci; MIXTURE, huMan-In-the loop eXpalainable artificial intelligence Through the Use of REcurrent training; UIP, usual interstitial pneumonia; WSI, whole slide imaging; HPSPF, Hermansky-Pudlak syndrome pulmonary fibrosis.

of selected features. In the hand-crafted approach, relevant features from data are manually selected. The domain knowledge is employed for features engineering, by close collaboration between pathologists and machine learning engineers to construct appropriate AI models. In contrast to DL-based unsupervised feature learning, hand-crafted based models offer some interpretability through incorporating the expertise of subject matter experts. Many high-level tasks such as prognosis or treatment response prediction which require a certain level of interpretability and hence hand-crafted, domain-inspired features may be favored by medical community to construct these models. Integration of DP in clinical workflow across major institutions poses a huge challenge, due to organizational structures, the cost of initial set-up, requirements of advanced security systems in hospitals and demands for storage of big data. Currently, most existing AI tools have been validated on retrospective data, which does not represent the current, real-world scenarios. Validating the algorithms in randomized controlled trials and prospective studies will be a crucial step towards clinical adoption of these AI tools.

Makela et al. [66] reported a study using AI to count fibroblast foci, a known prognostic factor in IPF, and other parameters to evaluate their prognostic significance. In this study, they trained a CNN to quantify fibroblast foci, interstitial mononuclear inflammation, and intra-alveolar macrophages to analyze the association of these parameters with survival [66]. Interstitial mononuclear inflammation and intra-alveolar macrophages were associated longer survival, while increased fibroblast foci were associated with poor prognosis.

Uegami et al. [67] proposed an original method to develop DL models for extracting pathologically significant findings based on expert pathologist's perspective with a small annotation effort. Their method named MIXTURE (huMan-In-the-loop eXplainable artificial intelligence Through the Use of REcurrent training) consisted three steps including (1) creating feature extractors for tiles from whole slide images using self-supervised learning, (2) clustering similar looking tiles based on output features, followed by integration of the pathologically synonymous clusters by pathologists, and (3) creation of DL models to classify tiles into pathological findings by using the integrated clusters as labeled data. They developed three models for different magnification. Their model predicted the diagnosis of UIP with a high accuracy, which was not possible to achieve without the step of integration of findings by pathologists. They proposed this model as the prototype for explainable AI that can collaborate with humans.

Testa et al. [68] reported a study that performed an automated digital quantification of pulmonary fibrosis in human histopathology specimens. They conducted a pilot sutdy to analyze a small number of specimens from patients with Hermansky-Pudlak syndrome pulmonary fibrosis (n = 3) or IPF (n = 9) using digital images of serial lung sections stained with picrosirius red, alcian blue or anti-CD68 antibody. Dedicated software was used to automatically quantify fibrosis, collagen, and macrophage content. Automated fibrosis quantification based on parenchymal tissue density and fibrosis score measurements were compared to the pulmonary function test values or Ashcroft score, a numerical scale with grades from 0 to 8, of the amount of fibrotic tissue in histological samples devised by Ashcroft et al. [69]. A high correlation coefficient was found between some automated quantification measurements and lung function values in the sample groups. They concluded that computerized image analysis can offer accurate, reader-independent pulmonary fibrosis quantification in human histopathology samples for various parameters such as fibrosis, collagen content, and immunostained cells. This approach may enhance the available tools to quantify and study fibrotic ILDs.

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CONCLUSION

Since Dr. Liebow introduced the diagnosis of UIP/IPF as a type of ILDs more than 50 years ago, histopathologic criteria have been refined and established. Antifibrotic therapy recently became available for UIP/IPF patients and brought modest improvement in its otherwise dismal clinical course. Partly based on the efficacy of antifibrotic therapy in other types of fibrosing ILDs, albeit limited, a proposal of UIP as a stand-alone entity was made to encompass all fibrosing ILDs with UIP pattern under the broad umbrella of UIP to be treated as UIP/IPF patients. Likewise, a concept of PPF that includes many types of fibrosing ILDs was endorsed as a prognostic entity (but not a specific diagnosis) by an international committee that also cited the similar therapeutic approach to that in UIP/IPF as the main reason for creating this category. Common and rare genetic variants identified in fibrosing ILD patients shed light in molecular pathways implicated in sporadic as well as familial cases of fibrosing ILDs. Whole slide imaging and AI might open the door to a new era provided accumulation of big histopathologic database and collective effort in this approach support the progress.

Ethics Statement

Not applicable.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Code Availability

Not applicable.

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Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

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