BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ESBRIET® (pirfenidone) oral
OFEV® (nintedanib) oral
Pirfenidone oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

Section A. Idiopathic Pulmonary Fibrosis (IPF):
ESBRIET (pirfenidone)
Pirfenidone
OFEV (nintedanib)

- **Criteria for initial therapy:** Ofev (nintedanib), Esbriet (pirfenidone), or generic pirfenidone is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist.

2. Individual is 18 years of age or older.

3. Individual has a confirmed diagnosis idiopathic pulmonary fibrosis (IPF) by **ONE** of the following:
    a. Findings on high-resolution computed tomography (HRCT), performed within the last 12 months, indicating usual interstitial pneumonia (UIP), a copy of HRCT must be submitted (See Table 1)

    b. If performed, a surgical lung biopsy demonstrating usual interstitial pneumonia (UIP), a copy must be submitted (See Tables 2 & 3)

    c. Specific HRCT and lung biopsy combinations, as per histopathological criteria for UIP pattern and HRCT and biopsy patterns, in patients with surgical lung biopsy, a copy of HRCT & biopsy results must be submitted (See Table 4)

4. **For Ofev (nintedanib)**: a negative pregnancy test in a woman of childbearing age, unless is using effective contraception.

5. Individual is a nonsmoker or has been abstinent from smoking for at least six weeks or is participating in a smoking cessation program.

6. Pulmonary function tests with evidence of **EITHER** of the following: (a copy of tests must be submitted)
    a. Most recent tests show **BOTH** of the following:
        i. FVC is ≥ 50% of the predicted value
        ii. DLCO is 30-79% of predicted value

    b. Longitudinal changes in the last six months show **EITHER** of the following:
        i. Decline in absolute FVC of 5-10%
        ii. Decline in absolute DLCO of 10-15%

7. Individual does not have hepatic impairment as defined below:
    a. **For Ofev (nintedanib)**: does not have moderate or severe hepatic impairment (Child-Pugh B or C)
    b. **For Esbriet (pirfenidone) or generic**: does not have severe hepatic impairment (Child-Pugh Class C)

8. Esbriet (pirfenidone) and Ofev (nintedanib) will not be used simultaneously.

9. Individual does not have renal impairment as defined below:
    a. **For Ofev (Nintedanib)**: does not have severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease
    b. **For Esbriet (pirfenidone) or generic**: does not have end-stage renal disease requiring dialysis

10. There are no significant interacting drugs
    a. For Ofev: rifampin, carbamazepine, phenytoin, and St. John's wort
    b. For pirfenidone: ciprofloxacin, fluvoxamine, phenytoin, rifampin, ritonavir, teriflunomide, others

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Ofev (nintedanib), Esbriet (pirfenidone), or generic pirfenidone is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist.

  2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
     a. Significant improvement in %FVC over baseline
     b. Absolute decline in FVC is less than 10%
     c. Absolute decline in DLCO is less than 15%
     d. Improved or no decline in symptoms for cough or shortness of breath

  3. Individual is a nonsmoker or is participating in a smoking cessation program.

  4. Individual has been adherent with the medication.

  5. Requested dose for Ofev is at least 100 mg twice daily.

  6. Individual has not developed any other significant adverse drug effects that may exclude continued use such as:
     a. Liver toxicity
     b. Severe and persistent GI reactions

  7. Esbriet (pirfenidone) or generic pirfenidone and Ofev (nintedanib) will not be used simultaneously.

  8. There are no significant interacting drugs
     a. For Ofev: rifampin, carbamazepine, phenytoin, and St. John's wort
     b. For pirfenidone: ciprofloxacin, fluvoxamine, phenytoin, rifampin, ritonavir, teriflunomide, others

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Section B. Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD): OFEV (nintedanib)

- **Criteria for initial therapy:** Ofev (nintedanib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist or Rheumatologist.

2. Individual is 18 years of age or older.

3. A confirmed diagnosis of Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD) as defined by the American College of Rheumatology/European League Against Rheumatism. (see Definitions section Tables 6 & 7)

4. Individual has **ALL** of the following:
    a. Disease onset (first non-Raynaud symptom) is less than 7 years
    b. High resolution computed tomography (HRCT) scan within the previous 12 months shows ≥ 10% fibrosis
    c. FVC is ≥ 40% of the predicted value
    d. DLCO is 30-89% of predicted value

5. Individual has documented failure (after 3 months of use), contraindication per FDA label, intolerance, or not a candidate for mycophenolate, cyclophosphamide or tocilizumab.

6. A negative pregnancy test in a woman of childbearing age, unless is using effective contraception.

7. Individual is a nonsmoker or has been abstinent from smoking for at least six weeks or is participating in a smoking cessation program.

8. Individual does not have moderate or severe hepatic impairment (Child-Pugh B or C).

9. Individual does not have severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease.

10. There are no significant interacting drugs such as rifampin, carbamazepine, phenytoin, and St. John's wort.

11. Esbriet (pirfenidone) or generic pirfenidone and Ofev (nintedanib) will not be used simultaneously.

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Ofev (nintedanib) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist or Rheumatologist.

2. Individual's condition has responded while on therapy with response is defined as **TWO** of the following:
    a. Significant improvement in %FVC over baseline
    b. Absolute decline in FVC is less than 10%
    c. Absolute decline in DLCO is less than 15%

d. Improved or no decline in symptoms for cough or shortness of breath

3. Individual is a nonsmoker or is participating in a smoking cessation program.
4. Esbriet (pirfenidone) or generic pirfenidone and Ofev (nintedanib) will not be used simultaneously.
5. Individual has been adherent with the medication.
6. Requested dose for Ofev is at least 100 mg twice daily.
7. Individual has not developed any significant adverse drug effects that may exclude continued such as:
   a. Liver toxicity
   b. Severe and persistent GI reactions
8. There are no significant interacting drugs such as rifampin, carbamazepine, phenytoin, and St. John's wort.

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

Section C. Chronic Fibrosing Interstitial Lung Disease with a Progressive Phenotype: OFEV (nintedanib)

- **Criteria for initial therapy:** Ofev (nintedanib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist or Rheumatologist.
2. Individual is 18 years of age or older.
3. A confirmed diagnosis of chronic fibrosing interstitial lung disease with a progressive phenotype by **BOTH** of the following:
   a. HRCT shows greater than 10% fibrotic features
   b. Clinical signs of progression defined as:
      i. FVC decline is ≥ 10%

ii. FVC decline is ≥ 5 % but <10% with worsening respiratory symptoms or with worsening fibrosis on chest imaging or worsening of respiratory symptoms and with worsening fibrosis on chest imaging

4. The individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. FVC ≥ 45% predicted
    b. DLCO ≥ 30% and < 80% of predicted
    c. A negative pregnancy test in a woman of childbearing age, unless is using effective contraception

5. Dependent upon the underlying cause of the fibrosing lung disease, the individual has documented failure (progressed on clinically appropriate medical management after 3 months of use), contraindication per FDA label, intolerance, or not a candidate for the following,
    a. Corticosteroid such as prednisone or methylprednisolone
    b. Mycophenolate mofetil
    c. Azathioprine
    d. Cyclophosphamide
    e. Cyclosporine or tacrolimus

6. Individual is a nonsmoker or has been abstinent from smoking for at least six weeks or is participating in a smoking cessation program.

7. Individual does not have moderate or severe hepatic impairment (Child-Pugh B or C).

8. Individual does not have severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease.

9. There are no significant interacting drugs such as rifampin, carbamazepine, phenytoin, and St. John's wort.

10. Esbriet (pirfenidone) or generic pirfenidone and Ofev (nintedanib) will not be used simultaneously.

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Ofev (nintedanib) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist or Rheumatologist.

2. Individual's condition has responded while on therapy with response is defined as **TWO** of the following:
    a. Improvement in %FVC over baseline or reduced rate of decline in FVC
    b. No worsening or development of dyspnea
    c. No new changes on imaging

3. Individual is a nonsmoker or is participating in a smoking cessation program.
4. Esbriet (pirfenidone) or generic pirfenidone and Ofev (nintedanib) will not be used simultaneously.
5. Individual has been adherent with the medication.
6. Requested dose for Ofev is at least 100 mg twice daily.
7. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Liver toxicity
    b. Severe and persistent GI reactions
8. There are no significant interacting drugs such as rifampin, carbamazepine, phenytoin, and St. John's wort.

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

Description:

Ofev (nintedanib) is indicated for the treatment of adults with idiopathic pulmonary fibrosis (IPF); it is indicated for the treatment of adults with chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; and it is indicated to slow the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). Pirfenidone (brand Esbriet and generic pirfenidone), a pyridone, is indicated for the treatment of idiopathic pulmonary fibrosis (IPF), a specific form of chronic progressive interstitial lung disease of the lower respiratory tract in which lung tissue becomes scarred or fibrotic over time.

Ofev (nintedanib) is a tyrosine kinase inhibitor that reduces fibroblast activity by binding to receptors for various growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). These pathways are implicated in the scarring of lung tissue. It blocks intracellular signaling, preventing proliferation, migration, transformation of fibroblasts implicated in IPF pathogenesis.

Pirfenidone exact mechanism of action is unknown, however, pirfenidone has anti-inflammatory and anti-fibrotic activity. Pirfenidone exerts anti-inflammatory effects by interfering with the production of transforming growth factor (TGF)-beta (involved in cell growth) and tumor necrosis factor (TNF)-alpha (involved in inflammation). It acts as an antifibrotic agent by altering the expression, synthesis, and possibly accumulation of collagen. Pirfenidone is available as 267 mg capsule or tablet and 801 mg tablet.

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Idiopathic Pulmonary Fibrosis (IPF)

IPF, also known as cryptogenic fibrosing alveolitis (CFA), is a specific and the most common type of idiopathic chronic, fibrosing interstitial pneumonia (IIP). IPF is defined as a specific form of chronic, progressive fibrosing of IIP unknown cause. IIPs are spontaneously occurring diffuse parenchymal lung diseases. Other IIPs include nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated interstitial lung disease (RB-ILD), acute interstitial pneumonia (AIP), lymphocytic interstitial pneumonia (LIP), and cryptogenic organizing pneumonia (COP). IIPs are classified based on their histopathologic appearances.

IPF is a progressive disease characterized by an irreversible decline in pulmonary function, worsening of pulmonary symptoms, and progressive fibrosis on high-resolution computed tomography (HRCT). As a result, patients with IPF experience shortness of breath, cough, and have difficulty participating in everyday physical activities. The exact cause of IPF is not known, but associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

IPF is a fatal lung disease with a variable and unpredictable course, in which progression occurs slowly in the majority of patients; a minority of patients experience rapid progression or stable disease, some experience episodes of acute respiratory worsening despite previous stability. The prognosis of IPF is poor, with only 20-30% of individuals are alive five years after diagnosis. Hospitalizations for respiratory problems are common and are frequently associated with death. No medication has been found to cure IPF, but nintedanib and pirfenidone, have been shown to slow disease progression, as evidenced by smaller decline in FVC, compared to placebo in adult patients with IPF.

Cigarette smoking is most strongly associated with IPF. Exposure to stone, metal, wood, and organic dusts has also been suggested as a risk factor as well as gastroesophageal reflux disease.

HRCT should be obtained in all patients suspected of having IPF. The presence of certain specific HRCT features in the appropriate clinical setting, may be sufficient to establish the diagnosis.

The characteristic HRCT features of IPF include peripheral (subpleural), bibasilar reticular opacities associated with architectural distortion, including honeycomb changes and traction bronchiectasis. While honeycombing is essential to making a definite diagnosis, it may be absent.
When the results of the clinical evaluation, laboratory testing, and HRCT do not allow for a confident diagnosis of IPF, lung biopsy may be indicated. When performed, lung biopsy results need to be correlated with the HRCT findings. For patients who require histopathologic confirmation of IPF, a surgical biopsy is preferred over transbronchial lung biopsy (TBLB).

The diagnosis of IPF requires exclusion of other known causes of ILD AND either definite features of UIP on HRCT or certain combinations of HRCT and lung biopsy features of UIP. The histologic hallmark and chief diagnostic criterion for UIP is a heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibroblast foci, and honeycomb changes. A UIP-like pattern of injury can also be seen in other fibrotic lung diseases, such as those associated with rheumatic diseases, chronic hypersensitivity pneumonitis, drug-toxicity, and pneumoconioses, such as asbestosis

There is no staging system for assessing the severity of IPF. Patients progress from mild to moderate to severe respiratory limitation. Disease severity is assessed on the basis of symptoms, HRCT, and pulmonary function testing. Surrogate markers for the disease include forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Use of the FVC as an efficacy measure is both supported and discouraged in the literature while the DLCO is considered a standard predictor of survival.

Moderate disease is characterized by: non-productive cough, dyspnea on moderate exertion (supplemental oxygen may be needed with exertion), and mild-to-moderate pulmonary function abnormalities: reduced FVC (50-70% of predicted), reduced DLCO (45-65% of predicted), and/or $P(A\text{-}a)O_2$ (21-30 mmHg).

Advanced disease is characterized by: dyspnea on mild exertion (walking < 300 feet or climbing more than one flight of stairs), oxygen desaturation (≥ 4%) during a six-minute walk test, requires supplemental oxygen at rest and/or with exertion, and

moderate to severe pulmonary function abnormalities: reductions in FVC (< 50% of predicted), reductions in DLCO (< 50% of predicted), and P(A-a)O_2 difference elevated (> 30 mmHg).

Clinical features associated with increased risk of mortality include: level of dyspnea, increasing degree of dyspnea, absolute decrease in FVC by ≥ 10%, absolute decrease in DLCO by ≥ 15%, DLCO < 40% of predicted, oxygen desaturation to ≤ 88% during a 6-minute walk test (6MWT), extent of honeycombing on HRCT, and worsening fibrosis on HRCT

IPF is defined by the American Thoracic Society in the following manner: a) exclusion of other known causes of interstitial lung disease (connective tissue disease, drug toxicity, domestic and occupational environmental exposure such as asbestos or beryllium exposure, hypersensitivity pneumonitis, systemic sclerosis, scleroderma, SLE, rheumatoid arthritis, radiation, sarcoidosis, bronchiolitis obliterans organizing pneumonia, HIV, viral hepatitis, or cancer) **and** b) presence of UIP pattern evidenced by HRCT alone or by a combination of surgical lung biopsy and HRCT.

Systemic sclerosis (SSc; scleroderma)
Systemic sclerosis (SSc; scleroderma) is a connective tissue disease characterized by excessive collagen deposition, autoimmunity, and extensive vascular damage that involves multiple organs. It is believed to involve an abnormal response to microvascular injury in individuals with genetic susceptibility and/or epigenetic modifications, which leads to immune dysregulation, inflammation, microvasculopathy and fibrosis.
Systemic sclerosis is a heterogeneous disease with a pathogenesis characterized by three hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix. The clinical manifestations and the prognosis of SSc are variable, with the majority of patients having skin thickening and variable involvement of internal organs.

Patients with SSc are classified according to the extent of skin involvement: limited SSc (lSSc), with no detectable skin involvement; limited cutaneous SSc (lcSSc) with skin involvement limited to the hands and face; and diffuse SSc (dSSc), with skin involvement proximal to the elbows and knees.

In patients with lcSSc, visceral involvement is rare, and the prognosis is good, with the exception of the 8-12% of patients in whom pulmonary arterial hypertension (PAH), ILD and/or bowel involvement eventually occur. Patients with dSSc experience visceral involvement, which is responsible for reduced life expectancy. In addition to diminishing life expectancy, SSc is responsible for skin, tendon, joint, and vessel damage, which leads to disability, handicap, and worsening of quality of life. ILD is more frequently associated with dSSc. Since SSc associated ILD may develop in the absence of dyspnea, HRCT must be performed systematically in SSc patients, together with pulmonary function tests (PFT).
The histological pattern most commonly observed in SSc-ILD is nonspecific interstitial pneumonia (NSIP), observed in approximately two-thirds of patients. UIP is present in a minority of individuals with SSc-ILD. The extent of fibrosis on HRCT predicts the progression of ILD. Decline in lung function is also a predictor of mortality in patients with SSc-ILD.

Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype
The term ILD includes a large group of more than 200 parenchymal pulmonary disorders that overlap in their clinical presentations and patterns of lung injury. A proportion of patients with ILDs develop a progressive-fibrosing phenotype. Progressive fibrosis is associated with worsening respiratory symptoms, decline in lung function, limited response to immunomodulatory therapies, decreased quality of life and, potentially, early death.
IPF and several other ILDs may present a progressive-fibrosing phenotype. These may include

- Hypersensitivity pneumonitis
- Autoimmune ILDs: includes RA-associated ILD, mixed connective tissue disease, systemic sclerosis-associated ILD, and others
- Idiopathic nonspecific interstitial pneumonia
- Unclassifiable idiopathic interstitial pneumonia
- Other ILDs: includes fibrosing ILDs not categorized above such as occupational exposure related ILD, sarcoidosis, and pleuro-parenchymal fibroelastosis

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IPF is the most common ILD that is characterized by progressive fibrosis, lung scarring, and a radiological pattern known as UIP

Definitions:

Interstitial Lung Diseases:

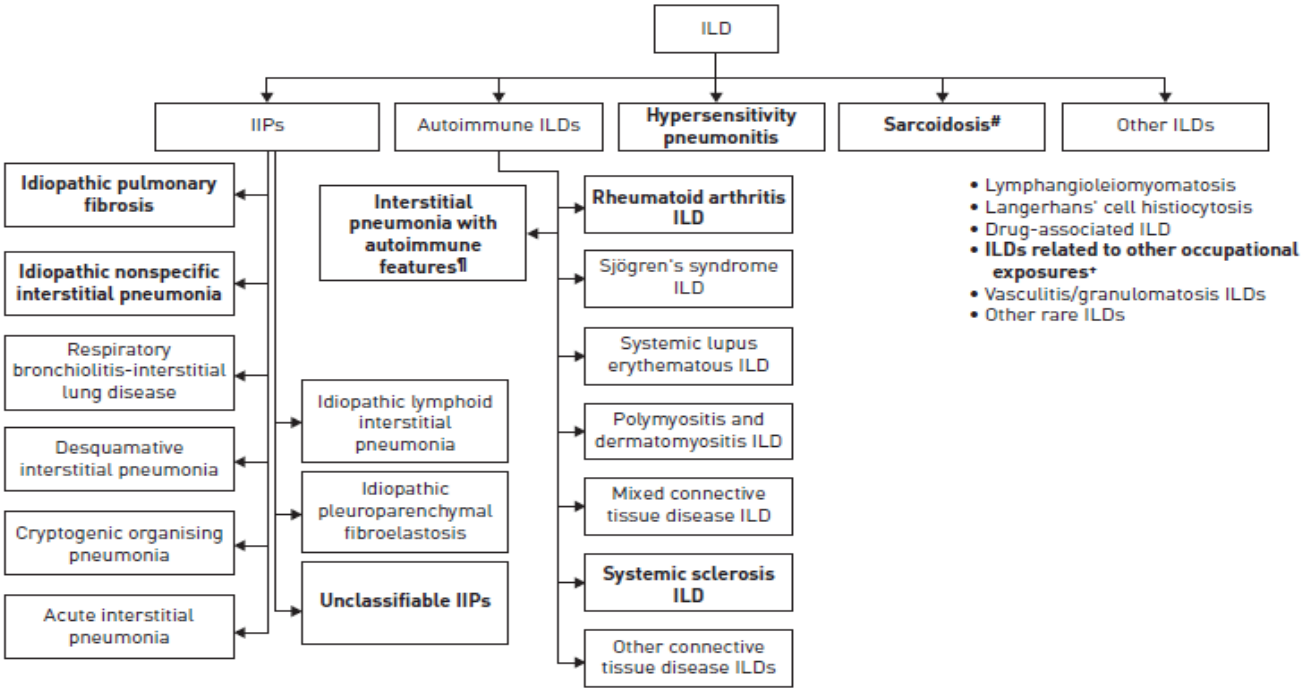

FIGURE 1 Types of interstitial lung disease (ILD) most likely to have a progressive-fibrosing phenotype (indicated in bold). IIPs: idiopathic interstitial pneumonias. #: stage IV sarcoidosis only; ¶: not an established clinical diagnosis; +: *e.g.* asbestosis, silicosis.

Idiopathic Pulmonary Fibrosis (IPF) Criteria from the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS, and the Latin American Thoracic Association (LATA):

- Exclusion of other know causes of interstitial lung disease (for instance, domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)
- Presence of a usual interstitial pneumonia (UIP) pattern on HRCT in patients without surgical lung biopsy, as evidenced by sub-pleural, basal predominance; reticular abnormality; honeycombing with or without traction bronchiectasis; and absence of any features inconsistent with UIP pattern. (See Table 1)
- Specific HRCT and lung biopsy combinations, as per histopathological criteria for UIP pattern and HRCT and biopsy patterns, in patients with surgical lung biopsy. (See Tables 2, 3, 4)

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Idiopathic Pulmonary Fibrosis:

HRCT Patterns and UIP Diagnosis:

Table 1: HRCT Patterns and UIP Diagnosis	
Pattern	Features
UIP – need all 4 features	• Sub-pleural, basal predominance; distribution is often heterogeneous • Reticular abnormality • Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis • Absence of feature listed in Inconsistent with UIP (see below)
Probable/Possible UIP – need all 3 features	• Sub-pleural, basal predominance; distribution is often heterogeneous • Reticular abnormality with peripheral traction bronchiectasis or bronchiolectasis • May have ground glass opacities • Absence of feature listed in Inconsistent with UIP (see below)
Indeterminant for UIP	• Subpleural and basal predominant • Subtle reticulations; may have mild ground glass opacities or distortion (“early UIP pattern”) • CT features and/or distribution of lung fibrosis that do not suggest any specific etiology (“truly indeterminate for UIP”)
Inconsistent with UIP/Alternative diagnosis	• Findings suggestive of another diagnosis, including: • CT features: Discrete cysts (multiple, bilateral, away from areas of honeycombing) Marked/diffuse mosaic attenuation/air-trapping (bilateral, in 3 or more lobes) Attenuation Predominant/extensive ground glass abnormality (extent > reticular abnormality) Profuse micronodules (bilateral, predominantly upper lobes) Centrilobular nodules Nodules Consolidation in bronchopulmonary segment(s)/lobe(s) • Predominant distribution: Peribronchovascular Perilymphatic Upper or mid-lung • Other: Pleural plaques (consider asbestosis) Dilated esophagus (consider CTD) Distal clavicular erosions (consider RA) Extensive lymph node enlargement (consider other etiologies) Pleural effusions, pleural thickening (consider CTD/drugs)

Histologic features of UIP:

Table 2: Histologic features of UIP	
Key feature	• Dense fibrosis causing remodeling of lung architecture with frequent honeycomb fibrosis • Fibroblastic foci typically scattered at the edges of dense scars • Patchy lung involvement • Frequent subpleural and parseptal distribution
Pertinent negative	• Lack of active lesions of other interstitial diseases (such as sarcoidosis or Langerhans cell histiocytosis) • Lack of marked interstitial chronic inflammation • Granulomas are inconspicuous or absent • Lack of substantial inorganic dust deposits such as asbestos bodies (except for carbon black pigment)

	• Lack of marked eosinophilia

Histological Criteria for UIP Pattern:

Table 3: Histologic Criteria for UIP Pattern from biopsy specimen	
	Criteria
UIP Pattern – need all 4 criteria	• Evidence of marked fibrosis/architectural distortion, +/- honeycombing in a predominantly sub-pleural/paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see Not UIP Pattern)
Probable UIP Pattern	• Evidence of marked fibrosis/architectural distortion, +/- honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see Not UIP Pattern) OR • Honeycomb changes only
Possible UIP Pattern – need all 3 criteria	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (see UIP Pattern) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see Not UIP Pattern)
Not UIP Pattern – need any of the 6 criteria	• Hyaline membranes • Organizing pneumonia • Granulomas • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

Combination of HRCT & Surgical Lung Biopsy (determined with multidisciplinary discussion):

Table 4: Combination of HRCT and Biopsy for Diagnosis of IPF			
Histopathology patterns and features			
UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) Predominant subpleural and/or paraseptal distribution of fibrosis Patchy involvement of lung parenchyma by fibrosis Fibroblast foci	Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF AND Absence of features to suggest an alternative diagnosis OR	Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause* Some histologic features from column 1, but with other features suggesting an alternative diagnosis	Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies Histologic findings indicative of other diseases (e.g., hypersensitivity pneumonitis, Langerhans cell histiocytosis, sarcoidosis, LAM)

Absence of features to suggest an alternate diagnosis		Honeycombing only			
IPF diagnosed based upon HRCT and biopsy patterns					
IPF suspected		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF diagnosis
	Probable UIP	IPF	IPF	IPF (likely)*	Non-IPF diagnosis
	Indeterminate for UIP	IPF	IPF (likely)*	Indeterminate for IPF	Non-IPF diagnosis
	Alternative diagnosis	IPF (likely)*/non-IPF diagnosis	Non-IPF diagnosis	Non-IPF diagnosis	Non-IPF diagnosis

* IPF is the likely diagnosis when any of the following features are present:
- Moderate-to-severe traction bronchiectasis/bronchiolectasis (defined as mild traction bronchiectasis/bronchiolectasis in four or more lobes including the lingual as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man over age 50 years or in a woman over age 60 years
- Extensive (>30%) reticulation on HRCT and an age >70 years
- Increased neutrophils and/or absence of lymphocytosis in BAL fluid
- Multidisciplinary discussion reaches a confident diagnosis of IPF

American Thoracic Society and European Respiratory Society (ATS/ERS):

Table 5: ATS/ERS Criteria for Diagnosis of IPF in the absence of surgical lung biopsy	
Major Criteria	• Exclusion of other known causes of ILD (certain drug toxicities, environmental exposure, and connective tissue diseases) • Abnormal PFT that include evidence of restriction (reduced VC, often with an associated increase in FEV1/FVC) and impaired gas exchange (increased $P(A\text{-}a)O_2$, decreased PaO_2 with rest or exercise, or decreased DLCO) • Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans • Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis
Minor Criteria	• Age > 50 years • Insidious onset of otherwise unexplained dyspnea on exertion • Duration of illness > 3 months • Bibasilar, inspiratory crackles (dry or Velcro-type in quality)
Presence of all Major with as at least 3 of the Minor criteria increases likelihood of a correct clinical diagnosis of IPF	

Systemic Sclerosis:

American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) Classification Criteria for Systemic Sclerosis (SSc):

Table 6: ACR-EULAR Criteria for the classification of Systemic Sclerosis
These criteria are ***not*** applicable to: a) Patients having a SSc-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic cheiropathy. b) Patients with `*Skin thickening sparing the fingers*' ***Patients having a total score of 9 or more are classified as having definite systemic sclerosis***

Items	Sub-items	Weight score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints is a sufficient criterion to classify as having SSc		9
Skin thickening of the fingers *(only count the highest score)*	Puffy fingers Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)	2 4
Finger-tip lesions *(only count the highest score)*	Digital Tip Ulcers Finger Tip Pitting Scars	2 3
Telangiectasia		2
Abnormal nail-fold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease (Maximum score is 2)	PAH ILD	2
Raynaud's phenomenon		3
Scleroderma related antibodies (any of anti-centromere, anti-topoisomerase I [anti-Sd 70], anti-RNA polymerase III) (Maximum score is 3)	Anti-centromere Anti-topoisomerase I Anti-RNA polymerase III	3
Total score		

PAH (pulmonary arterial hypertension) is defined as proven PAH by right heart catheterization

ILD (interstitial lung disease) is defined as pulmonary fibrosis on HRCT or chest radiograph, most pronounced in the basilar portions of the lungs, or presence of `velcro' crackles on auscultation not due to another cause such as congestive heart failure

Table 7: Definitions of the SSc classification criteria items

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits - a diffuse, usually non-pitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are narrowed distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other reasons such as inflammatory dactylitis
Finger-tip ulcers or pitting scars	Ulcers or scars distal to or at the PIP joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasia(e) in a scleroderma like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or large matt-like telangiectasia(e). Telangiectasiae are visible macular dilated superficial blood vessels; which collapse upon pressure and fill slowly when pressure is released; distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nail-fold capillary pattern consistent with SSc	Enlarged capillaries and/or capillary loss with or without peri-capillary hemorrhages at the nail-fold and may be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis on HRCT or chest radiograph, most pronounced in the basilar portions of the lungs, or presence of `Velcro' crackles on auscultation not due to another cause such as congestive heart failure.

Raynaud's phenomenon	Self-report or reported by a physician with at least a two-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
Scleroderma specific antibodies	Anti-centromere antibody or centromere pattern on antinuclear antibody (ANA) testing; anti-topoisomerase I antibody (also known as anti-Scl70 antibody); or anti-RNA polymerase III antibody. Positive according to local laboratory standards.

Resources:

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