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S2K Guideline for Diagnosis of Idiopathic Pulmonary Fibrosis

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Keywords
Idiopathic pulmonary fibrosis · Diagnosis · Guideline · Biopsy · High-resolution computed tomography · Bronchoalveolar lavage · Serology

Abstract
Idiopathic pulmonary fibrosis (IPF) is a severe and often fatal disease. Diagnosis of IPF requires considerable expertise and experience. Since the publication of the international IPF guideline in the year 2011 and the update 2018 several stud-

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ies and technical advances have occurred, which made a new assessment of the diagnostic process mandatory. The goal of this guideline is to foster early, confident, and effective diagnosis of IPF. The guideline focusses on the typical clinical context of an IPF patient and provides tools to exclude known causes of interstitial lung disease including standardized questionnaires, serologic testing, and cellular analysis of bronchoalveolar lavage. High-resolution computed tomography remains crucial in the diagnostic workup. If it is necessary to obtain specimens for histology, transbronchial lung cryobiopsy is the primary approach, while surgical lung biopsy is reserved for patients who are fit for it and in whom a bronchoscopic diagnosis did not provide the information needed. After all, IPF is a diagnosis of exclusion and multidisciplinary discussion remains the golden standard of diagnosis.

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11. Clinically Relevant Questions
Question 1: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo a detailed, prompted history of (previous) medication use and inhalational exposures at home and at work, to exclude potential causes of the ILD?

Question 2: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo serological testing to exclude or diagnose an underlying autoimmune disorder?

Question 3: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo cellular analysis of their BAL fluid?

Question 4: for patients with newly detected ILD of unknown cause who are clinically suspected of having IPF, should surgical lung biopsy (SLB) be performed to ascertain the histopathology diagnosis of UIP pattern?

Question 5: should a transbronchial lung biopsy (forceps) be performed for patients who are suspected of having IPF to ascertain the histopathology diagnosis of UIP pattern?

Question 6: for patients with newly detected ILD of unknown cause who are clinically suspected of having IPF, is transbronchial lung cryobiopsy (TBLC) a reasonable alternative to SLB to sufficiently ascertain the histopathology diagnosis of UIP pattern?

Question 7: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF be diagnosed in the context of an MDD?

Question 8: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo serum biomarker measurement to corroborate the IPF diagnosis?

1. About This Guideline

1.1. Responsible Professional Association
German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, DGP)
Robert-Koch-Platz 9
10115 Berlin.

1.2. Important Note
Medical science is continuously advancing. The information provided in this guideline – in particular concerning diagnostic and treatment procedures – can therefore only reflect the state of knowledge at the time of going to press. The application of therapy, medication, and dosage recommendations remains the responsibility of the user.

2. Scope of Application and Purpose of the Guideline

2.1. Rationale for Selecting the Guideline Topic
This guideline for the diagnosis of idiopathic pulmonary fibrosis (IPF) is an update to the [German] S2K guideline for diagnosis and therapy of IPF published in 2013 in PNEUMOLOGIE [1]. Since the publication of the guideline in 2013, an update on therapies was published in 2017 [2]. A relevant number of studies have been published in the meantime – particularly with respect to the diagnosis of IPF – which need to be considered. The body of scientific evidence has grown considerably, and this update only concerns the field of diagnosis and is published as a supplement to the original guideline.

2.2. Objective of the Guideline
The main objective of this guideline is to improve and standardize the diagnosis of IPF. It aims to achieve the highest possible diagnostic confidence with the lowest possible invasiveness of the diagnostic methods used. Another objective is to diagnose patients at an early stage. Improvements in the quality of care are intended to be achieved by the following:

- identifying affected patients at an early stage;
- standardizing diagnostic procedures;
- improving the interpretation of findings;
- streamlining the diagnostic strategy and prioritizing noninvasive investigational tests.

2.3. Target Patient Group
The guideline focuses on the group of patients suffering from IPF. However, it is also relevant for patients with any interstitial lung disease (ILD) as it is used to distinguish IPF from other types of ILD.

2.4. Coverage Area
The area covered by the guideline includes outpatient as well as inpatient structures responsible for diagnosing patients. The guideline is relevant for both general practitioners and specialists.

2.5. Target User Groups/Addressees
This guideline is intended for medical and nonmedical professionals (physicians and nonphysicians), who may be involved in the treatment of IPF in one way or the other. They include pneumologists, internal medicine specialists, cardiologists, radiologists, pathologists, thoracic surgeons, basic scientists, nurses, patients, patient advocacy groups, and interested laypersons). The guideline serves as a source of information for medical assistant professionals.

3. Composition of the Guideline Panel

3.1. Coordination and Editing
Prof. Dr. Med. Jürgen Behr, Coordinator and Editor
Department of Internal Medicine V, LMU University Hospital Munich and Asklepios Specialty Hospitals Munich-Gauting.

3.2. Professional Associations and Organizations Involved
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Delegated representative: K. Geißler

Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF*)
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10559 Berlin.
Delegated representative: H. Sitter.

3.3. Methodological Support

The methods for the development of this guideline were facilitated by AWMF (Association of the Scientific Medical Societies in Germany).

4. Accuracy of Methods

The methods used to develop the guideline are described in the guideline report. The guideline panel decided to lean on and adapt the 2018 ATS-ERS-JRS-ALAT clinical practice guideline which used the GRADE method characterized by the following: (a) systematic search with inclusion and exclusion criteria; (b) critical evaluation of the literature according to GRADE; (c) indication of recommendation levels and strength of evidence; (d) recognizable linking of recommendations and relevant literature; and (e) preparation of evidence tables for relevant studies [3].

The guideline and the associated document, including searches and evidence tables, are available as pdf files on the AWMF website (https://www.awmf.org/leitlinien/detail/ll/020-016.html). Complementary to the international guideline, publications published after September 2017 (and thus not available for the international guideline) were considered.

This guideline was supported throughout its development by AWMF (Association of the Scientific Medical Societies in Germany) (H.M.). Voting in the consensus meetings took place in line with the nominal group technique process and was facilitated by H.M. The consensus process for this S2K guideline included the following elements: logical analysis (clinical algorithm), formal consensus building, evidence-basing, and decision analysis. The rules for S2K guidelines state that a solution has to be based on a clearly defined set of questions and derived in several steps using conditional logic (if/then logic). Clinical trials and meta-analyses are included as evidence basis. The procedure is to be presented in a simple, clear, and concise manner using graphic algorithms.

4.1. Drafting of the Guideline/Consenting

The first version of the guideline was drafted under the direction of lead author Jürgen Behr by the authors of the individual chapters. This version was then circulated by e-mail among all members of the guideline panel, modified, and eventually provided the basis for the consensus meeting held in Munich on August 9, 2019.

4.2. Statements

Statements are presentations or explanations of specific facts or questions without a direct call for action. They are adopted in the context of a formal consensus process, in line with the approach taken for recommendations, and may be based either on study results or expert opinion.

4.3. Expert Consensus (EC)

In the context of the S2K guideline, recommendations are based on expert consensus; a comprehensive and systematic review of the entire available literature was not carried out. Expert consensus was graded not through

Table 1. Grading of recommendations

Level of recommendation	Description	Wording
A	Strong recommendation	Shall
B	Weak recommendation	Should
0	Conditional recommendation	Can

symbols or letters; rather, the strength of consensus is indicated by the wording used (shall/should/can), as shown in Table 1.

4.4. External Review and Approval

As part of the adoption process, the guideline is reviewed and consented by all medical societies involved.

5. Editorial Independence

The development of the guideline was funded by the German Respiratory Society (DGP) and the medical societies involved. Guideline development was editorially independent from the funding parties; there were no additional sponsors.

Funding was used exclusively to cover the cost of staff, office supplies, the procurement of literature, and for the consensus meeting (rent, technology, catering, facilitator fees, travel expenses, and accommodation costs).

Potential conflicts of interest were documented for all guideline panel members using standardized AWMF forms. The completed forms were reviewed and evaluated by the coordinators. The relationships and facts disclosed therein as well as the statemnets of conflicts of interest of the guideline panel members are presented in the guideline report published elsewhere (https://www.awmf.org/leitlinien/detail/ll/020-016.html). Where a potential conflict of interest was identified, the respective members were interviewed. In conclusion, there were no conflicts of interest relevant enough to justify the exclusion of a member on the grounds of bias.

The issue of conflicts of interest was jointly discussed at the beginning of the consensus meeting for the drafting process. Further potential risks of bias were reduced by the formal consensus building process, the interdisciplinary and multi-professional drafting process, and the possibility of public review. We would like to thank the representatives and experts for serving exclusively on a pro bono basis.

6. Preparation and Implementation

The guideline is published on the websites of the AWMF and the German Respiratory Society as well as in the medical journal "*Pneumologie*." It will also be presented at professional conferences of the participating professional societies and, thus, be brought to the attention of those involved in patient care as well as interested parties.

7. Validity and Updating Process

The S2K guideline will be valid until updated. The next update is scheduled to be made after 5 years, that is, in 2024. In the event of an urgent need for modification, a new version may be drafted earlier. Comments and suggestions for the updating process are explicitly encouraged, and can be addressed to the guideline secretariat:

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8. Clinical Presentation

IPF is a chronic, progressive, and irreversible ILD [4, 5]. Intensive research in recent years has led to numerous insights into the underlying pathophysiological processes. These include, without being limited to, faulty repair mechanisms in epithelial cell dysfunction, fibroblast activation, oxidative stress, vascular remodeling, genetic modifications, and aging processes (senescence). The exact pathogenesis remains unknown [6].

8.1. Epidemiology

Epidemiological data are inhomogeneous due to different statistical collection methods and disease definitions. The reported incidence rates in Europe and North America are between 2.8 and 19 cases per 100,000 people per year [7]. IPF is the most common form of idiopathic interstitial pneumonia. With a prevalence of 8.2 cases per 100,000, it is, however, a rare disease (orphan disease) [8]. Prevalence increases with age [7]. Familial clustering of IPF was observed in up to 11% of cases [9, 10].

Evaluations of randomized studies [11–13], as well as data from national and international patient registries [9, 14–18], show that the onset of the disease is usually in the sixth decade of life, with an age peak between 60 and 70 years. Men are more frequently affected than women, and the majority of patients have a history of smoking. This clinical constellation should lead to the suspicion of IPF and be considered in the differential diagnosis as an important indicator for the further diagnostic approach.

Earlier onset is possible in familial IPF and has been described repeatedly [17, 19]. The possibility of a pulmonary manifestation of an autoimmune disease should always be considered [20] if affected patients are younger.

8.2. Characteristic Features

The most common symptoms are shortness of breath (up to 85% of cases), initially on exertion, later also at rest, cough (up to 75%), tiredness, and loss of appetite [9, 14, 17, 21]. Symptoms usually are of insidious onset and increase over time. In exceptional cases, IPF may first present as an acute exacerbation, that is, acute worsening of dyspnea over just a few weeks.

Clinical examination reveals bibasilar inspiratory crackles (synonymous: velcro rales), a typical finding on auscultation that can be observed in 80–95% of patients [9, 14, 17]. Clubbing can be seen in 20–30% of patients [9, 14, 17]. The lung function parameters of forced vital capacity (FVC) and total lung capacity (TLC), as well as diffusion capacity (TLCO) of the lungs, may be within the reference range at the time of diagnosis or already be reduced and will typically deteriorate further as the disease progresses [9, 11, 13–16].

8.3. Risk Factors

Tobacco smoke undeniably increases the risk of developing IPF. Sixty to seventy percent of affected patients have a history of smoking [9, 12, 14, 15, 22]. IPF usually manifests years or decades after active smoking has been discontinued. According to data from the German INSIGHTS IPF registry, the average time between quitting smoking and the manifestation of IPF is 21 years [14]. At the time of diagnosis, only 1–6.8% of patients are still active smokers [9–11, 14–16].

Environmental factors such as exposure to asbestos, metal and wood dusts, chemicals, or contact with allergens usually found in hypersensitivity pneumonitis (HP; synonym: extrinsic allergic alveolitis), were found in up to 38% of IPF patients. However, a definite causal relationship could not be demonstrated [9, 14].

Genetic polymorphisms in the mucin 5B gene (MUC5B) promoter, for example, variant rs35705950, or mutations in the telomerase encoding genes, for example, TERT or TERC, which cause telomere shortening, or in the surfactant proteins are thought to be associated with the development of IPF [23]. However, genetic testing is not routinely done at present.

8.4. Comorbidities

Comorbidities are generally more prevalent in patients with IPF than in the general population and are relevant for prognosis [24, 25]. Relevant comorbidities are cardiovascular and thromboembolic diseases, gastroesophageal reflux, lung cancer, depression, sleep-related respiratory disorders, and diabetes [9, 26, 27]. IPF can be accompanied by COPD or pulmonary emphysema in one-third of cases, as these diseases result from years of smoking [9, 26, 27].

Lung cancer is diagnosed more frequently in IPF patients than in the general population, in 3% of patients within the first year of diagnosis of IPF. The cumulative incidence reaches 11% in a 4-year follow-up period and 54% in a 10-year follow-up period [27, 28]. A common risk factor for both diseases is not only smoking, but also similar pathophysiological mechanisms such as activation of the tyrosine kinase epidermal growth factor receptor, cellular aging processes, and genetic changes [23]. The presence of IPF limits the diagnostic and therapeutic options and goes along with a poorer prognosis of lung cancer and vice versa. This holds also true for the early stages of lung cancer [23, 29].

8.5. Progression and Follow-Up Monitoring

IPF progression is heterogeneous. Slow disease progression over several years and exacerbations are seen, as are rapidly progressing manifestations of the disease [21]. Follow-up assessments are usually performed at 3–4-month intervals.

Important parameters for assessing the course of the disease are lung function (FVC and TLC), blood gas analysis at rest and during exercise, TLCO, exercise tolerance (6-min walking test), quality of life (including the SGRQ or the K-BILD questionnaire) as well as imaging techniques (high-resolution computed tomography [HRCT]). In addition, cumulative scores such as the GAP and TORVAN index are used to assess disease severity and the associated prognosis [19]. Without treatment, FVC deteriorates by 200–280 mL per year [22, 26]. The deterioration is not a linear process; that is, past FVC deterioration does not predict the future FVC trend [16].

Managing patients with this highly complex clinical condition in specialized ILD centers allows the comprehensive diagnostic evaluation and case-by-case decision-making in the context of institutional multidisciplinary ILD boards at the time of initial diagnosis. Periodic follow-up visits at the centers will ensure that patients receive the best possible treatment (e.g., participation in clinical studies). A common approach is that patients are alternately seen by a pulmonologist and by the ILD center.

8.6. Prognosis

The cause of death in IPF patients is more frequently the underlying pulmonary fibrosis than any comorbidity. In large pivotal studies, 5.7–8.3% of patients in the placebo groups died within a year versus only 3.5–6.7% of patients in the verum groups [11, 13].

Frequent hospitalizations negatively affect the prognosis of the disease. Acute exacerbation of IPF is associated with an in-hospital mortality >50% and a median survival time of 3–4 months [30, 31].

8.7. Diagnosis

The diagnosis of IPF continues to be a diagnosis of exclusion. Given the different therapeutic approaches, the differentiation from other forms of chronic progressive pulmonary fibrosis is essential.

The diagnostic process requires detailed knowledge of differential diagnosis and a structured approach to reliably exclude known causes of ILDs [32].The differential diagnosis includes autoimmune diseases with pulmonary involvement, especially ILDs associated with rheumatoid arthritis or other types of connective tissue disease (CTD), drug-induced pneumonitis, pneumoconioses, chronic HP, chronic sarcoidosis, and, rarely, infections (e.g., tuberculosis). The average time from the onset of symptoms to the correct diagnosis is 1.5 years [13, 22].

9. Imaging

HRCT plays a central role in the diagnosis of IPF. A chest x-ray alone is not suitable for identifying and further characterizing ILD due to the subtle and complex parenchymal changes.

The optimal technique for evaluating ILD is outlined below:

- HRCT technique:
  - Spiral data, i.e., volumetric acquisition with smallest possible collimation, has largely replaced sequential CT acquisition. It ensures an accurate analysis of three-dimensional distribution patterns using multi-planar reformation and post-processing techniques such as MIP (maximum intensity projection) [33, 34]. In addition, the volumetric acquisition is more suitable for follow-up monitoring.
  - The fastest gantry rotation and pitch (ratio of table feed to 360° CT gantry rotation) should be used to reduce breathing and heart rate-related artifacts [35].
  - The DRG Working Group on Diagnostic Radiology of Occupational and Environmental Diseases (Arbeitsgemeinschaft Diagnostische Radiologie arbeits- und umweltbedingter Erkrankungen, AG DrauE) has delivered recommendations for the Low-Dose-Volume HRCT of the lungs to ensure standardization of CT examinations when using different scanners [36].
- Number of CT images:
  - The initial image is acquired under deep inspiration (volumetric acquisition) with the patient in supine position.
  - A second image should be acquired of the entire chest during exhalation (sequential CT acquisition), if a pathology within the small airways is to be confirmed/rejected (e.g., bronchiolitis, HP) [37].
  - Optionally, a third image in prone position (sequential CT acquisition only in the lower field, as necessary) can be acquired to rule out posture-induced changes of lung parenchyma (hypostasis) [38].
  - Breathing instructions must be given before each acquisition (preferably by the MTA rather than by automated voice messages) [39].
- CT scan in case of acute respiratory deterioration in patients with known ILD.
  - Acute pulmonary embolism should always be ruled out in patients presenting with acute respiratory deterioration. A chest CT angiography should, therefore, be obtained, either as a stand-alone procedure or in addition to a non-contrast HRCT protocol, if respective symptoms are present.
  - Acquisitions with the patient in supine position only are adequate to answer this question.
  - Acute IPF exacerbation should be excluded.

9.1. Usual Interstitial Pneumonia Pattern on HRCT

Usual interstitial pneumonia (UIP) is characterized by distinctive HRCT findings, including honeycombing, traction bronchiectasis, and/or traction bronchiolectasis, fine reticulation often in conjunction with ground-glass opacity (GGO) of the lung parenchyma [40, 41].

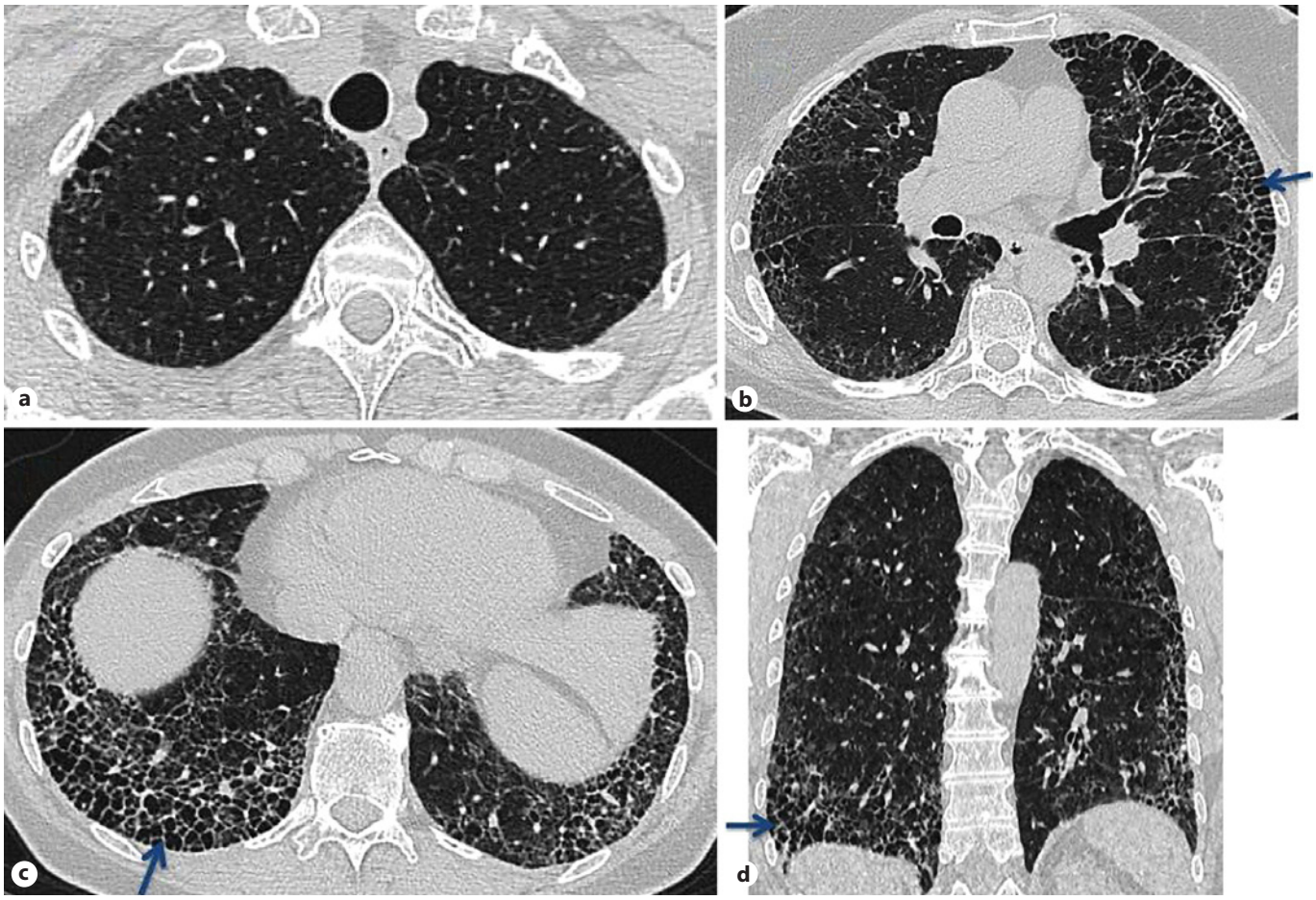


Fig. 1. UIP pattern on HRCT: axial (**a–c**) and coronal (**d**) CT image reconstructions of a patient with UIP pattern. Subpleural reticular abnormalities with traction bronchiectasis and honeycombing (arrows), and a distinct craniocaudal gradient in coronal reconstruction (**d**).

– Honeycombing:

Honeycombing is characterized by clustered, cystic airspaces of typically consistent diameter (3–10 mm, but occasionally larger). They are usually located in the subpleural parenchyma and have well-defined walls. Honeycombing is commonly accompanied by a reticular pattern containing traction bronchiectasis and bronchiolectasis. It often presents as multiple layers of subpleural cysts on top of each other but may also present as a single layer. In these cases, distinguishing between honeycombing and paraseptal emphysema or traction bronchiolectasis may be difficult. Interobserver agreement regarding the identification of honeycombing is moderate, with disagreement most commonly due to another, similar subpleural pathology (e.g., traction bronchiolectasis, paraseptal emphysema, and subpleural cysts) [42, 43].

– Traction bronchiectasis and bronchiolectasis:

Traction bronchiectasis and bronchiolectasis are characterized by irregular dilatations of the lumen of bronchi/bronchioles. It is usually peripheral/subpleural in UIP, often coexisting with honeycomb-like cysts, and may be best seen as peripheral traction bronchiolectasis. Traction bronchiectasis is considered a reliable sign of pulmonary fibrosis [44, 45]. It can present as pronounced airway irregularity and is also called varicose bronchiectasis.

– GGO:

GGO is a common feature in UIP, but usually less widespread than the reticular patterns. GGO is an increase in density of the low-density lung parenchyma, whereby vascular and bronchial walls can be identified within the densification. It is important to distinguish between "pure" GGO and GGO superimposed on fine re-

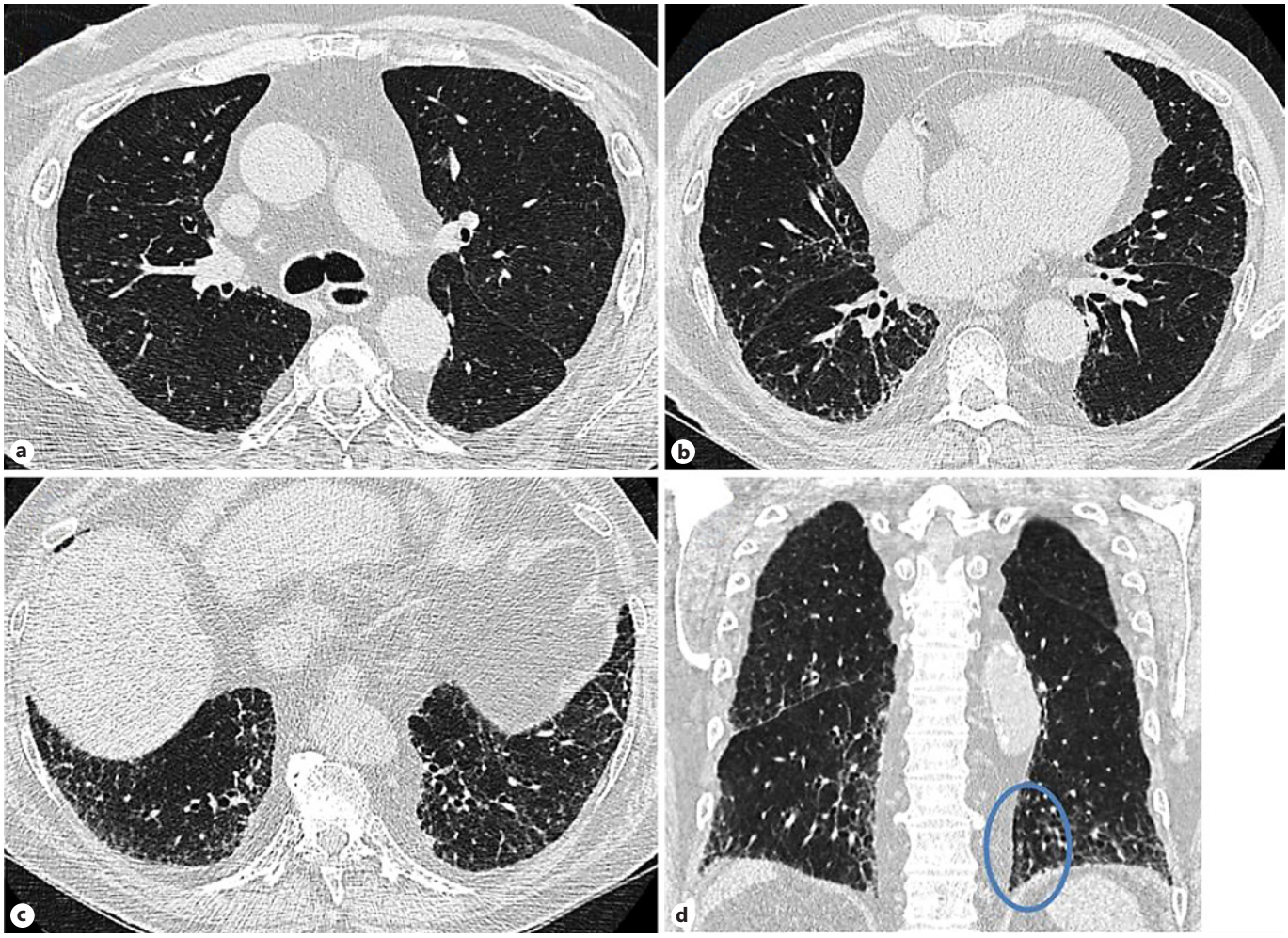


Fig. 2. Probable UIP pattern on HRCT: (**a–d**) the CT images show increased basal-predominant subpleural reticulation with peripheral traction bronchiectasis (circle in **d**) but without honeycombing.

ticular abnormalities [46]. "Pure" GGO is NOT a typical feature of UIP, and its presence in a patient with IPF could indicate an acute exacerbation [47, 48]. In contrast, GGO superimposed on fine reticular abnormalities indicates fibrosis and may be seen in patients with IPF. The combination with traction bronchiectasis/bronchiolectasis helps in the differentiation of these 2 patterns [42].

9.2. HRCT Patterns

We recommend using the 4 diagnostic categories described in the publication of the Fleischner Society. These categories are "UIP pattern," "probable UIP pattern," "pattern indeterminate for UIP," and "alternative pattern" (Fig. 1–4) [32].

9.3. UIP Pattern

UIP is the hallmark radiological pattern of IPF. Honeycombing is a distinguishing feature of UIP and must be present for a definite HRCT diagnosis of UIP to be made. It can be seen with or without peripheral traction bronchiectasis/bronchiolectasis. The typical distribution of UIP is subpleural with basal predominance although upper lobe involvement is common. In some cases, the craniocaudal distribution of UIP may be relatively uniform [49]. Asymmetric lung involvement can be seen in up to 25% of cases [50]. Several studies have documented that the positive predictive value of a UIP pattern on HRCT is between 90 and 100%. Therefore, a UIP pattern on HRCT is a highly accurate predictor of a UIP pattern in surgical lung biopsy [51, 52]. Other studies have demonstrated

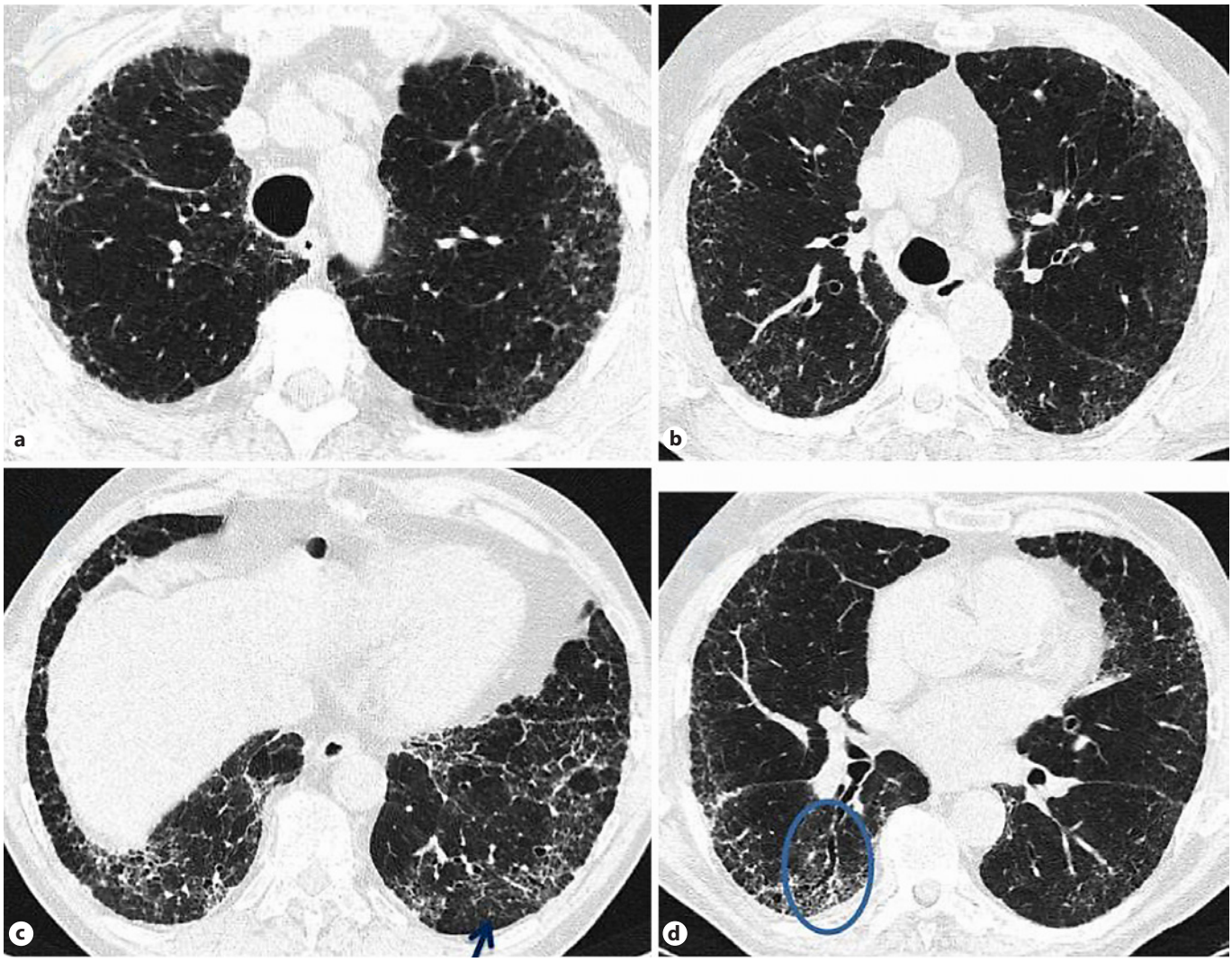


Fig. 3. Indeterminate for UIP: (**a–d**) the CT images show increased reticulation with traction bronchiectasis (circle), without honeycombing. There is no recognizable craniocaudal gradient. The findings are not typical of a UIP pattern due to the mosaic attenuation and subpleural sparing in the recess (arrow).

that a minority (approx. 30%) of patients with histopathologically confirmed UIP pattern did not meet the HRCT criteria for UIP pattern [53].

Mild mediastinal lymph node enlargement may be present [54]. GGO may be present but is usually less widespread than reticulation. It is usually superimposed by fine reticulation. Rarely, small ossified nodules within areas of fibrosis are observed, and these are more common in patients with UIP than in those with other fibrotic lung diseases (29%) [55, 56]. Patients with UIP pattern may, in addition, have some features of idiopathic pleuroparenchymal fibroelastosis at the lung apices [57]. However, there is no clear limit to the proportion of each pattern, and these cases should be regarded as UIP/IPF.

IPF patients can present for the first time with acute exacerbation, which makes a CT diagnosis more difficult. Combined features of emphysema are possible in the context of CPFE [58].

9.4. Probable UIP Pattern

In the earlier S2K guideline, an HRCT pattern of subpleural, basal-predominant reticular abnormalities without honeycombing was classified in the HRCT diagnostic

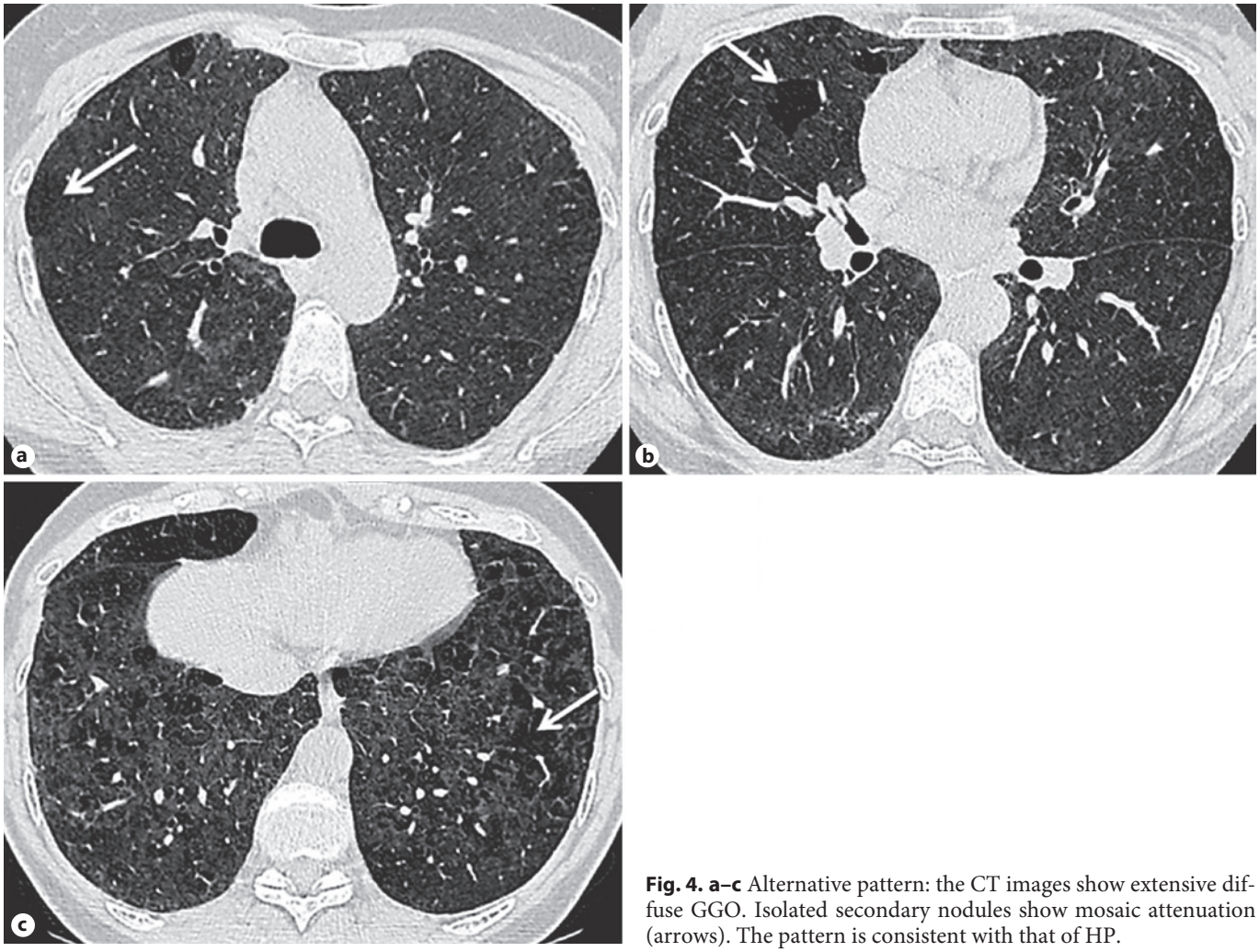


Fig. 4. a–c Alternative pattern: the CT images show extensive diffuse GGO. Isolated secondary nodules show mosaic attenuation (arrows). The pattern is consistent with that of HP.

category of "possible UIP." Since then, several studies have reported that patients with a "possible UIP" pattern on HRCT as per S2K guidelines are highly likely to have a histopathological UIP pattern, despite the absence of honeycombing in x-ray [59]. Therefore, subpleural, basal-predominant reticular abnormalities with peripheral traction bronchiectasis or bronchiolectasis should be regarded as "probable UIP." As with a UIP pattern, GGO may be present in probable UIP, but it is not a dominant feature [60].

9.5. Indeterminate for UIP

Atypical HRCT features frequently accompany a histopathological pattern of UIP (in about 30% of cases) [61]. The category "indeterminate for UIP pattern" should, therefore, be assigned when the HRCT shows features of pulmonary fibrosis without meeting the criteria of typical or probable UIP, and an alternative diagnosis cannot be explicitly suggested. This category also includes a subset of patients with minimal subpleural GGO or reticulation without obvious CT features of fibrosis, for these patients there is a suspicion that early UIP or probable UIP is present. In these cases, prone CT views should be used to confirm that the subpleural opacities do not represent hypostasis/position-dependent atelectasis of the lung parenchyma.

9.6. Alternative Pattern

There may be cases where IPF is clinically suspected, but the HRCT pattern suggests an alternative diagnosis. Examples include upper lobe-predominant peribronchial fibrosis with profuse mosaic attenuation of the lung parenchyma suggestive of HP, perihilar fibrotic retraction in sarcoidosis, or extensive GGO with subpleural sparing in fibrotic nonspecific interstitial pneumonia (NSIP).

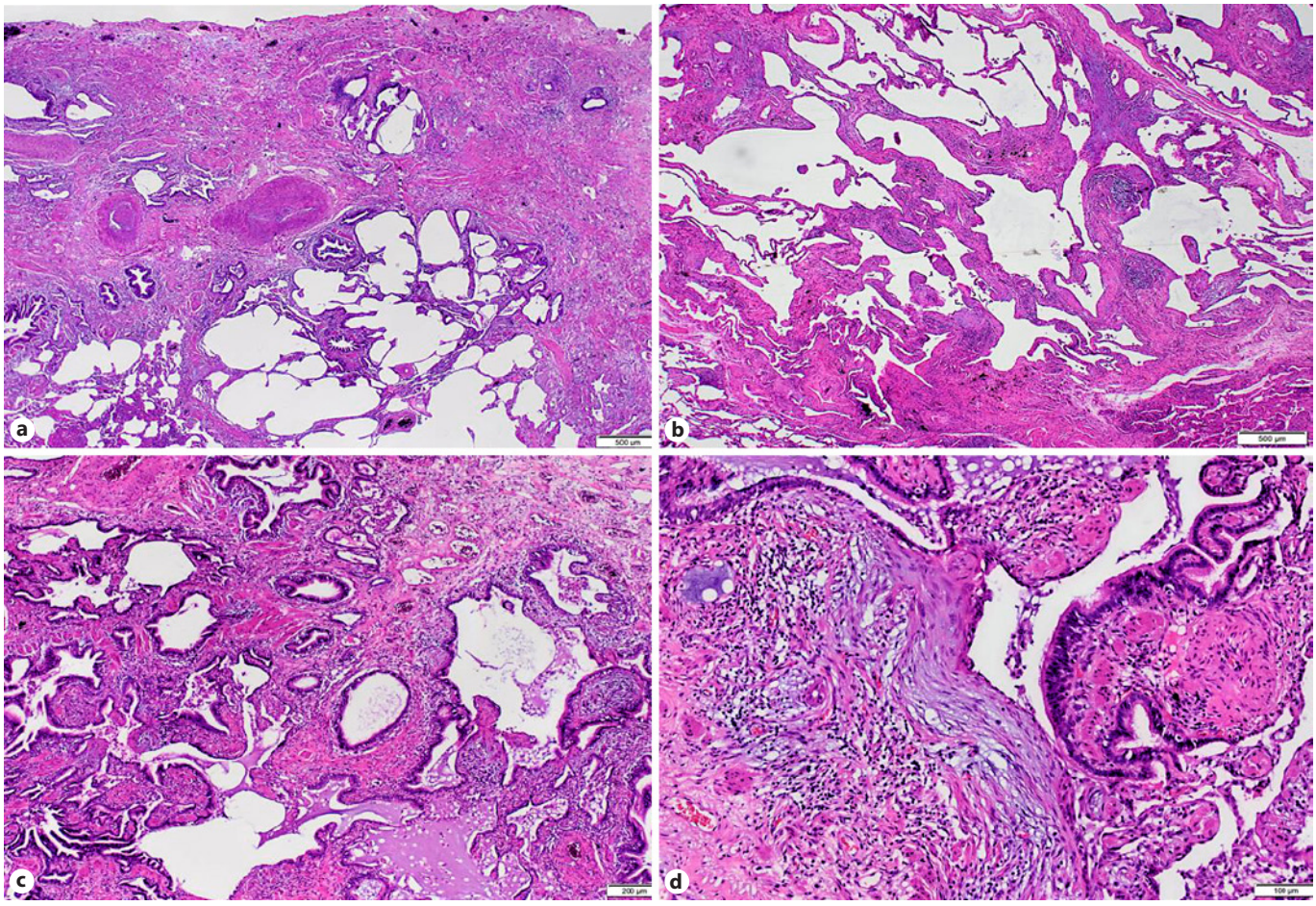


Fig. 5. UIP – histological patterns and features. Characteristic histopathological features of the UIP pattern include the following: prominent, heterogeneous fibrosis with extensive involvement of the visceral pleura and prominent smooth muscle (myogenic) metaplasia (**a**); abrupt transition between remodeled lung parenchyma and lung parenchyma (not yet) affected by fibrotic remodeling with inconspicuous alveolar septa (**b**); severe architectural distortion of lung parenchyma with extensive type II pneumocyte hyperplasia and mucus retention (**c**); defined subepithelial myofibroblast accumulation, so-called fibroblastic focus, adjacent to stroma with interspersed inflammation (**d**).

Occasionally, the HRCT presentation may be that of a typical, probable, or indeterminate UIP pattern, while ancillary findings suggest an alternative diagnosis. In such situations, an alternative diagnosis to IPF should be reconsidered.

9.7. CT Findings in Acute Exacerbation

Patients with acute IPF exacerbation have bilateral GGO of the lung parenchyma with or without consolidation on a background of pulmonary fibrosis. In the absence of a previous HRCT study, bilateral GGO and/or consolidation with additional UIP pattern is highly suggestive of an acute exacerbation and can be used to confirm underlying IPF diagnosis in the appropriate context.

Diagnostic Imaging Recommendations

Volumetric, high-resolution, non-contrast, inspiratory CT images shall be acquired for all patients with suspected IPF, with patients in supine position. Additional sequential HRCT slices in expiration should be acquired if a disease of the small airways is suspected (e.g., bronchiolitis and HP). Findings can be supplemented with prone scans. An existing CT that does not meet the above quality criteria shall not be used for diagnostic purposes.

We recommend using 4 HRCT diagnostic categories as described in the publication of the Fleischner Society [32]. These categories are "UIP pattern," "probable UIP pattern," "pattern indeterminate for UIP," and "alterna-

Table 2. HRCT pattern

	UIP	Probable UIP	Indeterminate for UIP	Alternative pattern
Distribution	Subpleural and basal predominant; distribution is often heterogeneous and asymmetric	Subpleural and basal predominant; distribution is often heterogeneous and asymmetric	Subpleural predominance	Peribronchovascular or perilymphatic distribution Upper or mid-lung predominance
Features	Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis	Reticular pattern with peripheral traction bronchiectasis or Bronchiolectasis	Subtle reticulation with or without GGO CT features and/or distribution of lung fibrosis that do not suggest any specific etiology	CT features suggestive of another diagnosis Cystic lung disease Marked mosaic attenuation Predominant GGO Profuse micronodules Nodules Consolidation Other features Pleural plaques Dilated esophagus (CTD) Distal clavicular erosions (RA) Extensive lymph node enlargement Pleural effusions

HRCT, high-resolution computed tomography; GGO, ground-glass opacity; CTD, connective tissue disease; RA, rheumatoid arthritis.

tive pattern." Radiology reports shall include an adequate description and apply the guideline-specific diagnostic criteria and classification system.

10. Histopathology Aspects

In (fibrosing) ILDs, a large number of noxious agents or triggers and pathological stimuli correspond to only a limited number of morphological injury patterns, each with significant overlap. Therefore, a correct diagnostic classification is only possible based on a synoptic consideration of clinical, radiological, and histopathological findings [62, 63].

The histological hallmark of UIP is a patchy mix of interstitial fibrosis with extensive remodeling of the original pulmonary architecture and areas with inconspicuous or only slightly remodeled parenchyma. As with most fibrosing ILDs, these changes are best identified on low magnification images (Fig. 5). Parenchymal remodeling begins in the subpleural and basal lung areas so that – especially in the early stages of disease – the subpleural compartments are most frequently affected in UIP. As the interstitial myofibroblast-driven remodeling progresses, also the centrilobular regions become increasingly affected. In addition to the heterogeneous distribution of fibrosed and non-fibrosed areas in terms of time and space, and the marked pleural/subpleural, as well as paraseptal fibrosis, an increasing number of honeycomb-like cysts with epithelial metaplasia (also known as "microscopic honeycombing"), accumulations of secretion and inflammatory infiltrates, are seen in the scarred areas. In most cases, this is associated with prominent type II pneumocyte hyperplasia and a pronounced so-called myogenic metaplasia with prominent interstitial smooth-muscle metaplasia and mostly mild chronic, occasionally even florid inflammation. Fatty tissue metaplasia or heterogeneous ossification can also occur. In addition, a varying number of localized proliferating myofibroblasts with cube-like epithelial lining, known as fibroblast foci and very typical for a fully developed UIP, can be found, especially in the transitional zone between the fibrotic and non-fibrotic areas [63, 64]. However, the detection of fibroblast foci is by no means specific for UIP.

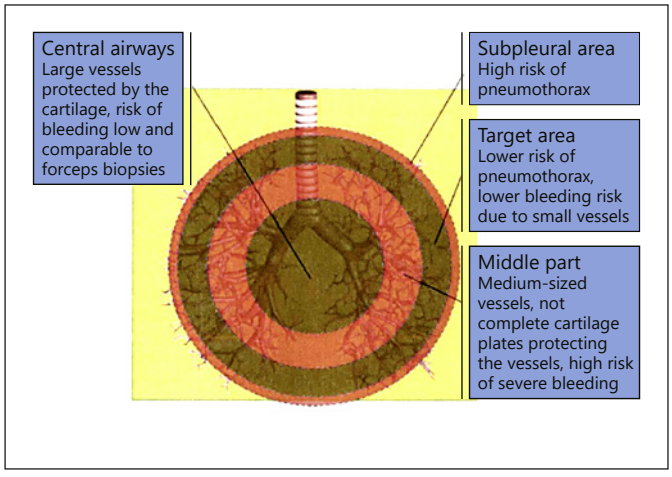
Annotation: it should be noted, however, that there is currently no generally accepted definition of fibroblast foci and that similar lesions are seen in a large number of fibrotic lung diseases.

Interstitial inflammation in UIP can range from discrete to prominent. In the absence of a granulocytic inflammatory component, the detection of prominent lymphofollicular aggregates in patients with otherwise typical

Table 3. Histopathology patterns and features

UIP	Probable UIP	Indeterminate for UIP	Alternative pattern
Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing)	Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF and	Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause[1]	Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies
Predominant subpleural and/or paraseptal distribution of fibrosis	Absence of features to suggest an alternative diagnosis, or honeycombing only	Some histologic features from column 1, but with other features suggesting an alternative diagnosis[2]	Histologic findings indicative of other diseases (e.g., Hypersensitivity pneumonitis, langerhans cell histiocytosis, sarcoidosis, LAM)
			Patchy involvement of lung parenchyma by fibrosis
			Fibroblast foci
			Absence of features to suggest an alternate diagnosis

IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; UIP, usual interstitial pneumonia. [1] Granulomas, hyaline membranes (other than those associated with acute IPF, exacerbation, which may be the presenting manifestation in some patients), prominent, airway-centered changes, areas of prominent interstitial inflammation without associated fibrosis, marked chronic fibrosing pleuritis, organizing pneumonia. Such features may not be easily seen by the untrained eye and often need to be specifically sought. [2] Changes that should raise concerns about the likelihood of an alternative diagnosis include inflammatory infiltrates away from areas of honeycombing, prominent lymphoid hyperplasia.



Color version available online

Fig. 6. Mathodological and safety aspects of TBLC (from Hetzel et al. [143] with permission).

UIP the pulmonary involvement of a primarily extrapulmonary condition, for example, a rheumatic disease, should be considered and/or discussed.

In line with the ATS/ERS criteria, the histopathological patterns shall be categorized as "UIP," "probable UIP," "indeterminate for UIP," or "alternative pattern" (see Table 3) [5]. The categories are based on defined positive and/or negative criteria. The categories as presented in this document have been modified/updated against the previous ATS/ERS statement of 2011 [62], and the S2K guideline based on it [1]. Given the high level of evidence for the specificity of HRCT in detecting a UIP pattern, lung biopsy continues not to be mandatory if a UIP pattern is identified on HRCT. Therefore, if an appropriate clinical context is met, an HRCT pattern of UIP is sufficient to diagnose IPF (Fig. 6, 7).

When assessing tissue samples, and before conclusively interpreting the identified morphological histopathological changes, the elements of parenchymal remodeling present should always be listed and the compartments affected by remodeling (affected lung areas, bronchi/bronchioles, alveolar space, interstitium, arterial and venous vascular branches, etc.) systematically described, to comprehensively document the intensity and spatial arrangement of such remodeling processes. This allows for a better comparison of a patient's findings over time or, if necessary, enables other institutions to reclassify the patient based on written documentation.

Also to be taken into account in this context are the inherent problems associated with different types of sampling, for example, the inherent inability to address pleural involvement in fibrotic remodeling in transbronchial biopsies, which by their very nature do not include the visceral pleura or the lung parenchyma next to it.

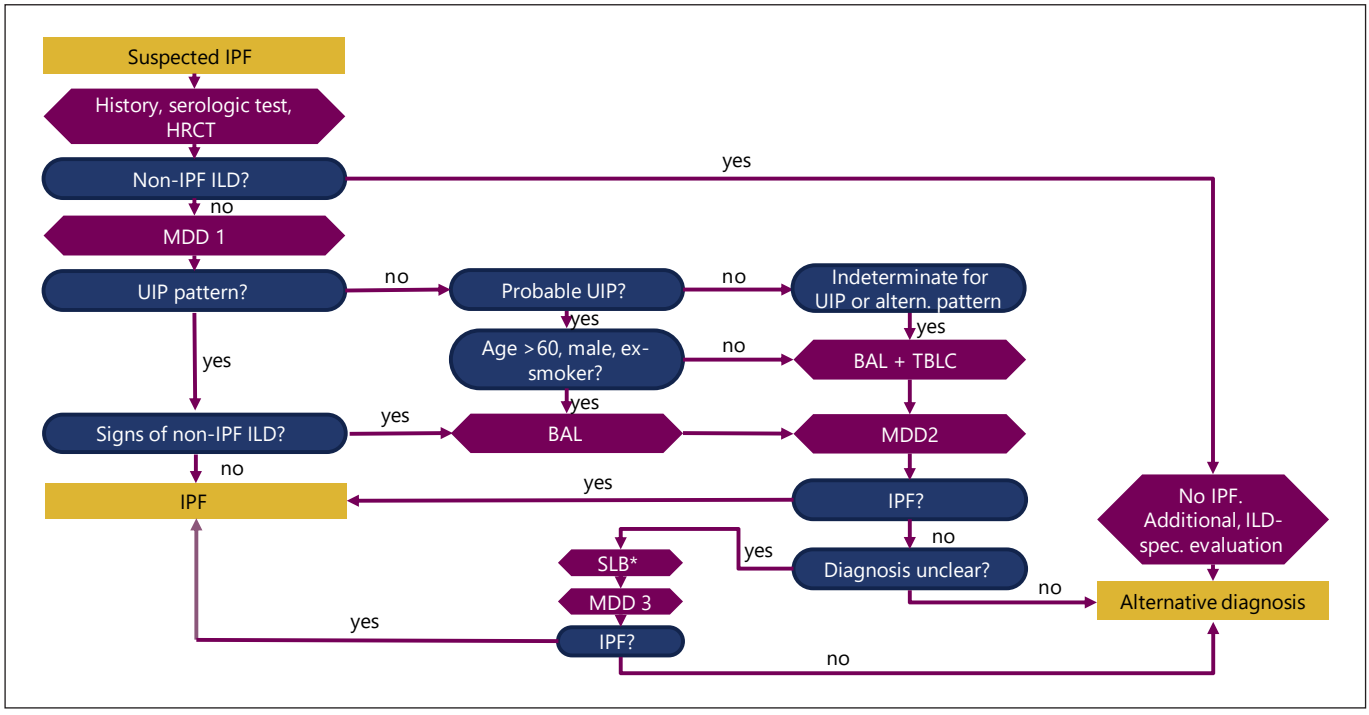


Fig. 7. Flow chart: process for diagnosing ILD. * Or TBLC if not already done and not contraindicated: the decision for surgical lung biopsy is to be based on the clinical condition of the respective patient. It is not indicated in patients at high risk of intra-, peri-, or postprocedural complications (for example, severe hypoxemia at rest and/or severe pulmonary hypertension and/or diffusing capacity of <40% [151].

If the histomorphological evaluation has to be done irrespective of imaging and clinical information (e.g., exposure to extrinsic noxious agents, drugs, presence of CTD, HP, or pneumoconioses), that is, if this information is not available at the time of diagnosis, the final diagnosis should only be made after clinicians, radiologists, and pathologists experienced in ILD diagnosis have assessed all the findings in the context of a multidisciplinary case conference (algorithm in Fig. 7), including secondary germinal centers, and a distinctly bronchiolocentric distribution pattern that can go along with extensive peribronchiolar metaplasia.

Histopathology Recommendation

The histopathology report shall include an adequate systematic description of alterations present and apply the diagnostic criteria and classification system of the guideline.

10.1. Diagnostic Procedure

The following questions refer explicitly to patients with clinically suspected IPF. Typically, this includes mostly male patients >60 years of age with symptomatic or asymptomatic bilateral ILD on imaging and bibasilar inspiratory crackles on auscultation. The questions should, however, also be applied to younger patients (40–60 years of age), especially for patients with a potential risk for familial IPF, as these patients may present with similar symptoms and clinical features. The following recommendations refer to patients with morphological changes suggestive of ILD on HRCT.

11. Clinically Relevant Questions

Question 1: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo a detailed, prompted history of (previous) medication use and inhalational exposures at home and at work, to exclude potential causes of the ILD?

Table 4. Advanced serological testing: recommended additional serological testing in case of clinical suspicion/positive ANA and screening test

Suspected diagnosis	Serological tests
Myositis	Muscle enzymes (Cr phosphokinase, myoglobin, and aldolase), myositis-specific autoantibodies: antisynthetase antibodies (anti-jo-1 and others), anti-MDA5, anti-mi-2, anti-NXP2, anti-TIF1-γ, anti-SRP, anti-HMGCR, and anti-SAE. Myositis-associated autoantibodies: anti-PM/Scl75, anti-PM/Scl100, anti-ku, and anti-U1RNP
Systemic sclerosis	Anti-Scl-70/topoisomerase-1, anti-centromere, anti-RNA polymerase III, anti-U1RNP, anti-Th/To, anti-PMScl, U3 RNP (fibrillarin), and anti-ku
Sjögren's syndrome	Anti-SSA/Ro and anti-SSB/La
Vasculitis	ANCA

HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; MDA5, melanoma differentiation-associated gene 5 antibody; NXP2, nuclear matrix protein 2; PM/Scl75, polymyositis/scleroderma 75; PM/Scl100, polymyositis/scleroderma 100; RNP, ribonucleoprotein; SRP, signal recognition particle; TIF1-γ, transcriptional intermediary factor 1 gamma; ANCA, anti-neutrophil cytoplasmic antibodies.

A detailed, complete review of (prior) medication use and inhalational exposures in the patient-specific environment provides an indispensable basis for identifying or excluding potential causes of the ILD (e.g., HP, pneumoconiosis, and drug toxicity). A retrospective study of 1,084 patients with newly diagnosed ILD of unknown cause shows that 47% of the patients could be diagnosed with HP on detailed assessment. The data show how important it is to accurately record inhalational triggers [65]. The guideline group agrees that identifying and removing potential causative environmental factors can have a positive impact on the course of the disease. Questionnaires can be useful in clinical practice to make a standardized assessment of exposures at home, at work, and in frequently visited places [65–67]. For German-speaking countries, the guideline panel recommends using the recently published questionnaire of Kreuter et al. [68].

Examples of relevant exposures include mold, birds including down feathers, other animals, metal dusts (e.g., brass, lead, and steel), wood dust or vegetable dust (e.g., pine trees), dust from stone polishing and cutting, medicines, cigarette smoke, current or recent occupation (e.g., hairdresser and dental technician), and hobbies [69–75]. Serological screening tests (for specific IgG antibodies) can help to identify a potentially triggering agent for HP that was not suspected based on the patient's clinical history. However, serum antibody tests are not standardized, and their specificity and sensitivity for the diagnosis of HP is unknown. Evidence of sensitization gained from in vitro testing alone is not indicative of disease. Conversely, negative antibody testing does not exclude HP. It is often impossible to fully prove a causal relationship between ILD and exposure.

Recommendation regarding History of Exposure

For patients with recently identified ILD of apparently unknown cause, who clinically meet the criteria of a presumptive IPF diagnosis, a detailed and complete history of both medication use and inhalational environmental exposure shall be obtained in a standardized format to exclude potential causes of ILD.

Question 2: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo serological testing to exclude or diagnose an underlying autoimmune disorder?

No reliable data are available on the role of serological screening in patients suspected of having IPF. However, the diagnosis of IPF requires exclusion of other causes of ILD. CTD-associated ILDs (or collagenosis-associated ILDs) which may be associated with a UIP pattern, constitute a differential diagnosis. There are patients with CTD in whom the ILD, that is, the lung involvement, is the first, dominant, or only feature. Criteria have been proposed for defining patients with clinically, serologically, and morphologically suspected autoimmune disease as having "interstitial pneumonia with autoimmune features"; this definition is currently in the process of being scientifically and clinically validated [76]. Serological screening is, therefore, recommended in all patients with newly identified ILD even if no other signs and symptoms of a CTD are found. Serological screening should include

testing for CRP, sedimentation rate, antinuclear antibodies (titers and interpretation of the fluorescence pattern, ENA), rheumatoid factor, myositis panel, anti-cyclic citrullinated peptide, and anti-neutrophil cytoplasmic antibodies [77]. Additional detailed serological testing is done on a case by case basis (see Table 4).

Patients with suspected CTD and those with characteristics atypical for IPF (e.g., female, <60 years), should be seen by a rheumatologist for further diagnostic evaluation (e.g., capillary microscopy). However, the guideline panelists do not generally recommend that all patients suspected of having IPF but who otherwise have no serological signs of systemic disease should be seen by a rheumatologist. By analogy, specific IgG antibodies (precipitins) against antigens known to be frequent triggers of HP can be measured; however, their significance is difficult to assess.

Recommendation regarding Serological Tests

For patients with newly identified ILD of yet unknown cause who are clinically suspected of having IPF, serological testing shall generally be performed to identify a CTD as a potential cause of ILD.

Question 3: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo cellular analysis of their BAL fluid?

The systematic literature search for the international guideline yielded 2,492 titles. However, no studies were identified that (1) compared clinical outcomes between patients who underwent BAL cellular analysis to those who did not or (2) reported the test characteristics of BAL cellular analysis for distinguishing IPF from other ILDs. Therefore, studies comparing BAL cell-type distribution across different ILDs were included; 8 of 14 studies were selected for analysis [78–85].

Annotation: the limitation of the international guideline is that only studies conducted since 2010 were taken into account. As a result, many older papers on BAL comparing the differential cytology of major lung diseases were not considered for the international guideline.

The included studies determined the percentage of neutrophils [78–83, 85], alveolar macrophages [78–82, 85], lymphocytes [78–85], and eosinophils [78, 80–83, 85], as well as the CD4/CD8 ratio [78, 80, 82, 83] in BAL. The data of IPF patients were then compared with those from patients with other ILD diagnoses such as HP [78, 79, 83], sarcoidosis [78, 82, 83], idiopathic NSIP [78, 80, 83–85], cryptogenic organizing pneumonia (COP) [78–80, 83], eosinophilic pneumonia [78], RB-ILD [79], and LIP [79]. Most studies reported the mean cell-type proportions, while some reported medians. The analysis compared the mean difference (MD) of the mean values between IPF and other groups of diseases; studies providing the median were, therefore, no longer considered.

Neutrophil Percentage

The percentage in healthy individuals is ≤3%. Patients with IPF had a mean value ranging from 5.9 to 22.1%. This was higher than that in HP (MD +4.84%; 95% CI, +1.70 to +7.98%), cellular NSIP (MD + 3.40%; 95% CI, 0.33 to +6.47%), eosinophilic pneumonia (MD + 16.8%; 95% CI, +1.96 to +31.62%), RB-ILD (MD + 11.8%; 95% CI, +9.04 to +14.56%), and LIP (MD + 7.40%; 95% CI, +3.3 to +11.5%). No differences were found when compared with patients with fibrotic NSIP, COP, or sarcoidosis.

Eosinophil Percentage

The percentage in healthy individuals is ≤1%. Patients with IPF had a mean value ranging from 2.39 to 7.5%. This was lower than that in patients with eosinophilic pneumonia (MD −48.94%; 95% CI, −62.58 to −35.30%). No differences were found when compared with patients with NSIP, HP, COP, sarcoidosis, RB-ILD, or LIP.

Lymphocyte Percentage

The percentage in healthy individuals is 10–15%. Patients with IPF had a mean lymphocyte percentage ranging between 7.2 and 26.7%. This was lower than that in patients with NSIP (MD −26.0%; 95% CI, −33.62 to 18.38%), sarcoidosis (MD −14.87%; 95% CI, −25.09 to −4.65%), COP (MD −31.43%; 95% CI, −38.78 to −24.08%), and LIP (MD −43.20; 95% CI, −48.83 to −37.7%). The lymphocyte percentage was higher in patients with IPF than in those with RB-ILD (MD 3.03%; 95% CI, +1.04 to +5.56%). No differences were found when compared with patients with HP or eosinophilic pneumonia.

Annotation: surprisingly, no difference was found with regard to HP. This was due to the selection of publications and the exclusion of older articles/studies (published before 2010) in the literature search. In the case of HP, only 2 studies were considered in the international guideline: a study by Schildge et al. [79], which found a lymphocyte percentage of 51.4% in HP and only 9.1% in IPF, and a study by Lee et al. [78] with a very small number of cases, in which the lymphocyte percentage in HP ($n = 9$) was only 19.9%, and in "UIP" ($n = 15$) was surprisingly high (21.2%). A study by Schildge et al. [86] from

2007, which was not considered, compared large numbers of patients with sarcoidosis, IPF, COP, CTD-ILD, RB-ILD, and HP. Here, the resulting mean lymphocyte value was 54.5% for HP versus only 10.2% for IPF.

CD4/CD8 Ratio

Healthy individuals have a ratio of 0.9–2.5. Patients with IPF had a mean ratio of 1.4–7.2. This was lower than that in patients with sarcoidosis (MD −5.49; 95% CI, −8.45 to −2.53) and higher than in patients with NSIP (MD +0.9; 95% CI, +0.43 to +1.47). No differences were found in comparison to HP, COP, eosinophilic pneumonia, RB-ILD, or LIP.

Evidence Assessment

The guideline panel had very low confidence in the estimated differences in BAL cell distribution between IPF and other ILDs. This was due to the small number of studies, the low number of cases, and the high variability of the distribution across the different studies. In addition, there was a risk of selection bias due to lack of consecutive patient enrollment, as well as detection bias due to different laboratory methods and bronchoscopy techniques used. The statistically significant differences were small and not considered clinically significant.

Positive Consequences

Cellular BAL analysis can help differentiate between IPF and a few other ILDs, especially in eosinophilic pneumonia and sarcoidosis.

Negative Consequences

Although no BAL-associated complications were reported in any of the studies, bronchoscopy is an invasive method that requires time, goes along with potential complications, and is uncomfortable for some patients.

Conclusion

Despite the very low confidence in the estimated effects, the guideline panel believes that the positive consequences outweigh the negative consequences of cellular BAL analysis in patients without a definite UIP pattern on HRCT. BAL is particularly useful if the radiological differential diagnosis includes eosinophilic pneumonia, sarcoidosis, HP, or infection. If a definite UIP pattern is present, BAL can provide relevant additional diagnostic information if there are concrete signs for an alternative etiology of the disease.

Recommendations regarding BAL

All patients with newly detected ILD of unknown cause and clinically suspected IPF shall undergo BAL if no definite UIP pattern is seen on HRCT. If a definite UIP pattern on HRCT is present, BAL can be performed if there are concrete signs of an alternative etiology of the disease.

Question 4: for patients with newly detected ILD of unknown cause who are clinically suspected of having IPF, should surgical lung biopsy (SLB) be performed to ascertain the histopathology diagnosis of UIP pattern?

There are 26 studies [87–112] of patients with unclear ILD in which the diagnostic accuracy of SLB was investigated and a multidisciplinary ILD board was used as the gold standard. In all cases, adequate tissue could be sampled by SLB (11 studies, 918 of 918, 100%; 95% CI, 99–100%), even though this may not always seem to be the case in a real-world scenario. In most cases, a specific diagnosis can be made based on SLB (26 studies; in 2,338 of 2,651 patients, 88.2%; 95% CI, 86.9–89.4%) and only rarely does an ILD remain unclassifiable (26 studies; 313 of 2,651 patients, 11.8%; 95% CI, 10.6–13.1%). Considering the final diagnosis of these patients, about one-third are classified as IPF (24 studies; 752 of 2,360 patients, 31.9%; 95% CI, 30.0–33.8%). Other diagnoses, some of which are potentially treatable, include infections, sarcoidosis, HP, eosinophilic pneumonia, LAM, COP, or pulmonary vasculitis.

The overall mortality of elective SLB is low (23 studies; 79 of 2,268 patients, 3.5%; 95% CI, 2.8–4.3%), the actual procedure-related mortality even lower (6 studies; 7 of 410 patients, 1.7%; 95% CI, 0.8–3.5%). Patient selection and the experience of centers in performing biopsies in some instances result in significant differences in the reported mortality rates. For example, a higher number of surgical lung biopsies per year leads to a decrease in the 30-day mortality rate (OR, 0.84; 95% CI, 0.73–0.97; p = 0.02), especially in nonelective procedures (OR, 0.84; 95% CI, 0.69–1.02; p = 0.08) and not so much in elective procedures (OR 0.94 95% CI, 0.74–1.18, p = 0.57) [113].

Additional complications and side effects of SLB include the following:

1. Acute exacerbations (15 studies; 6.1%; 95% CI, 5.1–7.3%)
2. Bleeding (7 studies; 0.8%; 95% CI, 0.4–1.7%)
3. Severe bleeding (4 studies; 0.2%; 95% CI, 0.04–1.2%)
4. Prolonged air leak (13 studies; 5.9%; 95% CI, 4.8–7.2%)

5. Respiratory infection (9 studies; 6.5%; 95% CI, 4.6–9.0%)
6. Neuropathic pain (1 study; 4.5%; 95% CI, 1.6–12.5%)
7. Delayed wound healing (4 studies; 3.3%; 95% CI, 2.0–5.4%).

Summary of Evidence

It can be assumed that the 1-year mortality rate of IPF is reduced from 8 to 5.5% by antifibrotic therapy, while the probability of slowing down disease progression increases from 60 to 68%. This would mean that in 1,000 surgical lung biopsies, in which 1,000 adequate tissue samples are obtained, 882 specific diagnoses will be made, and 319 of these patients will be determined to have IPF. Assuming that all receive therapy, the 1-year mortality of these 1,000 patients would be reduced from 26 to 18 patients, and disease progression would slow down in 217 instead of 192 patients. In addition, in many patients, a different, treatable ILD would be detected. However, it should be taken into account that 17 patients would die as a result of the surgical procedure, 61 patients would suffer acute exacerbation, and 65 respiratory infection.

If it appears necessary to confirm the histopathological findings of a UIP pattern in patients suspected of having IPF, the superior accuracy and sensitivity of SLB has to be weighed against its higher procedure-related mortality rate compared to bronchoscopic cryobiopsy, and factors such as the clinician's expertise and the number of procedures conducted at an institution need to be considered. In addition to the criteria to be applied to determine that patients are fit to undergo the procedure, the following contraindications to SLB should be considered for ILD patients:

1. Hypoxemia at rest, SpO_2 <90% on room air
2. TLCO <40% of predicted
3. Severe restriction with TLC <50% of predicted
4. Pulmonary hypertension with echocardiographically estimated systolic right ventricular pressure >40 mm Hg.

Recommendation regarding SLB

For patients with suspected IPF who have undergone the endoscopic diagnostic procedures but where the diagnosis still remains unclear after the multidisciplinary discussion (MDD), SLB shall be performed.

Question 5: should a transbronchial lung biopsy (forceps) be performed for patients who are suspected of having IPF to ascertain the histopathology diagnosis of UIP pattern?

The systematic literature search conducted in the context of the international guideline yielded 945 titles describing the diagnostic use of traditional transbronchial biopsy (TBB) in patients with ILD. However, no studies that compared clinical outcomes between patients with and without TBB could be identified.

Therefore, studies in which the diagnostic yield of TBB was determined using MDD-based decisions were included. Seven studies were selected in this respect, which included patients with ILDs of unknown cause, including patients with UIP pattern on HRCT [111, 114–119].

The analysis showed that TBB obtained an adequate sample in more than three-quarters of cases (78%). Among these adequate samples, a specific diagnosis was obtained from almost half (43%), while 57% were assessed as unclassifiable. Analyzing all the TBB samples (adequate and inadequate), a specific diagnosis could only be established in about one-third of the cases (36%). This rate (36%) corresponds to the diagnostic yield.

A significant limitation of these studies is that patients were not stratified by HRCT pattern. Observed complications included pneumothorax (1 study, 5 of 49, 10.2%; 95% CI, 4.4–21.8%) and prolonged air leak (1 study; 3 of 49, 6.1%; 95% CI, 2.1–16.5%). No procedure-related deaths were reported in this specific study.

Annotation: in the opinion of the German guideline group, complication rates cannot reasonably be derived from a study with only 49 patients. Older studies show a 30-day mortality rate of 0.2% and a complication rate of 12.8% [120].

Summary of Evidence

Using TBB to confirm a strong suspicion of IPF, the ILD remains unclassifiable in about 64% of patients. A specific diagnosis can be made in 36% of cases, thus avoiding surgical biopsy.

Positive consequence: surgical biopsy is avoided in 36% of cases. Negative consequence: a high percentage of patients remain undiagnosed (64%).

Recommendations regarding Transbronchial Forceps Biopsy

Transbronchial forceps biopsy shall not be performed for the diagnosis of IPF in patients with a definite UIP pattern on HRCT.

No recommendation is provided for patients with other HRCT patterns.

Assessment

Very little evidence is available regarding the diagnostic accuracy of TBB in patients with suspected IPF. The panel of experts agreed to advise against TBB in patients with a definite UIP pattern on HRCT. This was based on the low probability of identifying an alternative cause in patients with definite UIP pattern.

Question 6: for patients with newly detected ILD of unknown cause who are clinically suspected of having IPF, is transbronchial lung cryobiopsy (TBLC) a reasonable alternative to SLB to sufficiently ascertain the histopathology diagnosis of UIP pattern?

A systematic literature search for the international guideline yielded no studies comparing the clinical outcome of patients who underwent TLBC to those who underwent SLB. Therefore, studies that analyzed the diagnostic yield were selected. The analysis included 13 of 25 studies [109, 110, 116, 118, 119, 121–130] that enrolled patients with ILD of unknown cause and did not exclude patients with UIP pattern on HRCT.

The evidence reviewed by the international guideline panel showed that cryobiopsy obtained an adequate sample in the vast majority of cases (10 studies; 720 of 749: 96%; 95% CI, 94–97%). Among those cases where adequate samples were obtained, a specific diagnosis could be established in more than 4/5 of cases (13 studies; 692 of 833: 83%; 95% CI, 80–85%); the remaining cases were considered unclassifiable. The diagnostic yield was calculated at 80% (692 of 862 in 13 studies; 95% CI, 77–83%). The overall mortality rate was 2.7% (7 studies; 15 of 597, 95% CI, 1.7–4.3%); however, some deaths were considered to be related to the patient's underlying disease. Procedure-related mortality was 0.2% (3 studies; 1 of 427, 95% CI, 0.04–1.3%). Additional complications included acute exacerbations (3 studies; 1 of 82, 1.2%; 95% CI, 0.2–6.6%), bleeding (6 studies, 28 of 541, 5.2%; 95% CI, 3.6–7.4%) including severe bleeding (8 studies; 5 of 674, 0. 7%; 95% CI, 0.3–1.7%), prolonged air leak (2 studies; 47 of 352, 13.4%; 95% CI, 10.2–17.3%), and respiratory infections (3 studies; 3 of 409, 0.7%; 95% CI, 0.2–2.1%).

The international guideline's assessment of these data was as follows: for every 1,000 transbronchial cryobiopsy procedures performed, 950 adequate biopsies are obtained, and 790 diagnoses are made (thus avoiding surgical lung biopsies). Accordingly, 210 patients will remain undiagnosed despite TBLC, many of whom would then undergo surgical biopsy. Two patients would die as a result of the TBLC procedure, and 12 would suffer acute exacerbation.

In summary, the international guideline concluded that adequate material is obtained by TBLC in 96% (95% CI, 94–97%) of patients, from which a definitive diagnosis can be made and SLB avoided in 80% (95% CI, 77–83%) of cases. Compared with SLB, the rate of associated pulmonary infections is lower in TBLC, and a trend toward less procedural mortality is seen in TBLC. On the other hand, about 20% of patients (95% CI, 17–23%) remain undiagnosed after TBLC, and a higher rate of bleeding or prolonged air leak is observed compared to SLB.

A complementary literature search on TBLC was conducted for the German guideline. It looked for articles/studies published after the analysis date of the international guideline, and the results were analyzed to provide supplementary information. The search yielded 5 prospective and 8 retrospective studies.

A prospective study compared bleeding-related complications of conventional forceps and cryo-TBB and showed that the rate of clinically relevant bleeding events was higher after cryobiopsy (16.2 vs. 4.2%, $p < 0.05$) although no lethal hemorrhage was seen [131]. Safety aspects were addressed, among others, in a study by Hagmeyer et al. [132] who analyzed optional sequential SLB after TBLC. After initially high morbidity and mortality rates, the procedure was adjusted and significantly lower complication rates were observed.

Two prospective studies analyzed the agreement based on samples obtained by TBLC and by SLB; in both studies, SLB was performed immediately after TBLC in the same session. The study conducted by Romagnoli et al. [133] found agreement of histopathology results in $n = 21$ patients enrolled in 2 centers, with $\kappa = 0.22$ (95% CI, 0.01–0.44), concluding that, if SLB had not been performed after TBLC, this would have resulted in a different diagnosis and led to a different treatment in 51% of cases. In contrast, the multicenter study by Troy et al. [134] found histopathological agreement between TBLC and SLB of 70.8% in $n = 65$ patients, $\kappa = 0.70$ (95% CI, 0 55–0 86).

Annotation: a critical assessment of these studies concludes that the small number of cases in the Romagnoli study is a significant limitation and can easily result in overestimating the data. When adequate samples were obtained, TBLC contributed to the final MDD diagnosis as frequently as SLB in this study. Against the background of the generally low kappa values, the study by Troy et al. [134] on 65 patients with a kappa of 0.7 shows good agreement between TBLC and SLB.

In addition, a large monocenter cohort of 699 patients showed that at least 2 biopsies should be taken from different sites [135]. The size of the biopsies can differ great-

ly; according to a retrospective analysis, it ranges from 1.5 to 136.7 mm^2, with a mean value of 64.2 mm^2, while the diameter can range from 6 to 31 mm, with a mean value of 8.7 mm [129]. According to a state-of-the-art review, the cryobiopsy sample diameter should be at least 5 mm to allow for good histological analysis [136]. For the pathologist, cryobiopsy, as compared to TBB, offers the advantage that there are mostly no crushing artifacts.

The control of severe periprocedural hemorrhage can be improved by balloon insertion; the mortality rate was 0.4% [135]. Real-world data are now also available from Germany [137]. They confirm the published data concerning adequacy of material and diagnostic yield and show, in addition, that cryobiopsy is a feasible option in patients with significantly limited functional status. In the meantime, 30-day mortality data from retrospective monocenter studies have become available. They differ in the respective reports, ranging from 0% [137, 138] to 1.4% (outpatients) and 5.9% (inpatients) [135, 139–141]. Regarding the question of TBLC-associated costs versus those of TBB (forceps) and surgical biopsy, a systematic review found a diagnostic yield of 84.4 versus 64.3 versus 91.1% and cost savings for TBLC of £210 per patient in the first year and £647 in subsequent years [142].

Recommendations regarding TBLC

In summary, the members of the German guideline panel – in contrast to the international guideline – considered TBLC to be preferable over surgical biopsy for the following reasons:

a. When compared to SLB, the diagnostic significance and side effect rates are not considered inferior.
b. The cost of TBLC versus SLB is considered to be lower, and it is expected that far fewer patients will refuse to undergo TBLC than surgery.
c. Patients with significantly advanced ILD can undergo biopsy using TBLC rather than SLB. This may also be the case for elderly patients and possibly for patients with concomitant conditions. It is therefore expected that TBLC will reduce the percentage of unclassifiable ILDs.

The guideline panel, however, recommends that the technical and safety guidelines for cryobiopsy be strictly observed [143]. On a critical note, it should be pointed out that the procedure has not yet been internationally standardized and that only a few, partly contradictory data from controlled studies comparing TBLC versus SLB are available. Further research into this topic is encouraged.

TBLC – Method

An international expert panel has issued a detailed statement on the technical and safety aspects of TBLC [143], which the German guideline panel seconds with minor modifications.

The following safety aspects and contraindications should be observed when performing TBLC (cf. also Fig. 6):

a. We recommend TBLC to be performed in intubated patients under deep sedation or general anesthesia. Operating rooms for bronchoscopy should be fitted with emergency equipment.
b. We recommend using either a tube for airway management, ideally in combination with a bronchial blocker/Fogarty balloon for the (preventive) control of bleeding, or rigid bronchoscopy. Balloon may not be necessary in this case.
c. We recommend taking at least 2 biopsy samples from at least 2 segments at 1 cm from the visceral pleura. If possible, cryobiopsy samples with a diameter of no <5 mm should be obtained.
e. We recommend performing the biopsies under fluoroscopic guidance.
f. The site and number of biopsies should be determined in advance and not include areas of severe fibrosis.
g. The interventions should only be performed in centers that are highly experienced in these procedures and in managing-related complications.

The following safety aspects are relevant in TBLC:

a. The main risk factors are pneumothorax and bleeding. Acute exacerbation and death have been described in individual cases.
b. Contraindications for TBLC are bleeding diathesis, continued anticoagulation therapy with thienopyridines, other novel antiplatelet agents, and thrombocytopenia with platelet counts $<50 \times 10^9$/L.
c. Suspected pulmonary hypertension (sPAP >40 mm Hg) or confirmed pulmonary hypertension (mPAP ≥25mm Hg in the right heart catheter), as the risk of bleeding appears to be increased in these cases.
d. FVC <50% and/or target TLCO <30%, depending on clinical presentation
e. Relevant comorbidities (e.g., manifest heart failure and severe emphysema)

Question 7: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF be diagnosed in the context of a MDD?

Available data: the systematic search for the international guideline yielded 189 literature references. However, no studies could be identified that (1) compared the clinical results of single-discipline decision-making (SDD; either by a single clinician or by several clinicians from the same discipline) with those of MDD or (2) reported the test characteristics of SDD using MDD as reference standard. For this reason, studies were reviewed that reported agreement between SDD and MDD, and 5 out of 17 studies were selected for analysis [65, 144–147]. Numerous studies had to be excluded as they compared interindividual agreement but did not compare SDD to MDD. In 2017 and 2018, no new papers were published, which met the above criteria and would have needed to be considered for the German version of the guideline.

One study enrolled patients with IPF [65] diagnosed by SDD, and 4 studies enrolled patients with SDD diagnosis of different ILDs, including IPF [144–147]. An MDD diagnosis was consented and compared to the SDD diagnosis. In 3 studies, SDD was done by a single pneumologist [65, 144, 145], in one by either a single pneumologist or a single internist [146], and in another one by several pathologists [147]. In 3 studies, MDD was done by a pneumologist, a radiologist, and a pathologist [65, 144, 146]; in one by a radiologist together with a pathologist [65]; and in another one by a pneumologist and a pathologist [147].

Evidence assessment: out of 1,000 diagnostic decisions, agreement between MDD and SDD can be expected in 700 cases. If the MDD is accepted as the reference standard, it must be assumed that the remaining 300 patients are potentially subject to incorrect or delayed treatment or unnecessary diagnostic procedures.

Positive consequences: SDD is the more efficient diagnostic approach compared to the increased time and effort associated with MDD. Negative consequences. if MDD is the accepted reference standard, then SDD demonstrates suboptimal agreement of 70% (range: 47–87%).

Conclusion: the guideline panel recommends MDD as the preferred diagnostic approach, as the SDD-related risk of up to 30% of patients receiving incorrect or late treatment or requiring additional diagnostic testing deemed unacceptable. The panel believes that MDD provides the greatest benefit in patients whose HRCT pattern is probable UIP, indeterminate for UIP, or an alternative diagnosis, or when there are discordant clinical, radiological, and/or histological findings. There has been considerable discussion about what MDD should entail. Until further studies have been completed to optimize MDD, the guideline panel recommends that the group should consist of a pneumologist (and a rheumatologist, as necessary), a radiologist, and a pathologist (if cytology or histology results are available). The mode of operation is to be determined by the clinician. It may be in the form of a face-to-face meeting, telephone or web conference, or by circulating (annotated) documents by e-mail. A face-to-face meeting is recommended when discrepant findings need to be discussed.

When measured as proportion, the mean agreement between MDD and SDD was 70% (47–87%). When measured using Cohen's kappa coefficient, agreement was only moderate, $\kappa = 0.331$ (95% CI: 0.269–0.392). These estimates failed to convince the guideline panel. Contributing factors were as follows: the risk of a systematic recruitment bias by omitting diagnostic problem cases, nonconsecutive recruitment, the inconsistency of estimates, the small study sizes, and potential case selection.

Recommendation regarding MDD

The German guideline panel considers the MDD to be the diagnostic gold standard. An initial MDD conference shall be conducted with all available clinical information and HRCT findings to determine the further procedure.

After receiving the results of invasive diagnostic tests, the final diagnosis and further procedure shall then be determined in the context of a second MDD.

Question 8: should patients with newly detected ILD of unknown cause who are clinically suspected of having IPF undergo serum biomarker measurement to corroborate the IPF diagnosis?

The literature search for the international guideline was limited to 4 serum biomarkers based on expert decision: MMP7, SP-D, CCL18, and KL-6. A systematic literature search yielded 429 published articles. However, none of these studies compared clinical outcomes among patients who underwent the measurements of serum biomarkers compared to those who did not.

MMP7: several studies were reviewed that tested the diagnostic value of serum MMP7 concentrations for distinguishing IPF from other ILDs. Two of them were selected [148, 149]. One study tested the differentiation of IPF from a heterogeneous comparator group that included various other ILDs [148]. In another study, the serum MMP7 levels of IPF patients were compared to a group of patients with NSIP, HP, sarcoidosis, CTD-ILD, and drug-induced ILD [149]. Serum MMP7 values had a median sensitivity, specificity, accuracy, and diagnostic odds ratio of 71.7, 64.4, 68.4, and 4.7%, respectively.

Table 5. Combination of HRCT and histopathology patterns in diagnosing IPF

Suspected IPF	Histopathology			
	UIP	probable UIP	indeterminate for UIP	alternative diagnosis
HRCT pattern				
UIP	IPF	IPF	IPF	No IPF
Probable UIP	IPF	IPF	IPF (likely)[1]/no IPF	No IPF
Indeterminate for UIP	IPF	IPF (likely)[1]/no IPF	Unclassifiable ILD[2]	No IPF
Alternative diagnosis	IPF (likely)[1]/no IPF	No IPF	No IPF	No IPF

HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia; ILD, interstitial lung disease. [1] IPF is the likely diagnosis if – after excluding alternative causes – any of the following features are present: (a) Moderate to severe traction bronchiectasis and bronchiolectasis (defined as mild traction bronchiectasis/bronchiolectasis involving 4 or more lobes of the lung including lingula, or moderate to severe traction bronchiectasis in 2 or more lobes) in a male patient >50 years of age or a female patient >60 years of age; (b) Extensive (>30%) reticulation on HRCT, and >70 years of age; (c) Increased neutrophils and/or absence of lymphocytes in bronchoalveolar lavage; (d) The multidisciplinary case discussion agrees on a confident diagnosis of IPF. [2] Unclassifiable ILD: (a) Without adequate biopsy the diagnosis is unlikely to be IPF; (b) With an adequate biopsy, re-classification to a more specific diagnosis can be made based on multidisciplinary case discussion and/or additional consultation.

SP-D: 16 articles were reviewed that addressed the diagnostic accuracy of SP-D serum levels. Only one study was selected. It showed a sensitivity of 70.0% and specificity of 65.0%, an accuracy of 68.5%, and a diagnostic odds ratio of 3.1 to distinguish IPF from other types of ILD [148].

CCL18 and KL-6: no valid studies on the diagnostic accuracy of CCL18 and KL-6 serum levels to distinguish IPF from other ILDs were found. The serum levels of these markers do not allow the differentiation between IPF and other ILDs.

Conclusion

The data published on CCL18 and KL-6 do not suggest that one of these serum biomarkers has a diagnostic value with regard to differentiating IPF from other ILD diseases. For MMP7, 2 studies show a median sensitivity, specificity, accuracy, and diagnostic odds ratio of 71.7, 64.4, 68.4, and 4.7%, respectively. For SP-D, one study showed a sensitivity, specificity, accuracy, and diagnostic odds ratio of 70.0, 65.0, 68.5, and 3.1%, respectively. Translated into clinical practice, this implies that both MMP7 and SP-D serum levels indicate a correct IPF diagnosis in more than half of the patients while suggesting an incorrect classification in about one-third of patients. Based on these data, the diagnostic value of these serum biomarkers is currently considered insufficient to support clinical use.

Recommendation regarding the Use of Biomarkers to Diagnose IPF

In patients with newly diagnosed ILD of unknown cause and clinically suspected IPF, serum MMP7, SP-D, CCL18, or KL-6 levels shall not be measured for the purpose of IPF diagnosis and discrimination from other diseases.

12. Diagnostic Criteria

The required criteria for the diagnosis of IPF are criteria 1 and 2, or 1 and 3:

1. Exclusion of known causes of ILD (exposure to inhaled noxious agents, CTD and other systemic diseases, drug-induced ILD, etc.) and either 2 or 3,
2. Presence of UIP pattern on HRCT (see Fig. 1; Table 2),
3. Specific HRCT/histology combinations (see Table 5).

If IPF is suspected, all patients are screened for possible ILD etiologies. In German-speaking countries, we recommend the use of a standardized Interstitial Lung Disease Patient Questionnaire developed by the clinical section of the DGP [68]. If a potential cause can be identified, it should be confirmed or excluded through further investigation. If the cause or diagnosis remains unclear despite a thorough evaluation, then the findings are to be discussed in the MDD meeting. IPF is diagnosed if the appropriate combination of HRCT and histopathological patterns is present (see Table 5).

If an ILD is present and IPF is suspected (e.g., bilateral pulmonary infiltrates on chest X-ray or on CT, bibasilar inspiratory crackles, age ≥60 years, unexplained exercise-induced dyspnea, and/or cough), other causes of an ILD should be excluded first. This mainly relates to middle-aged patients (>40 and <60 years) and patients at risk for familial ILD. In such cases, other causes of ILD, for example, HP, CTD-ILD, pneumoconiosis, or medication use, should be thoroughly evaluated. This requires presenting the case in an initial MDD (Fig. 7). If no specific diagnosis is made, the clinical findings, the results of HRCT, and possibly bronchoalveolar lavage and/or cryobiopsy or SLB must be evaluated in a second MDD [150]. The diagnosis of IPF requires a specific combination of HRCT and (if available) histology (Table 5: combination of HRCT and histopathology).

Recommendations regarding the Diagnostic Process and BAL/Biopsy Procedures

1. For patients with suspected IPF and HRCT pattern of UIP without clinical signs of an alternative ILD diagnosis, no BAL and no biopsy shall be performed.
2. For patients with suspected IPF and HRCT pattern of UIP with clinical signs of an alternative ILD diagnosis (e.g., CTD-associated or chronic HP), BAL shall be performed.
3. For patients with suspected IPF and HRCT pattern of probable UIP, BAL but no biopsy shall be performed if the following criteria are met: >60 years of age, male, and ex-smoker. If the criteria are not met, a TBLC should be performed in addition.
4. For patients with suspected IPF who have an indeterminate for UIP or an alternative HRCT pattern, BAL and TBLC shall be performed.
5. For patients with suspected IPF who have undergone the endoscopic diagnostic procedures but where the diagnosis still remains unclear after the MDD, SLB shall be performed.

Annotation: all recommendations concerning cryobiopsy and SLB only apply if the patient-related safety criteria are fulfilled and if both the technical and personal expertise are available at the performing center.

13. Scientific Questions and Outlook

The expert panel sees an urgent need to further develop and validate the diagnostic procedures for ILDs. This concerns studies on the role of clinical parameters, HRCT, bronchoscopy, histopathology, and biomarkers.

Clinical Parameters

How should the disease behavior in individual patients be included in the diagnostic IPF algorithm? What is the role of patient-centered measurements like hand-held spirometry, accelerometry, or saturation measurements in this context? Could such patient-centered outcome measures, which in principle can be done at high frequency, possibly be even more sensitive than the periodic measurements of lung function and gas exchange at centers? Should systematic screening for comorbidities be part of the diagnostic evaluation to assess the prognosis? In patients with suspected IPF and probable UIP pattern on HRCT, to what extent does the observation of subsequent disease progression during the course of the disease contribute to validating the initial diagnosis of IPF and how does antifibrotic therapy influence this diagnostic implication?

A wait-and-watch approach for the natural course of the disease to confirm the diagnosis of IPF requires that the disease progresses in the majority of IPF patients within a certain time period. The inevitable consequence of such a strategy is that eligible patients do not receive antifibrotic therapy during this wait-and-watch period. The reliable identification of a "progressive chronic fibrosing" phenotype in patients based on one or clinical parameters or valid biomarkers is, therefore, of fundamental importance for IPF and beyond. Further studies will have to be conducted to answer these questions.

HRCT

What is the diagnostic significance of the extent and distribution pattern of traction bronchiectasis in patients with suspected IPF without visible honeycombing on HRCT? This also includes the question of the relative diagnostic value of central bronchiectasis and peripheral bronchiolectasis. Can the presence of mosaic attenuation, supported by a possibly obligatory expiratory CT scan, distinguish patients with chronic HP from IPF patients? How can mosaic attenuation be quantified, and can a standardized quantification contribute to differentiating the IPF-related UIP pattern from the UIP-like pattern of chronic HP? Can subgroups be formed based on the type and extent of GGO (by subjective assessment or automated methods) to estimate the probability of IPF? Does the craniocaudal distribution of fibrotic changes influence the probability of an IPF diagnosis? How is the HRCT interpretation influenced by the quality and quantity of available clinical information (concomitant diseases, inhaled noxious agents, etc.)? Can artificial intelligence be used to derive not only the correct diagnosis but

also a "progressive chronic fibrosing" phenotype from a single HRCT? Can the interstitial lung abnormalities frequently observed in the early detection of lung cancer be further differentiated, based on radiological criteria, into those representing early stages of IPF and therefore requiring further diagnosis and therapy, and others that may potentially be nonprogressive and as such be insignificant in the further course of the disease?

BAL and Transbronchial Lung Biopsy

Will novel diagnostic procedures that use artificial intelligence and molecular signatures from brush swabs, lavages, or forceps biopsies or chemical signatures, for example, in expired air (electric nose) or exhaled breath condensate be suitable for a reliable differential diagnosis of IPF and for differentiating IPF from other ILDs? How often do BAL differential cell counts, histopathology results from transbronchial lung biopsies, and molecular profiling of transbronchial lung biopsies using a machine-learning algorithm [121, 122] provide additional, relevant information for the diagnosis of IPF? Can an internationally consented definition of the fibroblast focus and also of microscopic honeycombing be reached, followed by the standardized application of this definition to histopathological findings?

Lung Cryobiopsy

Experts familiar with the methods should – based on already published recommendations [143] – further develop an internationally accepted standard for lung cryobiopsy to improve the risk/benefit ratio and achieve the best possible diagnostic yield with the lowest possible complication rate and create a basis for international, multicenter studies. This may require further comparative studies and prospective register studies.

Histopathology

How often do the results of a SLB or cryobiopsy change the final diagnosis depending on the underlying HRCT pattern? Are there any relevant differences in this regard between surgical biopsy and cryobiopsy? What influence does SLB or cryobiopsy have on lung function parameters and clinical end points at different points in time after a biopsy?

Genetic Markers and Counseling

Is IPF a hereditary disease? Which genetic markers are present in patients in whom clinical manifestation indicates familial IPF or familial interstitial pneumonia, but none of the markers or gene mutations identified to date have been found despite molecular genetic studies? What is the relationship between mutations or abnormal genetic markers and intrinsic (e.g., microaspiration, lung microbiome, abnormal gastroesophageal reflux) or extrinsic/environmental factors? Should all IPF patients receive genetic counseling? Although genetic variants account for part of the risk of developing sporadic IPF or a familial form of ILD (i.e., familial IPF or familial interstitial pneumonia), the clinical benefit and clinical applicability of these variants are unclear and need to be determined in future studies.

Other Biomarkers

What is the optimal procedure to exclude ILD in CTD and chronic HP? What is the role of specific serum antibodies in excluding or confirming suspected chronic HP? Studies of diagnostic molecular biomarkers are needed to (a) assess the diagnostic accuracy of new potential biomarkers; (b) use machine learning to diagnose IPF; and (c) integrate molecular markers into the current multidisciplinary diagnostic process for IPF. New biomarkers for diagnosing IPF (molecular classifiers) could include exhaled breath markers (e.g., electric nose and exhaled breath condensate), circulating markers (serum/plasma proteins, cellular markers, epigenetic markers [miRNAs], mitochondrial DNA, etc.), as well as the ability to identify IPF or molecular signatures from lung samples (BAL, transbronchial biopsy, TBLC, lung microbiome), whereby the least invasive methods should be used to obtain samples. What is the added value of routine screening for germline mutations or polymorphisms or routine measurement of telomere length in suspected or confirmed IPF? Other unresolved issues beyond the scope of this guideline include the best procedure for assessing the prognosis, the identification of risk factors for developing IPF, the optimal strategy for early detection of IPF, and the procedure for recording concomitant diseases and determining their impact on the course of the disease in IPF patients.

14. Summary of Recommendations

Recommendation regarding History of Exposure

For patients with recently identified ILD of apparently unknown cause, who clinically meet the criteria of a presumptive IPF diagnosis, a detailed and complete history of both medication use and inhalational environmental exposure shall be obtained in a standardized format to exclude potential causes of ILD.

Recommendation regarding Serological Tests

For patients with newly identified ILD of yet unknown cause who are clinically suspected of having IPF, serological testing shall generally be performed to identify a CTD as a potential cause of ILD.

Diagnostic Imaging Recommendations

Volumetric, high-resolution, non-contrast, inspiratory CT images shall be acquired for all patients with suspected IPF, with patients in supine position. Additional sequential HRCT slices in expiration should be acquired, if a disease of the small airways is suspected (e.g., bronchiolitis and HP). Findings can be supplemented with prone scans. An existing CT that does not meet the above quality criteria shall not be used for diagnostic purposes.

We recommend using the 4 HRCT diagnostic categories described in the publication of the Fleischner Society. These categories are "UIP pattern," "probable UIP pattern," "pattern indeterminate for UIP," and "alternative pattern." Radiology reports shall include an adequate description and apply the guideline-specific diagnostic criteria and classification system.

Histopathology Recommendation

The histopathology report shall include an adequate systematic description of alterations present and apply the diagnostic criteria and classification system of the guideline.

Recommendations regarding BAL

All patients with newly detected ILD of unknown cause and clinically suspected IPF shall undergo BAL if no definite UIP pattern is seen on HRCT.

If a definite UIP pattern on HRCT is present, BAL can be performed if there are concrete signs of an alternative etiology of the disease.

Recommendation regarding Transbronchial Forceps Biopsy

Transbronchial forceps biopsy shall not be performed for the diagnosis of IPF in patients with a definite UIP pattern on HRCT. No recommendation is provided for patients with other HRCT patterns.

Recommendation regarding SLB

For patients with suspected IPF who have undergone the endoscopic diagnostic procedures but where the diagnosis still remains unclear after the MDD, SLB shall be performed.

Recommendations regarding TBLC

In summary, the members of the German guideline panel – in contrast to the international guideline – considered TBLC to be preferable over surgical biopsy for the following reasons:

a. When compared to SLB, the diagnostic significance and side effect rates are not considered inferior.
b. The cost of TBLC versus SLB is considered to be lower, and it is expected that far fewer patients will refuse to undergo TBLC than surgery.
c. Patients with significantly advanced ILD can undergo biopsy using TBLC rather than SLB. This may also be the case for elderly patients and possibly for patients with multiple concomitant conditions. It is, therefore, expected that TBLC will reduce the percentage of unclassifiable ILDs.

The guideline panel, however, recommends that the following aspects of cryobiopsy, among others, be strictly observed [141]. On a critical note, it should be pointed out that the procedure has not yet been internationally standardized and that only little, partly contradictory data from controlled studies comparing TBLC versus SLB are available. Further research into this topic is encouraged.

Recommendations regarding the Diagnostic Process and BAL/Biopsy Procedures

1. For patients with suspected IPF and HRCT pattern of UIP without clinical signs of an alternative ILD diagnosis, no BAL and no biopsy shall be performed.
2. For patients with suspected IPF and HRCT pattern of UIP with clinical signs of an alternative ILD diagnosis (e.g., CTD-associated or chronic HP), BAL shall be performed.
3. For patients with suspected IPF and HRCT pattern of probable UIP, BAL but no biopsy shall be performed if the following criteria are met: >60 years of age, male, and ex-smoker. If the criteria are not met, a TBLC should be performed in addition.
4. For patients with suspected IPF who have an indeterminate for UIP or an alternative HRCT pattern, BAL and TBLC shall be performed.
5. For patients with suspected IPF who have undergone the endoscopic diagnostic procedures but where the diagnosis remains unclear after the MDD, SLB shall be performed.

Annotation: all recommendations concerning cryobiopsy and SLB only apply if the patient-related safety criteria are fulfilled and if both the technical and personal expertise are available at the performing center.

Recommendation regarding MDD

The German guideline panel considers the MDD to be the diagnostic gold standard. An initial MDD conference shall be conducted with all available clinical information and HRCT findings to determine the further procedure.

After receiving the results of invasive diagnostic tests, the final diagnosis and further procedure shall then be determined in the context of a second MDD.

Recommendation regarding the Use of Biomarkers for IPF Diagnosis

In patients with newly diagnosed ILD of unknown cause and clinically suspected IPF, serum MMP7, SP-D, CCL18, or KL-6 levels shall not be measured for the purpose of IPF diagnosis and discrimination from other diseases.

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16. Conflict of Interest Statement

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