IPF: A diagnostic approach

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Speaker Disclosure

- I do not have any significant or other financial relationships with industry or commercial supporters to disclose

What is necessary for diagnosis?

- All old imaging, dating back to first CT chest/abdomen
- Earliest pulmonary function test
- Re-review pathology slides
- Physical Exam

What is pulmonary fibrosis

Pulmonary fibrosis is a term used to describe scarring in the lung due to a multitude of causes

Idiopathic Pulmonary Fibrosis is a specific term used to describe a chronic, progressive, non-infectious process (pneumonia, or pneumonitis) in the lung of **unknown cause**

"Fibrosis" ≠ "Idiopathic Pulmonary Fibrosis"

Initial intake

- What are the severity, duration, and pace of the symptoms?
- Is there a relevant exposure, generally inhaled, known to result in the development of lung disease?
- Is the exposure significant? What was the intensity of the exposure?
- Did the exposure occur in the home or work environment?
- Is there a temporal association between the exposure and symptom onset?
- Is the occupation a known risk factor for the development of lung disease?
- What does the patient do specifically in their current job and previous jobs?

Home exposure history

- Inquire about pets, including birds
- Hobbies
- Water damage
- Infestations

Risk Factors

Does the patient use any medicines, herbs, vitamins, supplements, or recreational drugs that could account for the presence of lung disease?

- Vaping/electronic cigarettes
- Conventional cigarettes

Is there a family history of lung fibrosis?

Is there a history of premature graying, cirrhosis, low platelets or other blood count abnormalities?

Functional Testing

Pulmonary function testing

- FEV1 and FVC
- TLC
- DLCO

Walk test on room air

6 minute walk test

Blood Work

Auto-immune disease panel

- Rheumatoid Arthritis (ANA, RF, anti-CCP)
- Scleroderma (anti-scl-70)
- Mixed connective tissue disease (U1RNP, anti-smith, anti-SSA and –SSB)
- Vasculitis (ANCA)
- Myositis (CPK, aldolase, myositis panel, anti-jo1)
- Celiac Disease (with IPH – Lane Hamilton syndrome)

Environmental Disease Panel (aspergillus, pigeon, molds)

Telomere Panel

HRCT

- High resolution CT scan with thin slices through the chest
- Optimal quality CT scans have thin sections (<2mm)
- Images should be obtained at full inspiration to total lung capacity
- Inadequate inspiration increases lung attenuation, potentially leading to misinterpretation of key findings
- Prone CT may also facilitate the diagnosis of honeycombing
- Expiratory imaging is useful to identify air trapping, a feature that may suggest an alternative diagnosis such as chronic HP or CTD

Keys to CT diagnosis

What region of the lung is primarily affected (upper lung zones, lower lung zones or basal, diffuse)?

Specifically, is it basilar predominant and subpleural?

Is there evidence of early scarring (bronchiolectasis or bronchiectasis)?

Is there evidence of late scarring (honeycombing)?

Are there nodules? Where are they located?

Is there air trapping?

What is the pace of the change over time?

Usual Interstitial Pneumonia

A histopathologic and radiologic pattern of interstitial lung disease, which is the hallmark pattern for idiopathic pulmonary fibrosis (IPF)

This pattern can also be seen in other diseases associated with pulmonary fibrosis (e.g. rheumatoid arthritis)

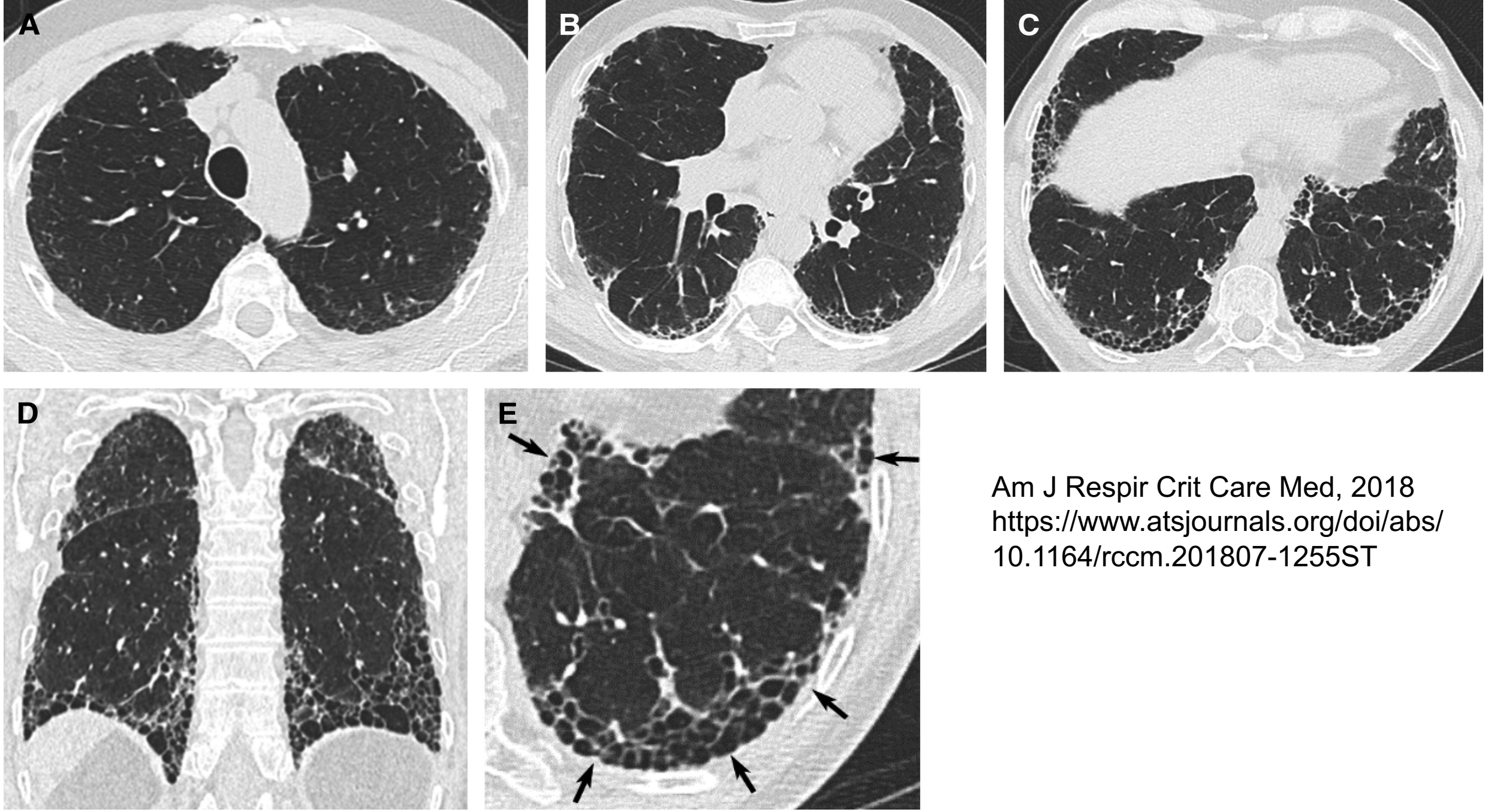
Current Classification by CT

Table 3: Diagnostic categories of UIP on CT

	Typical UIP CT pattern	Probable UIP CT pattern	CT pattern Indeterminate for UIP	CT features most consistent with non-IPF diagnosis
CT distribution	Basal (occasionally diffuse) and subpleural predominant. Distribution is often heterogeneous.	Basal and subpleural predominant. Distribution is often heterogeneous.	Variable or diffuse	Upper or mid lung predominant fibrosis Peribronchovascular predominance with subpleural sparing
CT features	Honeycombing. Reticular pattern with peripheral traction bronchiectasis/bronchiolectasis* Absence of features to suggest an alternative diagnosis	Reticular pattern with peripheral traction bronchiectasis/bronchiolectasis* Honeycombing is absent.	Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern*	Any of the following: Predominant consolidation Extensive pure ground glass opacity (without acute exacerbation) Extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration Diffuse nodules or cysts

*** Reticular pattern is superimposed on ground glass opacity, and in these cases is usually fibrotic. Pure ground glass opacity however would be against the diagnosis of UIP/IPF and would suggest acute exacerbation, hypersensitivity pneumonitis or other conditions**

Lancet Respir Med. 2018; 6: 138-153



Am J Respir Crit Care Med, 2018
https://www.atsjournals.org/doi/abs/10.1164/rccm.201807-1255ST

Multidisciplinary Discussion (MDD)

- The collaboration of multiple specialists with the ability to interpret and communicate complex clinical data patterns, and to synthesize uncertain or sometimes conflicting information
- Clinician, Thoracic Radiologist, Pathologist, ± Rheumatologist
- All this information must be shared using a common language, for clinical decision-making to occur
- Since “classic” clinical stories and patterns are uncommon, some degree of clinical uncertainty is often present; **acknowledgement of this limitation and a clear plan to address it are essential**

Lynch DA, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society white paper. *Lancet Respir Med.* 2018; 6: 138-153

“Typical UIP” CT Pattern

- Level of confidence for UIP histology: **>90%**
- There is a lower sensitivity (43%-78%)

ATS/ERS/JRS/ALAT Clinical Practice Guideline
Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults
Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

“Probable UIP” CT Pattern

- Typical appearance, but honeycombing absent
- **Provisional high confidence: 70-89%**
- The likelihood of UIP histology is greater in patients with age greater than 60, history of cigarette smoking, no history of other potential causes of fibrosis

When should we consider a biopsy?

- Indeterminate/inconsistent for UIP (level of confidence for UIP provisional low: **51-69%**
- Alternative diagnosis (low-very low $\leq$ 50%)
- Health and functional status of the patient (PFT, oxygenation, comorbidities)

Surgical Lung Biopsy

Tertiary care center by surgeons familiar with the diagnosis of interstitial lung disease

Typically involves a biopsy from three areas; at least 2-3 cm along the pleural axis and 1-2 cm deep

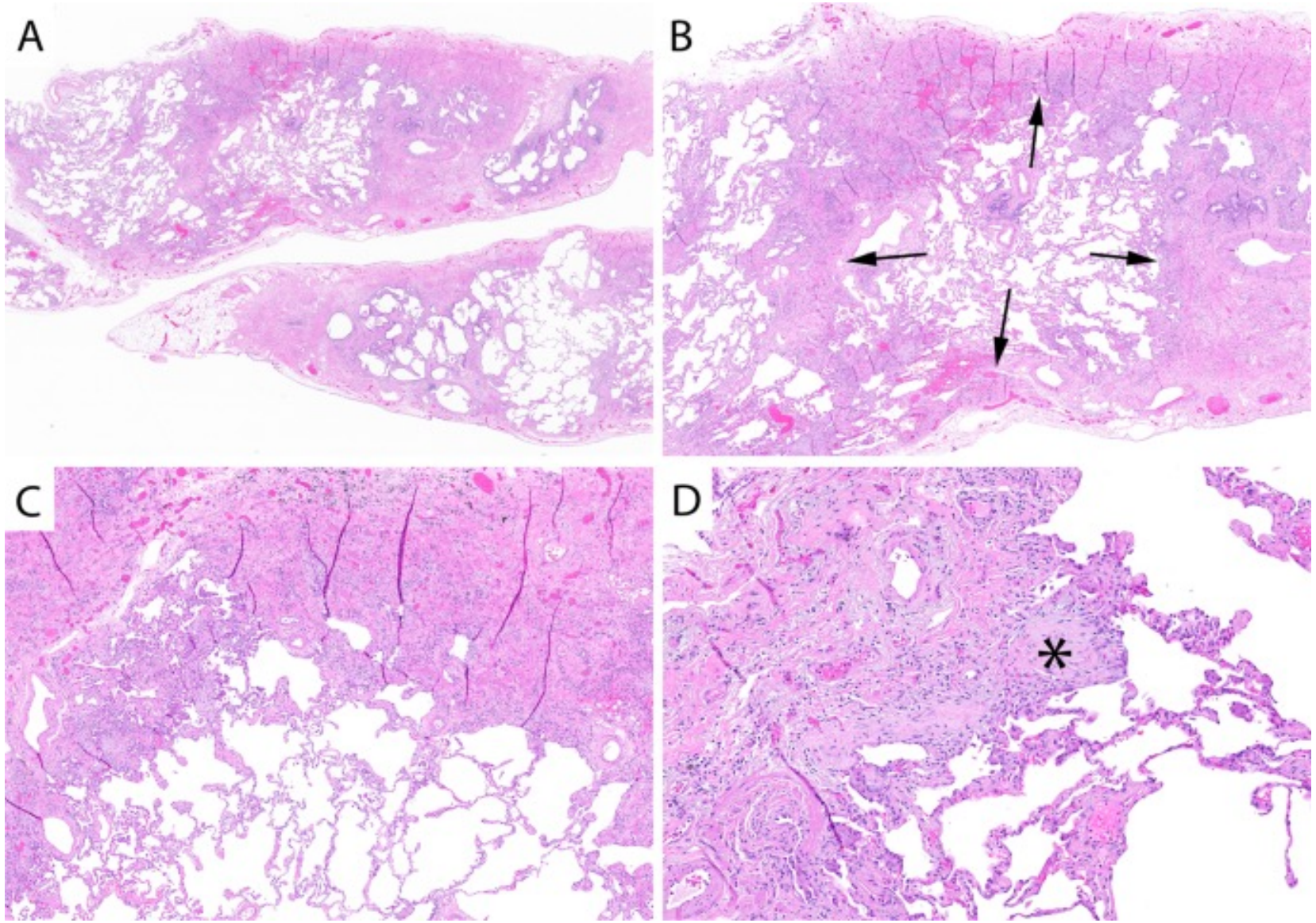
The proportion of biopsies yielding a specific diagnosis is high

Overall, in hospital mortality based on a US study was 1.7%

Histopathologic Criteria

	UIP
2018 ATS/ERS/JRS/ALAT Guidelines for UIP	• Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing) • Predominant subpleural and/or paraseptal distribution of fibrosis • Patchy involvement of lung parenchyma by fibrosis • Fibroblast foci • Absence of features to suggest an alternate diagnosis

American Journal of Respiratory and Critical Care Medicine
Volume 198 Number 5 | September 1 2018



Advanced fibrosis with architectural distortion (**A**)

Fibrosis at the periphery of the lobule (arrows) with sparing of the centrilobular regions (**B**)

Sharp demarcation between the advanced fibrosis and the normal appearing alveolar walls (**C**).

Evidence of active injury in the form of fibroblast foci (asterisks) (**D**).

Smith, M.L. The histologic diagnosis of usual interstitial pneumonia of idiopathic pulmonary fibrosis. Where we are and where we need to go. *Mod Pathol* **35** (Suppl 1), 8–14 (2022).

Alternative: Transbronchial Cryobiopsy

- Lower morbidity and mortality
- Smaller biopsies
- Diagnostic yield ~ 79 % v. SBL > 95%
- Central rather than peripheral
- Operator experience

TBLC

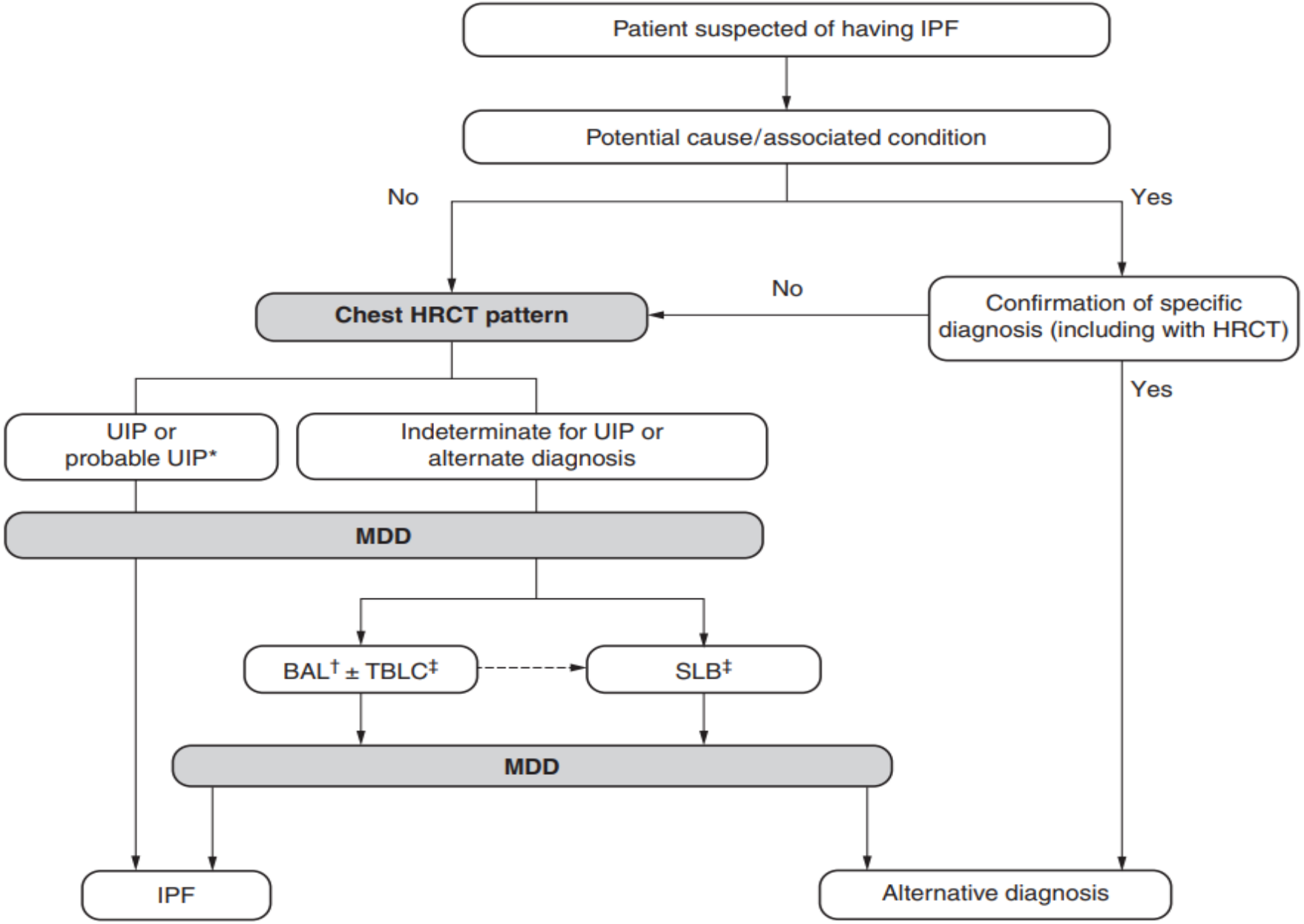
- Compared with surgical lung biopsy TBLC is more likely to demonstrate a **probable UIP pattern** than a definite UIP pattern given the limited sampling of subpleural lung
- However, it is an acceptable alternative to SLB for making a histopathological diagnosis in patients with ILD
- Conditional recommendation, very low-quality evidence

Genomic Classifier

- The available genomic classifier differentiates UIP from non-UIP pathology in transbronchial biopsies
- The test utilizes total RNA extracted from TBB samples to perform Next Generation RNA Sequencing. The gene count data from 190 genes are then input to the Envisia genomic classifier, a machine learning algorithm, to output either a UIP or non-UIP classification result
- The addition of a genomic classifier to TBLC and multidisciplinary discussion has been shown to increase diagnostic confidence in patients without a definitive UIP pattern

Genomic Classifier: Systematic Review

- Using histopathological diagnosis from samples obtained by SLB, TBLC, or MDD as the reference, the individual studies reported
  - **Sensitivity: 59% to 80%**
  - **Specificity: 78% to 100%**
- When aggregated by meta-analysis, genomic classifier testing identified the UIP pattern with sensitivity 68% and specificity of 92% in patients with ILD of unknown type
- The addition of a genomic classifier to TBLC and multidisciplinary discussion has been shown to increase diagnostic confidence in patients without a definitive UIP pattern
- 2022 Guidelines: no recommendation for or against the addition of genomic classifier testing due to insufficient agreement


Patient suspected of having IPF
Potential cause/associated condition
No
Yes
Chest HRCT pattern
No
Confirmation of specific diagnosis (including with HRCT)
Yes
UIP or probable UIP*
Indeterminate for UIP or alternate diagnosis
MDD
BAL† ± TBLC‡
SLB‡
MDD
IPF
Alternative diagnosis