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C.J. RYERSON ET AL.

Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement

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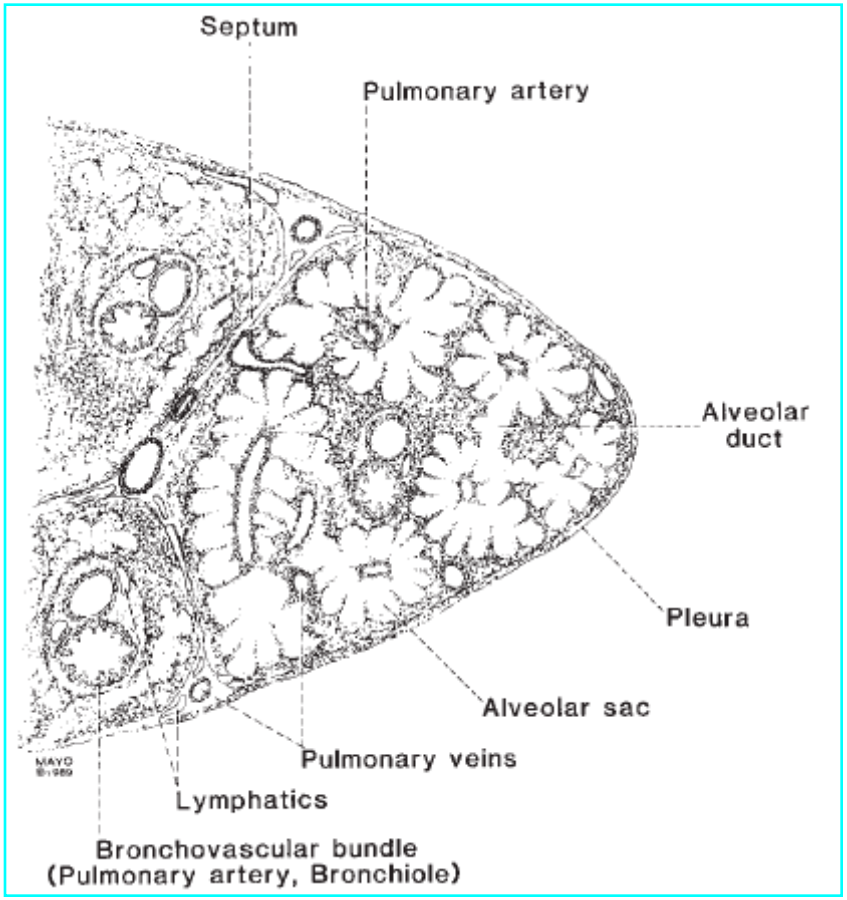
Interstitial pneumonia



Interstitium

: space between the epithelial & endothelial basement membrane

Interstitial pneumonia 유지

(interstitial lung dz)

- To maintain continuity with 2002 & 2013 documents
- To better include alveolar filling disorders (i.e. “pneumonia”)

Not addressed in this document

- pneumoconiosis, small airway dz, pul vv dz, sarcoidosis, infection, LAM, histiocytic dz

Not address Mx

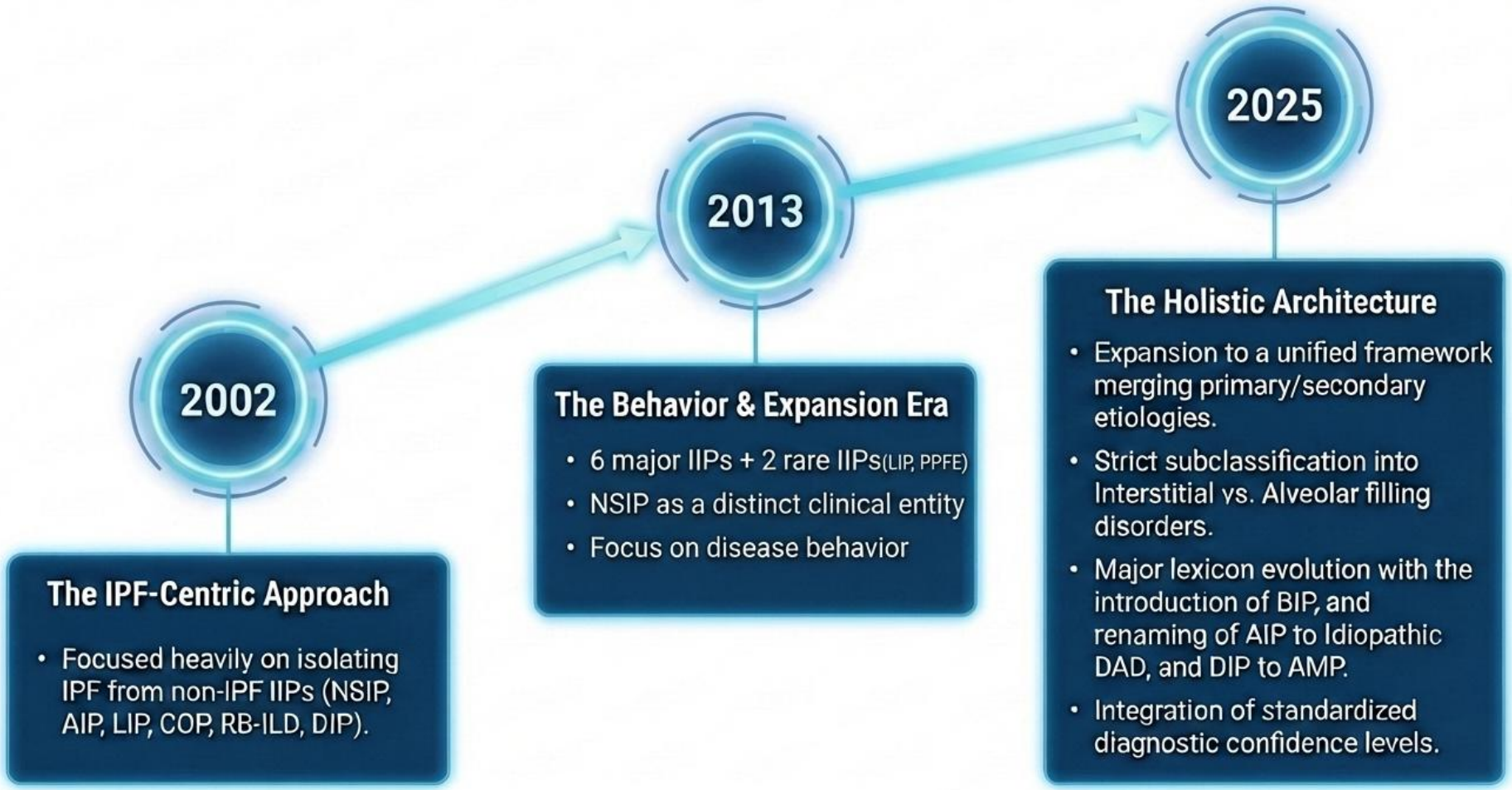
Methodology

- Committee(n=34)
  - Pulmonology(n=11) + Radiology(n=8) + Pathology (n=7) + Molecular(n= 6) + Patient representatives(n=2)
- Medical librarian(n=1)
- Ganesh Raghu, David Lynch, Martine Remy-Jardin and Jeffrey Myers requested to not be included as co-authors of the final document given the concerns that are described within the section on bronchiolocentric interstitial pneumonia(BIP).

- Not search systematically to identify literature

  Literature based on expert consensus by discussion
  - clinical experience, general clinical knowledge
  - if unclear → voting, 70% agreement necessary for consensus

Major changes in classification



Updated Terms

~~HP Pattern~~

BIP (Bronchiolocentric Interstitial Pneumonia)

Explanation: "HP" is now strictly a clinical multidisciplinary diagnosis. BIP is the underlying airway-centered morphological pattern seen on imaging/pathology.

~~AIP~~

iDAD (Idiopathic Diffuse Alveolar Damage)

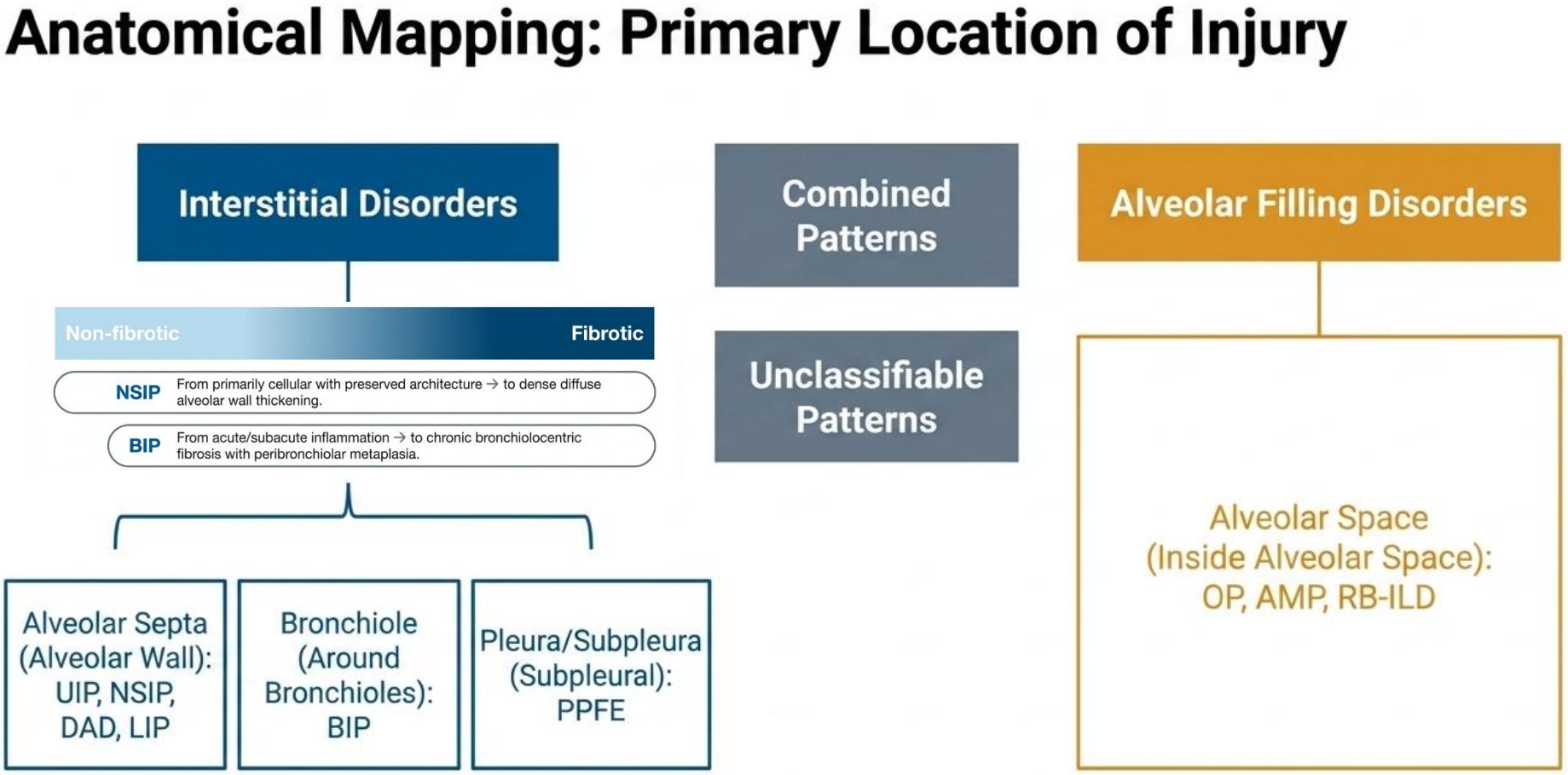
Explanation: Replaces AIP to better reflect the underlying pathology and acknowledge that other interstitial pneumonias can also present acutely.

~~DIP~~

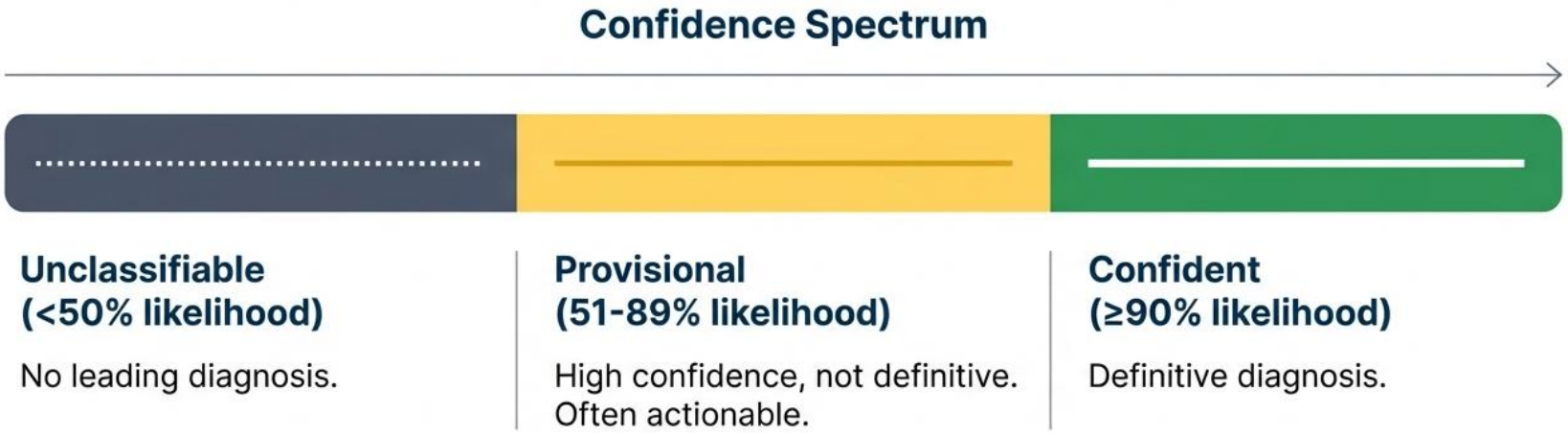
AMP (Alveolar Macrophage Pneumonia)

Explanation: Corrects a historical inaccuracy—disease is driven by excessive accumulation of macrophages, not alveolar pneumocyte "desquamation".

New classifications

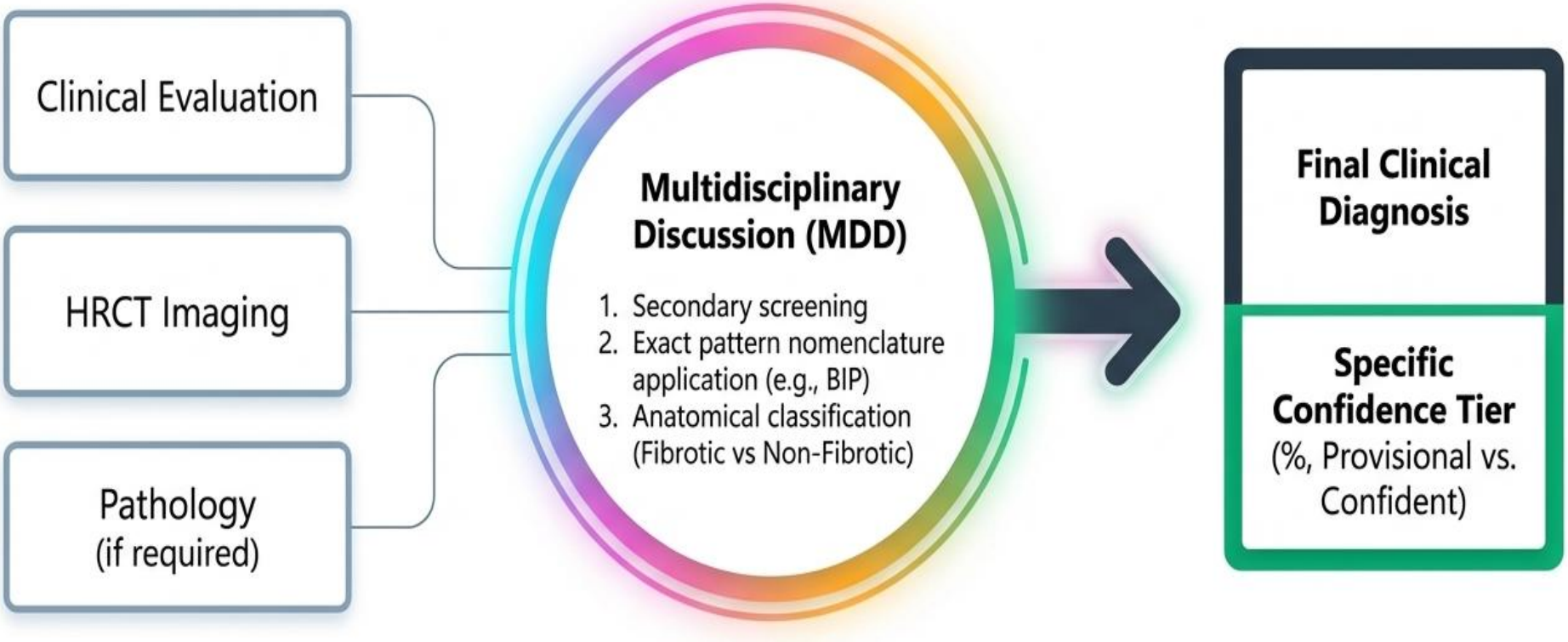


Diagnostic confidence



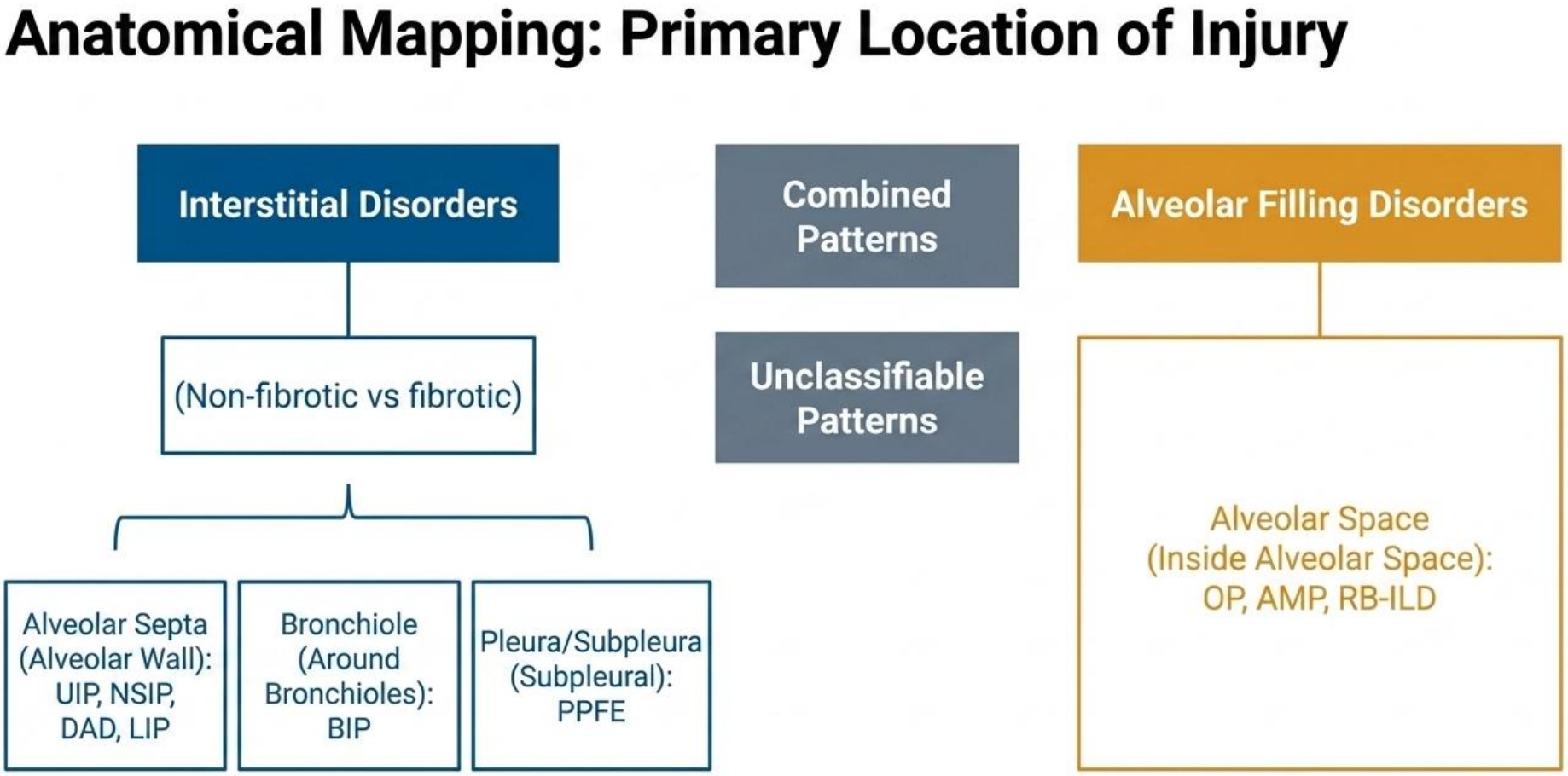
- This approach more appropriately acknowledges diagnostic uncertainty and calls attention to the need for careful reassessment of diagnoses over time!

Diagnostic approach

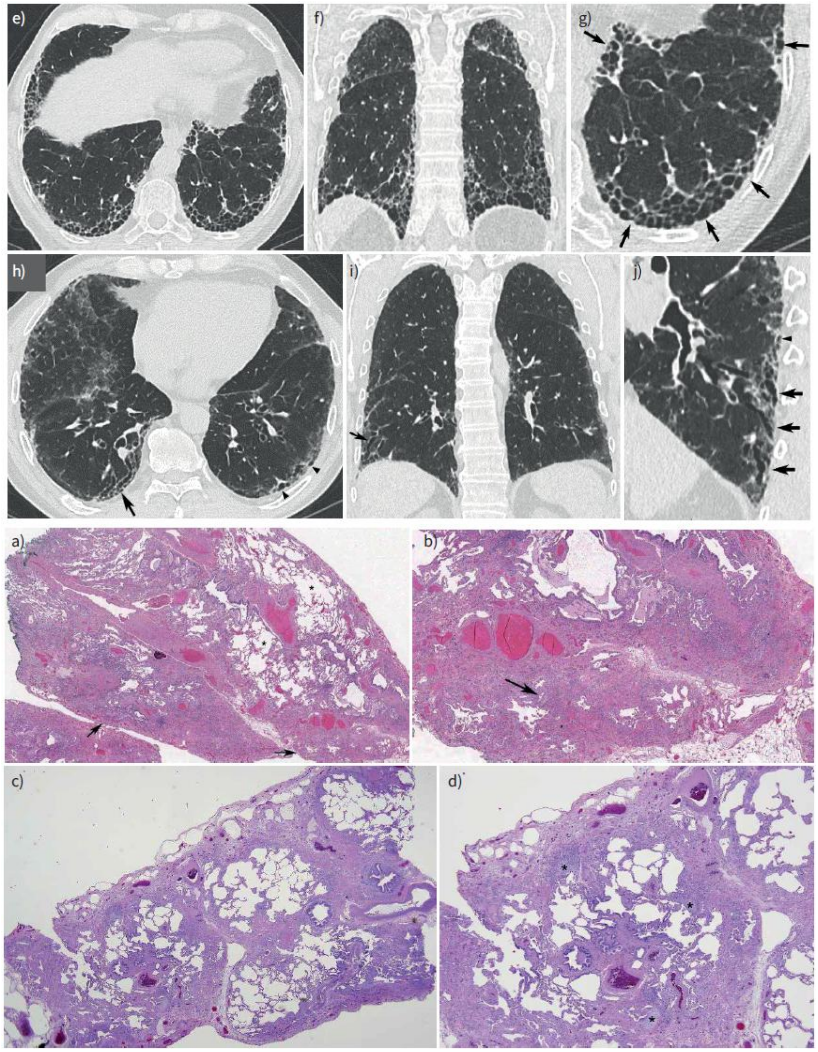


Major histopathological & radiological patterns

New classifications



Interstitial pattern 1-UIP



CT

- subpleural & basal predominant honeycombing

(-): cysts, marked mosaic attenuation, predominant GGO, nodules, consolidation

Bx

- temporal & spatial heterogeneity

subpleural & paraseptal predominant fibrosis

abrupt transition of normal to fibrotic lung

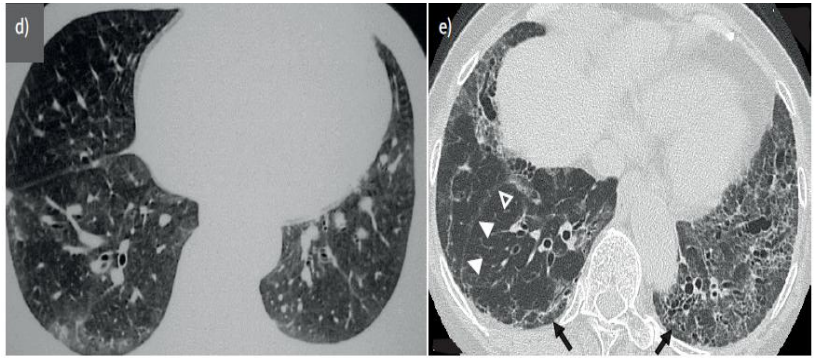
subepithelial fibroblastic foci, honeycombing

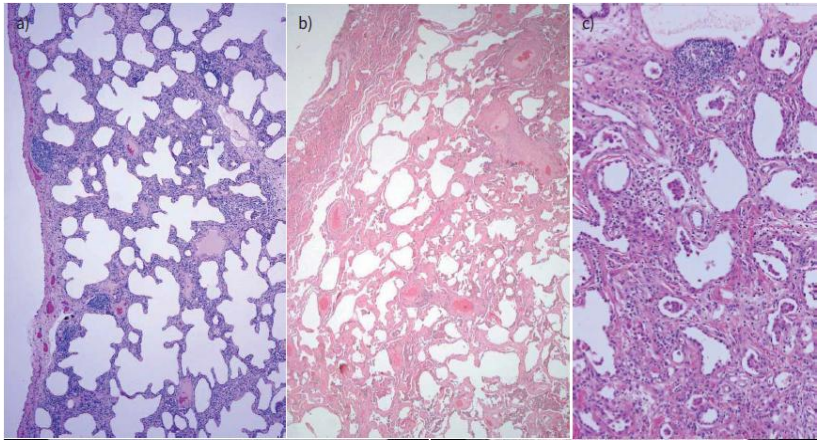
(-): predominant bronchiolocentricity, significant inflammation without fibrosis, granuloma

Interstitial pattern 1-UIP

- Primary : IPF
  Secondary : CTD-ILD, fibrotic HP, asbestosis
- Risk factors: old male c smoking Hx(IPF)
- CTD-UIP : often associated c sharply demarcated lower lobe honeycombing/ exuberant honeycombing(CT)
  prominent chronic inflammation c lymphoid aggregates containing germinal centers(Bx)
  patulous esophagus, mixed pattern(+ OP), pleuritis, pleural effusion
- HP-UIP : airway-centered abnormality (peribronchiolar granulomatous inflammation, extension of dz beyond peripheral& basal regions)

Interstitial pattern 2-NSIP





CT

- lower-lung-predominant GGO, reticulation, traction bronchiectasis

relative sparing of the subpleural lung (1/2 fibrotic NSIP)

lower lobe volume loss

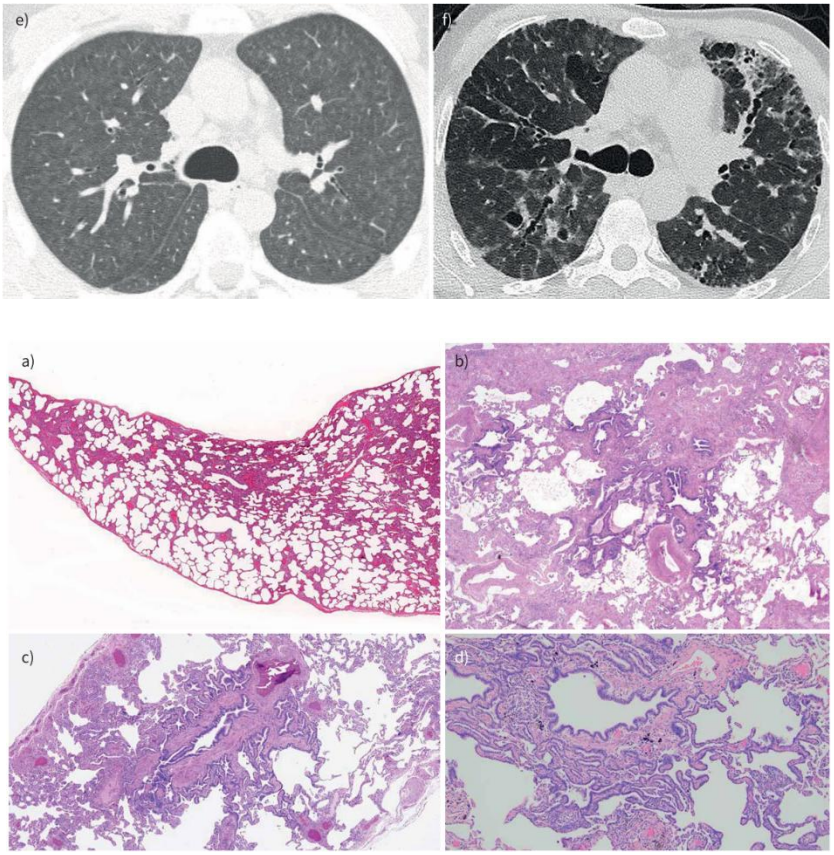
Bx

- homogeneous, uniform thickening of alveolar walls by interstitial inflammation/fibrosis

Interstitial pattern 2-NSIP

- Primary : iNSIP
  Secondary : CTD-ILD, drug toxicity, fibrotic HP, AMP, OP
- Risk factors: young females, often with a background of CTD
- Non-fibrotic(cellular) vs fibrotic pattern
- CTD/drug toxicity : OP+ NSIP
- CTD-NSIP : patulous esophagus, pleural thickening & effusion,
  prominent lymphoid follicles, plasma cell
- Bx is not indicated in typical fibrotic NSIP linked to
  CTD/medication exposure

Interstitial pattern 3-BIP



CT

- Non-fibrotic

  : profuse poorly defined centrilobular nodules,
  GGO, mosaic attenuation(3 density Sn)

- Fibrotic

  : less well characterized, GGO, reticulation,
  traction bronchiectasis, 3 density Sn,
  air trapping, peribronchovascular distribution

Bx

- Non-fibrotic(cellular)

  : Chronic Lympho-predominant inflammation
  surrounding bronchioles,
  non-necrotizing granuloma (suggestive HP)

- Fibrotic

  : bronchiolocentric fibrosis, peribronchiolar metaplasia

Interstitial pattern 3-BIP

- The term of BIP was originally proposed as a type of IP in 1969.
  Predominantly airway-centered IP ≈ HP
  (The term "HP" is used only to describe the Dx of HP, not pattern)

Table 6. Chest HRCT Scan Features of the Fibrotic HP Pattern

HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The "typical HP" pattern is suggestive of a diagnosis of HP. It requires *a*) an HRCT pattern of lung fibrosis (as listed below) in one of the distributions and *b*) at least one abnormality that is indicative of small airway disease	"Compatible-with-HP" patterns exist when the HRCT pattern and/or distribution of lung fibrosis varies from that of the typical HP pattern; the variant fibrosis should be accompanied by signs of small airway disease	The "indeterminate-for-HP" pattern exists when the HRCT is neither suggestive nor compatible with a typical and probable HP pattern

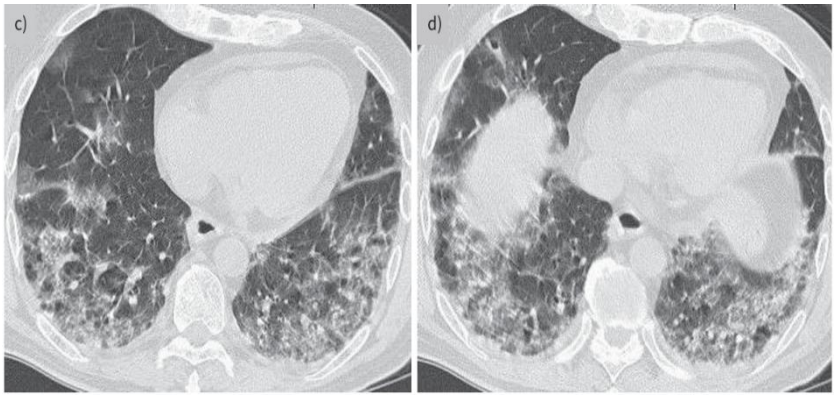
- Primary :iBIP (provisional)
  Secondary : HP, CTD-ILD, aspiration, inhalation, medication
  (e.g. "BIP pattern, strongly favor HP")

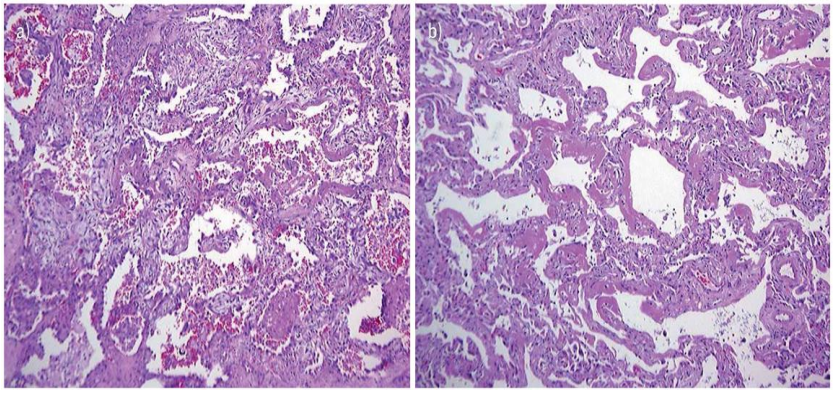
- Risk factors: no clear age or sex predilection

Interstitial pattern 3-BIP

- 4 members(committee) request not to be included as co-authors
  - 3 main concerns
    1) confusion c “typical HP pattern” (HP guidelines)
    2) HP could be diagnosed without definite etiological exposure
       → idiopathic BIP “should” remain a provisional
       and not be used a confident Dx of HP or another etiology.
    3) A need for more evidence / greater uptake of this term
       in the literature prior to it being suggested in this document
       and adopted in clinical practice
       ➔ need for a workshop to further study BIP,
       similar to the 2008 report on NSIP

Interstitial pattern 4-DAD





CT

- GGO (bilateral, patchy),
  consolidation(most dependent),
  traction bronchiectasis/bronchiolectasis

Bx

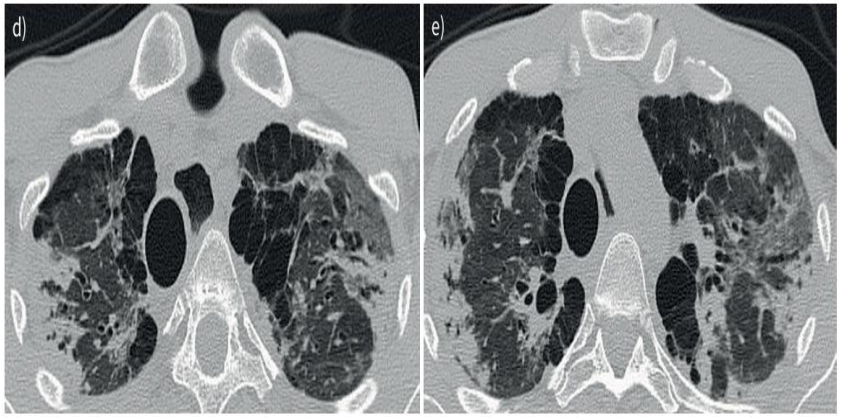
- thickened alveolar septa by interstitial edema,
  pneumocyte hyperplasia,
  surface hyaline membrane

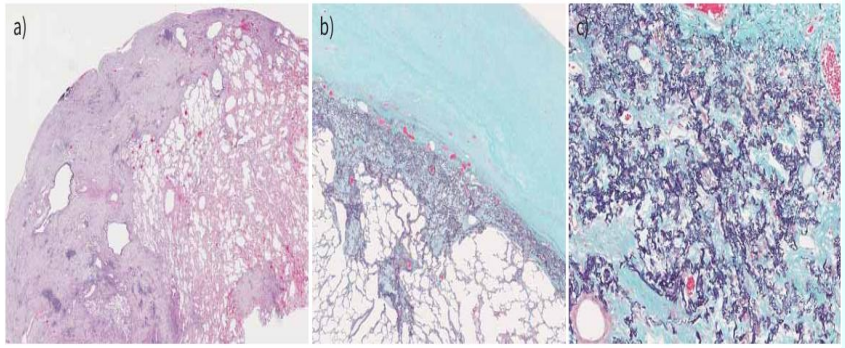
➔ loose connective tissue within alveolar wall

Interstitial pattern 4-DAD

- AIP → idiopathic DAD
  (d/t other IP can present acutely, most cases of AE of IP)
- Risk factors: vary with underlying etiology
  (e.g. sepsis, aspiration, pneumonia, CTD-ILD)
- Acute/subacute respiratory distress, high mortality
- Sometimes reversible
  irreversible fibrosis (61% of 23 pt of duration>3 wk
  24% of 54 pt of duration 1-3 wk)

Interstitial pattern 5-PPFE





CT

- biapical subpleural parenchymal fibrosis

  pleural thickening

  sharply demarcated dense consolidation,

  traction bronchiectasis, architectural distortion,

  reticulation in a subpleural distribution

- differentiated from apical caps

  1) upper lobe volume loss

  2) involvement of ant, post upper lobes,

  major fissure, middle/lober lobe

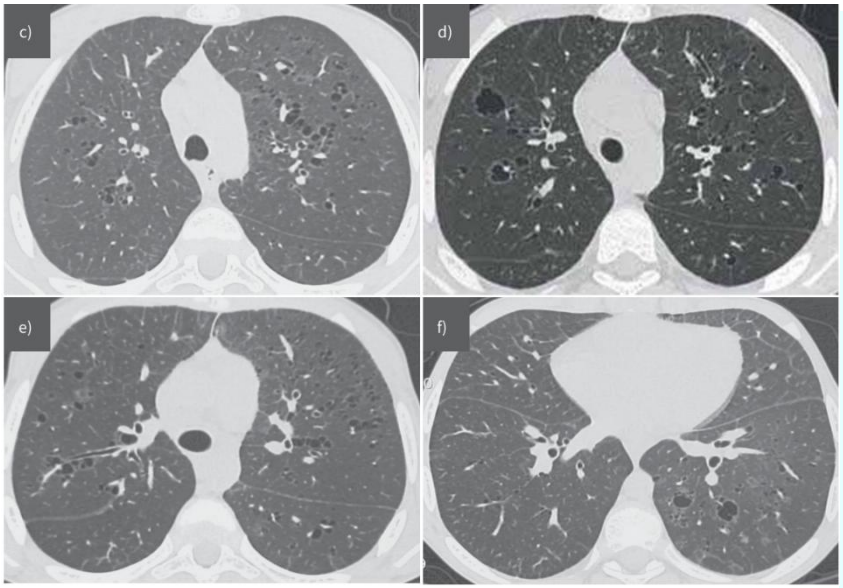
Bx

- subpleural intra-alveolar fibroelastosis,

  pleural fibrosis, marked subpleural thickening

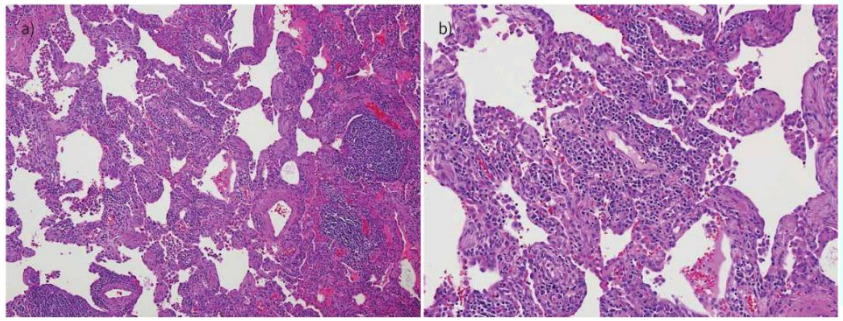
  associated with abundance of elastic fiber

Interstitial pattern 6-LIP



CT

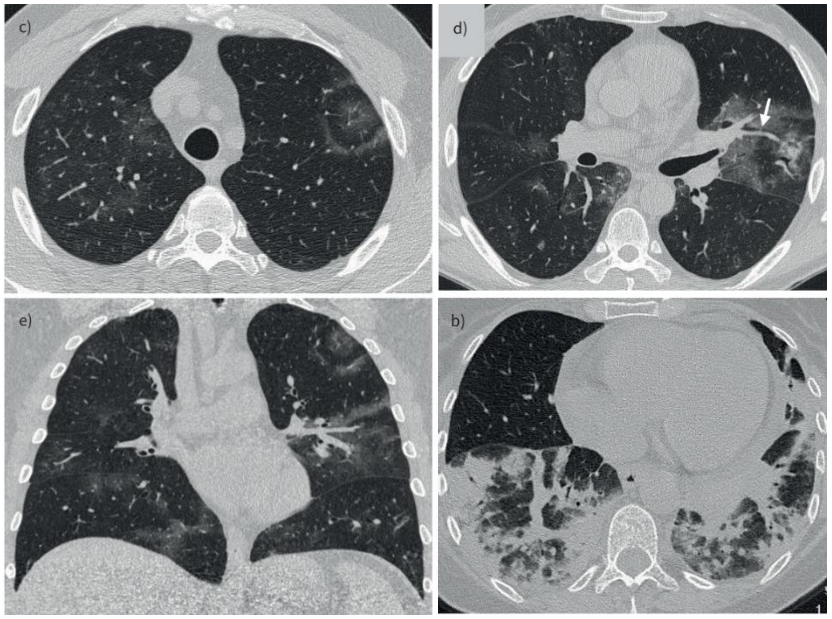
- bilateral GGO, diffuse,
  small centrilobular / subpleural nodules,
  bronchovascular thickening,
  randomly distributed thin-walled cysts

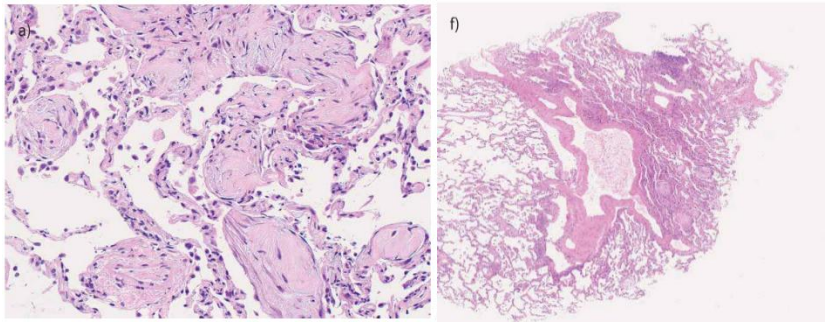


Bx

- dense diffuse infiltrate of lymphocytes, plama cells expanding and distorting the alveolar septa, lymphoid follicles, absent interstitial fibrosis

Alveolar filling pattern 1-OP





CT

- subpleural /peribronchial consolidation, GGO

  focal mass/nodules c an air-space pattern

  reverse halo, peribronchial thickening

  migratory on serial imaging

Bx

-polypoid plugs of loose fibroblastic connective

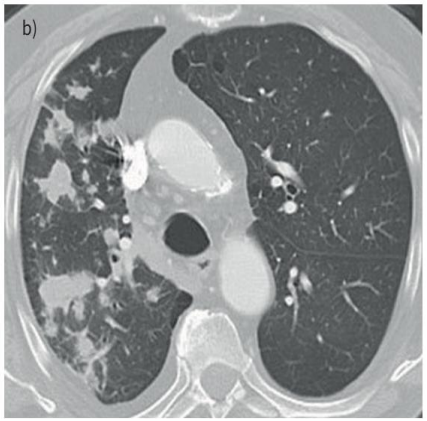
  tissue within the alveoli and alveolar ducts

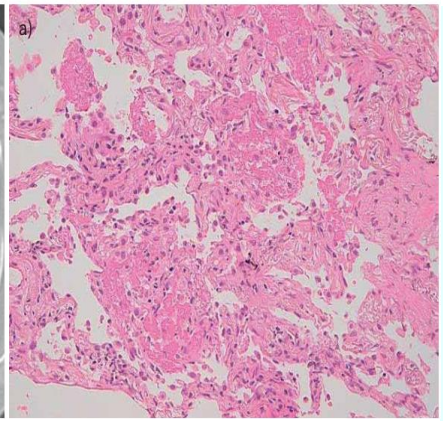
  patchy distribution, preserved lung architecture

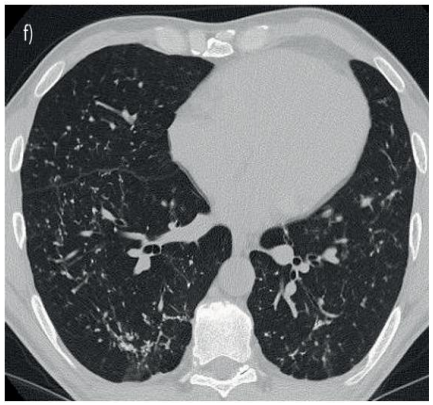
Alveolar filling pattern 1-OP

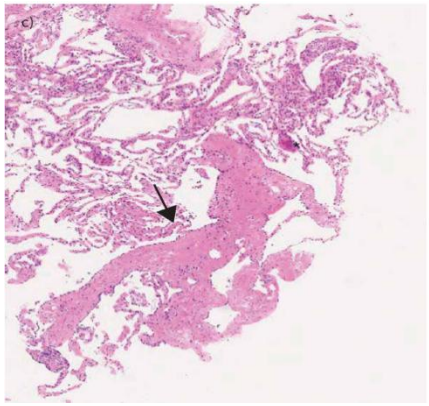
- Primary : cryptogenic
  Secondary : post-infectious, CTD, drug-induced
- Risk factors: no clear age or sex predilection for COP
  vary with underlying etiology for 2ndary OP
- BAL: lymphocytosis
- Sometimes complete response to steroid
  High potential for recurrence

Alveolar filling pattern 1-OP









AFOP

(Acute fibrinous and organizing pneumonia)

- manifestations raging from OP to DAD

patchy mass like lesions/GGO(CT)

intra-alveolar fibrin foaming balls(Bx)

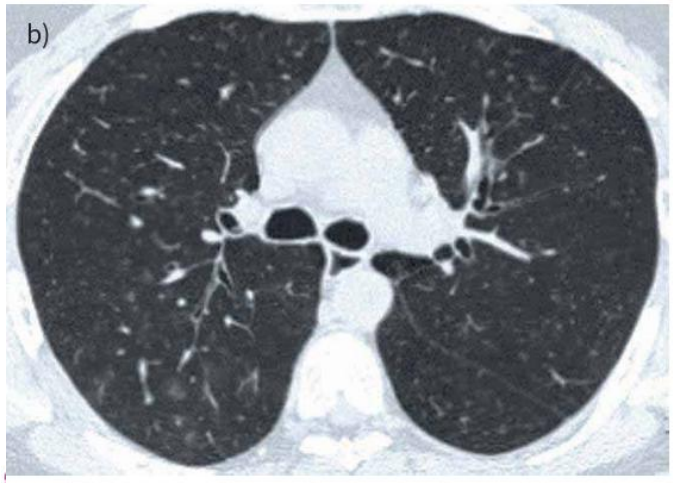
CiOP (Cicatrical organizing pneumonia)

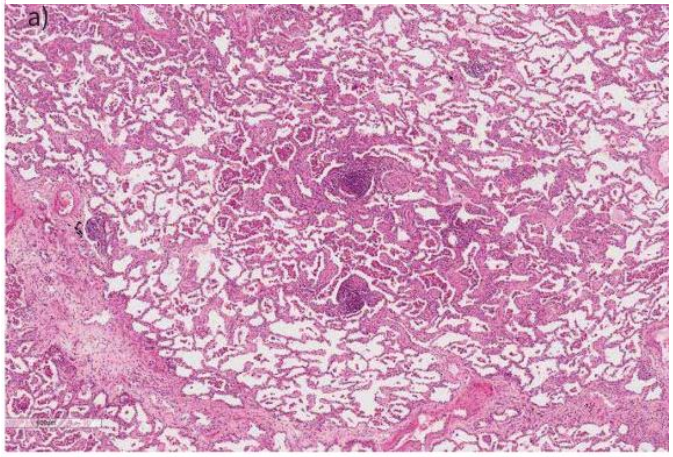
-polypoid plugs comprise dense established fibrous tissue,

dendriform ossification, perilobular distribution

dense fibrous bands, nodules(Bx)

Alveolar filling pattern 2-RBILD





CT

- patchy, poorly defined GGO,
  centrilobular distribution

Bx

-fibrosis is patchy, subpleural and within alveolar walls

temporally homogenous, pauci-cellular, dense & eosinophilic collagen causing alveolar wall thickening

bronchiolocentric distribution

clusters of lightly pigmented macrophges

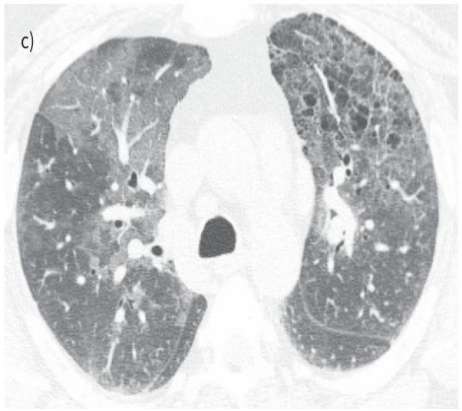
Alveolar filling pattern 2-RBILD

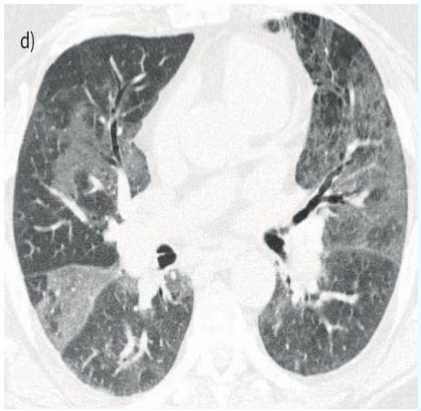
- Excessive accumulation of macrophages in alveoli, predominant features of bronchiolitis
- Primary : idiopathic
  Secondary : smoking related
- Risk factors: adult smokers, slight male predominance
- BAL: pigmented macrophages
- Smoking-related ILD

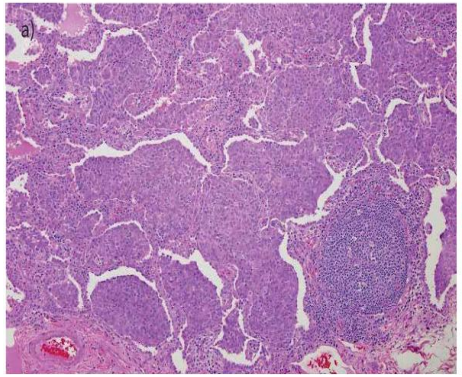
  (SR-ILD, airspace enlargement with fibrosis(AEF), smoking-related interstitial fibrosis(SRIF))

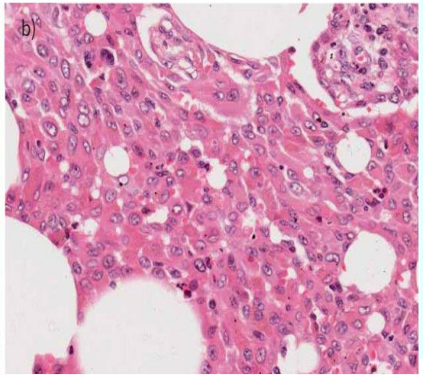
  : an umbrella term for being caused by exposure to cigarette smoke

Alveolar filling pattern 3-AMP









CT

-GGO,

mid & lower lobe, peripheral predilection

fine reticulation

rarely centrilobular nodules

Bx

- excessive of alveolar macrophages filling alveoli

diffuse, uniform distribution within airspace

alveolar walls may be fibrotic, variably inflamed,

including eosinophils, lymphoid aggregates

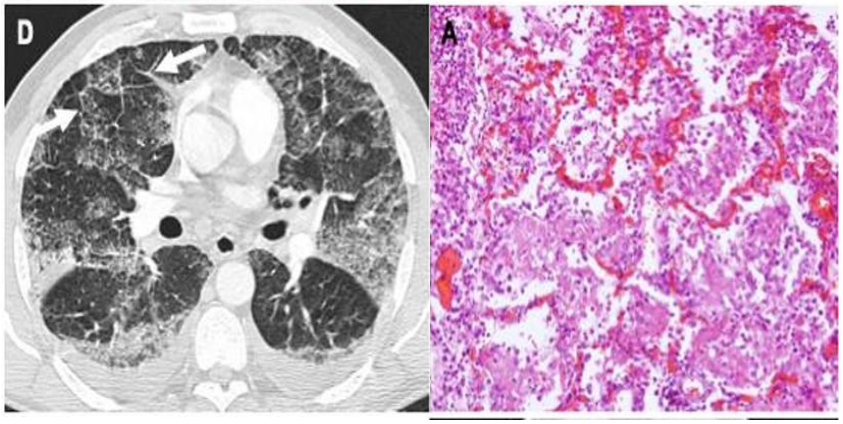
Alveolar filling pattern 3-AMP

- DIP → AMP(alveolar macrophage pneumonia)
  excessive widespread accumulation of macrophages with alveoli

- Primary : idiopathic
  Secondary : smoking, CTD, occupational dust inhalation,
  surfactant-protein dz (children)

- Risk factors: adult smokers, slight male predominance
  rare cases have been reported in nonsmokers

Alveolar filling pattern 4-Rare



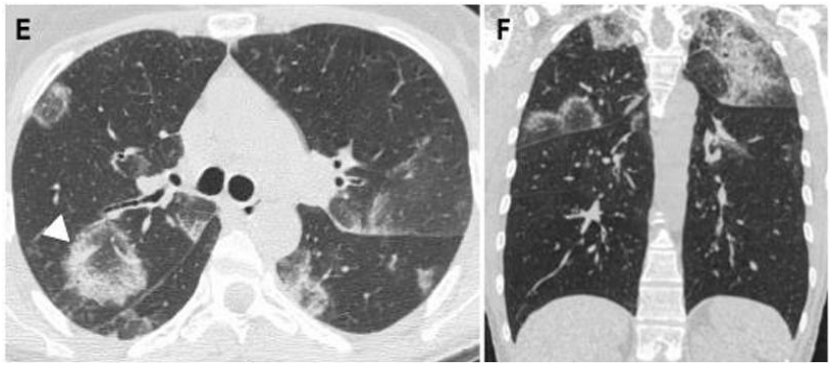
AEP:

- Variable craniocaudal/ axial distribution

  GGO/ consolidation with interlobular septal & bronchovascular thickening

  Pleural effusions, ill-defined centrilobular nodules

- DAD ± OP pattern, eosinophilic infiltrates (Bx)



CEP:

- Peripheral, middle or upper lung predominance

  Non-segmental consolidation, GGO

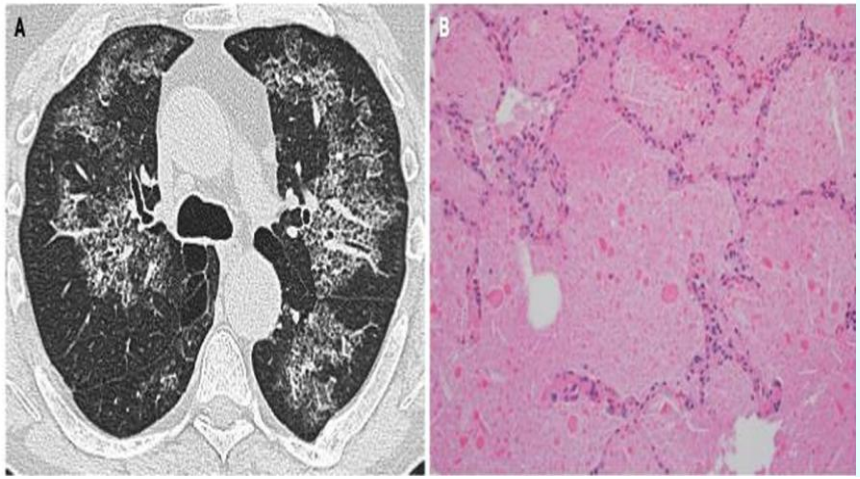
  centrilobular nodules, septal thickening, LAPs

  reticulation, traction bronchiectasis

- Scattered non-necrotizing granulomas,

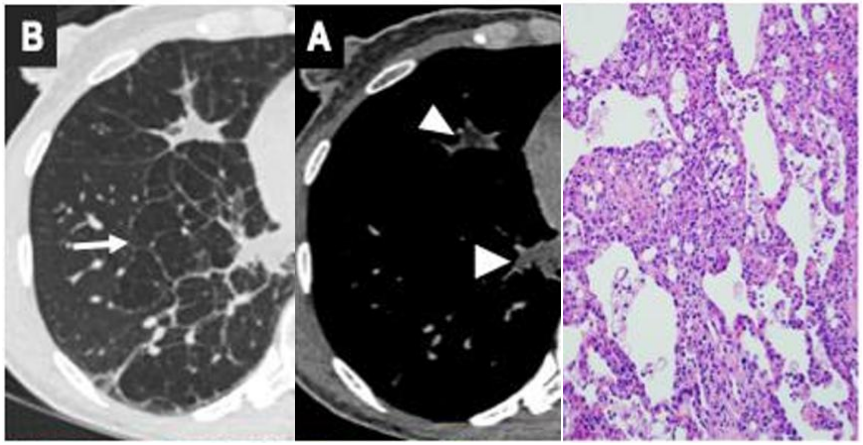
  necrotic eosinophilic microabscess (Bx)

Alveolar filling pattern 4-Rare



PAP:

- Central lung ground glass opacities with smooth interlobular and intralobular septal thickening in a crazy paving pattern
  relative apical and costophrenic angle sparing
- Diffuse or patchy intra-alveolar accumulation of acellular granular proteinaceous debris



LP:

- GGO, consolidation(dependent portions), irregular mass-like lesions, centrilobular nodules, low attenuation (negative HU values) within consolidated areas(reflecting fat content), crazy-paving pattern

-lipid-laden macrophages within alveoli, interstitium

Combined pattern

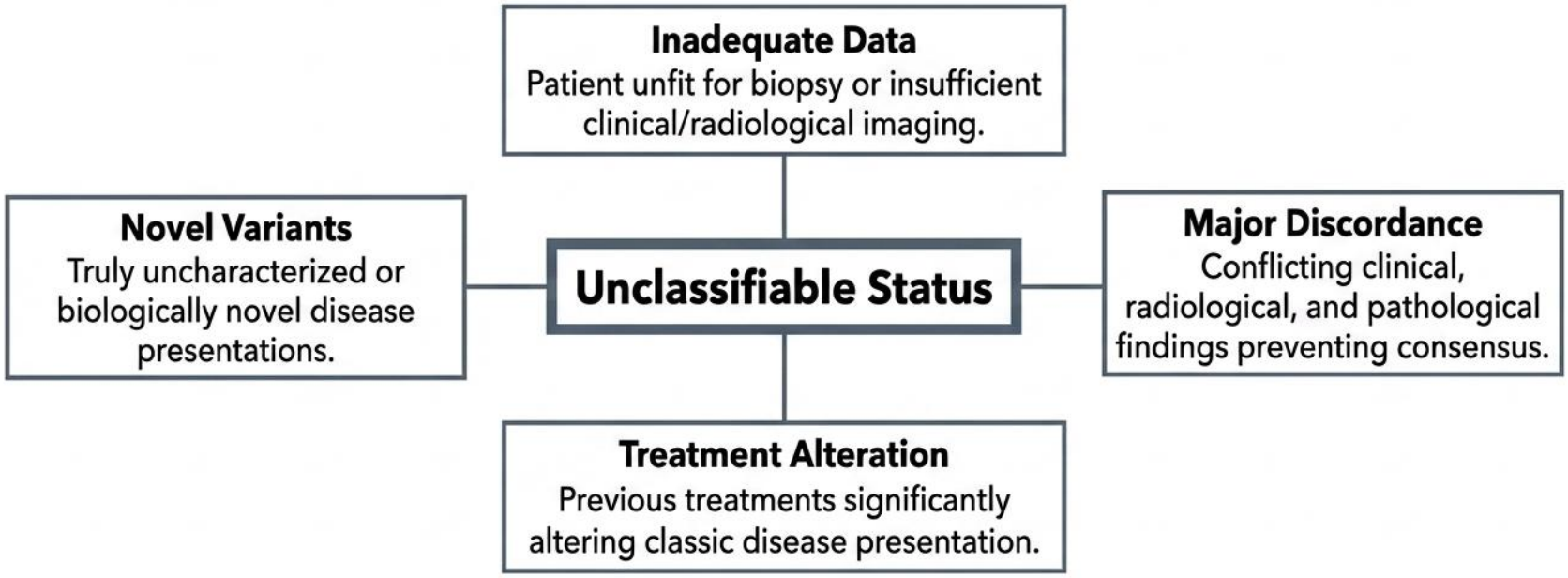
TABLE 4 Common combined radiological-histological patterns and key clinical differential diagnoses

Dominant and coexisting patterns[#]	Common differential diagnoses
UIP	
NSIP	IPF, CTD-ILD, HP
BIP	HP, CTD-ILD, coexistent airway injury of other cause
PPFE	Combined IPF and PPFE, CTD-ILD
DAD	Acute exacerbation of IPF or other secondary UIP (*e.g.* CTD-ILD)
AMP	IPF + smoking-related ILD
NSIP	
UIP	IPF, CTD-ILD, HP
Organising pneumonia	CTD-ILD, post-DAD, inhalation injury, HP, drug reaction
BIP	HP, CTD-ILD
LIP	CTD-ILD, drug-induced, post-viral (HIV, EBV)
PPFE	Idiopathic PPFE, CTD-ILD
BIP	
Organising pneumonia	CTD-ILD, HP
UIP	HP
NSIP	HP, CTD-ILD
LIP	CTD-ILD
PPFE	Idiopathic PPFE
Organising pneumonia	
NSIP	Post-infection, CTD-ILD, inhalation injury, HP, drug reaction
UIP	CTD-ILD, acute exacerbation of IPF
BIP	HP, CTD-ILD

Unclassifiable ILD

- Prevalence: 11.9% overall, 9.5% after MDD

➔ Inability to provide a specific Dx with > 50% confidence after MDD



Molecular Advances

TABLE 5 Molecular biomarkers in interstitial pneumonia

	Pathophysiology	Clinical accessibility	Clinical value		
			Diagnostic	Prognostic	Therapeutic
Genetic					
MUC5B rs35705950	Risk allele linked to increased pulmonary fibrosis susceptibility, but slower progression rate	Variably accessible	Unclear	Unclear	Unclear
Telomere-related genes (*TERT, TERC, RTEL1, PARN, DKC1, NAF1, ZCCHC8*)	Telomere-related gene variants linked to increased pulmonary fibrosis risk and rapid disease progression	Variably accessible	Potential value	Potential value	Unclear
Surfactant-related genes (*SFTPC, SFTPA1, SFTPA2*)	SRG variants linked to increased pulmonary fibrosis risk and to lung cancer	Variably accessible	Potential value	Unclear	Unclear
Other gene loci (including *DSP, KIF15, HLA-DRB1*)	Polymorphisms in these genes linked to increased pulmonary fibrosis risk	Variably accessible	Unclear	Unclear	Unclear
Short telomeres/telomeropathies					
Leukocyte telomere length	Leukocyte telomere length attrition associated with increased ILD susceptibility and rapid progression rate	Variably accessible	Potential value	Potential value	Emerging value in guiding post-lung transplant and ILD pharmacotherapy
Short telomere syndromes (including dyskeratosis congenita, Hoyeraal–Hreidarsson syndrome)	Clinical manifestation often at younger age, show Mendelian inheritance, have multiorgan involvement	Accessible	Potential value	Unclear	Unclear
Transcriptomic RNA signatures					
Lung biopsy-based Envisia Genomic Classifier	Integrates gene expression profiling with machine learning algorithms to recognise the genomic signature of a UIP pattern	Accessible in North America and Europe	Strengthens UIP diagnosis, but clinical utility unproven	Unclear	Unclear
Peripheral blood-based 52-gene RNA signature	Specific set of 52 genes whose combined expression pattern is indicative of IPF	Unclear	Unclear	Unclear	Unclear

Molecular Advances

Serum/plasma-based antibody panels					
Autoimmune serology (including ANA, dsDNA, anti-Sm, ACA, anti-Scl-70, anti-RNA polymerase III, anti-Jo-1, anti-MDA5, RF, anti-CCP, SS-A, SS-B, anti-RNP, ANCA, anti-U1 RNP, anti-PL-12 and anti-PL-7, anti-GM-CSF)	Identify the presence of discrete autoantibodies that target protein, nuclear or other cellular components which aid the diagnosis of specific autoimmune diseases	Accessible	Strengthens diagnosis of specific subtypes of CTD-ILD	Potential value	May guide choice of therapy
HP	Serum IgG testing against HP-associated antigens. Suboptimal sensitivity and specificity	Accessible	Positive test may support HP exposure	Unclear	Unclear
Other serum-/plasma-based protein markers					
Proteomics/specific proteins (including MMP-7, CCL18, SP-D, CA-125, CA19-9, KL-6, MMP-1, MMP-8, TGF-β, PDGF)	Tissue-derived glycoproteins, enzymes, and protein signatures linked to various pulmonary processes including innate immunity, tissue remodelling, extracellular matrix turnover and fibrosis	Variably accessible	Unclear	Unclear	Unclear
Inflammatory/immunological markers (CRP, ESR)	Acute-phase protein and proinflammatory markers that play pivotal roles in immune, autoimmune and inflammatory disorders	Globally accessible	Positive markers may support specific interstitial pneumonia diagnoses	Extent of positivity may predict outcomes (*e.g.* CRP)	May guide therapeutic response

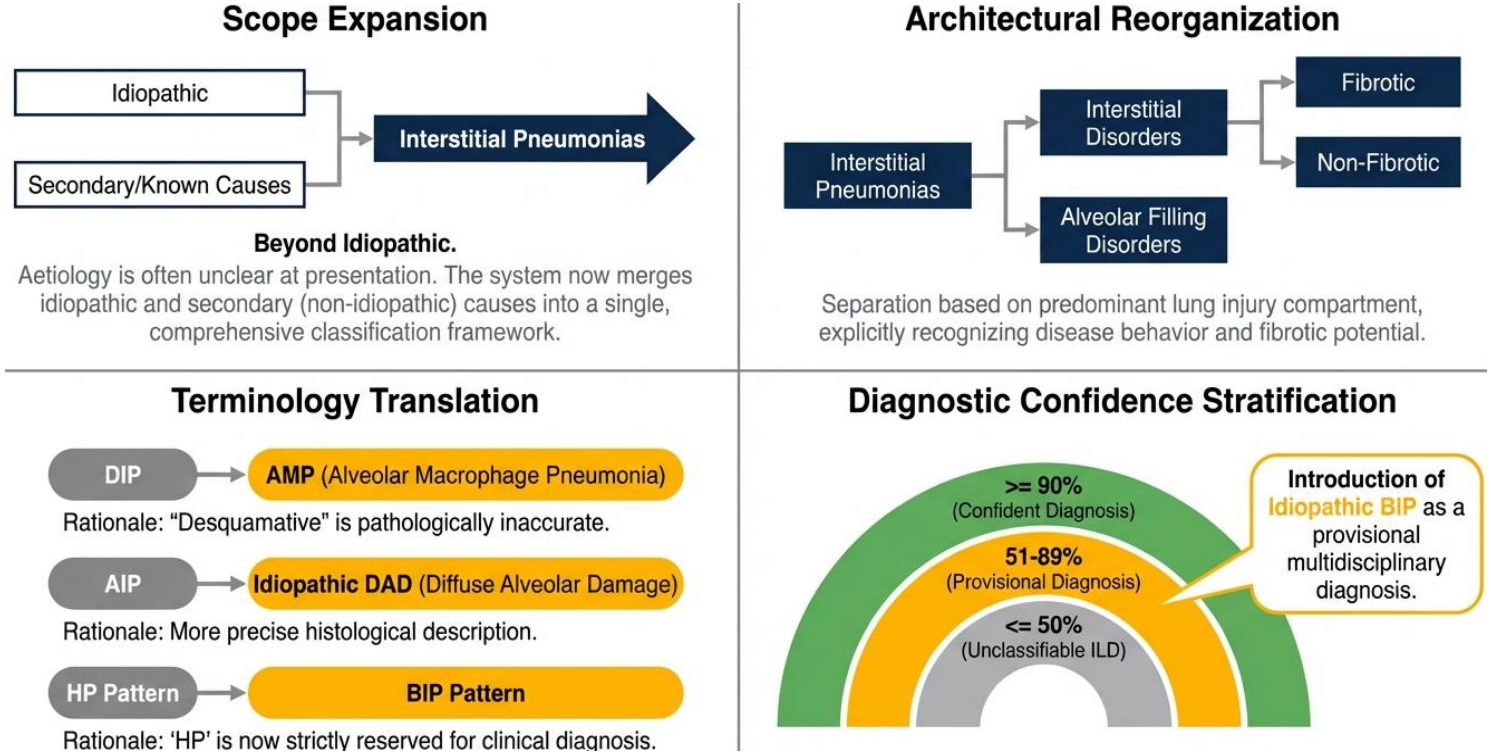
Research priorities

BOX 15 Overarching research priorities for all interstitial pneumonias

- Does photon-counting CT provide superior diagnostic information compared to HRCT?
- What is the role of artificial intelligence in the interpretation of existing diagnostic tools?
- What is the role of genetic testing?
- What molecular tests inform diagnosis, management, and prognosis?
- What is the diagnostic utility of optical coherence tomography?
- In what clinical settings is lung tissue sampling indicated?
- Are targeted interventions available for specific populations?
- What variables predict more rapid progression/relapse?

Summary

- 4 Major advances to the classification of interstitial pneumonia



- Update on the status of potential molecular tools and identified future research priorities

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