The Evolving Role of Pathologists in Diagnosis and Classification of Idiopathic Interstitial Pneumonias

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Unpaid scientific collaborator & advisor with Veracyte, Inc.
Diffuse Parenchymal Lung Diseases

- DPLD of known cause or association
  *(eg, drugs, CTD, occupational/environmental)*

- Other radiologically distinct DPLDs
  *(eg, LCH, LAM)*

- Granulomatous DPLD
  *(eg, HP, sarcoidosis)*

- Idiopathic interstitial pneumonias
Diffuse Parenchymal Lung Diseases

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Idiopathic interstitial pneumonias

Clinical & radiology

Pathology
# Idiopathic Interstitial Pneumonias

## Pathology Based Classification – 2016

<table>
<thead>
<tr>
<th>CPR Diagnosis</th>
<th>Morphologic “Pattern”</th>
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†Travis et al. Am J Resp Crit Care Med 2013; 188: 733
### Idiopathic Interstitial Pneumonias

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†Travis et al. Am J Resp Crit Care Med 2013; 188: 733
Idiopathic Interstitial Pneumonias - Myers

Evidence Based Guidelines for Diagnosis & Management†

“a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring in older adults, limited to the lungs, and associated with the **histopathologic** and/or **radiologic** pattern of UIP”

Usual Interstitial Pneumonia (UIP)
Histologic Criteria

• fibrosis
• heterogeneity (variegated pattern)
  – geographic heterogeneity
  – temporal heterogeneity
Idiopathic Interstitial Pneumonias - Myers

temporal heterogeneity

acute

chronic

fibroblast focus
Idiopathic Interstitial Pneumonias - Myers

Multiple microscopic foci of injury occurring over time

Focal fibroblast proliferation (fibroblast foci)

Alveolar collapse, collagen deposition, architectural distortion

Progressive clinical course

Death

Recurrent microscopic injury

Fibroblast Foci & The Pathogenesis of UIP
Fibroblastic Foci: Time To Be Counted?
Roland M. du Bois
Chest 2006;130;3-5

“there emerged a series of publications that explored the relationship between the number of fibroblast foci and individual outcome”
### Usual Interstitial Pneumonia (UIP) Fibroblast Foci as Prognostic Biomarker?

<table>
<thead>
<tr>
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<td>NO</td>
<td>NS</td>
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<tr>
<td>Hanak 2008</td>
<td>43</td>
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*includes patients with CTD
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Profusion of fibroblast foci has no established value as prognostic biomarker.

*includes patients with CTD
Usual Interstitial Pneumonia (UIP)
Histologic Criteria

- fibrosis
- heterogeneity (variegated pattern)
  - geographic heterogeneity
  - temporal heterogeneity
- architectural distortion
  - honeycomb change
  - fibrotic scarring
Usual Interstitial Pneumonia

Peripheral Honeycomb Change
Usual Interstitial Pneumonia (UIP) Histologic Criteria

- fibrosis
- heterogeneity (variegated pattern)
  - geographic heterogeneity
  - temporal heterogeneity
- architectural distortion
  - honeycomb change
  - fibrotic scarring
- peripheral/subpleural accentuation
Idiopathic Interstitial Pneumonias - Myers

- Geographic heterogeneity
- Temporal heterogeneity
- Architectural distortion
- Peripheral distribution

fibroblast foci
Idiopathic Interstitial Pneumonias - Myers

"a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP”

Usual Interstitial Pneumonia (UIP)/IPF
Radiological Findings

- subpleural, basilar
- reticulations
- honeycombing ± traction br’ectasis
- minimal ground glass
### Honeycombing in UIP

Histopathology ≠ Radiology†

<table>
<thead>
<tr>
<th>Microscopic Honeycombing</th>
<th>Absent</th>
<th>Rare</th>
<th>Present</th>
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<tbody>
<tr>
<td>None</td>
<td>8</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>Probable</td>
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<td>2</td>
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<td>8</td>
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**CT/SLBx concordance**

<table>
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<tr>
<th></th>
<th>50%</th>
<th>49%</th>
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†Chung et al. *CT scan findings of probable usual interstitial pneumonitis have a high predictive value for histologic usual interstitial pneumonitis.* CHEST 2015; 147: 450
Usual Interstitial Pneumonia (UIP)/IPF Survival After Diagnosis†

Survival (%)

Years following diagnosis

mean age ≈ 58 years
M:F ≤ 2:1

Bjoraker et al.: AJRCCM 1998
"Nonspecific interstitial pneumonia must be separated from the three main forms of idiopathic interstitial pneumonia because of better prognosis and different treatment options."

"Sixty-four cases of interstitial pneumonia were identified that could not be classified into one of the three main categories of idiopathic interstitial pneumonia."
“It should not be considered a specific disease, however, because it may have varying etiologies . . .; less often it may reflect a nonrepresentative biopsy of another process.”
**Nonspecific Interstitial Pneumonia**

**Histologic Criteria**

- chronic interstitial pneumonia
  - with (“fibrotic NSIP”) or without (“cellular NSIP”) fibrosis
- *temporally uniform* without architectural distortion
- lacking other features (e.g. granulomas, pigmented [“smoker’s”] alveolar histiocytes) to allow more specific classification

"cellular" NSIP
"fibrotic" NSIP
“fibrotic” NSIP
Idiopathic Interstitial Pneumonias - Myers
Idiopathic Interstitial Pneumonias - Myers

NSIP
The final diagnosis in the 67 [of 193] cases was established when,

• the surgical lung biopsy showed a NSIP pattern (cellular or fibrosing);

• the HRCT showed a pattern consistent with NSIP and not diagnostic of other entities such as UIP or chronic hypersensitivity pneumonitis; and

• there were no clinical features of another chronic ILD, such as collagen vascular disease, drug, or inhaled antigen exposure at the time of diagnosis.

†Travis et al. Am J Resp Crit Care Med 2008; 177: 1338
The final diagnosis in the 67 [of 193] cases was established when,

- the surgical lung biopsy showed a NSIP pattern (cellular or fibrosing);

**key learning point**

SLBx necessary but insufficient for diagnosis of NSIP

†Travis et al. Am J Resp Crit Care Med 2008; 177: 1338
Idiopathic Nonspecific Interstitial Pneumonia

Definition†

The final diagnosis in the 67 [of 193] cases was established when,

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Histopathologic Variability in UIP/IPF†

109 patients with UIP or NSIP who underwent biopsy of ≥ 2 lobes

- **concordant** UIP (UIP + UIP) 51
- **NSIP** (NSIP + NSIP) 30
- **discordant** UIP (UIP + NSIP) 28

†Flaherty et al. Am J Respir Crit Care Med 2001; 164: 1722
Histopathologic Variability in UIP/IPF†

Cumulative proportion surviving

Years

0 1 2 3 4 5 6 7 8 9

NSIP

Discordant UIP

Concordant UIP

†Flaherty et al. Am J Respir Crit Care Med 2001; 164: 1722
Idiopathic Interstitial Pneumonias - Myers

Histopathologic Variability in UIP/IPF

- **Flaherty et al. 2001**
  - UIP is a specific diagnosis that defines natural history

- **Monaghan et al. 2004**
  - **key learning point**
  - SLBx necessary but insufficient for diagnosis of NSIP

Cumulative Proportion Surviving

- concordant NSIP
- discordant UIP
- concordant UIP

Percentage survival

- concordant NSIP
- discordant UIP
- concordant UIP

Time (years)

Time (months)

- concordant UIP (n=25)
- discordant UIP-NSIP (n=8)
- concordant NSIP (n=31)
“our CRP consensus review revealed diagnoses of hypersensitivity pneumonitis, organizing pneumonia, and UIP in cases in which lung biopsies showed a definite or probable NSIP pattern.”

†Travis et al. Am J Resp Crit Care Med 2008; 177: 1338
Idiopathic Interstitial Pneumonias

Idiopathic Nonspecific Interstitial Pneumonias
Diagnosis of Exclusion

NSIP ‘94

- UIP
- HP
- late/persistent/resolving DAD
- fibrotic/“healed” LCH
- non-diagnostic/non-classifiable lesions
- SRIF?

NSIP ‘16

Multidisciplinary review

? systemic CVD?
Idiopathic Nonspecific Interstitial Pneumonia
Clinical Features†

women > men (2:1)
mean age 52 yrs
69% never smokers

5 yrs – 82.3%
10 yrs – 73.2%

N = 67

†Travis et al. Am J Resp Crit Care Med 2008; 177: 1338
### Usual Interstitial Pneumonia/IPF
Role of HRCT in Separating from NSIP†

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<tbody>
<tr>
<td>UIP*</td>
<td>UIP</td>
<td>27</td>
<td>0</td>
<td>27</td>
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<tr>
<td></td>
<td>NSIP</td>
<td></td>
<td></td>
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<tr>
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<td>Total</td>
<td>27</td>
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*includes “definite” and “probable” diagnoses

†data from Flaherty et al. Thorax 2003; 58: 143
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<td>5</td>
<td>25</td>
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<tr>
<td><strong>NSIP</strong>*</td>
<td><strong>26 (59%)</strong></td>
<td>18</td>
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Pathology diagnosis was the single most powerful predictor of disease specific mortality

Combining HRCT and pathology resulted in greater prognostic precision

Patients with “discordant” HRCT (NSIP) and pathology (UIP) findings may have earlier stage disease

† Flaherty et al. Thorax 2003; 58: 143
**Idiopathic Interstitial Pneumonia**

What Is the Effect of a Multidisciplinary Approach to Diagnosis?

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<td>Diagnosis &amp; Confidence</td>
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<td>Radiologists</td>
<td>Confidence of IPF</td>
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<tr>
<td><strong>Step 2 - Individual</strong></td>
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<td>Radiologists</td>
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<td>Pathologists</td>
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<td><strong>Step 5 - Group Discussion</strong></td>
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<td>Consensus Diagnosis &amp; Confidence</td>
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<tr>
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- $n = 58$ consecutive patients
- independent pathology review before step 1
- weekend in Michigan
**Frequency of UIP/IPF diagnosis**

<table>
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<tr>
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<th>Clinician C</th>
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*AJRCCM 2004; 170: 904-10*
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- **SLBx results**
  - Step 3: \( \kappa 0.60 \)
  - Step 4: \( \kappa 0.92 \)
  - Step 5: \( \kappa 0.50 \)

\( \kappa \) values:
- Step 1: \( \kappa 0.75 \)
- Step 2: \( \kappa 0.86 \)
- Step 3: \( \kappa 0.75 \)
- Step 4: \( \kappa 0.92 \)
- Step 5: \( \kappa 0.79 \)

*AJRCCM 2004; 170: 904-10*
**Idiopathic Interstitial Pneumonia**

What Is the Effect of a Multidisciplinary Approach to Diagnosis?


AJRCCM 2004; 170: 904-10

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### Frequency of UIP/IPF diagnosis

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<th>Radiologist B</th>
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<td>15</td>
<td>15</td>
<td>0.92</td>
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<td>Step 2</td>
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<td>15</td>
<td>15</td>
<td>0.90</td>
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<tr>
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<td>30</td>
<td>15</td>
<td>16</td>
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**What Is the Effect of a Multidisciplinary Approach to Diagnosis?**


AJRCCM 2004; 170: 904-10

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\[ \kappa = 0.92 \]

\[ \kappa = 0.95 \]

\[ \kappa = 0.20 \]

\[ \kappa = 0.84 \]

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\[ \kappa = 0.98 \]

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\[ \kappa = 0.88 \]
Histopathologic Diagnosis in Diffuse Lung Disease
An Ailing Gold Standard†

“The essential assumption underlying the present study is that there is no gold standard for diagnosis in diffuse lung disease, merely the silver standards of clinical, radiologic, and histopathologic evaluation.

†Athol Wells. Am J Respir Crit Care Med 2004; 170: 828
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†Athol Wells. Am J Respir Crit Care Med 2004; 170: 828
argentiferous

adjective | ar·gen·tif·er·ous | \\är-jən-ˈti-f(ə)rəs\\

Definition of ARGENTIFEROUS

: containing silver

http://www.merriam-webster.com/dictionary/argentiferous
October 20, 2015 at 07:00 hrs
Idiopathic Interstitial Pneumonias - Myers

HRCT consensus clinical data SLBx
CONSENSUS!
Histopathologic Diagnosis in Diffuse Lung Disease
An Ailing Gold Standard†

“The recent view that a final diagnosis should be made by consensus between histopathologist, radiologist, and clinician is a radical departure from the diagnostic thinking of the late twentieth century.”

†Athol Wells. Am J Respir Crit Care Med 2004; 170: 828
Idiopathic Interstitial Pneumonia - Myers

Idiopathic Interstitial Pneumonia
What Is the Effect of a Multidisciplinary Approach to Diagnosis?

AJRCCM 2004; 170: 904-10

Frequency of UIP/IPF diagnosis

<table>
<thead>
<tr>
<th>Step</th>
<th>Clinician A</th>
<th>Clinician B</th>
<th>Clinician C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>28</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Step 2</td>
<td>28</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Step 3</td>
<td>24</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>SLBx results</td>
<td>κ 0.60</td>
<td>κ 0.55</td>
<td>κ 0.50</td>
</tr>
<tr>
<td>Step 4</td>
<td>32</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>consensus</td>
<td>κ 0.92</td>
<td>κ 0.89</td>
<td>κ 0.79</td>
</tr>
<tr>
<td>Step 5</td>
<td>31</td>
<td>29</td>
<td>30</td>
</tr>
</tbody>
</table>
Idiopathic interstitial pneumonias

Diffuse Parenchymal Lung Diseases

- DPLD of known cause or association
  (e.g., drugs, CTD, occupational/environmental)

- Other radiologically distinct DPLDs
  (e.g., LCH, LAM)

- Granulomatous DPLD
  (e.g., HP, sarcoidosis)

- Idiopathic interstitial pneumonias
Idiopathic Interstitial Pneumonias - Myers

suspected UIP/IPF -> identifiable causes?

no -> HRCT

yes -> DPLD of known cause or association (eg, drugs, CTD, occupational/environmental)

other clinically/radiologically distinct DPLDs (eg, LCH, LAM)

other histologically distinct DPLDs (eg, LCH, NSIP)

granulomatous DPLD (eg, HP, sarcoidosis)

IPF/Not IPF -> Not IPF!
A subset (majority?) of patients with SLBx diagnoses of UIP/IPF will have an “NSIP-pattern” on HRCT.

A subset of patients (minority) with UIP/IPF will have SLBx diagnoses of NSIP ("pattern") as a consequence of sampling bias.

Therefore, a subset of patients with UIP/IPF will be diagnosed as idiopathic NSIP even after multidisciplinary review.
Idiopathic Interstitial Pneumonias - Myers

Lung, [site], wedge biopsy: UIP

. . . *sufficient* to establish the diagnosis of, although not the clinical context for, UIP.

Lung, [site], wedge biopsy: NSIP

. . . *necessary* but *insufficient* to establish the diagnosis of NSIP.
**Molecular Profiling**

Application of genotyping strategies to identify unique signatures in smaller & smaller samples

2938 most differentially expressed genes that distinguished idiopathic pulmonary fibrosis samples from “healthy” control lung tissue

(n = 3 lung explants)

*Kim et al. Lancet Respir Med 2015*
Classification of usual interstitial pneumonia in patients with interstitial lung disease: assessment of a machine learning approach using high-dimensional transcriptional data

Su Yeon Kim, James Diagons, Dan Pankratz, Jing Huang, Moraima Pagan, Nicole Sindy, Ed Tom, Jessica Anderson, Yoonha Choi, David A Lynch, Mark P Steele, Kevin R Flaherty, Kevin K Brown, Humam Farah, Michael J Bukstein, Annie Pardo, Moisés Selman, Paul J Wolters, Steven D Nathan, Thomas V Colby, Jeffrey L Myers, Anna-Luise A Katzenstein, Ganesh Raghu, Giulia C Kennedy

- RNA expression levels on microarrays in 125 surgical lung biopsies from 86 patients
- Classifier algorithm was trained on one set of samples (n=77) and tested in a second set (n=46).
- Next-generation RNA sequencing (RNAseq) in a subset of samples (n=36); assessed a classifier trained on RNAseq data by cross-validation
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<table>
<thead>
<tr>
<th>Classifier</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microarray classifier</td>
<td>82%</td>
<td>92%</td>
</tr>
<tr>
<td>RNAseq classifier</td>
<td>59%</td>
<td>95%</td>
</tr>
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"consensus"

clinical & radiology

pathology
Idiopathic Interstitial Pneumonias - Myers