

- Reproducibility of the ATS/ERS Classification of IIPs -

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Does interobserver agreement of IIPs matter?

- Prognostic differences
 - UIP vs. others
 - DAD vs. others
- Therapeutic differences
 - New clinical trials
 - IIPs vs. CTD-ILD / Others
- Scientific reasons
 - Identifying biomarker
 - Possible subset analysis for new agents

1. Pirfenidone for IPF
King et al, NEJM 2014
2. Nintedanib (BIBF) for IPF
Richeldi L, et al, NEJM 2014
3. NO steroid/azathioprine for IPF
Rague et al, NEJM 2012

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Interobserver agreement of ILD Dx.

UIP...
No!! NSIP!

Dx. accurately given only by limited Experts
Cannot accomplish Science

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Reasons of diagnostic difficulty

1. Diagnosis is given mostly based on combination of "Non-specific findings"
2. The biopsy shows changes of a moment, although the diseases have dynamic changes on their course
3. The biopsies have size limitation compared to the whole lung in which the biopsy may not represent the major pathology of the whole lung
4. Lack of robust criteria for the pathological judgment of each disease.
5. Separations of histological patterns and etiological causes are often mixed up.

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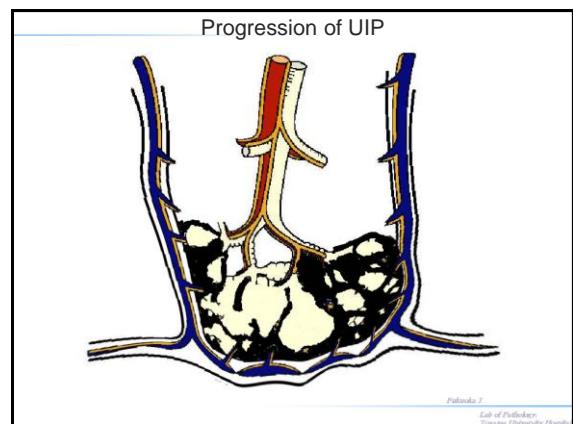
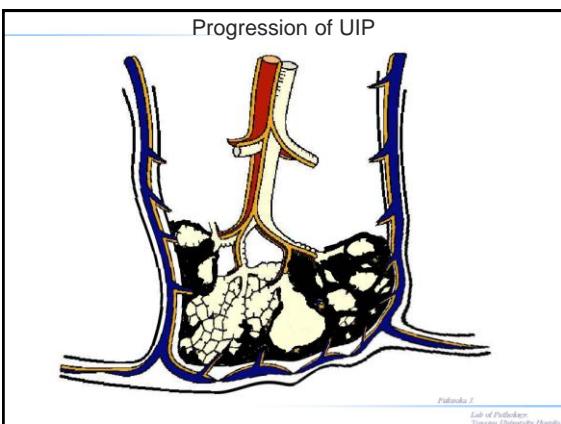
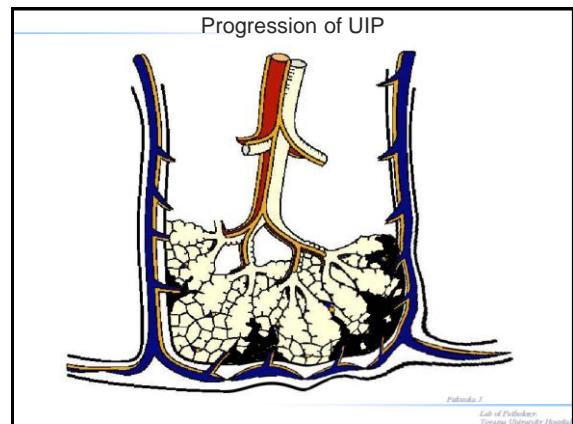
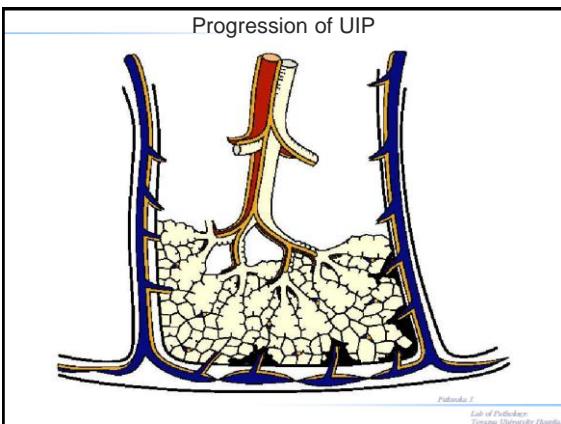
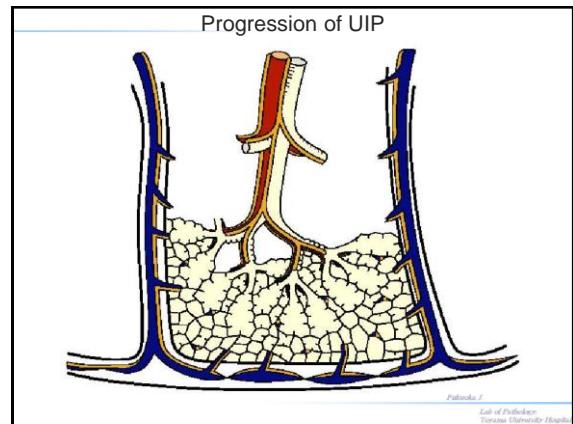
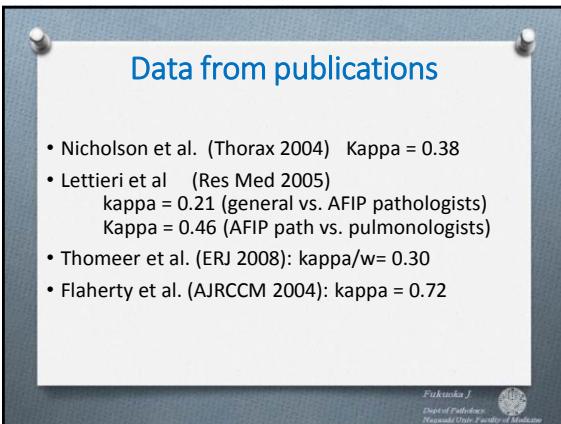
Issues of
“Histological Patterns”

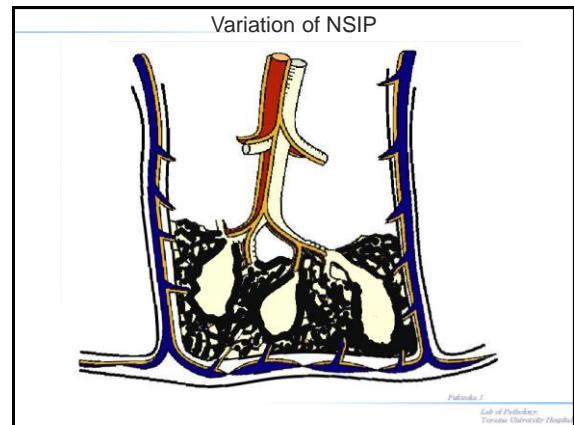
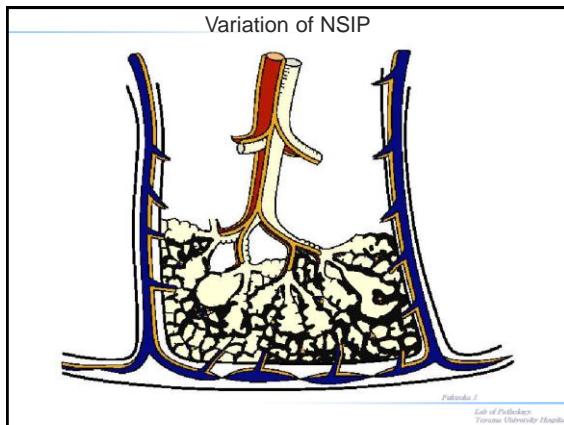
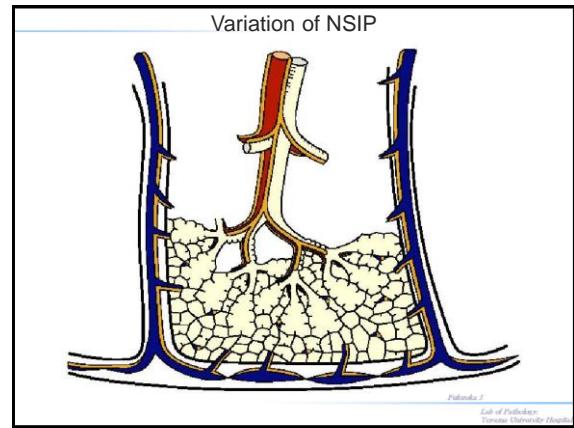
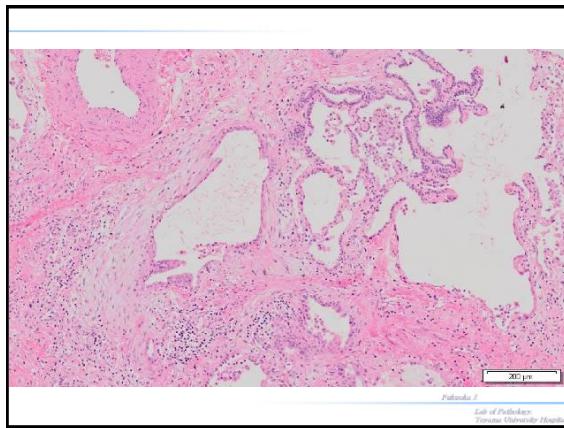
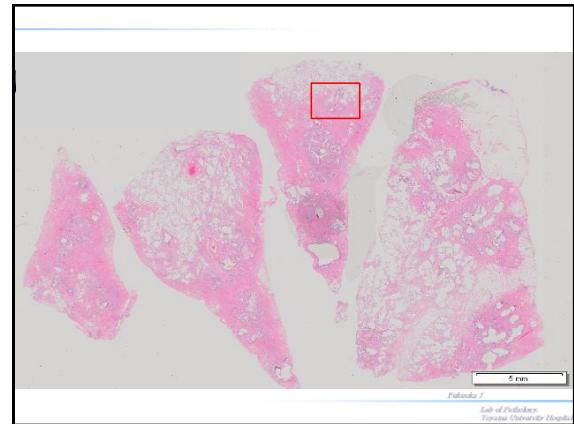
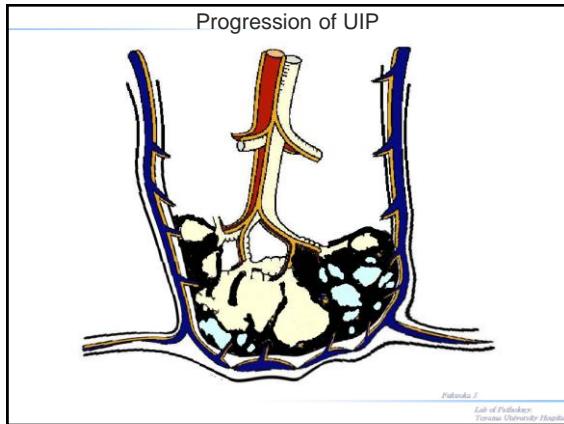
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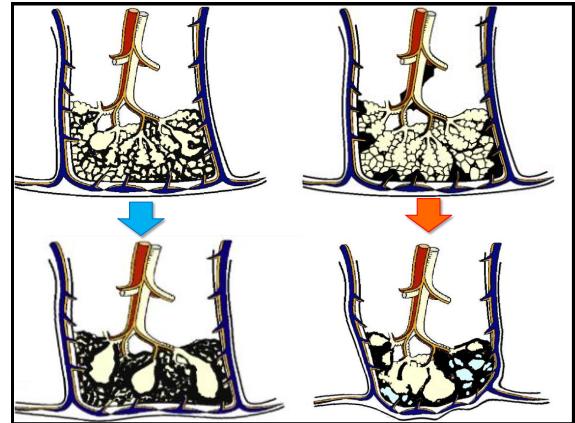
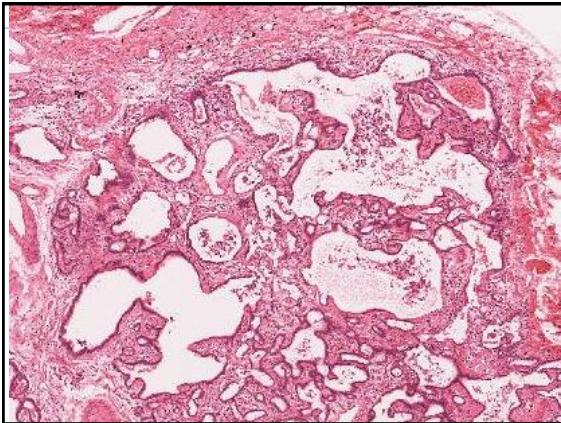
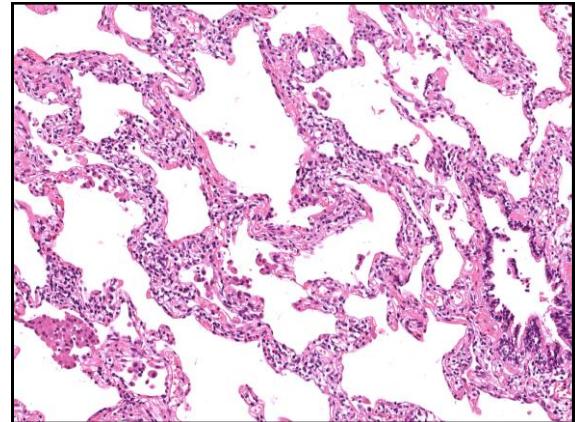
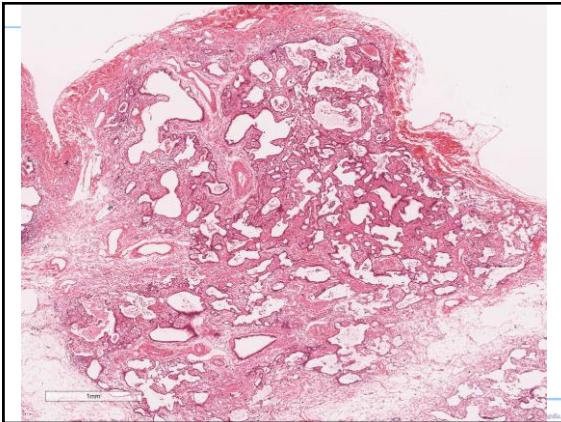
But the Real Case is like...

<p>+</p> <ul style="list-style-type: none"> • Dense fibrosis • Peripheral accentuation • Fibroblastic focus • lower lung predominance • Architectural destruction • Honeycombing • Smooth muscle hyperplasia • Adjacent normal lung area 	<p>-</p> <ul style="list-style-type: none"> • Atelectatic indulation • Bronchiocentricity • Diffuse involvement • Non-specific predominance • Non-specific involvement with architectural sparing from IPF • Granuloma • Marked OP • Granular eosinophilia • Marked pleuritis
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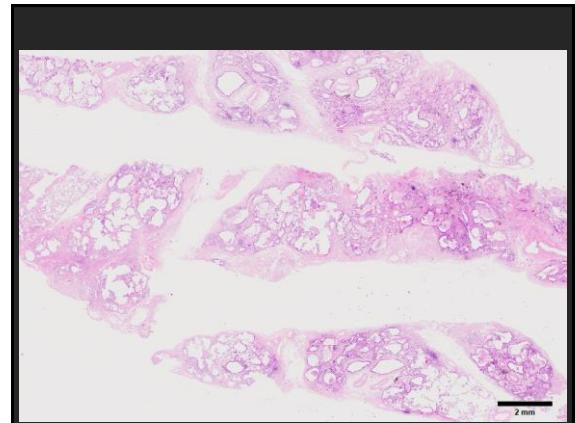




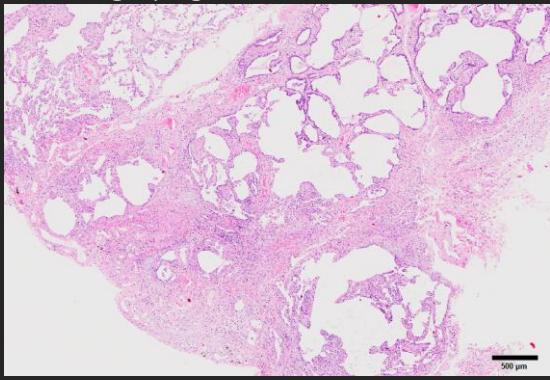
Let's look at cases.

- 72 year old man
- Ex-smoker
- Progressing chronic cough and dyspnea on exertion for a year
- CT: Bilateral lower lung abnormality showing Interstitial pneumonia (possible UIP)

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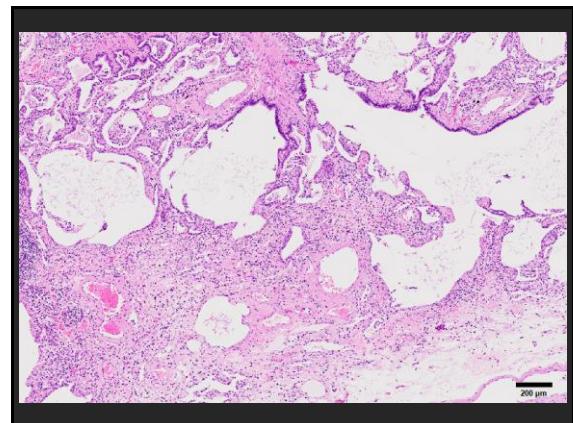
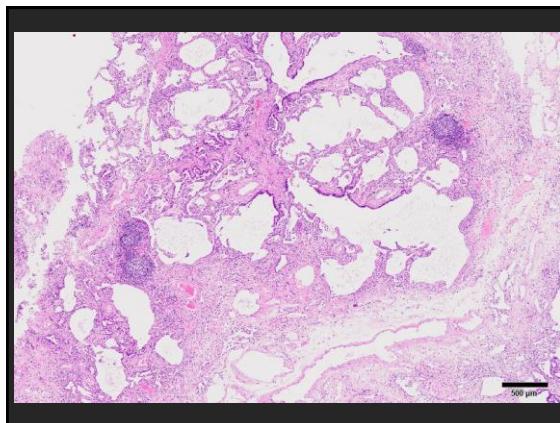
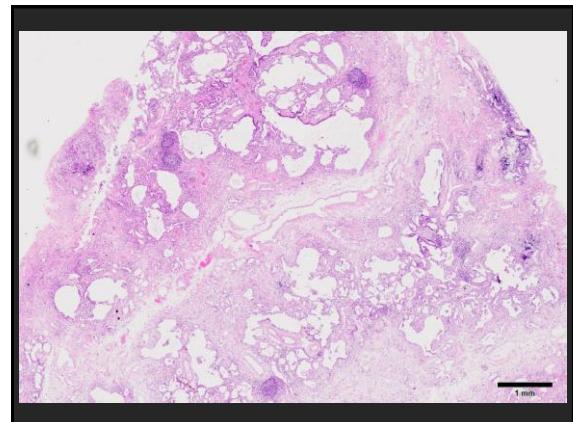
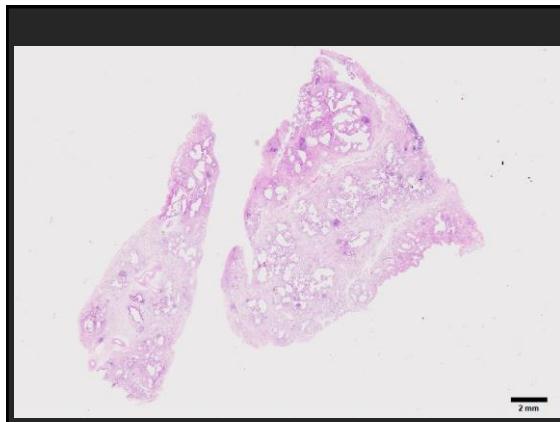
Highly agreed: UIP 28, NSIP 1

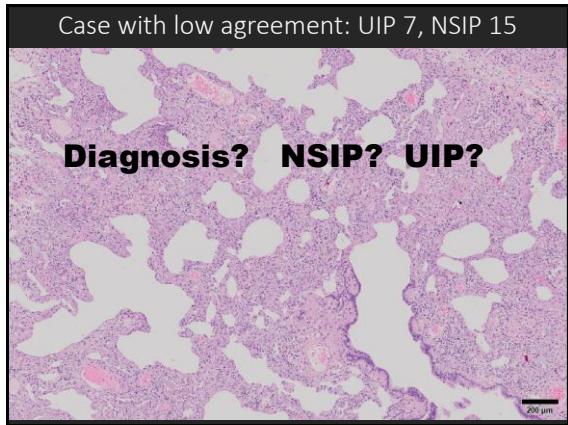
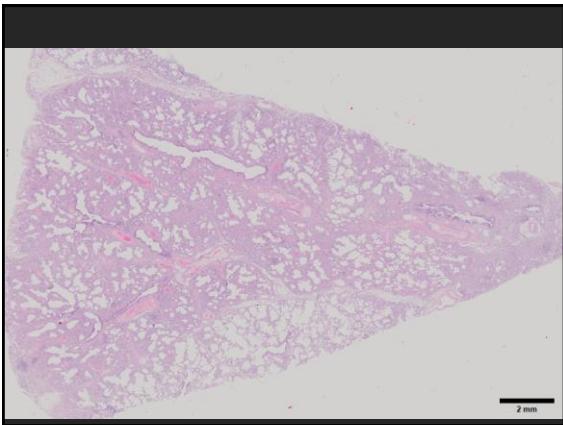
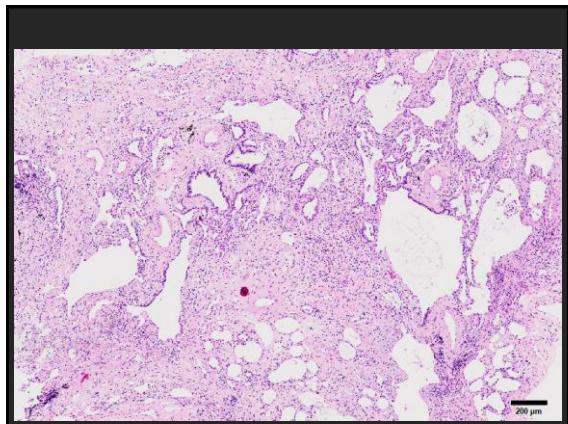
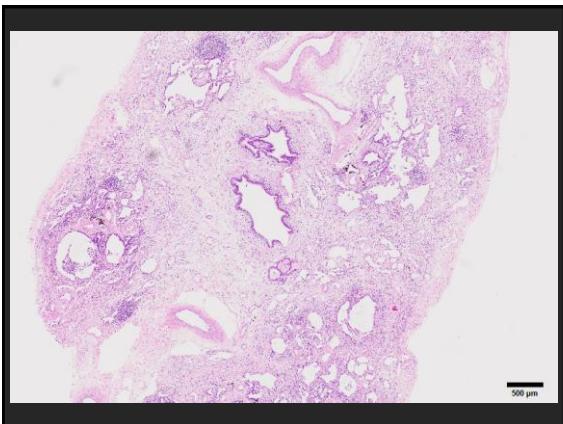
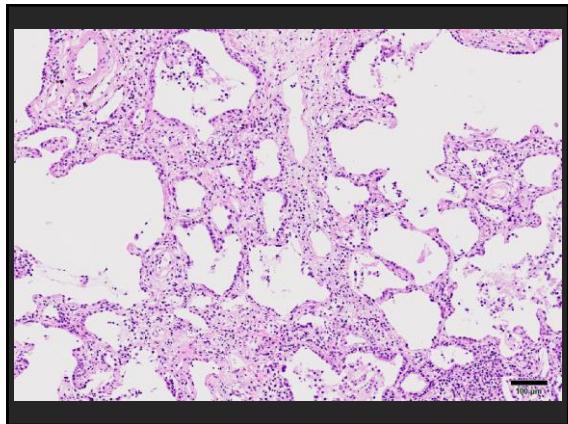
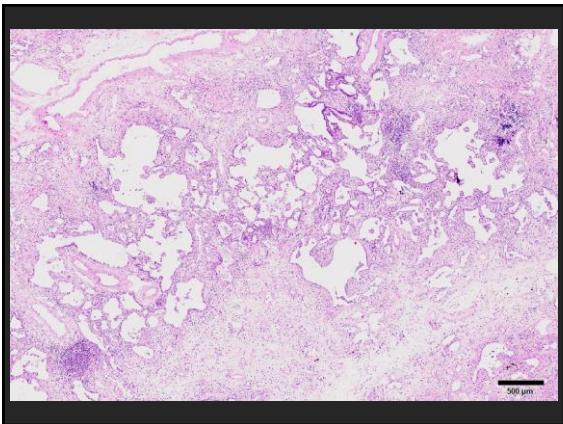


Another case.

- 67 year old man
- Ex-smoker
- Progressing dyspnea during a year
- CT: Bilateral lower lung abnormality showing Interstitial pneumonia (possible UIP)

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(Materials and Methods)

- 20 VATS of fibrotic interstitial pneumonia
⇒ 29 pathologists
- ATS/ERS Path pattern (2002 classification)
- Possible background etiologies
- Analyze inter-observer agreements

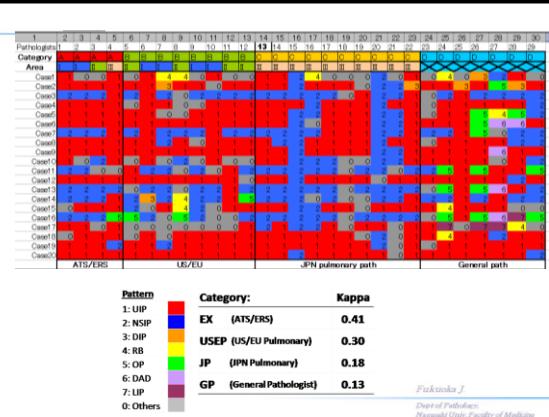
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- Gratitude to the Panelists -

Colby TV, Travis WD, Brambilla EB, Abrahams N, Allen T, Beasley MB, English JC, Galateau-Salle F, Gomes MM, Jones K, Kerr K, Murer B, Tazelaar HD,

Kitaichi M, Takemura T, Fukuda Y, Hayashi S, Hayashi T, Hebisawa A, Ishizawa S, Kawabata Y, Nomoto K, Oka T, Shimizu S, Takahashi H, Tsutsumi Y, Yamadori I, Yamasaki F, Tanaka T, Fukuoka J

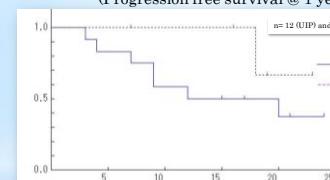
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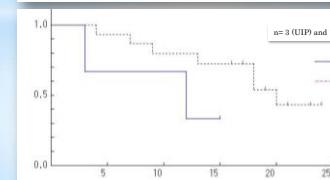
Cluster Analysis



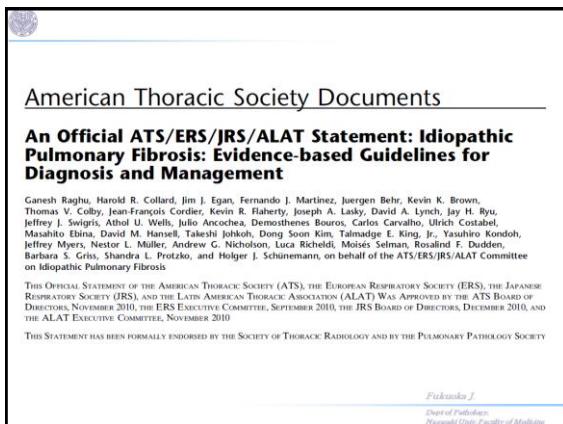
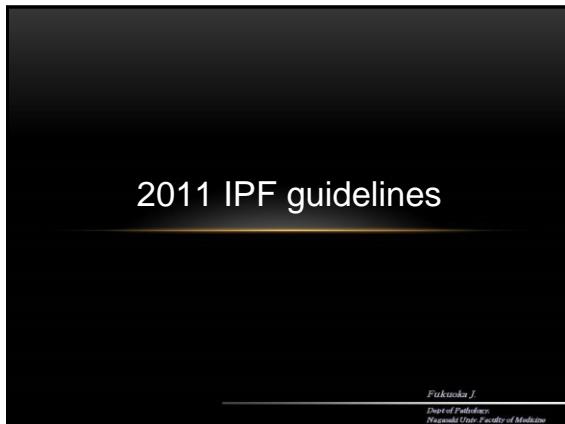
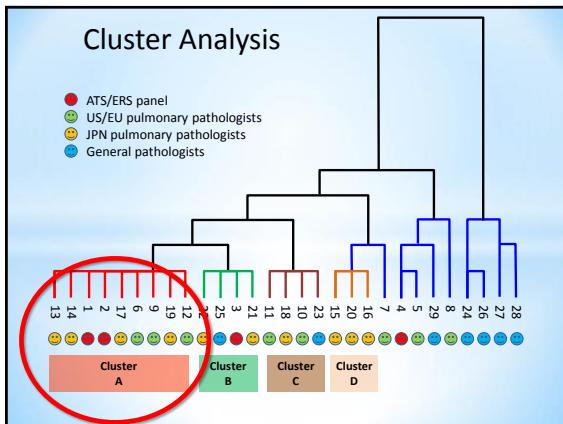
• K-M curve created by consensus diagnosis within panels of cluster A & D (Progression free survival @ 1 year follow up)



Cluster A



Cluster D

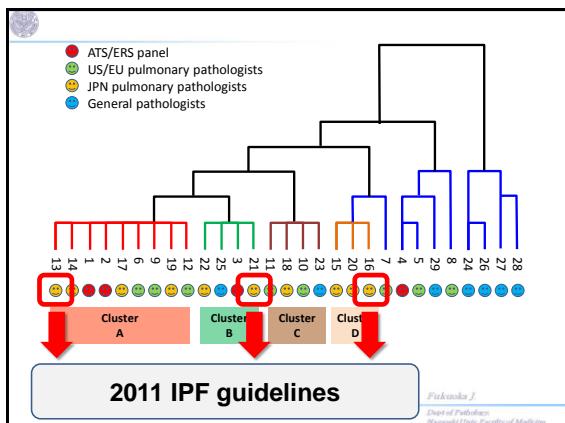
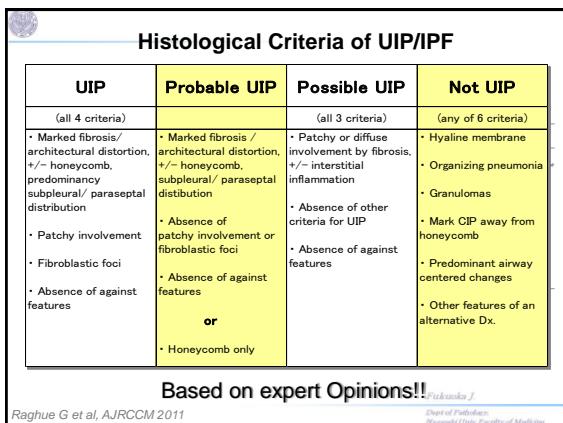


Raghue G et al, AJRCCM 2011

TABLE 6. COMBINATION OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY AND SURGICAL LUNG BIOPSY FOR THE DIAGNOSIS OF IPF (REQUIRES MULTIDISCIPLINARY DISCUSSION)

HRCT Pattern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis of IPF?
UIP	UIP Probable UIP Possible UIP Nonclassifiable fibrosis [†]	YES
Possible UIP	Not UIP UIP Probable UIP	No YES
Inconsistent with UIP	Possible UIP Nonclassifiable fibrosis Not UIP	Probable [‡] No Possible [‡]
	Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP	No

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	pathologist1 (cluster A)	Pathologist2 (cluster B)	Pathologist3 (cluster D)
Case1	2	2	0
Case2	3	0	0
Case3	1	1	1
Case4	3	3	3
Case5	3	2	3
Case6	2	2	2
Case7	1	1	0
Case8	1	2	2
Case9	2	3	0
Case10	3	1	3
Case11	0	0	0
Case12	2	2	2
Case13	0	0	0
Case14	1	1	0
Case15	0	0	0
Case16	0	0	0
Case17	0	0	0
Case18	0	0	0
Case19	2	3	3
Case20	2	3	3

Kappa in
4 categories
= 0.52

Not UIP
possible UIP
probable UIP
UIP

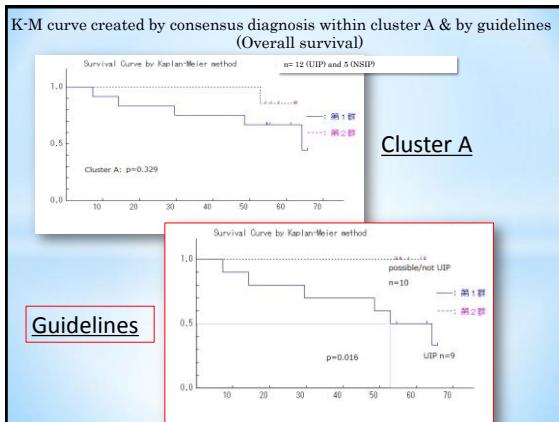
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	pathologist1 (cluster A)	Pathologist2 (cluster B)	Pathologist3 (cluster D)
Case1	UIP	UIP	Not UIP
Case2	UIP	Not UIP	Not UIP
Case3	Not UIP	Not UIP	Not UIP
Case4	UIP	UIP	UIP
Case5	UIP	UIP	UIP
Case6	UIP	UIP	UIP
Case7	Not UIP	Not UIP	Not UIP
Case8	Not UIP	UIP	UIP
Case9	UIP	UIP	Not UIP
Case10	UIP	Not UIP	UIP
Case11	Not UIP	Not UIP	Not UIP
Case12	UIP	UIP	UIP
Case13	Not UIP	Not UIP	Not UIP
Case14	Not UIP	Not UIP	Not UIP
Case15	Not UIP	Not UIP	Not UIP
Case16	Not UIP	Not UIP	Not UIP
Case17	Not UIP	Not UIP	Not UIP
Case18	Not UIP	Not UIP	Not UIP
Case19	UIP	UIP	UIP
Case20	UIP	UIP	UIP

Kappa in
2 categories
= 0.66

Not UIP
possible UIP
prob UIP
UIP

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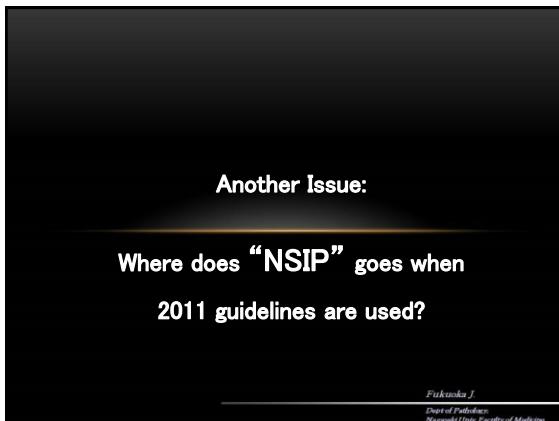


Please join to our project!!

2011 IPF guidelines (histologic criteria)

2011 IPF guidelines (histologic criteria)

Case No.	Your Histological level	level of certainty	Alternative dx	Likely etiology	2011 IPF certainty guidelines	Reasons for NOT UIP
1	UIP	Possible	UIP	UIP	UIP	None of the above
2	UIP	Possible	UIP	UIP	UIP	None of the above
3	UIP	Possible	UIP	UIP	UIP	None of the above
4	UIP	Possible	UIP	UIP	UIP	None of the above
5	UIP	Possible	UIP	UIP	UIP	None of the above
6	UIP	Possible	UIP	UIP	UIP	None of the above
7	UIP	Possible	UIP	UIP	UIP	None of the above
8	UIP	Possible	UIP	UIP	UIP	None of the above
9	UIP	Possible	UIP	UIP	UIP	None of the above
10	UIP	Possible	UIP	UIP	UIP	None of the above
11	UIP	Possible	UIP	UIP	UIP	None of the above
12	UIP	Possible	UIP	UIP	UIP	None of the above
13	UIP	Possible	UIP	UIP	UIP	None of the above
14	UIP	Possible	UIP	UIP	UIP	None of the above
15	UIP	Possible	UIP	UIP	UIP	None of the above
16	UIP	Possible	UIP	UIP	UIP	None of the above
17	UIP	Possible	UIP	UIP	UIP	None of the above
18	UIP	Possible	UIP	UIP	UIP	None of the above
19	UIP	Possible	UIP	UIP	UIP	None of the above
20	UIP	Possible	UIP	UIP	UIP	None of the above



CRP Dx.	Panel A	Panel B	Panel C	Panel D
cfnSIP	Possible	Possible	Not UIP	Not UIP
Not UIP	Not UIP	Not UIP	Not UIP	Possible
cfnSIP	Not UIP	Not UIP	Not UIP	Not UIP
cfnSIP	Not UIP	Not UIP	Not UIP	Probable
cfnSIP	Not UIP	Not UIP	Not UIP	Not UIP
cfnSIP	Not UIP	Not UIP	Not UIP	Not UIP
cfnSIP	Not UIP	Not UIP	Not UIP	Not UIP
cfnSIP	Not UIP	Not UIP	Not UIP	Not UIP
cfnSIP	Probable	Possible	Possible	Possible
cfnSIP	Possible	Not UIP	Possible	Possible
cfnSIP	Probable	Not UIP	Possible	Possible
cfnSIP	Possible	Not UIP	Possible	Possible
cfnSIP	Possible	Probable	Probable	Probable
cfnSIP	Probable	Not UIP	Possible	Possible
fnsIP	Possible	Not UIP	Possible	Not UIP
fnsIP	Probable	probable	Not UIP	Not UIP
fnsIP	Not UIP	Not UIP	Not UIP	Probable
fnsIP	Probable	Possible	Possible	Possible
fnsIP	Possible	Not UIP	Possible	Possible
fnsIP	Possible	Not UIP	Possible	Definite UIP
fnsIP	Possible	Possible	Probable	Possible

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		Majority of NSIP are now Possible UIP			
Original Path Dx	consensus Hx pattern	Agreement			
		4/4	3/4	2/4	
cellular and fibrotic	Probable	3	0	2	1
	Possible	5	0	4	1
	Not UIP	6	3	3	0
Fibrotic	Probable	0	0	0	0
	Possible	4	0	2	2
	Not UIP	1	0	1	0

CRP Dx.	Panel A	Panel B	Panel C	Panel D	majority
cNSIP	Possible	Possible	Not UIP	Not UIP	NSIP
cNSIP	Not UIP	Not UIP	Not UIP	Possible	NSIP
cNSIP	Not UIP	Not UIP	Not UIP	Not UIP	NSIP
cNSIP	Not UIP	Not UIP	Not UIP	probable	NSIP
cNSIP	Not UIP	Not UIP	Not UIP	Not UIP	NSIP
cNSIP	probable	Not UIP	Not UIP	Not UIP	NSIP
cNSIP	Not UIP	Not UIP	Not UIP	Not UIP	NSIP
cNSIP	probable	Possible	Possible	Possible	NSIP
cNSIP	Possible	Not UIP	Possible	Possible	NSIP
cNSIP	probable	Not UIP	Possible	Possible	NSIP
cNSIP	Possible	Possible	Possible	Not UIP	NSIP
cNSIP	Possible	Not UIP	Possible	Possible	NSIP
cNSIP	Possible	probable	probable	probable	probable
cNSIP	probable	Not UIP	probable	Possible	probable
cNSIP	Possible	Not UIP	Possible	Not UIP	NSIP
fNSIP	probable	probable	Not UIP	Not UIP	disagreed
fNSIP	Not UIP	Not UIP	Not UIP	probable	NSIP
fNSIP	probable	Possible	Possible	Not UIP	disagreed
fNSIP	Possible	Not UIP	Possible	Possible	NSIP
fNSIP	Possible	Not UIP	Possible	Possible	NSIP
fNSIP	Possible	Not UIP	Possible	UIP	UIP
fNSIP	Possible	Possible	probable	Possible	NSIP

Problem is ... Criteria of “NOT UIP”

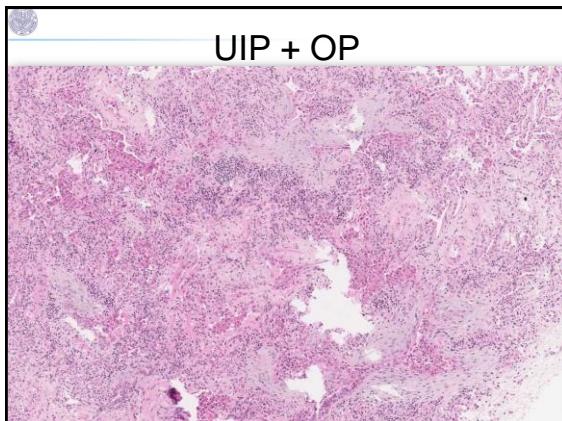
- Hyaline membranes
- OP
- Granulomas
- Marked CIP away from honeycomb
- Predominant airway centered change
- Features suggestive of an alternate Dx

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Criteria of “NOT UIP”

- Hyaline membranes ⇒ If not ac-ex clinically, then...
- OP
- Granulomas
- Marked CIP away from honeycomb
- Predominant airway centered change
- Other features suggestive of an alternate Dx

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Criteria of “NOT UIP”

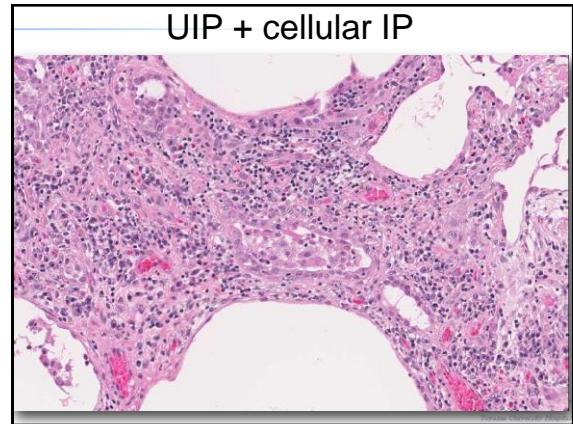
- Hyaline membranes
- OP
- Granulomas ⇒ How many in how much tissue?
- Marked CIP away from honeycomb
- Predominant airway centered change
- Other features suggestive of an alternate Dx

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Criteria of “NOT UIP”

- Hyaline membranes
- OP
- Granulomas
- Marked CIP away from honeycomb
- Predominant \Rightarrow “Possible UIP” allows CIP in its criterion though
- Other features suggestive of an alternate Dx

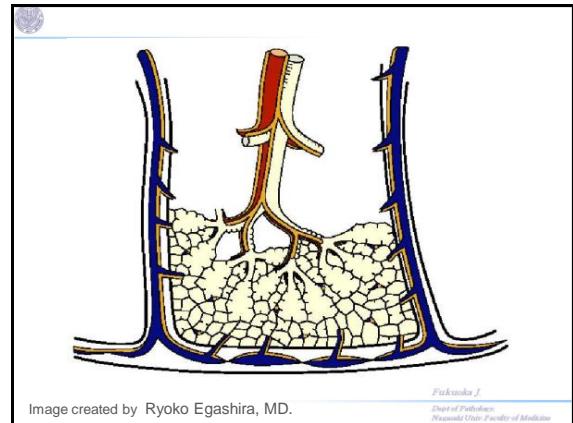
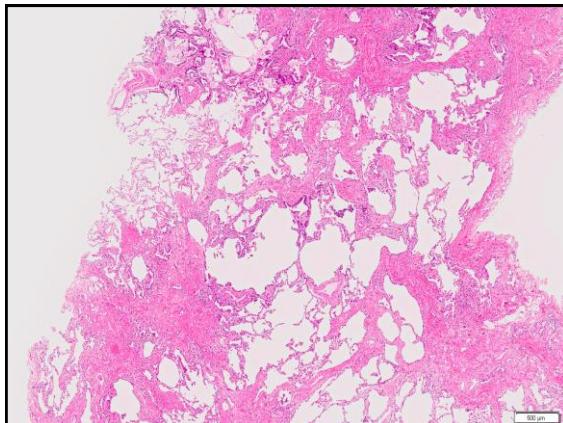
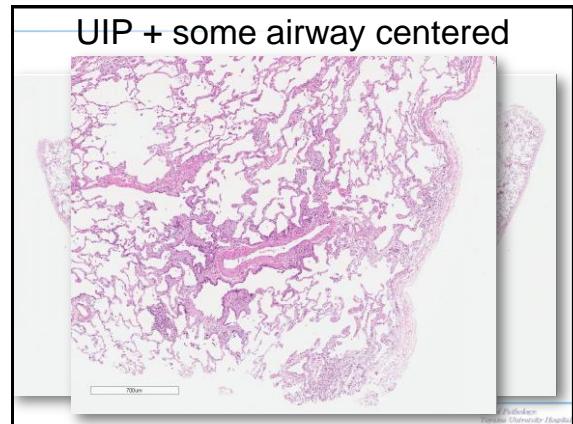
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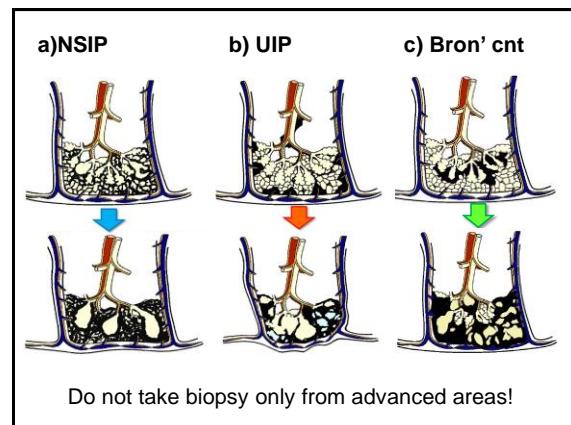
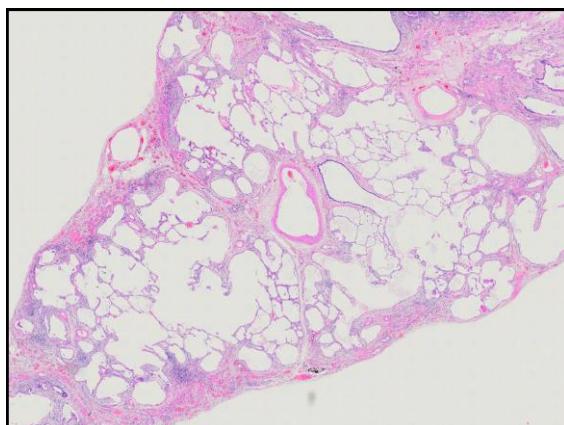
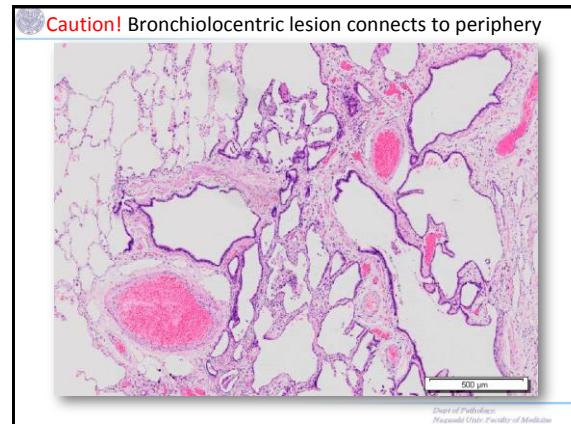
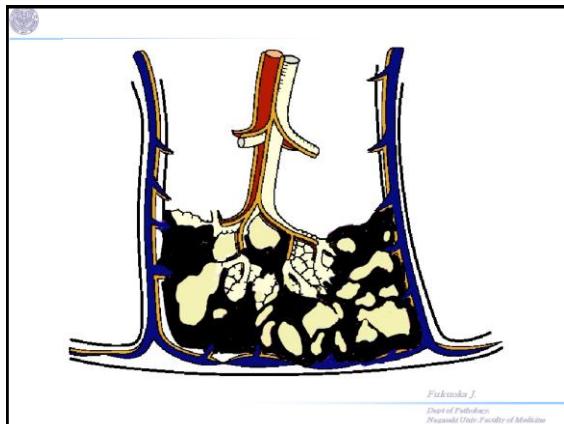
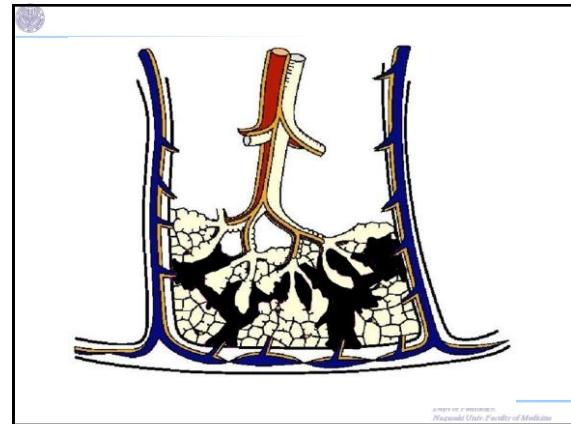
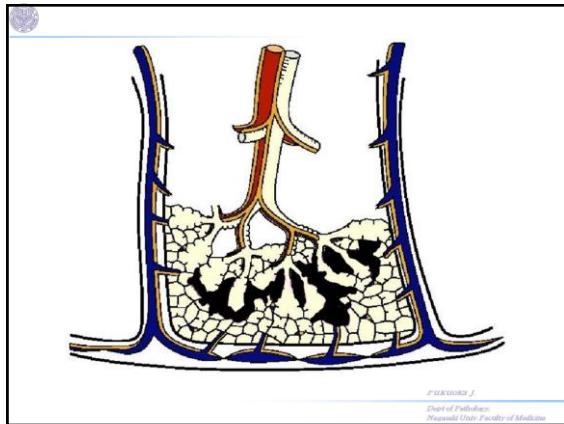


Criteria of “NOT UIP”

- Hyaline membranes
- OP
- Granulomas
- Marked CIP away from honeycomb
- Predominant airway centered change
 \Rightarrow How much would be “predominant”? How about UIP + ACIF (UIP > ACIF)?

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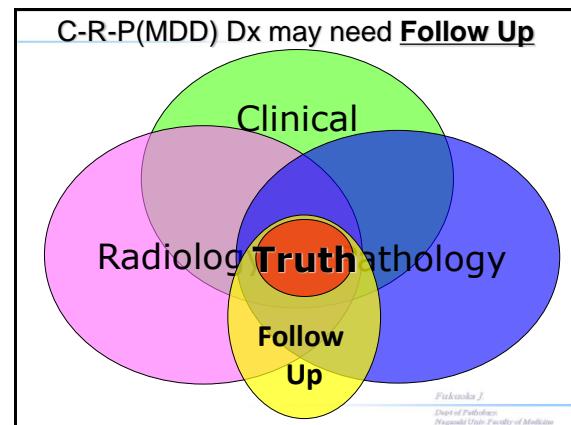
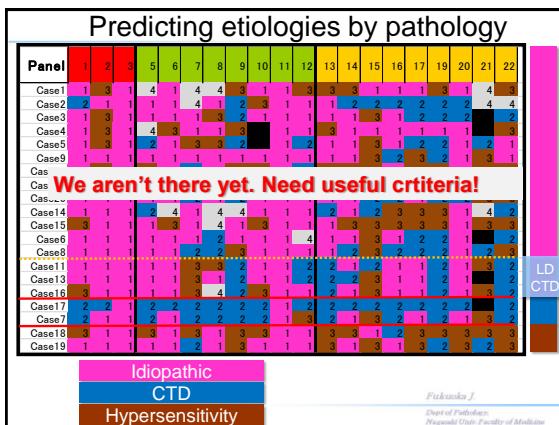
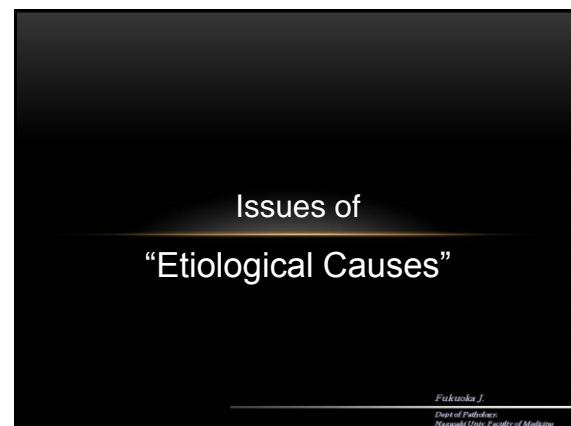
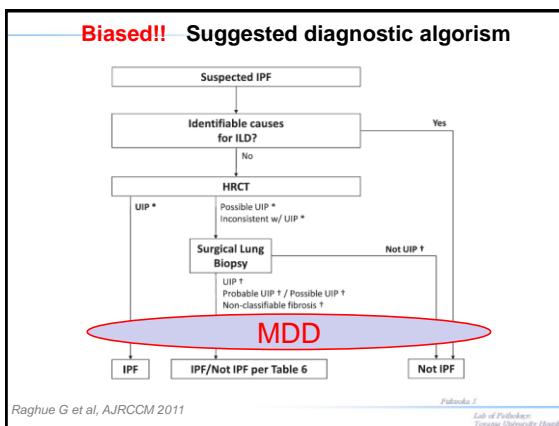
Criteria of “NOT UIP”

- Hyaline membranes
- OP
- Granulomas
- ⇒ Features of autoimmune, then? Can we reproducibly separate them by pathology?
- Features suggestive of an alternate Dx

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UIP/P	Probable UIP/P	Possible UIP/P	Not UIP/P
(all 4 criteria)			(any of 6 criteria)
<ul style="list-style-type: none"> Marked fibrosis/architectural distortion, +/- honeycomb, predominance subpleural/interlobular distribution Patchy involvement Fibroblastic foci Absence of against features <p><i>Caution!! Biased & personal opinion!</i></p>	<ul style="list-style-type: none"> Absence of patchy involvement or fibroblastic foci Absence of against features <p><i>or</i></p> <ul style="list-style-type: none"> Honeycomb only <p><i>or</i></p> <ul style="list-style-type: none"> UIP + weak “NOT” features 	<ul style="list-style-type: none"> Patchy or interlobular inflammation Organizing pneumonia Granulomas Other alternative diseases <p><i>or</i></p> <ul style="list-style-type: none"> UIP/probUIP + “NOT” features 	<ul style="list-style-type: none"> Organizing pneumonia Granulomas Other alternative diseases <p>Add “Severe”</p>

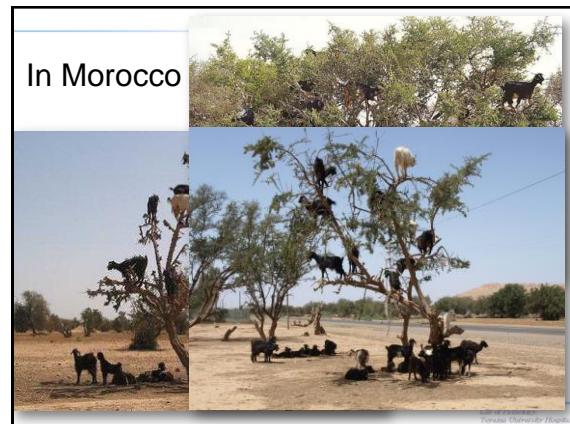
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What does this mean?

- CG (computer graphic)?
- Illusion?
- Goat on the Tree?
- Goat jumps?
- Goat hanging on the tree?

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Like a case you may call “Probable UIP??” ...

But if you know that CT is this...

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Summary of the Talk

- Criteria of IPF guidelines are reasonable.
- Criteria of “NOT UIP” has a problem.
Consider definite UIP + probable UIP as UIP.
(possible UIP is “prob NOT” UIP)
- Etiological cause can be guessed by limited expert.
- Do MDD, but may need Follow UP for final Dx.
- Please join “inter-observer agreement study”.

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