ONLINE SUPPLEMENT

Supplemental Table 1. Categorization of unique histopathologic interpretations as usual interstitial pneumonia (UIP), possible UIP/Unclassifiable pulmonary fibrosis, or not UIP

	Pathology Designation					
	Definite/Probable UIP		**Possible UIP/Unclassifiable pulmonary fibrosis**		**Not UIP**	
	UCSF (n=113)	**Mayo (n=111)**	**UCSF (n=26)**	**Mayo (n=7)**	**UCSF (n=246)**	**Mayo (n=48)**
Pathology Interpretation	UIP	UIP	• Fibrosing interstitial pneumonia – unclassifiable Clinical diagnosis (n=23): o IPF, n=5 o HP, n=2 o SR-ILD, n=1 Unclassifiable, n=12 o UCTD, n=3 • UIP + Bronchiolocentric fibrosis o Clinical diagnosis (n=3): o IPF, n=1 o Antisynthetase syndrome, n=1 o Unclassifiable, n=1	• Diffuse interstitial fibrosis, n=1 • Fibrosing interstitial pneumonia with mixed UIP and DIP features, n=2 • Possible UIP with airspace disease with possible aspiration/infection, n=1 • Interstitial subpleural and bronchiolocentric fibrosis and chronic inflammation, n=1 • possible UIP with severe emphysema and pleural fibrosis with foreign body reaction, n=1 • UIP with granulomas, n=1	• UIP + organizing pneumonia (n=1, clinical diagnosis RA-ILD) • Fibrosing interstitial pneumonia – unclassifiable, Bronchiolocentric fibrosis (n=1, clinical diagnosis Unclassifiable ILD) • UIP, Bronchiolocentric fibrosis, Non-necrotizing granulomatous inflammation –Favor HP • UIP, Non-necrotizing granulomatous inflammation – Favor HP • Interstitial fibrosis with extramedulary hematopoiesis • Acute bronchopneumonia • Amyloidosis/LCDD • Aspiration • Bland DAH • Bronchiolocentric fibrosis • Bronchiolocentric fibrosis, non-necrotizing granulomatous inflammation • Cellular bronchiolitis • Cellular interstitial pneumonia • Constrictive bronchiolitis • DAD/ALI • DIP • Eosinophilic pneumonia • Follicular bronchiolitis	• DIP • HP • Mixed Unclassifiable • NSIP

					• LIP • NSIP – cellular • NSIP – cellular & fibrotic • NSIP – cellular with granulomas • NSIP – fibrotic • Necrotizing granulomas • Non-necrotizing granulomatous inflammation • Normal • OP • OP, Emphysema • Other Granulomatous Disease • Pleuritis • Pulmonary alveolar proteinosis • RB • RB, OP • Adenocarcinoma • Apical fibrous cap • Diffuse panbronchiolitis • Increased microphages, apical fibrosis • other bronchiolitis	

Supplemental Table 2. Histopathologic interpretation and final clinical diagnosis of the 24 patients with HRCT possible UIP pattern but not definite/probable UIP on surgical lung biopsy in the derivation cohort and validation cohorts

UCSF (n=24)	**Histopathologic Interpretation**	**Final Clinical Diagnosis**
	Bronchiolocentric fibrosis, Non-necrotizing granulomatous inflammation – Favor HP	HP
	Non-necrotizing granulomatous inflammation – Favor HP	HP
	Organizing pneumonia	HP
	NSIP with granulomas (suggest HP)	HP
	UIP, Bronchiolocentric fibrosis	IPF
	Non-necrotizing granulomatous inflammation – Favor HP	HP
	Bronchiolocentric fibrosis	HP
	Fibrosing interstitial pneumonia – unclassifiable	IPF
	Bronchiolocentric fibrosis	HP
	Necrotizing granulomas	ANCA-associated vasculitis
	Fibrosing interstitial pneumonia – unclassifiable	Unclassifiable ILD
	Fibrotic NSIP	HP
	Fibrotic NSIP	Unclassifiable ILD
	Fibrotic NSIP	Idiopathic NSIP
	NSIP with granulomas (suggest HP)	HP
	Fibrotic NSIP	UCTD
	Fibrosing interstitial pneumonia – unclassifiable	IPF
	Fibrotic NSIP	UCTD
	NSIP with granulomas (suggest HP)	HP
	UIP, Bronchiolocentric fibrosis	Antisynthetase syndrome
	Fibrosing interstitial pneumonia – unclassifiable	Unclassifiable ILD
	Fibrosing interstitial pneumonia – unclassifiable	Unclassifiable ILD
	Fibrosing interstitial pneumonia – unclassifiable	IPF
	Fibrotic NSIP	Antisynthetase syndrome
Mayo (n=4)	Possible UIP with severe emphysema and pleural fibrosis with foreign body reaction	IPF
	HP	HP
	HP	HP
	Possible UIP with airspace disease with possible aspiration, infection	IPF

Supplemental Table 3. Individual features of inconsistent with UIP pattern on HRCT

	Histopathologic Diagnosis			
	Definite/ Probable UIP n (%)	**Possible UIP, Unclassifiable PF, or Not UIP** n (%)	**Odds Ratio* (95% CI)**	**P-value***
Mosaic perfusion/Air-trapping				
UCSF				
Yes	24 (27.3)	64 (72.7)	0.80 (0.45-1.43)	0.46
No	49 (21.0)	184 (79.0)		
Mayo				
Yes	15 (46.9)	17 (53.1)	0.48 (0.17-1.34)	0.16
No	29 (46.0)	34 (54.0)		
Micronodules				
UCSF				
Yes	1 (2.4)	40 (97.6)	0.07 (0.01-0.50)	0.008
No	72 (25.7)	208 (74.3)		
Mayo				
Yes	0 (0)	11 (100)	--	--
No	44 (52.4)	40 (47.6)		
Ground glass opacities				
UCSF				
Yes	27 (17.9)	124 (82.1)	0.39 (0.23-0.66)	<0.001
No	46 (27.1)	124 (72.9)		
Mayo				
Yes	19 (33.9)	37 (66.1)	0.09 (0.04-0.23)	<0.001
No	25 (64.1)	14 (35.9)		
Consolidation				
UCSF				
Yes	3 (10.7)	25 (89.3)	0.27 (0.08-0.95)	<0.001
No	70 (23.9)	223 (76.1)		
Mayo				
Yes	3 (60.0)	2 (40.0)	0.54 (0.07-3.85)	0.54
No	41 (45.6)	49 (54.4)		
Cysts				
UCSF				
Yes	9 (34.6)	17 (65.4)	1.33 (0.55-3.23)	0.53
No	64 (21.7)	231 (78.3)		
Mayo				
Yes	1 (100.0)	0 (0)	--	--
No	43 (45.7)	51 (54.3)		
Upper-mid lung predominance				
UCSF				
Yes	8 (13.3)	52 (86.7)	0.44 (0.19-1.01)	0.053
No	65 (24.9)	196 (75.1)		
Mayo				
Yes	12 (46.2)	14 (53.8)	0.22 (0.08-0.62)	0.004
No	32 (46.4)	37 (53.6)		
Peribronchovascular distribution				
UCSF				
Yes	33 (19.6)	135 (80.4)	0.54 (0.33-0.90)	0.017
No	40 (26.1)	113 (73.9)		
Mayo				
Yes	7 (43.8)	9 (33.1)	0.19 (0.05-0.66)	0.009
No	37 (46.8)	42 (53.2)		

*Odds ratio and p-value for association with histopathologic definite/probable UIP pattern using logistic regression adjusted for the other inconsistent features

Abbreviations: UIP = usual interstitial pneumonia, HRCT = high-resolution computed tomography, PF = pulmonary fibrosis; CI = confidence interval

Supplemental Table 4. Test characteristics by UIP score for histopathologic UIP

	UCSF (n=385)		Mayo Clinic (n=167)	
Prevalence of histopathologic UIP	29%		67%	
UIP Score	**LR+**	**PPV (%)**	**LR+**	**PPV (%)**
1	1.16	32	1.17	70
2	1.27	35	1.40	74
3	1.52	39	1.59	76
4	2.30	49	3.65	88
6	5.33	69	14.12	97
7	5.74	70	13.87	97
8	6.22	72	13.63	96
9	6.02	71	12.64	96
10	45.7	95	17.84	97
C-statistic (95% CI)	0.74 (0.69-0.78)		0.83 (0.76-0.89)	

*The UIP score is calculated as follows: Age 50-59 (+2 points) or Age ≥60 (+3 points), Male sex (+1 points), HRCT Possible UIP pattern with total traction bronchiectasis score ≥ 4 (+6 points) for a total of 10 possible points

Abbreviations: LR+, likelihood ratio for a positive test; PPV, positive predictive value; NPV, negative predictive value; UIP, usual interstitial pneumonitis

Supplemental Table 5. Sensitivity analyses included (1) including cases with possible UIP/unclassifiable PF on histopathology as "positive" outcomes (i.e. equivalent to definite/probable UIP cases), (2) using a clinical diagnosis of IPF rather than histopatholgic UIP as the outcome, and (3) inclusion of patients with diagnosis of a defined CTD prior to biopsy who were excluded from the primary analysis.

Sensitivity Analysis	**PPV** (95% CI)	**LR+** (95% CI)
Population: Primary study population Outcome: pathology UIP includes possible UIP/unclassifiable PF Predictor: HRCT Possible UIP pattern	75.0 (62.6-85.0)	5.31 (3.14-8.99)
Population: Primary study population Outcome: pathology UIP includes possible UIP/unclassifiable PF Predictor: HRCT Possible UIP pattern + traction score ≥ 4	80.0 (65.4-80.4)	7.08 (3.51-14.3)
Population: Primary study population Outcome: IPF Predictor: HRCT Possible UIP pattern	60.9 (47.9-72.9)	4.70 (3.01-7.34)
Population: Primary study population Outcome: IPF Predictor: HRCT Possible UIP pattern + traction score ≥ 4	66.7 (51.0-80.0)	6.02 (3.39-10.7)
Population: Primary study population plus patients with CTD diagnosis prior to biopsy Outcome: pathology UIP Predictor: HRCT Possible UIP pattern	61.5 (48.6-73.3)	4.05 (2.58-6.35)
Population: Primary study population plus patients with CTD diagnosis prior to biopsy Outcome: pathology UIP Predictor: HRCT Possible UIP pattern + traction score ≥ 4	68.9 (53.4-81.8)	5.60 (3.1-10.1)

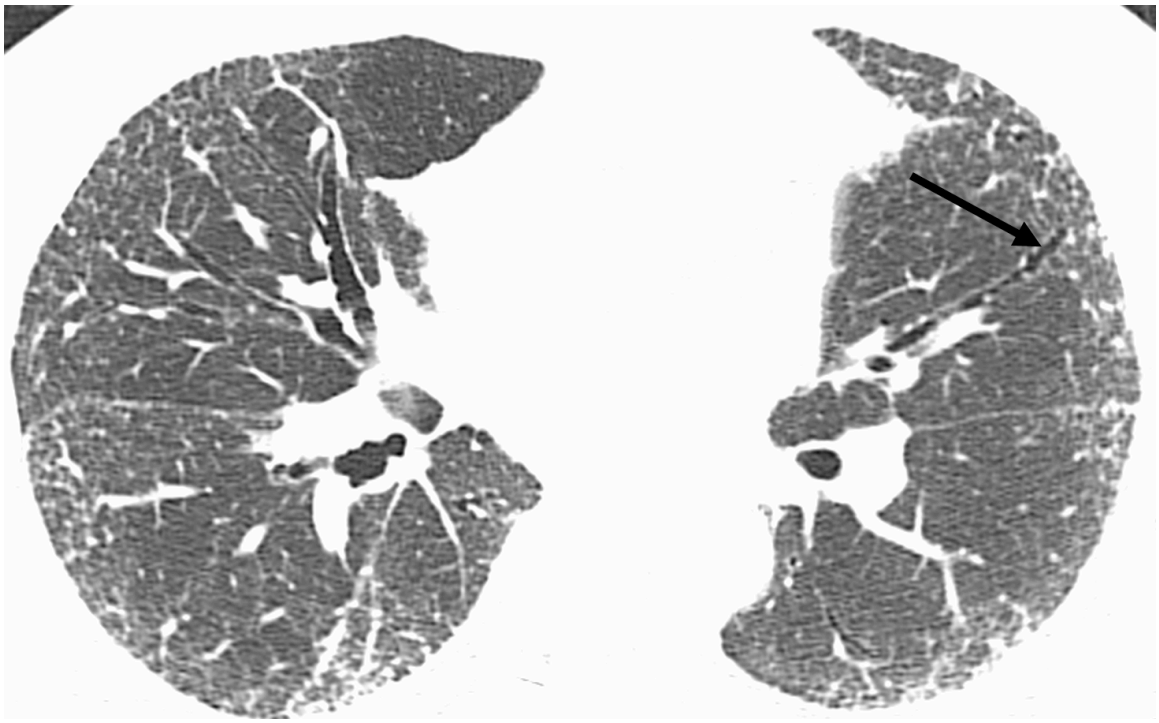
Supplemental Table 6. Diagnostic characteristics of HRCT Possible UIP pattern for pathologic UIP by individual radiologist for the primary analysis

Radiologist	Sensitivity	Specificity	PPV	NPV	AUROC	LR+
1	35.4 (26.6-45.0)	91.2 (87.2-94.3)	62.5 (49.5-74.3)	77.3 (72.3-81.7)	0.63 (0.58-0.68)	4.01 (2.54-6.33)
2	40.7 (31.6-50.4)	91.9 (88.0-94.9	67.6 (55.2-78.5)	78.9 (74.0-83.2)	0.66 (0.61-0.71)	5.03 (3.18-7.96)

Abbreviations: HRCT, high resolution computed tomography; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under receiver operating curve; LR+, likelihood ratio of positive test; UIP, usual interstitial pneumonitis

Supplemental Figure 1.

a.



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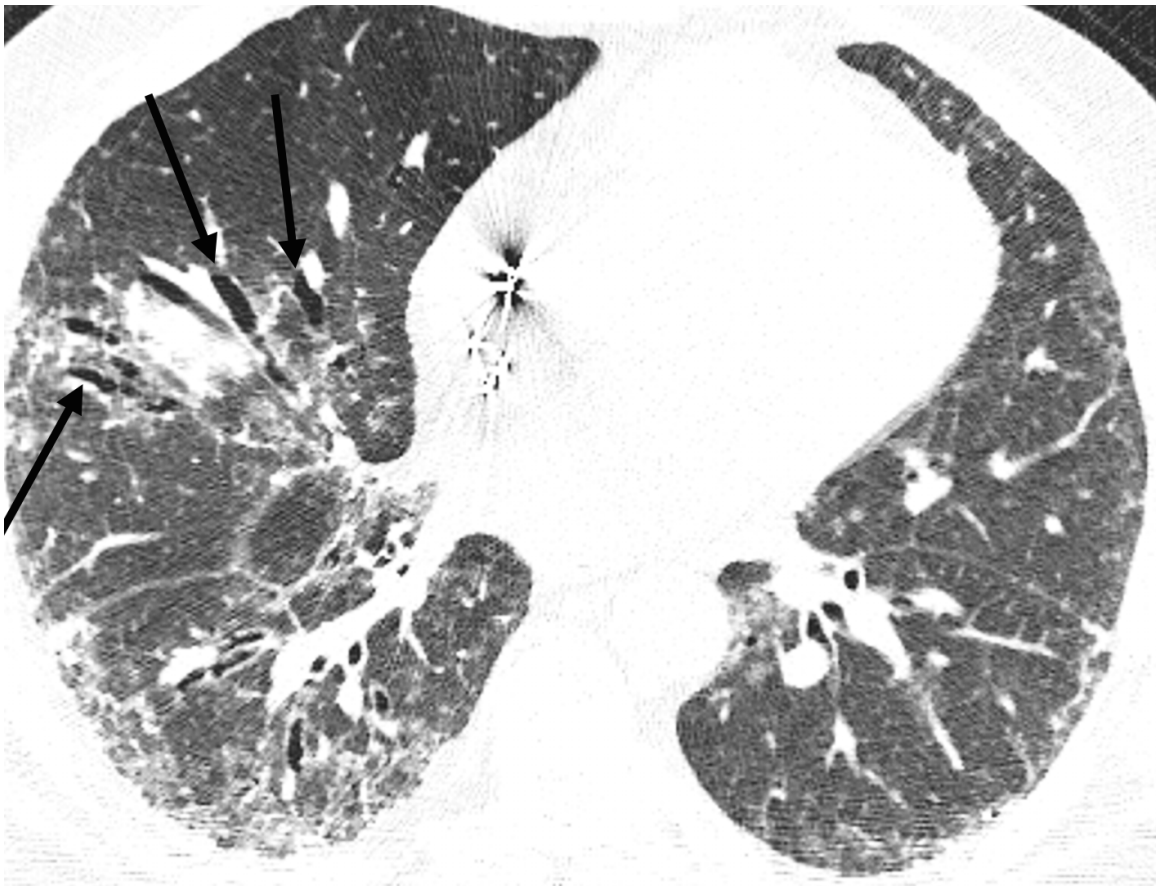

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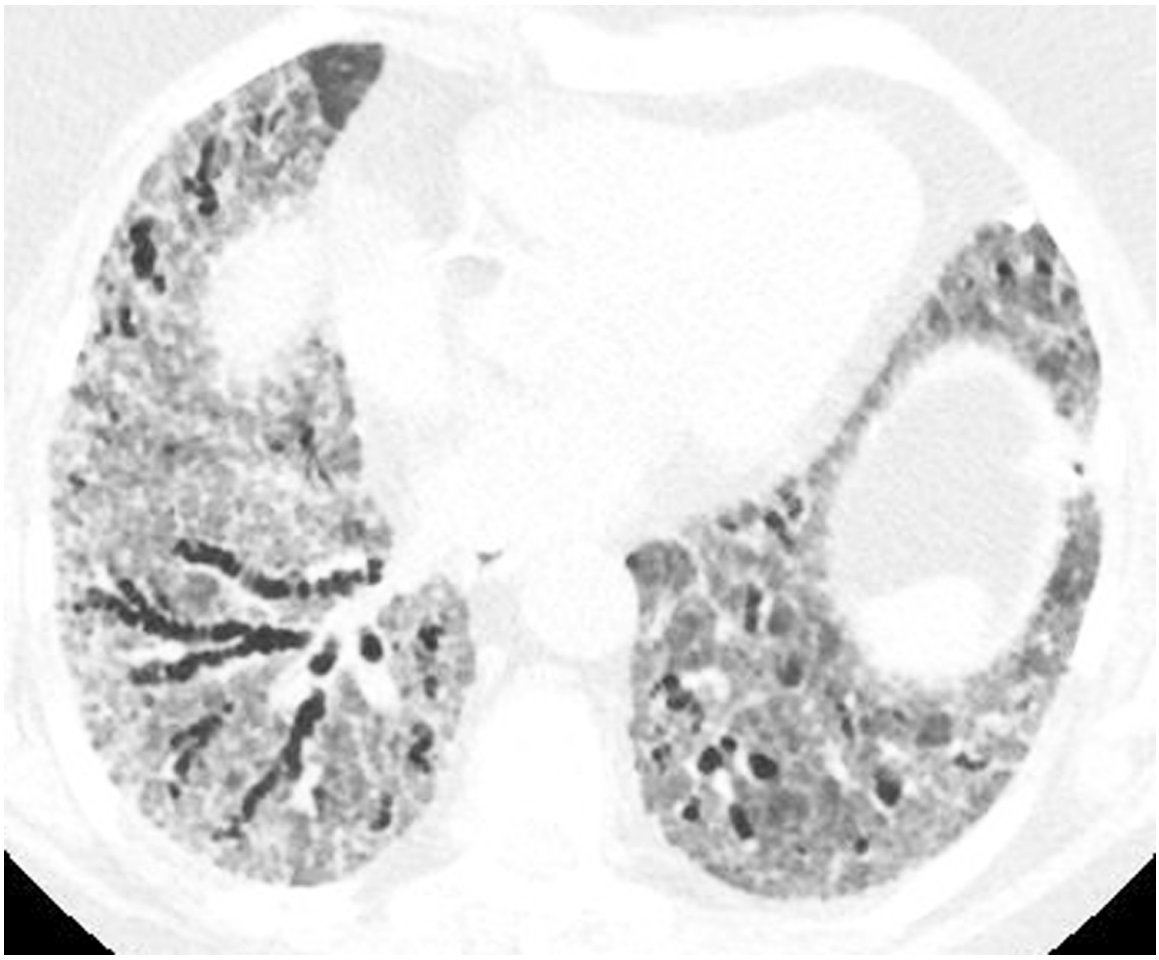

Figure 1a-Mild Traction Bronchiectasis (traction score for lobe = 1)
Figure 1b-Moderate Traction Bronchiectasis (traction score for lobe = 2)
Figure 1c-Severe Traction Bronchiectasis (traction score for lobe = 3)

Supplemental Figure 2.

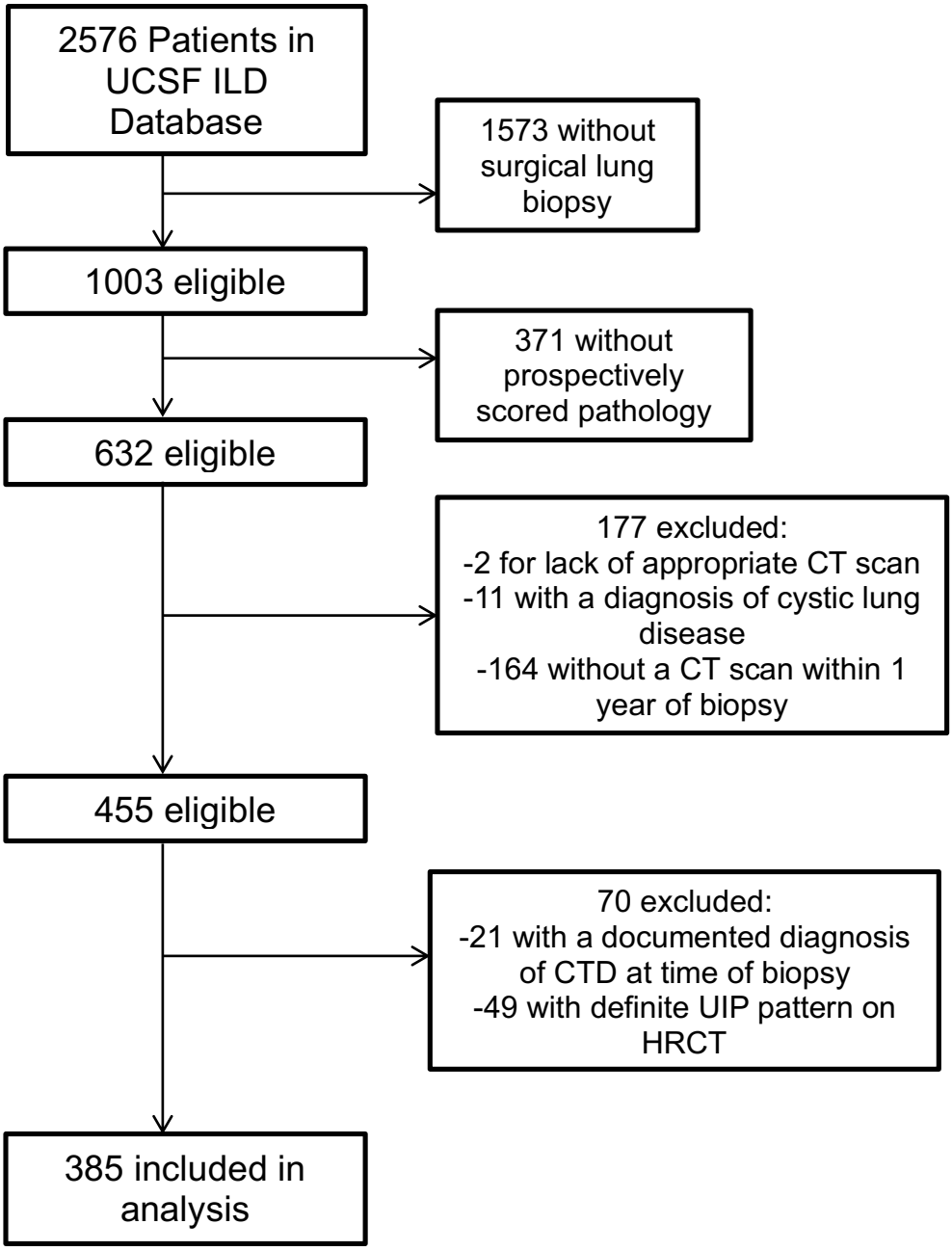

Figure 2. Derivation Cohort Patient selection flow chart

Supplemental Figure 3.

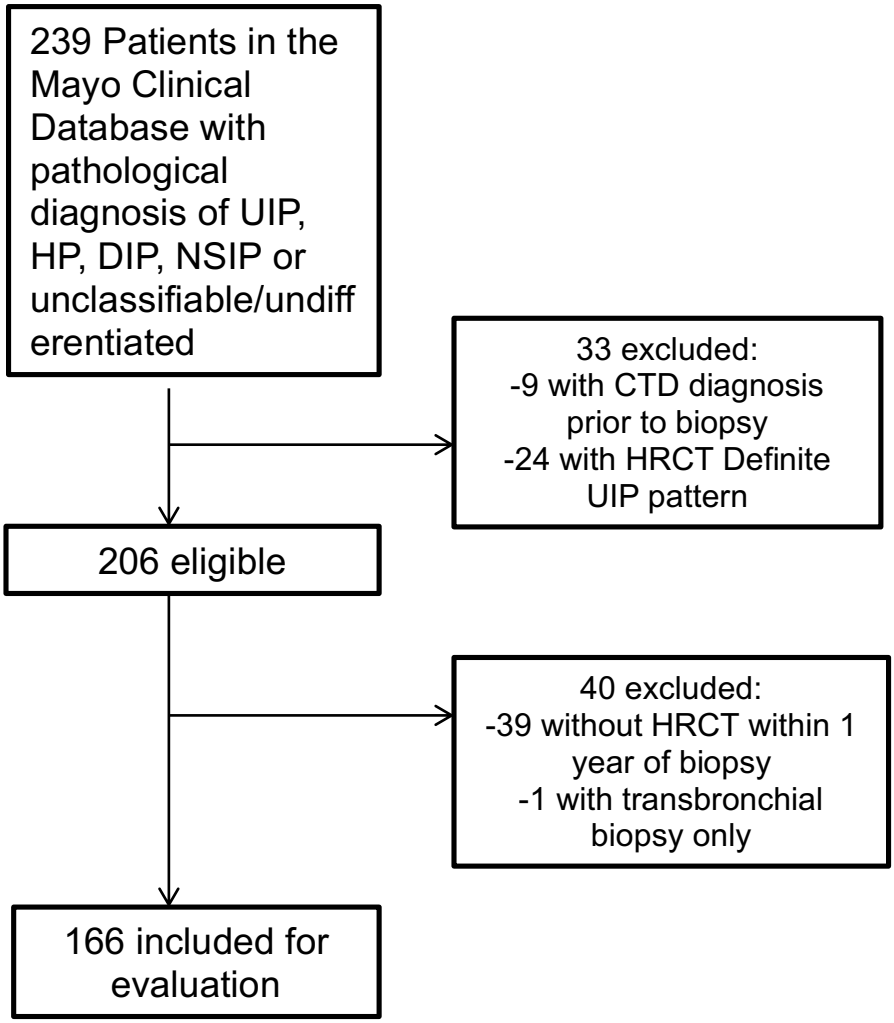

Figure 3. Validation Cohort Patient selection flow chart