Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Eur Respir J. Author manuscript; available in PMC 2023 June 23.

Published in final edited form as:

Eur Respir J. 2023 April ; 61(4): . doi:10.1183/13993003.01245-2022.

Interstitial Lung Disease Progression after Genomic Usual Interstitial Pneumonia Testing

Sachin Chaudhary[1], **S. Sam Weigt**[2], **Manuel L. Ribiero Neto**[3], **Bryan S. Benn**[4], **Janelle Vu Pugashetti**[5], **Rebecca Keith**[6], **Arista Chand**[1], **Scott Oh**[2], **Fayez Kheir**[7], **Vijaya Ramalingam**[4,8], **Joshua Solomon**[6], **Richart Harper**[5], **Joseph A. Lasky**[9], **Justin M. Oldham**[10,11]

[1.]Division of Pulmonary and Critical Care Medicine, University of Arizona

[2.]Division of Pulmonary and Critical Care Medicine, University of California at Los Angeles

[3.]Department of Pulmonary Medicine, Cleveland Clinic

[4.]Division of Pulmonary and Critical Care Medicine; Medical College of Wisconsin

[5.]Division of Pulmonary, Critical Care and Sleep Medicine Medicine; University of California at Davis

[6.]Division of Pulmonary and Critical Care and Sleep Medicine, National Jewish Health

[7.]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital

[8.]Northeast Georgia Physicians Group

[9.]Division of Pulmonary and Critical Care Medicine, Tulane University

[10.]Division of Pulmonary and Critical Care Medicine; University of Michigan

[11.]Department of Epidemiology; University of Michigan

Abstract

A genomic classifier for usual interstitial pneumonia (gUIP) has been shown to predict histologic UIP with high specificity, increasing diagnostic confidence for idiopathic pulmonary fibrosis (IPF). Whether those with positive gUIP classification exhibit a progressive, IPF-like phenotype remains unknown.

A pooled, retrospective analysis of patients who underwent clinically indicated diagnostic bronchoscopy with gUIP testing at seven academic medical centers was performed. We assessed the association between gUIP classification and eighteen-month progression-free survival (PFS) using Cox proportional hazards regression. PFS was defined as the time from gUIP testing to

Corresponding author Justin M Oldham, MD MS, 1150 W. Medical Center Drive, MSRB III, Ann Arbor, MI 48109, oldhamj@med.umich.edu.

Author Contributions: Study design (SC, JMO), bronchoscopy and sample acquisition (SC, SSW, MRN, BSB, RK, SO, FK, VR, JS, RH, JAL, JMO), data collection (SC, SSW, MRN, BSB, RK, AC, FK, VR, JS, JAL, JMO), data analysis (JMO), interpretation of results (SC, SSW, MRN, BSB, JS, JAL, JMO), manuscript preparation (SC, SSW, MRN, BSB, JS, JAL, JMO).

Publisher's Disclaimer: This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

death from any cause, lung transplant, ≥10% relative decline in forced vital capacity (FVC) or censoring at the time of last available FVC measure. Longitudinal change in FVC was then compared between gUIP classification groups using a joint regression model.

Of 238 consecutive patients who underwent gUIP testing, 192 had available follow-up data and were included in the analysis, including 104 with positive gUIP classification and 88 with negative classification. In multivariable analysis, positive gUIP classification was associated with reduced PFS (HR 1.58, 95% CI 0.86-2.92; p=0.14), but this did not reach statistical significance. Mean annual change in FVC was −101.8mL (95% CI −142.7mL, −60.9mL; p<0.001) for those with positive gUIP classification and −73.2mL (95% CI −115.2mL, −31.1mL; p<0.001) for those with negative classification (difference 28.7mL; 95% CI −83.2mL, 25.9mL; p=0.30).

Genomic UIP classification was not associated with differential rates of PFS or longitudinal FVC decline in a multi-center ILD cohort undergoing bronchoscopy as part of the diagnostic evaluation.

Introduction

The Envisia® genomic classifier (Veracyte, South San Francisco, CA USA) is a commercially available, gene expression-based molecular diagnostic tool developed to predict histologic usual interstitial pneumonia (UIP) in patients undergoing transbronchial biopsy.(1, 2) With high specificity for histologic UIP,(1, 2) this tool has been shown to increase diagnostic confidence for idiopathic pulmonary fibrosis (IPF),(1-5) a fatal interstitial lung disease (ILD) without cure other than lung transplant.(6) As a surrogate for histologic UIP, genomic UIP (gUIP) testing may obviate the need for surgical biopsy in those without a confident IPF diagnosis. It remains unclear however, whether the phenotype identified by gUIP approximates that of IPF, characterized by progressive lung function decline and early death.(6)

Uncertainty around the phenotype identified by gUIP testing stems from the fact that several non-IPF interstitial lung diseases (ILDs) can result in radiologic and histologic UIP,(7-9) which has unclear overlap with gUIP. An accurate ILD diagnosis has important prognostic and treatment implications, as immunosuppressive agents may stabilize lung function in patients with autoimmune ILD(10) and chronic hypersensitivity pneumonitis,(11) but harm patients with IPF.(12) IPF is instead treated with anti-fibrotic therapy, as these agents slow lung function decline.(13, 14) Anti-fibrotic therapy also benefits those with progressive non-IPF ILD,(15, 16) but the ability to reliably predict a progressive phenotype remains elusive. Because gUIP testing is likely to influence therapeutic decision-making, it is critical to better understand the phenotype identified by this molecular diagnostic tool.

In this investigation, we conducted a pooled, retrospective analysis of patients who underwent clinically indicated diagnostic bronchoscopy with gUIP testing at seven academic institutions across the United States to determine whether gUIP classification informed clinical outcomes. We hypothesized that positive gUIP classification would be associated with a higher risk of categorical ILD progression and higher rate of longitudinal forced vital capacity decline. Secondary analysis of key subgroups according to radiologic pattern and diagnostic classification was also performed.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Methods

Study Population

This study was performed at the Cleveland Clinic, Medical College of Wisconsin, National Jewish Health, University of Arizona, University of California at Davis, University of California at Los Angeles, and Tulane University. A waiver of consent was provided by institutional review boards at each institution given the retrospective nature of the study. Consecutive ILD patients without a definite UIP pattern on high resolution computed tomography (HRCT) who underwent clinically indicated bronchoscopy with gUIP testing as part of the diagnostic evaluation from April 2018 to July 2021 were eligible for inclusion. Patients without baseline spirometry and those lost to follow-up were excluded.

Clinical data were extracted from the electronic medical record and included baseline demographics, HRCT pattern determined by a chest radiologist at each center according to Fleischner Society criteria(17), and pulmonary function testing (forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO)). Longitudinal data obtained from the medical record included serial lung function, immunosuppressant exposure (prednisone, azathioprine, mycophenolate mofetil, rituximab, cyclophosphamide, tacrolimus, leflunomide, tocilizumab) and anti-fibrotic exposure (nintedanib and pirfenidone). Vital status was determined through review of the medical record and telephone communication with referring providers, patients, and family members of patients.

Statistical Analysis

Continuous variables are reported as means with standard deviation (SD) and compared using the Student's t-test given a normal distribution. Categorical variables are reported as counts with percentage and compared using a Chi-square test or Fischer's exact test, as appropriate. The primary endpoint assessed was progression-free survival (PFS), defined as the time from bronchoscopy to death from any cause, lung transplant, ≥10% relative FVC decline or censoring. Patients were censored at 18 months or the date of last available FVC if performed <18 months after bronchoscopy. PFS was compared between gUIP classification groups using mixed effects univariable and multivariable Cox proportional hazards regression. Both models included center as a random effect to control for center-level heterogeneity in outcomes and patient-level covariates that were collinear with center. (18, 19) The multivariable model also included age, sex and percent predicted FVC, percent predicted DLCO, anti-fibrotic treatment exposure, immunosuppressant treatment exposure and radiologic pattern on high-resolution computed tomography as fixed effects. The proportional hazards assumption was checked and confirmed for each model. A similar mixed effects multivariable logistic regression model (was used to assess the odds of positive gUIP classification among groups stratified by baseline HRCT and odds of IPF diagnosis after positive gUIP classification.

Annual change in FVC (relative and absolute) was then determined using a joint model, which includes a mixed effects submodel to estimate longitudinal change in FVC and a survival submodel to account for the effect of informative dropout (death or lung transplant)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

on the repeated FVC measures.(20-22) Each submodel was adjusted for the same covariates included in the multivariable Cox model described above, along with covariates for time, gUIP classification and time-by-classification interaction term to assess the difference in FVC change between gUIP classification groups. Statistical significance was set at $p<0.05$. All analyses were performed in Stata (StataCorp. 2018. Release 16. College Station, TX).

Results

Patient Characteristics

Two hundred and thirty-eight patients underwent bronchoscopy with gUIP testing (Figure 1). Among eligible patients, 46 were excluded due to missing baseline PFT (n=17) or one-year progression status (n=29). Of the 192 patients included in the final analysis, 104 (54%) were classified as positive for gUIP classification and 88 (46%) were classified as negative. Compared to those with negative gUIP classification, those with positive classification were older and had a higher percentage of males (Table 1). Baseline lung function was similar between groups. A higher proportion of those with positive gUIP classification were diagnosed with IPF and received anti-fibrotic therapy, while a higher proportion of those with negative gUIP classification were diagnosed with non-IPF ILD and received immunosuppressant therapy (Table 1). Among cases diagnosed with non-IPF ILD after gUIP testing, fibrotic hypersensitivity pneumonitis was most common, followed by unclassifiable ILD, connective tissue disease associated ILD, idiopathic non-specific interstitial pneumonia and fibrotic sarcoidosis.

When stratifying the cohort by baseline HRCT pattern, a positive gUIP classification was most common in those with a probable UIP pattern (80.3%, n=57/71), followed by indeterminate (49.2%, n=30/61) and alternate diagnosis patterns (28.3%, n=17/60) (Figure 2). Compared to those with an HRCT pattern indeterminate for UIP, those with a probable UIP pattern had greater than four-fold higher odds of positive gUIP classification (OR 4.74; 95% CI 1.95-11.50; p=0.001), while those with a pattern suggestive of an alternate diagnosis had greater than 2-fold lower odds of having a positive gUIP classification (OR 0.40; 95% CI 0.17-0.93; p=0.03).

When assessing post-bronchoscopy ILD diagnosis, a positive gUIP classification was associated with >30-fold increased odds of an IPF diagnosis (OR 33.75; 95% CI 12.72-89.52; $p<0.001$), but this varied depending on baseline HRCT pattern (Figure 3). Positive gUIP classification was associated with a 7-fold increase in odds of an IPF diagnosis (OR 7.00, 95% CI 0.52-94.96; p=0.14) in those with an alternate diagnosis pattern, but this did not reach statistical significance. Positive gUIP classification was associated with greater than 70-fold increase in odds of an IPF diagnosis among those with an indeterminate pattern (OR 72.16, 95% CI 5.65-922.23; p=0.001) and 60-fold increased odds among those with a probable UIP pattern (OR 60.83, 05% CI 8.56-432.41; $p<0.001$).

Survival Analysis

Over the 18-month follow-up period, PFS was similar between groups ($p_{logrank} = 0.28$) (Figure 4). Positive gUIP classification was associated with nearly 30% increased risk of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

ILD progression in univariable analysis (HR 1.29, 95% CI 0.81-2.07; p=0.29) (Figure 4), but this did not reach statistical significance. After multivariable adjustment, the association between positive gUIP classification and ILD progression nearly doubled (HR 1.58, 9% CI 0.86-2.92; p=0.14), but still did not cross the statistical significance threshold (Table 2). Inclusion of gUIP classification in a multivariable Cox regression model adjusted for age, sex, percent predicted FVC, percent predicted DLCO and IPF diagnosis did not significantly improve PFS prediction (C=0.685 vs 0.687; p=0.16) Radiologic and diagnostic subgroups were then assessed (Table 2). Positive gUIP classification was not associated with increased ILD progression risk in those with probable UIP and indeterminate patterns on HRCT but was associated with increased risk for those with an alternate diagnosis pattern on HRCT (OR 2.74, 95% CI 1.12-6.69; p=0.03) (Table 2). Similar results were observed when stratifying by post-bronchoscopy diagnosis. Positive gUIP classification was not associated with increased ILD progression risk in those diagnosed with IPF, but was associated with increased progression risk in those diagnosed with a non-IPF ILD diagnosis (OR 2.51, 95% CI 1.16-5.45; p=0.02) (Table 2).

Longitudinal Change in FVC

The mean annual change in FVC following genomic UIP testing for all patients was −3.61% (95% CI - 4.77%, −2.45%; p<0.001), which corresponded to an absolute change of −88.8mL (95% CI - 119.1mL, −56.5mL; p<0.001). Those with a negative gUIP classification experienced a mean annual change in FVC of −73.2mL (95% CI −115.2mL, −31.1mL; p<0.001), while those with positive gUIP classification displayed a change of −101.8mL (95% CI −142.7mL, −60.9mL; p<0.001), with a between-group difference of 28.7mL (95% CI −83.2mL, 25.9mL; p=0.30). Subgroup analysis according to HRCT pattern was not performed as model convergence could not be achieved due to small sample size.

Discussion

In this multi-center investigation, we showed that a positive gUIP classification was strongly associated with baseline HRCT pattern and subseqeunt IPF diagnosis, but did not predict differential eighteen-month progression-free survival or longitudinal change in FVC. In subgroup analysis, positive gUIP classification was associated with reduced PFS in those with an alternative diagnosis pattern on HRCT and those diagnosed with non-IPF ILD following gUIP testing, but these subgroups were small. Little difference in outcomes was observed among gUIP classification strata in those with probable UIP or indeterminate patterns on HRCT or those diagnosed with IPF. To our knowledge, these findings are the first to assess clinical outcomes as they relate to gUIP classification and suggest that gUIP testing does not predict a progressive ILD phenotype.

The Envisia® gUIP classifier is the first commercially available molecular diagnostic tool marketed to predict histologic UIP,(1-5) the hallmark feature of IPF on surgical lung biopsy.(6) By applying a machine learning algorithm to transcriptomic data generated from homogenized lung tissue acquired via transbronchial biopsy, this tool has been shown to predict histologic UIP with high specificity and positive predictive value, increasing diagnostic confidence for IPF.(1-5) Our data support this, as gUIP classification was strongly

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

associated with subsequent IPF diagnosis, especially among those with a probable UIP or indeterminate pattern on HRCT, increasing the odds of an IPF diagnosis by greater than 60-fold in each group.

While this tool was developed to obviate the need for surgical lung biopsy, it remains unclear whether the histologic UIP identified by gUIP testing is specific to IPF, as this pattern can be observed in other forms of fibrosing ILD, including chronic hypersensitivity pneumonitis,(23), asbestosis(24) and ILD due to connective tissue disease.(25-28) Discriminating between these conditions and IPF remains important given potential differences in survival and treatment approach.(8-10) Those with some forms of non-IPF ILD benefit from immunosuppressant therapy,(10, 11) while those with IPF are harmed by this approach.(12) Recent anti-fibrotic clinical trials suggest that this class of therapy provides benefit for those with progressive non-IPF ILD,(15, 29) but their utility in those without a clearly progressive phenotype is unclear. While IPF is an invariably progressive disease, non-IPF ILD is not and the ability to predict a progressive phenotype among these patients remains elusive. Most anti-fibrotic trials performed in non-IPF ILD have required objective evidence of ILD progression prior to trial enrollment and payors may require similar findings before approval of anti-fibrotic therapy for non-IPF ILD. As such, efforts to identify at-risk patients prior to ILD progression are critically needed.

Patients for this study were recruited while surgical lung biopsy was still recommended to diagnose IPF in patients with probable UIP on HRCT.(30) This practice is likely to change, as recently released IPF diagnostic guideline now allow patients with probable UIP to receive a diagnosis of IPF in the appropriate clinical context.(6) This change in diagnostic classification reflects studies showing strong correlation between histologic UIP and probable UIP pattern on HRCT, (17, 31-33) and similar rates of FVC decline between those with definite and probable UIP on HRCT.(34) Our data also support this approach, as 77% of those with probable UIP on HRCT had positive gUIP classification, leading nearly all to be diagnosed with IPF. These findings, along with the recent update to the IPF diagnostic guideline suggest little reason to pursue bronchoscopy and gUIP testing in those with a probable UIP pattern on HRCT. Outcomes also did not vary in those with an indeterminate pattern on HRCT. Whether this reflects a true absence of association, or an indication bias that led cohort enrichment with patients likely to progress irrespective of gUIP classification remains unclear.

While gUIP classification is unlikely to influence diagnosis in those with an alternate pattern on HRCT, our data suggest that a positive classification could potentially predict a progressive non-IPF ILD phenotype in such patients. These results must be viewed with caution however, as the number of patients with positive gUIP classification and alternate diagnosis pattern on HRCT was small (n=17). At present, bronchoscopy only contributes meaningful information in a minority of patients with ILD, namely those with hypersensitivity pneumonitis(35) and sarcoidosis(36). There exists little reason to perform bronchoscopy in those diagnosed with connective tissue-disease associated ILD, as results are unlikely to change management.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

We defined ILD progression as death, lung transplant or ≥10% FVC decline in this study. This was necessary given the low mortality often observed with short-term studies. While death and lung transplant invariably suggest a progressive phenotype, categorical declines in FVC of ≥10% often precede these terminal events and serves as a reliable measure of ILD progression.(37, 38) We also assessed longitudinal change in FVC, which is used in clinical trials assessing drug efficacy, as this provides a more easily measured variable of clinical change compared to categorical events.(13-16) While this cohort represented the largest real-world cohort with gUIP testing reported to date, the direction of effect for gUIP classification suggest that the study was potentially power limited. However, nearly 800 patients would be required to observe a statistical difference between groups based on 12-month PFS of 0.76 in the gUIP negative group and 0.67 in the gUIP positive group.

This investigation has several limitations. First, the retrospective nature of the study resulted in variable follow-up times. Consecutive inclusion of patients from centers across the US is assumed to have resulted in a representative sample, but incomplete follow-up could have influenced results. Further, the relatively short follow-up time may have also impacted our findings, as differences in outcomes may have become more apparent over several years of follow-up. Next, variability in clinical practice across these centers may have also influenced our results. While all patients underwent bronchoscopy as part of the ILD diagnostic evaluation, the rationale for bronchoscopy and pre-test diagnosis likely varied across centers, especially as some centers received direct referrals for gUIP testing without antecedent evaluation through an ILD program. Variability in practice patterns also likely extended to interpretation of HRCT pattern, along with treatment decisions. Only 60% of patients with a positive gUIP classification, most of which were diagnosed with IPF, received anti-fibrotic therapy. The reason underpinning this remains unclear, but low anti-fibrotic adoption is a known problem in the United States.(39) We attempted to adjust for this by modeling center as a random effect, which controls for center-level outcome heterogeneity and patient-level covariates that correlated with center.(18, 19).

Conclusion

While gUIP may serve as a reliable surrogate for histologic UIP, gUIP classification was not associated with differential outcomes or FVC decline. These findings suggest that patients referred for gUIP testing have a high pre-test probability of developing a progressive ILD, whether IPF or a non-IPF ILD. These findings did vary according to baseline HRCT pattern, leaving open the possibility that gUIP may serve as a prognostic biomarker in a subgroup of patients with ILD. But until such a group is identified, our results suggest that gUIP testing has diagnostic value, but little prognostic value.

Funding:

NHLBI (K23HL138190)

References

1. Pankratz DG, Choi Y, Imtiaz U, Fedorowicz GM, Anderson JD, Colby TV, Myers JL, Lynch DA, Brown KK, Flaherty KR, Steele MP, Groshong SD, Raghu G, Barth NM, Walsh PS, Huang

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

J, Kennedy GC, Martinez FJ. Usual Interstitial Pneumonia Can Be Detected in Transbronchial Biopsies Using Machine Learning. Ann Am Thorac Soc 2017; 14: 1646–1654. [PubMed: 28640655]

2. Raghu G, Flaherty KR, Lederer DJ, Lynch DA, Colby TV, Myers JL, Groshong SD, Larsen BT, Chung JH, Steele MP, Benzaquen S, Calero K, Case AH, Criner GJ, Nathan SD, Rai NS, Ramaswamy M, Hagmeyer L, Davis JR, Gauhar UA, Pankratz DG, Choi Y, Huang J, Walsh PS, Neville H, Lofaro LR, Barth NM, Kennedy GC, Brown KK, Martinez FJ. Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study. Lancet Respir Med 2019; 7: 487–496. [PubMed: 30948346]
3. Richeldi L, Scholand MB, Lynch DA, Colby TV, Myers JL, Groshong SD, Chung JH, Benzaquen S, Nathan SD, Davis JR, Schmidt SL, Hagmeyer L, Sonetti D, Hetzel J, Criner GJ, Case AH, Ramaswamy M, Calero K, Gauhar UA, Patel NM, Lancaster L, Choi Y, Pankratz DG, Walsh PS, Lofaro LR, Huang J, Bhorade SM, Kennedy GC, Martinez FJ, Raghu G. Utility of a Molecular Classifier as a Complement to HRCT to Identify Usual Interstitial Pneumonia. Am J Respir Crit Care Med 2020.
4. Kheir F, Alkhatib A, Berry GJ, Daroca P, Diethelm L, Rampolla R, Saito S, Smith DL, Weill D, Bateman M, Abdelghani R, Lasky JA. Using Bronchoscopic Lung Cryobiopsy and a Genomic Classifier in the Multidisciplinary Diagnosis of Diffuse Interstitial Lung Diseases. Chest 2020.
5. Lasky JA, Case A, Unterman A, Kreuter M, Scholand MB, Chaudhary S, Lofaro LR, Johnson M, Huang J, Bhorade SM, Kennedy GC. The Impact of the Envisia Genomic Classifier in the Diagnosis and Management of Patients with Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc 2022; 19: 916–924. [PubMed: 34889723]
6. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers JL, Nicholson AG, Ryerson CJ, Strek ME, Troy LK, Wijsenbeek M, Mammen MJ, Hossain T, Bissell BD, Herman DD, Hon SM, Kheir F, Khor YH, Macrea M, Antoniou KM, Bouros D, Buendia-Roldan I, Caro F, Crestani B, Ho L, Morisset J, Olson AL, Podolanczuk A, Poletti V, Selman M, Ewing T, Jones S, Knight SL, Ghazipura M, Wilson KC. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022; 205: e18–e47. [PubMed: 35486072]
7. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, Frankel SK, Hobbs SB, Huie TJ, Ketzer J, Mannina A, Olson AL, Russell G, Tsuchiya Y, Yunt ZX, Zelarney PT, Brown KK, Swigris JJ. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016; 47: 588–596. [PubMed: 26585429]
8. Salisbury ML, Gu T, Murray S, Gross BH, Chughtai A, Sayyouh M, Kazerooni EA, Myers JL, Lagstein A, Konopka KE, Belloli EA, Sheth JS, White ES, Holtze C, Martinez FJ, Flaherty KR. Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory. Chest 2019; 155: 699–711. [PubMed: 30243979]
9. Ryerson CJ, Urbania TH, Richeldi L, Mooney JJ, Lee JS, Jones KD, Elicker BM, Koth LL, King TE Jr., Wolters PJ, Collard HR. Prevalence and prognosis of unclassifiable interstitial lung disease. Eur Respir J 2013; 42: 750–757. [PubMed: 23222877]
10. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet 2012; 380: 689–698. [PubMed: 22901890]
11. Morisset J, Johannson KA, Vittinghoff E, Aravena C, Elicker BM, Jones KD, Fell CD, Manganas H, Dube BP, Wolters PJ, Collard HR, Ryerson CJ, Ley B. Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis. Chest 2017; 151: 619–625. [PubMed: 27816444]
12. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012; 366: 1968–1977. [PubMed: 22607134]
13. King TE Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, Group AS. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2083–2092. [PubMed: 24836312]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

14. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR, Investigators IT. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2071–2082. [PubMed: 24836310]
15. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzlaff K, Stowasser S, Coeck C, Clerisme-Beaty E, Rosenstock B, Quaresma M, Haeufel T, Goeldner RG, Schlenker-Herceg R, Brown KK, Investigators IT. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med 2019.
16. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, Axmann J, Kirchgaessler KU, Cottin V. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: design of a double-blind, randomised, placebo-controlled phase II trial. BMJ Open Respir Res 2018; 5: e000289.
17. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, Goldin JG, Hansell DM, Inoue Y, Johkoh T, Nicholson AG, Knight SL, Raoof S, Richeldi L, Ryerson CJ, Ryu JH, Wells AU. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med 2018; 6: 138–153. [PubMed: 29154106]
18. Todd JL, Neely ML, Kopetskie H, Sever ML, Kirchner J, Frankel CW, Snyder LD, Pavlisko EN, Martinu T, Tsuang W, Shino MY, Williams N, Robien MA, Singer LG, Budev M, Shah PD, Reynolds JM, Palmer SM, Belperio JA, Weigt SS. Risk Factors for Acute Rejection in the First Year after Lung Transplant. A Multicenter Study. Am J Respir Crit Care Med 2020; 202: 576–585. [PubMed: 32379979]
19. Austin PC. A Tutorial on Multilevel Survival Analysis: Methods, Models and Applications. Int Stat Rev 2017; 85: 185–203. [PubMed: 29307954]
20. Crowther MJ, Abrams KR, Lambert PC. Flexible parametric joint modelling of longitudinal and survival data. Stat Med 2012; 31: 4456–4471. [PubMed: 23037571]
21. Hogan JW, Laird NM. Model-based approaches to analysing incomplete longitudinal and failure time data. Stat Med 1997; 16: 259–272. [PubMed: 9004396]
22. Oldham JM, Lee CT, Wu Z, Bowman WS, Vu Pugashetti J, Dao N, Tonkin J, Seede H, Echt G, Adegunsoye A, Chua F, Maher TM, Garcia CK, Strek ME, Newton CA, Molyneaux PL. Lung function trajectory in progressive fibrosing interstitial lung disease. Eur Respir J 2021.
23. Myers JL. Hypersensitivity pneumonia: the role of lung biopsy in diagnosis and management. Mod Pathol 2012; 25 Suppl 1: S58–67. [PubMed: 22214971]
24. Gulati M, Redlich CA. Asbestosis and environmental causes of usual interstitial pneumonia. Curr Opin Pulm Med 2015; 21: 193–200. [PubMed: 25621562]
25. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, Haslam PL, Vassilakis DA, Black CM, du Bois RM. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002; 165: 1581–1586. [PubMed: 12070056]
26. Fischer A, Swigris JJ, Groshong SD, Cool CD, Sahin H, Lynch DA, Curran-Everett D, Gillis JZ, Meehan RT, Brown KK. Clinically significant interstitial lung disease in limited scleroderma: histopathology, clinical features, and survival. Chest 2008; 134: 601–605. [PubMed: 18403656]
27. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, Kitaichi M. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest 2005; 127: 2019–2027. [PubMed: 15947315]
28. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjogren syndrome. Chest 2006; 130: 1489–1495. [PubMed: 17099028]
29. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, Bonnet R, Grohe C, Held M, Wilkens H, Hammerl P, Koschel D, Blaas S, Wirtz H, Ficker JH, Neumeister W, Schonfeld N, Claussen M, Kneidinger N, Frankenberger M, Hummler S, Kahn N, Tello S, Freise J, Welte T, Neuser P, Gunther A, investigators R. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med 2021.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

30. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldan I, Selman M, Travis WD, Walsh S, Wilson KC, American Thoracic Society ERSJRS, Latin American Thoracic S. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018; 198: e44–e68. [PubMed: 30168753]

31. Chung JH, Montner SM, Adegunsoye A, Lee C, Oldham JM, Husain AN, MacMahon H, Noth I, Vij R, Strek ME. CT Findings, Radiologic-Pathologic Correlation, and Imaging Predictors of Survival for Patients With Interstitial Pneumonia With Autoimmune Features. AJR Am J Roentgenol 2017; 208: 1229–1236. [PubMed: 28350485]

32. Chung JH, Oldham JM, Montner SM, Vij R, Adegunsoye A, Husain AN, Noth I, Lynch DA, Strek ME. CT-Pathologic Correlation of Major Types of Pulmonary Fibrosis: Insights for Revisions to Current Guidelines. AJR Am J Roentgenol 2018; 210: 1034–1041. [PubMed: 29547052]

33. Raghu G, Lynch D, Godwin JD, Webb R, Colby TV, Leslie KO, Behr J, Brown KK, Egan JJ, Flaherty KR, Martinez FJ, Wells AU, Shao L, Zhou H, Pedersen PS, Sood R, Montgomery AB, O'Riordan TG. Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial. Lancet Respir Med 2014; 2: 277–284. [PubMed: 24717624]

34. Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, Stowasser S, Schlenker-Herceg R, Hansell DM. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria. Am J Respir Crit Care Med 2017; 195: 78–85. [PubMed: 27331880]

35. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, Bargagli E, Chung JH, Collins BF, Bendstrup E, Chami HA, Chua AT, Corte TJ, Dalphin JC, Danoff SK, Diaz-Mendoza J, Duggal A, Egashira R, Ewing T, Gulati M, Inoue Y, Jenkins AR, Johannson KA, Johkoh T, Tamae-Kakazu M, Kitaichi M, Knight SL, Koschel D, Lederer DJ, Mageto Y, Maier LA, Matiz C, Morell F, Nicholson AG, Patolia S, Pereira CA, Renzoni EA, Salisbury ML, Selman M, Walsh SLF, Wuyts WA, Wilson KC. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 202: e36–e69. [PubMed: 32706311]

36. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, Abston E, Bernstein RC, Blankstein R, Chen ES, Culver DA, Drake W, Drent M, Gerke AK, Ghobrial M, Govender P, Hamzeh N, James WE, Judson MA, Kellermeyer L, Knight S, Koth LL, Poletti V, Raman SV, Tukey MH, Westney GE, Baughman RP. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 201: e26–e51. [PubMed: 32293205]

37. Collard HR, King TE Jr., Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003; 168: 538–542. [PubMed: 12773325]

38. Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, Hansell DM, du Bois RM, Wells AU. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35: 830–836. [PubMed: 19840957]

39. Dempsey TM, Payne S, Sangaralingham L, Yao X, Shah ND, Limper AH. Adoption of the Antifibrotic Medications Pirfenidone and Nintedanib for Patients with Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc 2021; 18: 1121–1128. [PubMed: 33465323]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

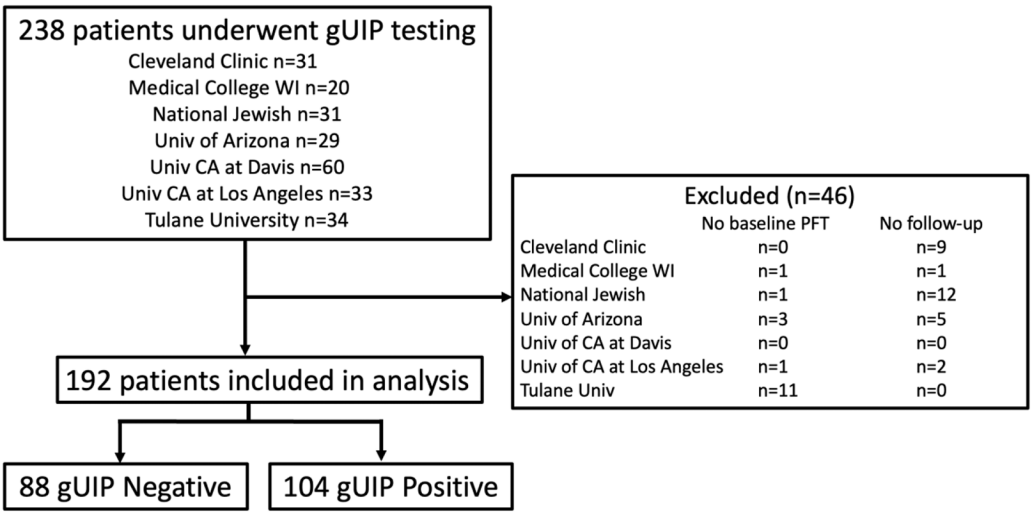

Figure 1.
Strobe diagram

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

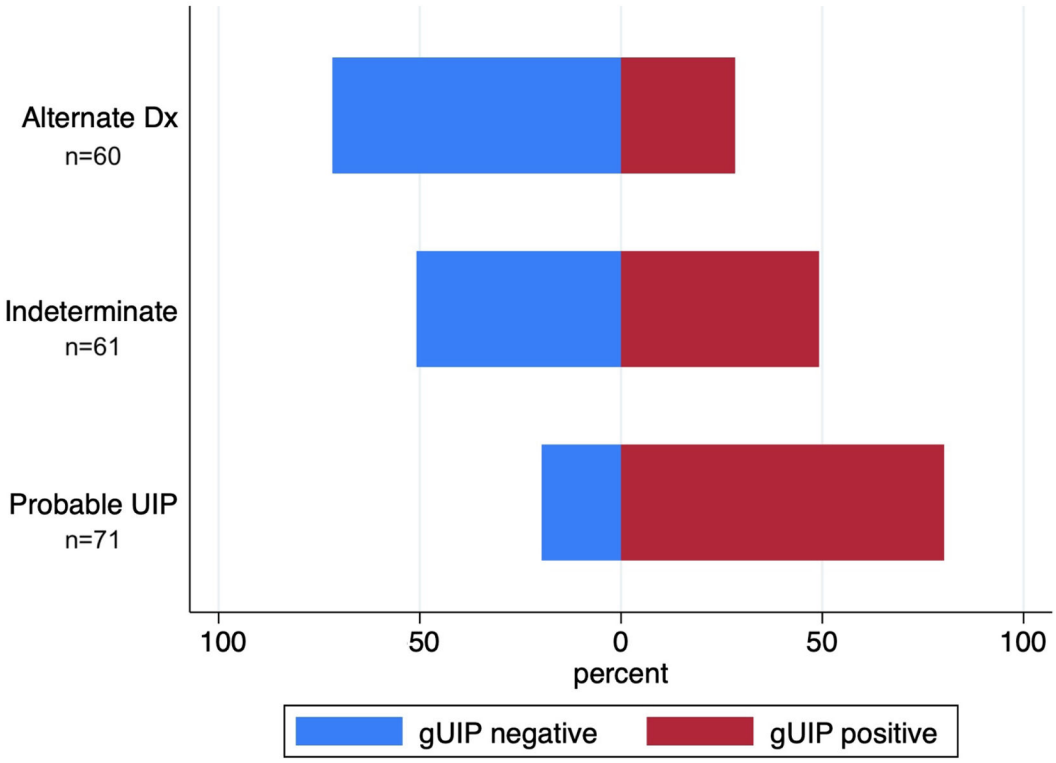

Figure 2.
Genomic UIP classification stratified by baseline HRCT pattern

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

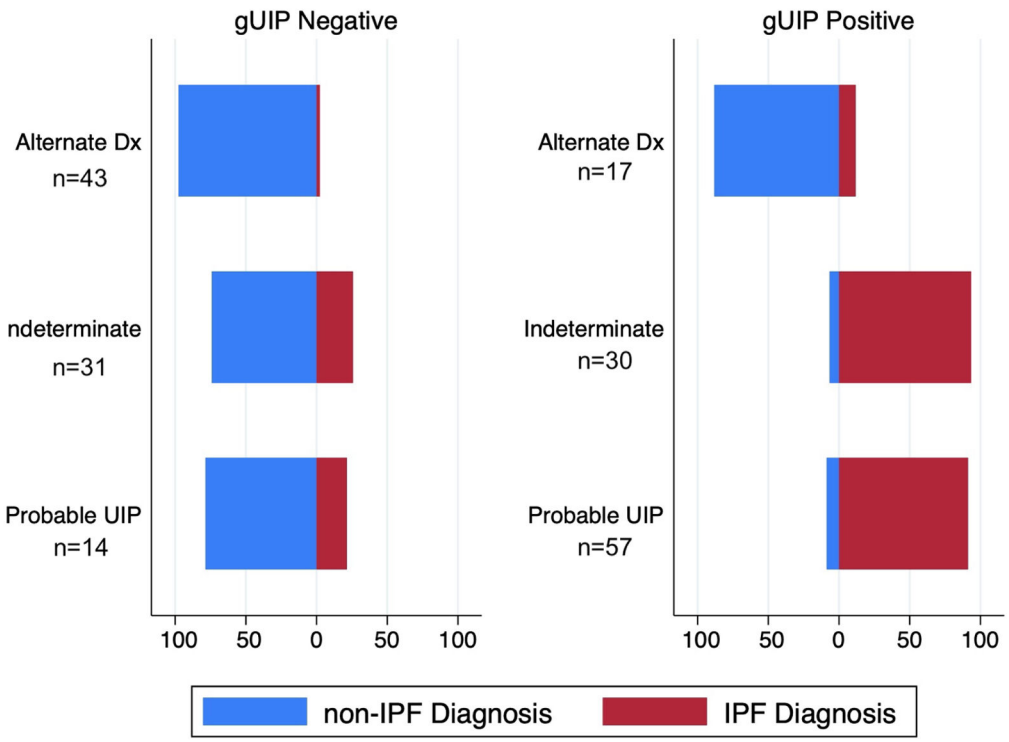

Figure 3.
ILD diagnosis following gUIP testing stratified by baseline HRCT pattern

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

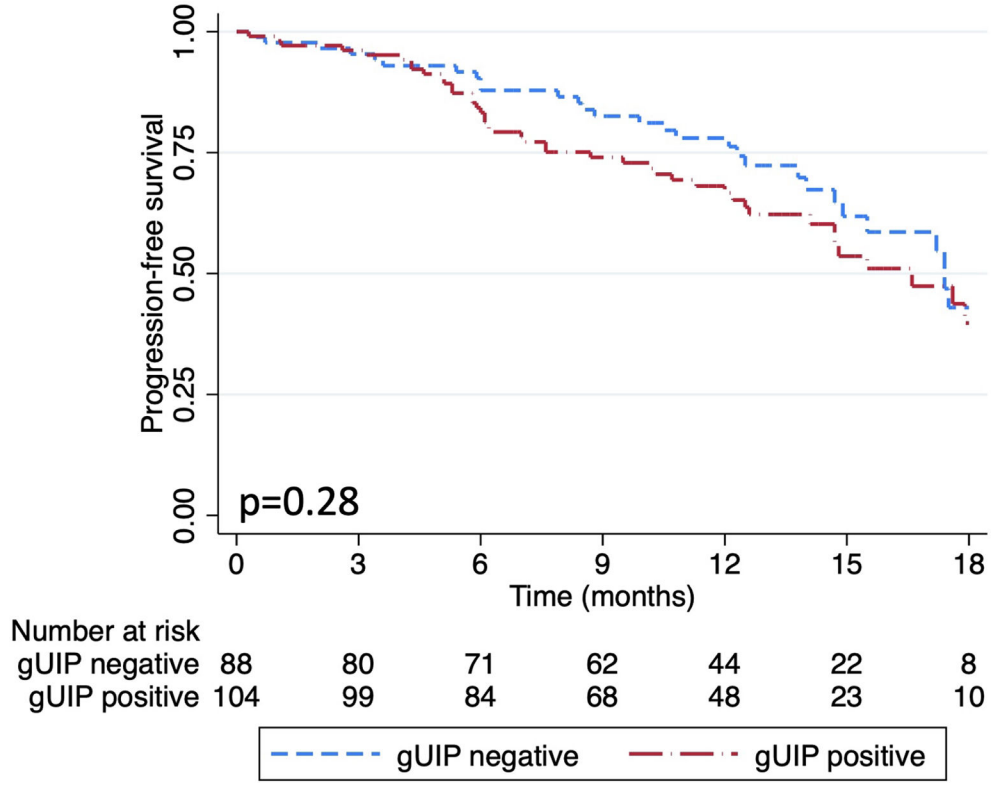

Figure 4.

Kaplan-Meier survival curve comparing progression-free survival between groups stratified by genomic UIP classification.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Patient characteristics, treatments, diagnoses and outcomes stratified by genomic UIP classification

Baseline characteristics	**gUIP Negative (n=88)**	**gUIP Positive (n=104)**	**p-value**
Age, mean (SD)	68.5 (9.6)	71.2 (7.2)	0.03
Male sex, n (%)	46 (52.3)	76 (73.1)	0.003
Pulmonary Function			
FVC % predicted, mean	72.2 (18.6)	73.6 (19.6)	0.61
DLCO % predicted, mean *	56.4 (19.2)	54.3 (18.2)	0.45
Diagnosis after gUIP testing			
Idiopathic Pulmonary Fibrosis	12 (13.6)	82 (78.9)	<0.001
Non-idiopathic pulmonary fibrosis	76 (86.4)	22 (21.1)	<0.001
Fibrotic Hypersensitivity pneumonitis	29 (33.0)	11 (10.6)	
Unclassifiable ILD	26 (29.5)	6 (4.8)	
Connective tissue disease associated ILD	8 (9.1)	4 (3.8)	
Idiopathic non-specific interstitial pneumonia	5 (5.7)	1 (1.0)	
Sarcoidosis	3 (3.4)	0 (0)	
Other ILDs	5 (5.7)	0 (0)	
Treatment after gUIP testing			
Anti-fibrotic	18 (20.5)	61 (58.7)	<0.001
Immunosuppressant **	46 (52.3)	11 (10.6)	<0.001
Outcomes after gUIP testing			
Death	10 (11.4)	8 (7.7)	0.39
Lung transplant	1 (1.1)	2 (1.9)	1.00
FVC decline ≥10% relative to baseline	18 (20.5)	33 (31.7)	0.08
Follow-up months, median (IQR)	11.9 (7.4-15.2)	11.5 (6.9-14.7)	0.84

* missing data: gUIP negative n=84; gUIP negative n=103

** mycophenolate mofetil, azathioprine, leflunomide, tacrolimus or prednisone ≥20mg daily

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2.

Risk of ILD progression associated with genomic UIP classification

Group	gUIP Negative (n=88)		gUIP Positive (n=104)		Progression risk*					
					Unadjusted			Adjusted		
	stable	progressive	stable	progressive	HR	95%CI	p	HR	95%CI	p
All patients	59	29	61	43	1.29	0.81-2.07	0.29	1.58	0.86-2.92	0.14
HRCT Pattern										
Alternate Diagnosis	31	12	6	11	2.52	1.11-5.71	0.03	2.74	1.12-6.69	0.03
Indeterminate	19	12	18	12	1.07	0.42-2.72	0.79	0.98	0.29-3.30	0.98
Probable UIP	9	5	37	20	1.13	0.40-3.18	0.82	1.6	0.39-6.51	0.51
Diagnosis after gUIP classification										
IPF	6	6	52	30	1.06	0.40-2.77	0.91	1.55	0.40-5.97	0.53
Non-IPF ILD	53	23	9	13	2.05	1.04-4.05	0.04	2.51	1.16-5.45	0.02

*Estimated using a mixed effects Cox proportional hazards regression model with center included as a random effect. The adjusted model additionally included age, sex, percent predicted FVC, percent predicted DLCO, anti-fibrotic exposure, immunosuppressant expose and high-resolution computed tomography pattern as fixed effects.