ORIGINAL ARTICLE

Diagnostic Likelihood Thresholds That Define a Working Diagnosis of Idiopathic Pulmonary Fibrosis

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Abstract

Rationale: The level of diagnostic likelihood at which physicians prescribe antifibrotic therapy without requesting surgical lung biopsy (SLB) in patients suspected of idiopathic pulmonary fibrosis (IPF) is unknown.

Objectives: To determine how often physicians advocate SLB in patient subgroups defined by IPF likelihood and risk associated with SLB, and to identify the level of diagnostic likelihood at which physicians prescribe antifibrotic therapy with requesting SLB.

Methods: An international cohort of respiratory physicians evaluated 60 cases of interstitial lung disease, giving: *1*) differential diagnoses with diagnostic likelihood; *2*) a decision on the need for SLB; and *3*) initial management. Diagnoses were stratified according to diagnostic likelihood bands described by Ryerson and colleagues.

Measurements and Main Results: A total of 404 physicians evaluated the 60 cases (24,240 physician–patient evaluations). IPF was part of the differential diagnosis in 9,958/24,240 (41.1%) of all physician–patient evaluations. SLB was requested in 8.1%, 29.6%, and 48.4% of definite, provisional high-confidence and provisional low-confidence diagnoses of IPF, respectively. In 63.0% of provisional high-confidence IPF diagnoses, antifibrotic therapy was prescribed without requesting SLB. No significant mortality difference was observed between cases given a definite diagnosis of IPF (90–100% diagnostic likelihood) and cases given a provisional high-confidence IPF diagnosis (hazard ratio, 0.97; $P = 0.65$; 95% confidence interval, 0.90–1.04).

Conclusions: Most respiratory physicians prescribe antifibrotic therapy without requesting an SLB if a provisional high-confidence diagnosis or "working diagnosis" of IPF can be made (likelihood $\geq$ 70%). SLB is recommended in only a minority of patients with suspected, but not definite, IPF.

Keywords: working diagnosis; idiopathic pulmonary fibrosis; surgical lung biopsy; clinical practice guidelines; antifibrotic therapy

At a Glance Commentary

Scientific Knowledge on the Subject: The current clinical practice guideline for idiopathic pulmonary fibrosis (IPF), published in 2018 as a joint statement from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society, sets criteria for making a definite IPF diagnosis. This guideline includes a conditional recommendation to perform surgical lung biopsy (SLB) in patients if a definite IPF diagnosis cannot be made. The influence of diagnostic likelihood in nondefinitive IPF cases on the decision to perform SLB and initiate antifibrotic therapy is not known.

What This Study Adds to the Field: Our findings suggest that most respiratory physicians managing patients with IPF prescribe antifibrotic therapy without requesting an SLB if a "working diagnosis" of IPF can be made (defined as a diagnostic likelihood of 70% or more).

The value of making a diagnosis of idiopathic pulmonary fibrosis (IPF) is that it informs patients and physicians as to the correct treatment, natural history, and treated course. The current clinical practice guideline for IPF, published in 2018 as a joint statement from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society sets criteria for making a definite IPF diagnosis (1). However, in a large subgroup of patients with IPF who cannot undergo surgical lung biopsy (SLB), a definite diagnosis is not possible (2, 3). In these patients, a physician must decide to either prescribe antifibrotic therapy empirically, treat for an alternative disorder, or to monitor without initiating any treatment (2). Many of these patients with IPF are prescribed antifibrotic therapy based on a "working diagnosis" (defined as a nondefinite diagnosis made with sufficient confidence to justify disease-specific therapy), a concept recently endorsed by the Fleischner Society (4). However, the level of diagnostic likelihood that defines a working diagnosis has not been formally evaluated.

In 2017, Ryerson and colleagues (5) devised an ontological framework for classifying diagnostic likelihood in fibrotic interstitial lung disease (ILD). We examined the influence of the perceived likelihood of a diagnosis of IPF on biopsy and treatment decisions, made by a large, international cohort of nonacademic and university-affiliated respiratory physicians. Our primary goals were *1*) to determine how often physicians advocate SLB in patient subgroups defined by IPF likelihood and risk associated with SLB and *2*) to identify the level of diagnostic likelihood at which physicians choose to institute antifibrotic therapy.

Methods

Case Collection and Participating Physicians

The National Health Service Health Research Authority approved the study protocol, and, for this retrospective examination of clinically indicated data, the need for patient consent was waived. Full details on the patient selection methodology and identification of participating physicians are described in the Methods section of the online supplement and in a previous report (6).

Scoring Protocol

Evaluation of cases took place on a custom-built, Web-based application. Physicians answered a preliminary survey regarding their clinical practice (Table E1 in the online supplement). For each case, they were presented with the patient's history, findings

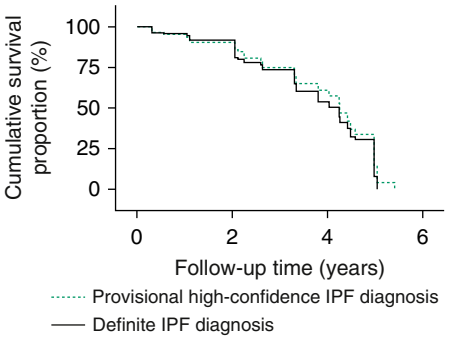

Figure 1. Kaplan-Meier survival curves for definite and provisional high-confidence idiopathic pulmonary fibrosis (IPF) diagnoses based on 24,240 physician–patient evaluations (hazard ratio, 0.97; $P = 0.65$; 95% confidence interval = 0.90–1.04).

on physical examination, and standardized baseline clinical information, extracted from the electronic patient records (Table E2), and the patients' high-resolution computed tomography (HRCT) scan at presentation. This information included patients' comorbidities if they were documented in the electronic patient records at presentation. The original HRCT report was not provided. SLB information was not provided, because this would confound responses by physicians on the need for SLB and conflate the clinical skill of the surveyed physician with the expertise of the host institution.

The scoring protocol has been described previously (6, 7). Briefly, for each case, physicians were required to select up to five differential diagnoses and provide a diagnostic likelihood level (censored at 5% and summing to 100% in each case) from a drop-down menu of diffuse lung diseases (Table E3). For each case, physicians were asked if they would perform SLB (yes/no) and how they would initially treat the patient, selecting from six options: *1*) observation; *2*) IPF-specific therapy (i.e., nintedanib and/or pirfenidone—one or both are available); *3*) IPF-specific therapy (i.e., nintedanib and/or pirfenidone), assuming the patient satisfies local prescribing criteria; *4*) IPF-specific therapy (i.e., nintedanib and/or pirfenidone), if it were available in my country; *5*) immunomodulation; and *6*) other (e.g., granulocyte/macrophage colony–stimulating factor for alveolar proteinosis; physicians were asked to specify in this case). The only stipulation to scoring the cases was that each case was evaluated in isolation without interspecialty consultation.

Statistical Analysis

Statistical analyses were performed using the Python package SciPy version 0.19.1 (https://www.scipy.org/). Data are given as means with SDs, medians with interquartile range (IQR), or the number of patients and percentage where appropriate. Group comparisons were made using the Student's *t* test, Wilcoxon rank sum, χ^2 statistics, and Fisher's exact test where appropriate. *P* values less than 0.05 were considered statistically significant.

Cohen's κ coefficient (κ) was used to evaluate interobserver agreement for biopsy decisions and stated as the median with IQR. κ values were categorized as follows: poor ($0 < \kappa \leq 0.20$), fair ($0.20 < \kappa \leq 0.40$), moderate ($0.40 < \kappa \leq 0.60$), good ($0.60 < \kappa \leq 0.80$), or excellent ($0.80 < \kappa \leq 1.00$).

IPF diagnoses were placed in IPF diagnostic confidence categories based on their assigned diagnostic likelihood using Ryerson's ontology as follows: *1*) category 0, "unclassifiable ILD" (0–50% diagnostic likelihood); *2*) category 1, provisional diagnosis of IPF with low confidence (51–69% diagnostic likelihood); *3*) category 2, provisional diagnosis of IPF with high confidence (70–89% diagnostic likelihood); and *4*) category 3, definite diagnosis of IPF (90–100% diagnostic likelihood) (5). IPF diagnoses in category 0 (0–50% diagnostic likelihood) were those cases assigned a first IPF diagnosis made with 50% or lower confidence or those where IPF was part of the differential diagnosis (e.g., first-choice diagnosis hypersensitivity pneumonitis, 70%; second choice diagnosis IPF, 30%). Regression analysis was performed to determine which clinical factors were associated with an increased perceived likelihood of IPF, taking IPF diagnostic confidence categories as the dependent variable (0–3) and age, % predicted D_{LCO}, sex, smoking history, exposure history, and autoantibody positivity as the independent variables.

Logistic regression, clustering physicians' responses within each patient case, was performed to identify clinical factors associated with the decision to perform SLB, taking diagnostic confidence category, age, and D_{LCO} as the independent variables. For this analysis, the 0–50% diagnostic confidence category was modified by: *1*) altering the confidence threshold to 1–50% to ensure that IPF was part of the differential; and *2*) eliminating cases where the first-choice diagnosis was a non-IPF disorder made with 70% or greater diagnostic likelihood and, therefore, less likely to require SLB (e.g., hypersensitivity pneumonitis, 80%; IPF, 20%). An age threshold of 65 years or older and % predicted D_{LCO} threshold of 40% were selected based on previous studies reporting the risk of mortality in patients with IPF undergoing SLB (8, 9). This % predicted D_{LCO} threshold (40%) was also close to the median value in the cohort (43.6%).

Mortality distinctions between IPF and other diffuse lung diseases were used to validate and compare diagnostic accuracy for IPF in different diagnostic confidence

Table 1. Frequency of Idiopathic Pulmonary Fibrosis Diagnoses Stratified on the Basis of Ryerson Diagnostic Likelihood Thresholds

Diagnostic Likelihood Category	Physician–Patient Evaluations (*n*)
Total (evaluations where IPF was part of differential)	9,958
Definite IPF diagnosis (90–100%)	2,440
Provisional high-confidence IPF diagnosis (70–89%)	2,123
Provisional low-confidence IPF diagnosis (51–69%)	797
First choice IPF diagnosis, 1–50% confidence	948
Not first choice IPF diagnosis, 1–50% confidence*	3,650

Definition of abbreviation: IPF = idiopathic pulmonary fibrosis.
*First-choice diagnoses were: connective tissue disease–related (interstitial lung disease = 801; idiopathic nonspecific interstitial pneumonia = 899; hypersensitivity pneumonitis = 561; and other diagnoses = 1,389).

Table 2. Factors Associated with the Perceived Increasing Likelihood of Idiopathic Pulmonary Fibrosis Quantified Using Ryerson's Diagnostic Likelihood Bands*

Variable	*n*	OR	*P* Value	95% CI
Age	24,240	1.04	0.014	1.01–1.07
D_{LCO}	24,240	0.96	<0.001	0.94–0.98
Sex, M	13,736	3.85	0.001	1.73–8.61
Smoking, ever	14,948	4.09	<0.001	2.09–8.01
Exposure history, yes/no	4,444	0.70	0.359	0.33–1.50
Autoantibody positivity	8,080	0.66	0.246	0.33–1.33

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
The 0–50% band was included in this analysis but did not necessarily indicate an "unclassifiable" level of diagnostic likelihood. In this band, 10,036/18,880 (53.2%) physician–patient evaluations were assigned a first diagnosis of a non–idiopathic pulmonary fibrosis disorder with diagnostic likelihood of 70% or greater. *n* = number of physician–patient evaluations.
*Definite or guideline-based diagnosis (90–100% confidence), a high-confidence provisional diagnosis (70–89% confidence), a low-confidence provisional diagnosis (51–69%), and "unclassifiable interstitial lung disease" (0–50% confidence).

categories (6, 7, 10). Cox proportional hazards modeling, clustering physicians' responses within each patient case, was then used to determine crude and adjusted (for age and % predicted D_{LCO}) hazard ratios (HRs) in the regression model. We controlled for disease severity using % predicted D_{LCO} rather than FVC, because D_{LCO} best captures the impact of IPF, supervening pulmonary hypertension and emphysema, whereas FVC is spuriously preserved when IPF and emphysema coexist, and it does not capture pulmonary hypertension. Time to death was the outcome for survival analyses, and the survival period for each patient was calculated from the date of referral to the host institution to January 1st, 2015. We tested the assumptions of proportional hazards by visual inspection of the log–log plot of survival, comparison of the Kaplan-Meier observed survival curves with the Cox predicted curves for the same variable, and graphical and formal analysis of Schoenfeld residuals (analysis not shown). Results are reported as HRs, 95% confidence intervals (CIs), and *P* values.

Results

Patient Population and Participating Physicians

The study cohort of cases was made up of 60 patients, including 22 (36.7%) with a diagnosis of IPF. SLB was required by the host institution in five cases (three IPF, one alveolar proteinosis, and one obliterative bronchiolitis). Vital status was known at the end of the study period for all cases, and there were 26/60 (43.4%) deaths. For details of patient exclusions and diagnoses, *see* Figure 1 and the online supplement (Results and Table E4). Between July 7th, 2016 and January 1st, 2017, 404 physicians representing 57 countries enrolled and completed the evaluation of all 60 cases (giving a total of 24,240 physician–patient evaluations). A summary of physician institution type and access to multidisciplinary team meetings based on country is shown in the Table E5.

Factors Associated with the Perceived Likelihood of IPF

IPF was part of the differential diagnosis in 9,958/24,240 (41.1%) of all patient-case evaluations. The mean age and % predicted D_{LCO} of these patients were 68.7 (±12.1) years and 41.2 (±14.5) units, respectively. Definite (90–100% diagnostic likelihood), provisional high-confidence (70–89% diagnostic likelihood), and provisional low-confidence (51–69% diagnostic likelihood) diagnoses first choice IPF diagnoses were made in 2,440 (25.2%), 2,123 (22.0%), and 797 (8.2%) of patient-case evaluations, respectively (Table 1). In 948 patient-case evaluations, first-choice diagnoses of IPF were made with 50% or lower diagnostic likelihood. In 3,650 patient-case evaluations, IPF was part of the differential diagnosis (but not the first-choice diagnosis) with 50% or lower diagnostic likelihood. Increasing age, decreasing % predicted D_{LCO}, male sex, and a positive smoking history (ex- or current smoker) were independently associated with an increased perceived likelihood of IPF using the Ryerson diagnostic likelihood thresholds (Table 2).

Factors Associated with Biopsy Decisions in IPF

A total of 4,598 patient-case evaluations included IPF with a diagnostic likelihood of 1–50%, and 1,164 of these had non-IPF first-choice diagnoses made with 70% or greater diagnostic likelihood (connective tissue disease–related ILD = 285, idiopathic non-specific interstitial pneumonia (NSIP) = 257, hypersensitivity pneumonitis = 163, and other diagnoses = 459). Decreasing perceived likelihood of IPF based on Ryerson diagnostic likelihood thresholds, decreasing age and increasing % predicted D_{LCO} were independently associated with the decision to perform SLB (*see* Table E6).

Biopsy Decisions in IPF Stratified by Diagnostic Likelihood

SLB was requested in 8.1%, 29.6%, and 48.4% of definite, provisional high-confidence, and provisional low-confidence diagnoses of IPF, respectively (Tables 3–5]). For patients defined as low-risk biopsy candidates (age < 65 yr and % predicted D_{LCO} > 40 units; *n* = 19 [11]), SLB was requested in 26.2%, 59.9%, and 83.1% of definite, provisional high-confidence, and provisional low-confidence diagnoses of IPF, respectively (Table 4). The 26.2% of definite IPF diagnosis among low-risk biopsy candidates represented 17 physicians evaluating three patients. These three patients were male, aged 44, 55, and 60 years of age with a probable usual interstitial pneumonia pattern on HRCT (based on the host institutions evaluation), no exposure history, and negative connective tissue disease serology. In 63.0% and 41.5% of provisional high-confidence diagnoses and provisional low-confidence IPF diagnoses, respectively, antifibrotic therapy was prescribed without requesting SLB (Table 3). The probability of seeking SLB was highest in low-risk patients (i.e., age < 65 yr and % predicted D_{LCO} > 40 units) with a provisional low-confidence diagnosis of IPF (odds ratio, 3.85; $P < 0.0001$; 95% CI, 2.49–5.94) (Table 4).

Prognostic Accuracy of IPF Diagnoses Stratified by Diagnostic Likelihood

The Ryerson diagnostic confidence categories for IPF were predictive of mortality (HR, 1.42; $P < 0.0001$; 95% CI,

Table 3. Total Cohort

IPF Confidence Band	*n*	SLB Requested [*n* (%)]	SLB Not Requested [*n* (%)]	Treated with IPF Therapy [*n* (%)]	Not Treated with IPF Therapy [*n* (%)]	Treated with IPF Therapy without Requesting SLB [*n* (%)]	Treated with IPF Therapy and Requesting SLB [*n* (%)]	OR for Requesting Biopsy*	*P* Value for Requesting Biopsy*
1–50%†	3,434†	2,123 (61.8%)	1,311 (38.2%)	1,212 (35.3%)	2,222 (64.7%)	526 (15.3%)	686 (20.0%)	3.08	<0.0001
51–69%	797	386 (48.4%)	411 (51.6%)	638 (80.1%)	159 (19.9%)	331 (41.5%)	307 (38.5%)	1.58	<0.0001
70–89%	2,123	628 (29.6%)	1,495 (70.4%)	1,889 (89.0%)	234 (11.0%)	1,338 (63.0%)	551 (26.0%)	0.68	<0.0001
90–100%	2,440	198 (8.1%)	2,242 (91.9%)	2,307 (94.5%)	133 (5.5%)	2,116 (86.7%)	191 (7.8%)	0.13	<0.0001

Definition of abbreviations: IPF = idiopathic pulmonary fibrosis; *n* = number of physician–patient evaluations; OR = odds ratio; SLB = surgical lung biopsy. Requested SLB with OR for requesting an SLB and number of patients treated with antifibrotic therapy patients, where IPF was a first-choice diagnosis or diagnosed with a confidence of ⩽50%. Proportion of patients treated with antifibrotic therapy with and without requesting SLB are also shown.
*Controlled for age and D_{LCO}.
†A total of 1,164 physician–patient evaluations was assigned a first-choice diagnosis of a non-IPF disorder with diagnostic likelihood of 70% or higher.

1.22–1.65) and remained predictive of mortality once disease severity, as judged by the % predicted D_{LCO}, was accounted for (HR, 1.31; $P < 0.0001$; 95% CI, 1.14–1.49). To evaluate the relative prognostic accuracy of IPF diagnoses in each diagnostic confidence category, bivariate analyses of adjacent categories was performed (e.g., definite IPF diagnoses vs. provisional high-confidence IPF diagnoses; *see* Table E7). Although each diagnostic confidence category provided improved prognostic discrimination compared with the preceding diagnostic likelihood category, once disease severity (as judged by % predicted D_{LCO}) and age were accounted for, no significant mortality difference was observed between physician–patient evaluations given a definite diagnosis of IPF (90–100% confidence) and those given a provisional high-confidence IPF diagnosis (70–89% confidence) (HR, 0.97; $P = 0.65$; 95% CI, 0.90–1.04; Figure 1 and Table E7). This result was maintained on subgroup analysis of university-affiliated ($n = 288$; HR, 0.97; $P = 0.64$; 95% CI, 0.83–1.11) and nonacademic physicians' ($n = 116$; HR, 0.97; $P = 0.79$; 95% CI, 0.80–1.18) IPF diagnoses.

Interobserver Agreement on the Decision to Perform SLB

Overall agreement between physicians on the decision to perform SLB was poor ($\kappa = 0.15$; IQR, 0.05–0.26). On subgroup analysis, interobserver agreement between the expert panel members was fair ($n = 35$; $\kappa = 0.30$; IQR, 0.20–0.40) and poor between the remaining physician group ($n = 369$; $\kappa = 0.14$; IQR, 0.04–0.24). Interobserver agreement between the university physicians was poor ($n = 288$; $\kappa = 0.16$; IQR, 0.05–0.26) and between nonuniversity physicians was poor ($n = 116$; $\kappa = 0.13$; IQR, 0.03–0.24). In both University and nonuniversity physicians, interobserver agreement was improved by access to weekly multidisciplinary team meetings (*see* Table E8). Nonuniversity physicians performed SLB more frequently than university physicians ($P = 0.001$). Physicians without access to multidisciplinary team meetings performed SLB more frequently than physicians with access to weekly multidisciplinary team meetings (in both University and nonuniversity hospital groups, $P < 0.001$ and $P < 0.001$, respectively). Of the four most prevalent first-choice diagnoses, IPF, connective tissue disease–related ILD, hypersensitivity pneumonitis, and idiopathic NSIP, SLB was requested in 27.7%, 45.1%, 53.5%, and 73.1% of cases, respectively.

Discussion

We have shown in an international cohort of more than 400 respiratory physicians, that, across the spectrum of patients with suspected IPF, once the diagnostic likelihood of IPF reaches 70%, most physicians will prescribe antifibrotic therapy without requesting SLB. Furthermore, using adjusted mortality to validate diagnostic accuracy, no significant outcome distinction was observed between patients given a provisional high-confidence diagnosis of IPF and those who received a definite diagnosis of IPF.

In 2017, Ryerson and colleagues (5) devised an ontological framework that standardizes thresholds of diagnostic likelihood in fibrotic ILD for clinical care and research. Previous studies of diagnostic performance in diffuse lung diseases have evaluated agreement on the probability of a specific diagnosis; however, the impact of diagnostic likelihood on biopsy decisions is unknown (6, 7, 12, 13). Using these thresholds, we established a broad view on the need for SLB in patients with suspected IPF across the diagnostic likelihood spectrum. With regard to risk factors for SLB, the clinical characteristics of patients with suspected IPF in our study (mean age, 68.7 ± 12.1 yr; mean D_{LCO}, 41.2 ± 14.5) are similar to the typical clinical presentation of IPF; therefore, physicians' decisions in this study are likely to reflect decisions made by physicians in the real world (14). SLB was requested in only 34.7% of patients with a provisional diagnosis of IPF (provisional high confidence, 29.6% [628/2,123]; provisional low confidence 48.4% [386/797]) and 67.9% of patients with a provisional diagnosis of IPF considered lower risk for SLB (provisional high confidence, 59.9% [100/167]; provisional low confidence, 83.1% [74/89]). The current clinical practice guideline for IPF makes a conditional recommendation for SLB in patients with suspected IPF when an imaging-based definitive diagnosis cannot be made (1). When SLB is considered low-risk (age < 65 yr and % predicted $D_{LCO} > 40$), this recommendation does appear to reflect physician views, although only by a small majority in provisional high-confidence IPF diagnoses (59.9%). However, across the whole range of patients with suspected IPF to which the guideline recommendation applies, SLB was requested in a minority of provisional high-confidence IPF diagnoses (29.6%). These data suggest that there is a discrepancy, at least in this patient cohort, between the majority opinion of the more than 400 physicians who participated in this study

Table 4. Low-Risk Biopsy Cases*

IPF Confidence Band	*n*	SLB Requested [*n* (%)]	SLB Not Requested [*n* (%)]	Treated with IPF Therapy [*n* (%)]	Not Treated with IPF Therapy [*n* (%)]	Treated with IPF Therapy without Requesting SLB [*n* (%)]	Treated with IPF Therapy and Requesting SLB [*n* (%)]	OR for Requesting Biopsy†	*P* Value for Requesting Biopsy†
1–50%‡	650‡	526 (80.9%)	124 (19.1%)	193 (29.7%)	457 (70.3%)	47 (7.2%)	146 (22.5%)	3.68	<0.0001
51–69%	89	74 (83.1%)	15 (6.9%)	68 (76.4%)	21 (23.6%)	14 (15.7%)	54 (60.7%)	3.85	<0.0001
70–89%	167	100 (59.9%)	67 (40.1%)	142 (85.0%)	25 (15.0%)	59 (35.3%)	83 (49.7%)	1.15	<0.379
90–100%	65	17 (26.2%)	48 (73.8%)	63 (96.9%)	2 (3.1%)	48 (73.8%)	15 (23.1%)	0.27	<0.0001

For definition of abbreviations, *see* Table 3.
Requested SLB with OR for requesting an SLB and number of patients treated with antifibrotic therapy patients where IPF was a first-choice diagnosis or diagnosed with a confidence of ⩽50%. Proportion of patients treated with antifibrotic therapy with and without requesting SLB are also shown.
*Age < 65 yr and/or D_{LCO} > 40, 19/60 patients.
†Controlled for age and D_{LCO}.
‡A total of 199 physician–patient evaluations was assigned a first-choice diagnosis of a non-IPF disorder with diagnostic likelihood of 70% or higher.

and the current clinical practice guideline recommendation of SLB in nondefinite IPF diagnoses. It should be highlighted, however, that interobserver agreement on the decision to perform SLB was poor to fair among participating physicians, which may limit application of these results in individual patients. It also highlights the need for consensus on when SLB is actually required, particularly in patients with suspected hypersensitivity pneumonitis and idiopathic NSIP.

In patients with suspected IPF, when a noninvasive diagnosis cannot be made and SLB is not possible, physicians are required to speculate between three management strategies: prescribe antifibrotic therapy empirically if a high-confidence, "working diagnosis" of IPF can be made; treat according to an alternative disorder; or continue to monitor without initiating therapy (3). The essence of a working diagnosis of IPF is that it is not definitive but made with sufficient confidence such that IPF-specific therapy is the only logical treatment choice, and it is a concept formally recognized in a recent White Paper statement on IPF diagnosis by the Fleischner Society (2, 4). In the current study, once a diagnostic likelihood of IPF reached 70%, most physicians (63.0%) prescribed antifibrotic therapy without requesting an SLB. These results suggest that this level of diagnostic likelihood equates to a working diagnosis of IPF. In patients with a provisional low-confidence diagnosis of IPF, antifibrotic therapy was prescribed in 41.5% without requesting SLB; therefore, a provisional low-confidence diagnosis of IPF may also represent a working diagnosis of IPF, although, in a small majority of diagnoses, SLB may be required. Three observations warrant further discussion. First, SLB was requested in 26.2% (17/65) of definite IPF diagnoses made in patients considered low risk for biopsy (Table 4). These biopsy decisions relate to three male patients aged 44, 55, and 60 years with probable usual interstitial pneumonia on HRCT of unknown cause. The apparently paradoxical decision to request biopsy when the diagnostic likelihood of IPF was considered 90–100% suggests that more consensus is required on when SLB is needed in young patients who otherwise present with clinical and imaging features compatible with IPF. Second, nonuniversity hospital physicians requested SLB more frequently than university hospital physicians, highlighting the importance of referring cases to specialist centers, when SLB is considered necessary. Third, by demonstrating improved agreement on biopsy decisions between physicians who have access to regular multidisciplinary team meetings, our

Table 5. High-Risk Biopsy Cases*

IPF Confidence Band	*n*	SLB Requested [*n* (%)]	SLB Not Requested [*n* (%)]	Treated with IPF Therapy [*n* (%)]	Not Treated with IPF Therapy [*n* (%)]	Treated with IPF Therapy without Requesting SLB [*n* (%)]	Treated with IPF Therapy and Requesting SLB [*n* (%)]	OR for Requesting Biopsy†	*P* Value for Requesting Biopsy†
1–50%‡	2,784‡	1,597 (57.4%)	1,187 (42.6%)	1,019 (36.6%)	1,765 (63.4%)	479 (17.2%)	540 (19.4%)	2.88	<0.0001
51–69%	708	312 (44.1%)	396 (55.9%)	570 (80.5%)	138 (19.5%)	317 (44.8%)	253 (35.7%)	1.44	<0.001
70–89%	1,956	528 (27.0%)	1,428 (73.0%)	1,747 (89.3%)	209 (10.7%)	1,279 (65.4%)	468 (23.9%)	0.65	<0.001
90–100%	2,375	181 (7.6%)	2,194 (92.4%)	2,244 (94/5%)	131 (5.5%)	2,068 (87.1%)	176 (7.4%)	0.13	<0.001

For definition of abbreviations, *see* Table 3.
Requested SLBs with OR for requesting an SLB and number of patients treated with antifibrotic therapy patients where IPF was a first-choice diagnosis or diagnosed with a confidence of ⩽50%. Proportion of patients treated with antifibrotic therapy with and without requesting SLB are also shown.
*Age ⩾ 65 yr and/or D_{LCO} ⩽ 40, 41/60 patients.
†Controlled for age and D_{LCO}.
‡A total of 973 physician–patient evaluations was assigned a first-choice diagnosis of a non-IPF disorder with diagnostic likelihood of 70% or higher.

results suggest that multidisciplinary team meetings may have a training effect and benefit physicians when evaluating patients in isolation.

An obstacle to validating diagnostic accuracy in diffuse lung diseases is that there is no accepted diagnostic reference standard. Because inexorably progressive disease associated with increased mortality is, in general, a distinguishing feature of IPF, diagnostic accuracy for IPF can be validated against outcome. This approach has been used in several studies that have examined the accuracy of first-choice diagnoses of IPF (6, 7). In the current study, using Ryerson's diagnostic confidence categories, we were able to apply the same method to test the relative accuracy of IPF diagnoses made with different levels of diagnostic likelihood. Once disease severity and age were accounted for, no significant mortality difference was observed between definite IPF diagnoses and provisional high-confidence diagnoses of IPF, and this was maintained on subgroup analysis of university-affiliated and nonacademic physicians' IPF diagnoses.

Interpretation of our results, in the context of the current clinical practice guideline for IPF, requires caution. Our study represents a Delphi-type exercise in 404 physicians on diagnostic and treatment decisions in routine clinical practice. Its principal objective was to determine the level of diagnostic likelihood of IPF at which physicians choose to initiate antifibrotic therapy without requiring SLB. This, based on the recent Fleischner Society White Paper, defines a working diagnosis of IPF (4). In contrast, the current joint IPF guideline statement is a clinical practice guideline developed by a panel of experts based on a systematic review of evidence, and it sets the bar for making a definite diagnosis of IPF; it does not make any recommendation on treatment in patients with IPF when the diagnosis is provisional (1). Therefore, our conclusions regarding accepting a working diagnosis for treatment purposes rather than requiring diagnostic certainty with the performance of an SLB do not conflict with the joint guideline. Regarding SLB decisions, the majority of the participating physicians chose not to biopsy in provisional high-confidence IPF diagnoses (i.e., 70–89% confidence in a final IPF diagnosis), which differs from the guideline recommendation. However, this result highlights that many physicians do not require a guideline level of diagnostic certainty before recommending initiation of antifibrotic therapy, and is also, therefore, neither concordant nor discordant with the current joint guideline recommendations.

Our study has several limitations, common to previous studies of diagnostic performance (7, 12, 15). Physicians did not have an opportunity to engage in face-to-face consultation with patients to take a clinical history or examine patients themselves. In complex disease, direct contact with the patient may influence a physician's impression in a manner that is not easy to quantify objectively. However, direct patient contact in a study of this size would have been impracticable. Our methodology of Web-based case reviews is instead similar to that of previously published studies of diagnostic agreement and accuracy (6, 7). Second, although poor outcome separates IPF from non-IPF disorders, the natural history of IPF is heterogeneous, and therefore some overlap between the two disease groupings (IPF vs. non-IPF) is likely (16). Third, we did not evaluate how the availability of cryobiopsy might have influenced management decisions, as it is not yet available at many institutions, and neither the joint IPF clinical practice guideline nor the Fleischner Society White Paper make a final statement on its use in patients with suspected ILD (1, 4). Future studies could address the impact of cryobiopsy in this setting, if and when it becomes more uniformly available. Fourth, our selection of cases from 2010 meant that mortality differences between patients with IPF and other ILDs were not confounded by treatment with antifibrotic therapy. However, we did not investigate the potentially confounding impact of immunosuppressive therapy (which may be harmful in patients with IPF) on mortality. Lastly, our results reflect the clinical practice of participating physicians in this dataset, which consisted of 60 patients, including 22 patients with IPF. A similar study in a larger cohort of patients may be needed to confirm our findings.

In conclusion, our findings suggest that most respiratory physicians managing IPF prescribe antifibrotic therapy without requesting an SLB if a "working diagnosis" of IPF can be made (with a likelihood of $\geqslant$70%). SLB was recommended in only a minority of patients with suspected, but not definite, IPF. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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