Integrating Clinical Probability into the Diagnostic Approach to Idiopathic Pulmonary Fibrosis: An International Working Group Perspective

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Abstract (241 words)

Background. When considering the diagnosis of idiopathic pulmonary fibrosis (IPF), experienced clinicians integrate clinical features that help to differentiate IPF from other fibrosing interstitial lung diseases, thus generating a “pre-test” probability of IPF. The aim of this international working group perspective was to summarize these features using a tabulated approach similar to chest HRCT and histopathologic patterns reported in the international guidelines for the diagnosis of IPF, and to help formally incorporate these clinical likelihoods into diagnostic reasoning to facilitate the diagnosis of IPF.

Methods. The committee group identified factors that influence the clinical likelihood of a diagnosis of IPF, which was categorized as a pre-test clinical probability of IPF into “high” (70-100%), “intermediate” (30-70%), or “low” (0-30%). After integration of radiological and histopathological features, the post-test probability of diagnosis was categorized into “definite” (90-100%), “high confidence” (70-89%), “low confidence” (51-69%), or “low” (0-50%) probability of IPF.

Findings. A conceptual Bayesian framework was created, integrating the clinical likelihood of IPF (“pre-test probability of IPF”) with the HRCT pattern, the histopathology pattern when available, and/or the pattern of observed disease behavior into a “post-test probability of IPF”. The diagnostic probability of IPF was expressed using an adapted diagnostic ontology for fibrotic interstitial lung diseases.

Interpretation. The present approach will help incorporate the clinical judgement into the diagnosis of IPF, thus facilitating the application of IPF diagnostic guidelines and, ultimately improving diagnostic confidence and reducing the need for invasive diagnostic techniques.

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Introduction: diagnostic limitations in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is the archetypal chronic, progressive interstitial lung disease (ILD), characterized by a high-resolution computed tomography (HRCT) and/or histopathological pattern of usual interstitial pneumonia (UIP). Differentiating IPF from other conditions within the spectrum of fibrotic ILD has management implications. The diagnosis of IPF is made by a multidisciplinary team, with clinicians, radiologists, and pathologists experienced in ILD discussing all relevant information collected(1). Clinicians experienced in ILD integrate all clinical and HRCT features and, if necessary and appropriate, lung histopathology. Past and/or future observation of disease behavior may also support refinement of diagnostic confidence, especially in situations of diagnostic uncertainty.

In the 2018 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society (ATS/ERS/JRS/ALAT) guidelines for the diagnosis of IPF(2), chest HRCT and histopathological patterns were described using tabulated criteria to help evaluate the probability of IPF; however, clinical patterns were not expressed in the same way despite the clinical evaluation playing a pivotal role in the multidisciplinary diagnostic approach to IPF. For example, some clinical features, particularly when present in certain combinations, substantially increase or decrease the likelihood of an IPF diagnosis, influencing the decision to proceed with further investigations, including lung biopsy(3). A majority of respiratory physicians make similar management decisions in patients with a provisional high confidence or “working diagnosis” of IPF compared to those with a definite diagnosis(4), corresponding to a diagnostic probability of 70% or more based on clinical and HRCT data(5), highlighting the relevance of the clinical probability of disease. However, it may be challenging for clinicians with limited experience in ILD to conceptualize when the probability of IPF is sufficient to make management decisions, and to obviate the need for lung biopsy. A Bayesian approach (i.e., updating diagnostic confidence as new information becomes available) is helpful in this situation, yet showing that the positive predictive value of HRCT for a UIP

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pattern is highly dependent on the clinician's pre-test probability of disease(6), putting further emphasis on the importance of clinical judgement.

The aim of this international working group perspective is to incorporate clinical likelihoods into diagnostic reasoning, applying IPF diagnostic guidelines in common patient scenarios, with the ultimate goals of improving diagnostic confidence and reducing the need for invasive diagnostic techniques. Herein, we propose a conceptual framework for integrating clinical (pre-test) probability into the diagnostic algorithm for IPF, expanding upon the radiological and histopathological patterns described in recent international guidelines.

Methods

Conception and development of the framework

After review of the literature, the main clinical features that help differentiate IPF from other fibrosing ILDs were summarized. A discussion was conducted by email and teleconference, with several rounds of amendment and editing until a consensus was reached on a framework that could be used to integrate these clinical features and generate a probability of IPF. The clinical probability of disease was tabulated based on published evidence(7), with a focus on evidence generated using a Bayesian approach(6). This was integrated into the diagnostic evaluation using an adapted diagnostic ontology for fibrotic ILD that emphasizes the importance of documenting diagnostic confidence and the differential diagnosis, rather than simply labeling patients with a single clinical entity that ignores the certainty in that diagnosis(8). This approach was based on the concepts of positive/negative predictive value, where post-test probability is estimated on the basis of pre-test probability (clinical evaluation), and "test" is represented sequentially by HRCT evaluation, histopathology, and additional investigations if available. The pre-test clinical probability of IPF was categorized into "high" (70-100%), "intermediate" (30-70%), or "low" (0-30%) based on the clinical approach. After integration of radiological and histopathological features, the post-test probability of diagnosis was then categorized into "definite" (90-100%), "high confidence" (70-89%), "low

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confidence" (51-69%), or "low" (0-50%) probability of IPF as adapted from previously proposed categories(8). Probabilities are a subjective estimation based on the inference of data integrated in the dynamic scenario of the multidisciplinary discussion of cases.

An electronic vote was conducted on the key components of the framework. Committee members were invited to vote on each factor potentially influencing the clinical likelihood of IPF, using a 5-point Likert scale as follows: major factor [+/-2] or minor factor [+/-1] increasing/decreasing the likelihood of IPF, or neutral factor [0]. Committee members next voted on each situation whereby the clinical likelihood of IPF was integrated with data from HRCT, histopathology, and outcome. For each situation, they had to choose the option from the following categories that best corresponded to the post-test probability of IPF: definite diagnosis of IPF, high-confidence diagnosis of IPF, low-confidence diagnosis of IPF, probability of IPF comparable to that of other ILD diagnoses (i.e., IPF and non-IPF diagnoses have similar likelihoods), probability of ILD other than IPF greater than that of IPF, or 'I prefer not to vote'. Responses were dichotomized between votes in favor of a diagnosis of IPF (definite diagnosis of IPF or high-confidence diagnosis of IPF), and votes indicating insufficient confidence in the diagnosis of IPF or probability of another diagnosis comparable to or greater than a diagnosis of IPF (other categories).

Proposed framework

The conceptual framework applies to patients in whom the diagnosis of IPF is contemplated, i.e. with chronic, fibrotic ILD, considered idiopathic prior to formal diagnostic evaluation. Contained within this group are diagnoses of IPF, idiopathic nonspecific interstitial pneumonia, other idiopathic interstitial pneumonias, and also a sub-group of patients ultimately diagnosed with fibrotic hypersensitivity pneumonitis (in whom there is no evident antigen exposure) or connective tissue disease-ILD (in whom formal criteria for an individual connective tissue disease are not satisfied. The conceptual framework was divided into four assessments: 1/ clinical likelihood of IPF, 2/ integration

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of the HRCT pattern, 3/ integration of the histopathological pattern and/or additional items when available, and 4/ integration of the pattern of observed disease behavior (**Figure 1**).

Clinical likelihood of IPF

Key features that increase the likelihood (pre-test probability) of IPF in a patient with a fibrotic ILD include older age, male sex(2, 6), tobacco smoking history(9-13), presence of Velcro crackles at auscultation(14, 15), chronic onset of disease, and patient-reported familial pulmonary fibrosis(16-18). In contrast, the likelihood of IPF is lower in the presence of relevant antigen exposure potentially causing hypersensitivity pneumonitis, clinical or serology autoimmune features not fulfilling criteria of connective tissue disease, as per the research statement on interstitial pneumonia with autoimmune features), and wheezes or squeaks at auscultation(20). Digital clubbing was historically considered to increase the likelihood of IPF; however, previous studies suggest the presence of clubbing may not be particularly helpful (21).

Table 1 presents the main features that impact the clinical likelihood of IPF; 62% to 100% of committee members voted that these features influenced the likelihood of IPF (**Figure S1)**). Factors that were considered the most strongly associated with an increased likelihood of IPF were increasing age and the absence of a plausible differential diagnosis. To read the table, features (rows) are classified into two categories (columns). The more features of the right column are present in a patient, the higher the clinical likelihood of IPF. The more features of the left column are present in a patient, the lower the clinical likelihood of IPF. For example, velcro crackles when present increases the likelihood of IPF. The end-result at this stage can be considered a pre-test probability of IPF, with “test” being the HRCT, and other potential investigations. It is proposed that clinicians may use this table to integrate all data available into a “high” (70-100%), “intermediate” (30-70%), or “low” (0-30%) pre-test clinical likelihood of IPF, either using gestalt evaluation or in the future using a clinical diagnostic scoring system (22). The probability of IPF is considered high when several features that increase the likelihood of IPF are present, with the probability considered low

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when several features that decrease the likelihood of IPF are present. When features from different columns are present, the clinical likelihood of IPF is considered low or intermediate.

Integrating the radiologic assessment

According to guidelines(23), HRCT findings are integrated into four patterns: UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and HRCT patterns suggesting alternative diagnoses.

In a patient with an intermediate likelihood of IPF based on the clinical evaluation (pre-HRCT probability), an HRCT pattern of UIP or probable UIP increases the confidence in the diagnosis of IPF, whereas an HRCT pattern indeterminate for UIP may not substantially impact the pre-test likelihood of IPF, and a pattern suggesting an alternative diagnosis would decrease the likelihood of IPF. The probability of IPF at this stage can be expressed using a diagnostic ontology as described above(8), i.e. as “definite diagnosis of IPF”, “high-confidence provisional diagnosis of IPF”, “low-confidence provisional diagnosis of IPF”. In some case scenarios, the probability of a diagnosis of ILD other than IPF is comparable to, or greater than, the probability of IPF, in which case IPF would not be considered the working diagnosis. It is anticipated that the categories of “definite diagnosis of IPF” and of “high-confidence provisional diagnosis of IPF”(8) will often lead to similar management decisions by most physicians, including choice of antifibrotic pharmacotherapy without acquisition of a surgical lung biopsy(5).

Table 2 presents the probability of a non-invasive diagnosis of IPF based on integrating the clinical assessment in **Table 1** with the radiologic assessment using international HRCT guideline categories(2). Results of the votes and agreement among committee members are indicated in **Figure S2**. The result at this stage is an evaluation of the post-HRCT probability of IPF. In addition to establishing a diagnosis of IPF in some patients, this scheme can be used to evaluate the need to perform a bronchoalveolar lavage, seek histologic confirmation of the diagnosis using lung biopsy (video-assisted thoracoscopic lung biopsy or transbronchial cryobiopsy), or pursue other potential

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investigations (e.g. search for arguments in favor of a diagnosis of hypersensitivity pneumonitis, connective tissue disease-associated ILD, etc).

Additional information may modulate the estimated probability of IPF in selected cases when available, including results of bronchoalveolar lavage(24), a molecular classifier(25), or genetic tests (**Table 3**), none of which, however, are widely available. Votes by committee members are indicated in **Figure S3**. The factor that was considered the most strongly associated with a decreased likelihood of IPF was the presence of lymphocytosis at bronchoalveolar lavage, for which several thresholds were proposed(24, 26). Carriage of the *MUC5B* promoter variant rs35705950 is associated with increased risks of IPF(27), rheumatoid arthritis-associated ILD(28), and fibrotic hypersensitivity pneumonitis(29), but not systemic sclerosis-associated ILD(8, 30), sarcoidosis(31), or anti-synthetase syndrome(32). Clinical manifestations commonly associated with mutations of the telomerase related genes and/or the identifications of such mutation increase the probability of IPF at a young age(31, 33, 34); but they may also be associated with a diagnosis of ILD other than IPF, including fibrotic hypersensitivity pneumonitis(29, 35), connective tissue disease-associated ILD(36), and unclassifiable ILD(33). It remains unclear whether the presence of the *MUC5B* promoter variant, telomeropathy, or short telomeres increases the probability of IPF to a greater extent compared to other fibrotic ILDs.

Integrating histopathological and other assessments

According to international guidelines(23), histopathological features are integrated into four patterns: UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and histopathological pattern suggesting an alternative diagnosis.

Table 4 presents the probability of a diagnosis of IPF based on integration of the clinical and radiologic assessment with the histopathological pattern using international guideline categories(2). Results of the votes and agreement among committee members are indicated in **Figure S4**. Here, the clinical and radiological evaluation, as integrated in **Table 2**, is now considered the pre-biopsy

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probability of disease, and **Table 4** suggests a post-biopsy probability of IPF taking into account all information available including the biopsy, if performed. In cases in which an alternative diagnosis is considered on the biopsy, the probability of IPF is low (<50%), with the potential for an alternative working diagnosis or, potentially, a designation of unclassifiable ILD. In a patient with a low-confidence provisional diagnosis of IPF based on the clinical-radiologic evaluation, a histopathological pattern of UIP or of probable UIP increases the confidence in the diagnosis of IPF, whereas a histopathological pattern indeterminate for UIP may not substantially alter the probability of IPF (although it may decrease the probability of alternative diagnoses), and a pattern suggesting an alternative diagnosis decreases the probability of IPF.

Integrating the assessment of observed disease behavior

Information about disease behavior helps refine the probability of IPF when available, either prior to patient referral or following the initial diagnostic assessment (**Table 5**). Results of the votes and agreement among committee members are indicated in **Figure S5**. Patients diagnosed with IPF should not receive high-dose glucocorticoids or immunosuppressive drugs for the long-term treatment of IPF(23); however, such treatment is sometimes prescribed in patients with other ILDs, when the diagnosis remains uncertain, or in the setting of an acute exacerbation(1). A past clear and objective response to glucocorticoids decreases the likelihood of IPF, whereas a progressive worsening of disease despite therapy increases its probability. Such “longitudinal disease behavior” has been included in the classification of idiopathic interstitial pneumonias(37), and can contribute to a working diagnosis of IPF(38); however, a trial of glucocorticoids should not be used as a diagnostic discriminator between IPF and non-IPF ILDs given the potential harm associated with this treatment in patients with IPF(39).

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Case examples

Case #1 (**Figure 2a**). A 68-year-old male ex-smoker who used to work as a builder is referred for fibrotic ILD with chronic onset of shortness of breath. Fine Velcro crackles are present on auscultation. He has no significant exposure or connective tissue disease features, no familial history of ILD, and no telomeropathy. Pulmonary function tests show restrictive physiology. The diagnosis would be categorized as a high clinical likelihood of IPF (**Table 1**), meaning that IPF is the most likely diagnosis at this stage. The HRCT demonstrates a pattern of probable UIP, therefore allowing a diagnosis of IPF (**Table 2**), and biopsy is then considered unnecessary by the multidisciplinary team.

Case #2 (**Figure 2b**). A 61-year-old female ex-smoker is referred for fibrotic ILD with chronic onset of shortness of breath and dry cough. Velcro crackles are present on lung auscultation. The patient has Raynaud' phenomenon, but no other feature of connective tissue disease, and autoimmune serology is negative. Pulmonary function tests show restrictive physiology. The clinical likelihood of IPF is considered intermediate (**Table 1**). The HRCT demonstrates a pattern of probable UIP, therefore providing a low-confidence provisional diagnosis of IPF (**Table 2**). The transbronchial cryobiopsy showed a probable UIP pattern and a high-confidence diagnosis of IPF was made (**Table 4**). Hypothesizing that the patient declines lung biopsy, it is still possible to make a confident IPF diagnosis if the follow-up demonstrates deterioration (in Figure 2b, forced vital capacity declines of 90 mL over 6 months, then 140 mL over 9 months), without new significant autoimmune features **(Table 5).**

Case #3 (**Figure 2c**). A 63-year-old female never-smoker is referred for fibrotic ILD with insidious onset of shortness of breath and dry cough. Velcro crackles are present on lung auscultation. The patient has no clinical feature of connective tissue disease, and autoimmune serology is negative. Pulmonary function tests show mild restrictive physiology. The clinical likelihood of IPF is considered intermediate (**Table 1**). The HRCT demonstrates a pattern indeterminate for UIP, therefore indicating that the probability of IPF is not greater than that of

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another ILD diagnosis (**Table 2**). A video-assisted thoracoscopic lung biopsy demonstrates a pattern indeterminate for UIP, not altering the probability of IPF (**Table 4**), and leading to a label of unclassifiable ILD. The patient receives oral glucocorticoids with tapering doses, with objective improvement at 6 and 12 months (**Table 5**), leading to IPF being considered an unlikely diagnosis.

Discussion

This international working group perspective provides a conceptual framework that can be used to assess the probability of a diagnosis of IPF, which would be of particular use for clinicians. We propose a step-by-step Bayesian approach, successively integrating the clinical manifestations, the radiologic pattern, the histopathological pattern, and the observed disease behavior into a synthetic probability of a diagnosis of IPF. This should be viewed as a complement to the ATS/ERS/JRS/ALAT guidelines for the diagnosis of IPF(2) and the Fleischner society white paper on this same topic(4). This proposed approach also follows on from the prior published ontological framework for classification of fibrotic ILD(8). It facilitates real-world integration of clinical judgement with existing guideline criteria, and further provides a structure for future studies to quantify specific probabilities of IPF associated with each clinical, radiological, and histopathological feature.

The clinical assessment of the probability of IPF as proposed here does not substitute for an expert clinical gestalt, but is instead a way of attempting to generalize how committee members make the diagnosis. In other words, it helps to delineate an IPF clinical syndrome in a more reproducible manner. In the future, the gestalt evaluation of the clinical probability could be replaced by clinical scores developed based on large datasets from registries and incorporating most of the items listed here, as recently reported(18). This also applies to the radiologic and histopathological assessment of the disease, which conceivably could be refined and translated into numerical variables (e.g. a likelihood ratio could be calculated for each of the categories of HRCT or histopathology), a scoring system, or benefit from artificial intelligence developments. Similarly, this

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approach could be applied to scores obtained for multiple individual radiological features (e.g. a score could be calculated to reflect the increasing probability of histopathologic UIP with increasingly extensive traction bronchiectasis on HRCT(6)), akin to an approach that has been described for the histopathological separation of IPF from fibrotic hypersensitivity pneumonitis(40). These types of tools would allow calculation of a pre- and post-test probability of IPF, with less interobserver variability compared to the current more qualitative integration of features.

The categories of “definite diagnosis of IPF” as per international guidelines (i.e. cases with UIP on HRCT in the appropriate clinical context)(2), and of “high-confidence provisional diagnosis of IPF”(8) frequently lead to similar decisions regarding management and follow-up by most physicians(5). This approach is supported by the retrospective analysis of data from the INPULSIS trials, which did not show any difference in outcome according to higher versus lower confidence in the diagnosis of IPF (i.e. UIP at HRCT and/or biopsy performed versus possible UIP or no biopsy)(41), and by registry data(42). However, in real-world data, there is some heterogeneity within the category of probable UIP on CT, which does not always correspond to histopathologic UIP(43) especially when the clinical likelihood of IPF is low.

Evaluation of the relative risk and benefit of lung biopsy is more complex than the mere assessment of the probability of a non-invasive diagnosis of IPF(44). The present framework could guide the multidisciplinary discussion regarding the theoretical utility of a lung biopsy(5), especially obviating the need of a biopsy in patients with high clinical probability of IPF. In contrast, a lung biopsy is likely to inform the diagnosis and may be helpful in cases where the clinico-radiological evaluation leads to a low-confidence diagnosis of IPF, i.e. with significant diagnostic uncertainty potentially impacting management decisions. However, decisions cannot be solely based on this assessment, as the risk of biopsy also needs to be taken into account(18, 45, 46). Furthermore, a high-confidence diagnosis of IPF may not be required in every case. For example, a low-confidence provisional diagnosis of IPF may be considered sufficient for management decisions in an elderly

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patient with mild clinical and functional impairment and in whom follow-up is the only option currently contemplated by the treating clinician. Information provided by bronchoalveolar lavage and/or molecular classifiers on transbronchial biopsy samples, if available, may conceptually be processed after HRCT evaluation. Per 2018 guidelines (2), bronchoalveolar lavage is indicated in patients with an HRCT pattern distinct from UIP; the current approach may help in both confirming the indication for bronchoalveolar lavage and integrating the information of the lavage into the diagnostic algorithm.

By contributing to diagnostic certainty, this approach may also be used to inform management decisions beyond IPF. Specifically, since nintedanib demonstrated efficacy in patients with a progressive phenotype of fibrosing ILD(47), and pirfenidone slows disease progression in progressive unclassifiable ILD(48, 49), indications for antifibrotic therapy may not be limited to IPF, pending international recommendations. However, an accurate diagnosis remains key to best management(1). It is proposed that categories of definite diagnosis of IPF and high-confidence diagnosis of IPF be managed as per IPF guidelines(2, 23). The present document may contribute to increased diagnostic confidence, underpinning management decisions in patients who otherwise run the risk of being disenfranchised from treatment(50). Flexibility is needed here(38, 50), as not all medical situations can be foreseen in such a perspective. However, this approach does not apply to interstitial lung abnormalities(51), which in essence are mostly subclinical. In the case of interstitial lung abnormalities, the first step is an assessment of whether clinically significant ILD is present, in which case the present approach can apply. It is likely that the delineation of “early UIP pattern” and of “interstitial lung abnormalities” may evolve in the coming years, and the present framework may then need to be updated.

All items listed in **Tables 1 and 3** may increase or decrease the likelihood of IPF when present, but none are sufficiently specific or sensitive for IPF to justify their use in isolation, and the degree to which each one influences the diagnosis varies. For example, the diagnosis of IPF should

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not be denied to female patients although male sex increases the clinical likelihood of IPF. The diagnostic value of several of them needs to be quantified in future studies. For example, it is unclear whether the probability of IPF is altered by the clinical context of familial fibrotic ILD, the presence of the *MUC5B* rs allele, and/or the identification of telomeropathy in the index case or in the family (clinically or by demonstration of rare variants of the telomerase related genes). These items have nevertheless been included in **Table 3** for benchmarking and to foster future research. It is similarly unclear how much emphasis should be placed on occupational exposures and on subtle exposures or autoimmune features that are insufficient to support an alternative diagnosis of hypersensitivity pneumonitis(52) or connective tissue disease(19), respectively.

The previously described "longitudinal disease behaviour" classification(37) has also been included in the approach. Although response to glucocorticoids and/or immunosuppressive therapy may provide useful information regarding the likelihood of IPF when prescribed prior to the formal diagnostic evaluation for IPF, this should not be taken as a suggestion to prescribe these medications in patients with a high clinical likelihood of IPF. We reiterate that high-dose glucocorticoids and immunosuppressive drugs are contra-indicated in patients with IPF(23). Conversely, long-term stability (2-3 years) decreases the probability of IPF in a patient with a low confidence provisional diagnosis of IPF, whilst progressive, irreversible disease progression despite immunosuppressive treatment increases the likelihood of IPF in a patient with idiopathic, fibrotic ILD. In other words, longitudinal disease behaviour may inform the probability of disease, but this does not justify a trial of glucocorticoids nor a watch-and-wait approach to nuance IPF diagnostic likelihood when IPF is the favoured diagnosis.

This approach has some limitations. The clinical assessment may be subject to interobserver variability, similar to the HRCT assessment(53). As not all likelihood ratios are known for the tests considered, probabilities are necessarily coarse estimates, providing a framework for broad judgements of high versus low probability of IPF at every step of the diagnosis approach. The

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probability of IPF varies inversely with the likelihood of an alternative diagnosis. Therefore, although the goal of clinical precision is highly desirable, probabilities indicated in this framework need to be interpreted with caution. The way in which clinical likelihood might be applied in individuals may vary somewhat depending upon realistic differentials, e.g. whether the differential is connective tissue disease-associated ILD, hypersensitivity pneumonitis, or another disease. This approach does not apply to non-idiopathic ILD. Furthermore, diagnostic categories may evolve in the future with the update of the international guidelines and implementation into clinical practice, which is beyond the scope of the present conceptual perspective that is to provide a framework rather than a definitive working document.

In conclusion, this international working group perspective provides a conceptual framework for how the clinical probability of IPF can be incorporated into the current diagnostic guidelines. A similar approach could be applied to evaluation of other ILD subtypes. We anticipate that progress in the clinical assessment, radiology, and newer diagnostic techniques will provide objective specific probabilities for IPF that apply to individual clinical, radiographic, and genetic features that will serve as a basis for the refinement and improvement of this approach. We also expect that this framework will serve the goal of better incorporating the clinical judgement into diagnostic reasoning, thereby resulting in more prudent decision-making on the need for invasive diagnostic tests and the choice of subsequent management.

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All submissions must include disclosure of all relationships in which there is a potential or actual conflict of interest, even if it not directly relevant to the submitted work.

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TABLES

Table 1. Clinical likelihood of IPF based on demographics, clinical features, etiological assessment, lung function, and disease onset. Items listed may increase or decrease the probability of the clinical category (high, intermediate, or low clinical probability). As this evaluation corresponds to the clinical evaluation, it can be considered a "pre-test" evaluation, i.e. before analysis of the HRCT scan.

How to read the table? Features (rows) are classified into two categories (columns). The more features of the right column are present in a patient, the higher the clinical likelihood of IPF. The more features of the left column are present in a patient, the lower the clinical likelihood of IPF. For example, velcro crackles when present increases the likelihood of IPF. The committee voted that age, and the absence of an alternative diagnosis more likely than IPF, have the greatest weight in assessing the clinical likelihood of IPF.

	Clinical likelihood of IPF		
	Likelihood decreased if present		**Likelihood increased if present**
Sex	Female sex		Male sex
Age	< 50 years		> 60 years
Tobacco history	Never smoker		Ex-smoker (or current smoker)
Auscultation	Absence of crackles Presence of squeaks or wheezing		Velcro crackles
Clubbing	Absent		Present
Exposure to significant antigens that may cause hypersensitivity pneumonitis	Present		Absent
Autoimmune features*	Present		Absent
Plausible differential diagnosis	Yes		No
Familial aggregation of fibrotic ILD	No		Yes
Lung function	Airflow obstruction or mixed physiology not ascribable to emphysema		Restrictive physiology
Onset	Acute or subacute onset		Chronic onset

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Note. *as per criteria of interstitial pneumonia with autoimmune features (19). IPF diagnostic confidence categories based on their assigned diagnostic likelihood can be estimated as follows: “high” diagnostic likelihood (70-100%), “intermediate” diagnostic likelihood (30-70%), or “low” diagnostic likelihood (0-30%) of IPF.

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Table 2. Assessment of the probability of a non-invasive diagnosis of IPF based on the clinical assessment (see Table 1) and the HRCT pattern as per international guidelines(2). The vertical column on the left is the product of table 1 (clinical likelihood of IPF), and the horizontal column consists of HRCT categories defined in international guidelines(2). The table boxes are the intersections of these two columns defining diagnostic likelihoods. As this evaluation takes into account both the clinical evaluation and the HRCT pattern, it can be considered a "post-test" evaluation, i.e. after analysis of the HRCT scan. Whether a biopsy is likely to inform diagnosis reflects expert opinion.

		HRCT pattern			
		UIP	**Probable UIP**	**Indeterminate for UIP**	**Alternative diagnosis**
Clinical likelihood	**High** (70% or more)	**Definite diagnosis of IPF** (biopsy not indicated)	**Definite diagnosis of IPF** (biopsy not indicated)	**Low-confidence provisional diagnosis of IPF** (biopsy is likely to inform diagnosis)	**Probability of IPF comparable to that of other ILD diagnosis** (biopsy, if performed, is highly likely to inform diagnosis)
	Intermediate for IPF (30-70%)	**High-confidence provisional diagnosis of IPF** (biopsy generally not indicated)	**Low-confidence provisional diagnosis of IPF** (biopsy is likely to inform diagnosis)	**Probability of IPF comparable to that of other ILD diagnosis** (biopsy, if performed, is highly likely to inform diagnosis)	**Probability of ILD other than IPF greater than IPF** (biopsy, if performed, is highly likely to inform diagnosis)
	Low (30% or less)	**Low-confidence provisional diagnosis of IPF** (further evaluation needed to make a diagnosis)	**Probability of IPF comparable to that of other ILD diagnosis** (biopsy, if performed, is highly likely to inform diagnosis)	**Probability of ILD other than IPF greater than IPF** (biopsy, if performed, is highly likely to inform diagnosis)	**Probability of ILD other than IPF greater than IPF** (biopsy, if performed, is highly likely to inform diagnosis)

Note. IPF diagnostic confidence categories based on their assigned diagnostic probability using a previously proposed ontology(8) can be estimated as follows : definite diagnosis of IPF (90-100% diagnostic probability; high-confidence provisional diagnosis of IPF (70–89% diagnostic probability); low-confidence provisional diagnosis of IPF (51–69% diagnostic probability); probability of IPF not greater or lower than that of an alternative diagnosis (0-50% diagnostic probability).

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Table 3. Clinical probability of IPF based on additional assessment, when available. When assessed, items listed may increase or decrease the probability of IPF. This evaluation would typically take place after the clinic-radiological assessment.

	Likelihood of IPF		
	Likelihood decreased if present		**Likelihood increased if present**
Pre-diagnostic disease behavior*	Long-term stability over years		Progression over months-years despite treatment
Pre-diagnostic short-term response to glucocorticoids or immunosuppression*	Present		Absent
Bronchoalveolar lavage if performed	Lymphocyte count increased (>30%)		Lymphocyte count not increased (<15%)
Genetics if performed	Absent		*Single nucleotide polymorphisms (e.g. MUC5B)* *Pathogenic gene variants related to surfactant metabolism and telomere maintenance.* Syndromic ILD (e.g. short telomere syndrome)
Molecular classifier on transbronchial lung biopsy	Molecular classifier « Not UIP »		Molecular classifier « UIP »

* Although short-term response to glucocorticoids may increase the likelihood of a non-IPF diagnosis, the authors do not endorse a trial of therapy as a diagnostic test given the potential harm associated with glucocorticoids in patients with IPF. The potential utility of glucocorticoids in establishing a diagnosis of IPF refers to the prescription of glucocorticoid that occasionally occurs prior to the formal diagnostic evaluation for ILD.

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Table 4. Assessment of the probability of a diagnosis of IPF based on the clinical and radiologic assessment (see Table 2) and on the histopathological pattern as per international guidelines(2). The vertical column on the left is the product of table 2 (likelihood of IPF based on clinical and radiologic assessment), and the horizontal column consists of histopathologic categories defined in international guidelines(2). The table boxes are the intersections of these two columns defining diagnostic likelihoods. Here, the clinical and radiological evaluation as integrated in Table 2 is now considered the pre-test probability of disease, where the test is the biopsy (surgical lung biopsy or transbronchial cryobiopsy), and Table 3 suggests a post-test probability of IPF taking into account all information available including the biopsy.

		Pathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
Clinical and radiologic likelihood of IPF (before biopsy)	Definite diagnosis of IPF or high confidence provisional diagnosis of IPF	Not applicable. A biopsy is generally not indicated if a high-confidence diagnosis has already been obtained based on the clinical and radiological evaluation			
	Low confidence provisional diagnosis of IPF	Definite diagnosis of IPF	High-confidence provisional diagnosis of IPF	Low-confidence provisional diagnosis of IPF (disease behavior likely to inform diagnosis)	Alternative diagnosis (including unclassifiable ILD)
	Probability of IPF comparable to that of other ILD diagnosis	High-confidence provisional diagnosis of IPF	Low-confidence provisional diagnosis of IPF (disease behavior likely to inform diagnosis)	Probability of IPF comparable to that of other ILD diagnosis	Alternative diagnosis (including unclassifiable ILD)

Note. All situations may be discussed in MDD. IPF diagnostic confidence categories based on their assigned diagnostic probability using a previously proposed ontology(8) can be estimated as follows: definite diagnosis of IPF (90-100% diagnostic probability; high-confidence provisional diagnosis of IPF (70–89% diagnostic probability); low-confidence provisional diagnosis of IPF (51–69% diagnostic probability); probability of IPF not greater or lower than that of an alternative diagnosis (0-50% diagnostic probability).

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Table 5. Assessment of the probability of a diagnosis of IPF based on the pattern of observed disease behaviour. Here, the clinical and radiological evaluation as integrated in Table 2 or 3 is now considered the pre-test probability of disease, where the test is the pattern of disease behaviour, and Table 5 suggests a post-test probability of IPF taking into account all information available including disease behaviour. Disease behaviour comprises information about potential improvement in response to immunomodulation and the rate of physiological worsening.

		Observed disease behavior		
		Progressive, irreversible disease despite treatment	Long term stability (without antifibrotic therapy)	Response to immunomodulation therapy if prescribed
Likelihood of IPF based on multidisciplinary assessment	Definite diagnosis of IPF or high confidence provisional diagnosis of IPF	Not applicable. This situation is not further discussed, as a high-confidence diagnosis has already been obtained based on the multidisciplinary assessment		Not applicable. Immunomodulation therapy is not appropriate in this situation
	Low confidence provisional diagnosis of IPF	**High confidence provisional or definite diagnosis of IPF**	**Probability of IPF comparable to that of other ILD diagnosis**	
	Probability of IPF comparable to that of other ILD diagnosis	**Low-confidence provisional diagnosis of IPF**	**Probability of IPF comparable to that of other ILD diagnosis**	**Alternative diagnosis (including unclassifiable ILD)**

Note. All situations may be discussed in MDD. IPF diagnostic confidence categories based on their assigned diagnostic probability using a previously proposed ontology(8) can be estimated as follows: definite diagnosis of IPF (90-100% diagnostic probability; high-confidence provisional diagnosis of IPF (70–89% diagnostic probability); low-confidence provisional diagnosis of IPF (51–69% diagnostic probability); probability of IPF not greater or lower than that of an alternative diagnosis (0-50% diagnostic probability).

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Figure legends

Figure 1. Steps to the diagnosis

Figure 2. Schematic representation of probability of diagnosis at each step of the evaluation.

Figure 2a. Example 1: patient with high clinical likelihood of IPF and probable UIP at HRCT. A high-confidence diagnosis of IPF was made; biopsy was not necessary.

Figure 2b. Example 2: patient with intermediate clinical likelihood of IPF, and probable UIP at HRCT. The patient underwent a lung cryobiopsy showing a probable UIP pattern and allowing a diagnosis of IPF with high-confidence. Alternatively, follow-up of the patient declining the lung biopsy would show progressive, irreversible disease, and lead to a high-confidence diagnosis of IPF (without a lung biopsy).

Figure 2c. Example 3: patient with intermediate clinical likelihood of IPF, and HRCT pattern indeterminate for UIP. Lung biopsy showing a pattern indeterminate for UIP did not alter the probability of IPF. Objective improvement at 6 and 12 months was seen with glucocorticoids. The disease was labelled with unclassifiable ILD, with a probability of IPF < 50%.

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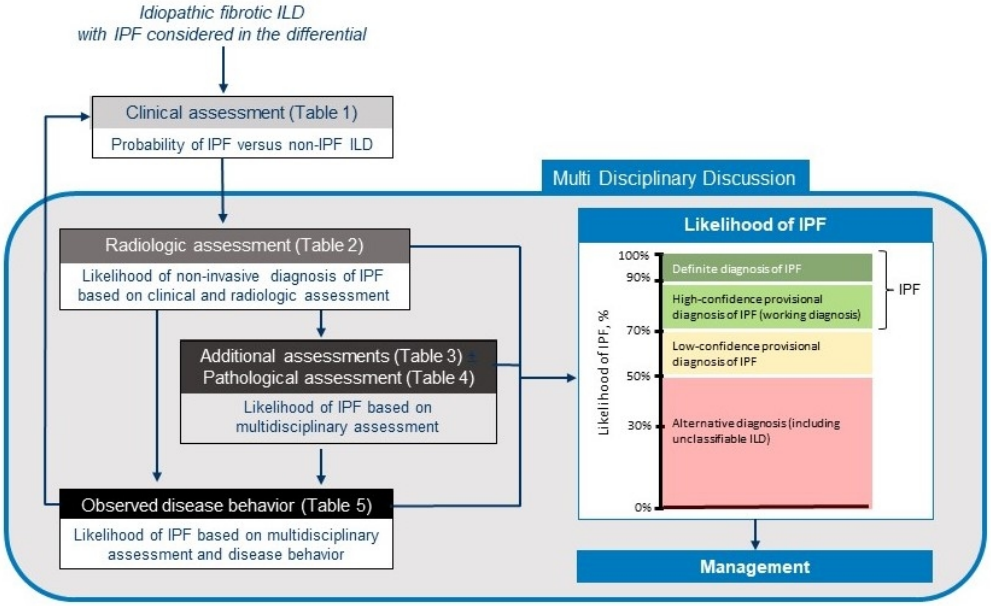

Figure 1. Steps to the diagnosis

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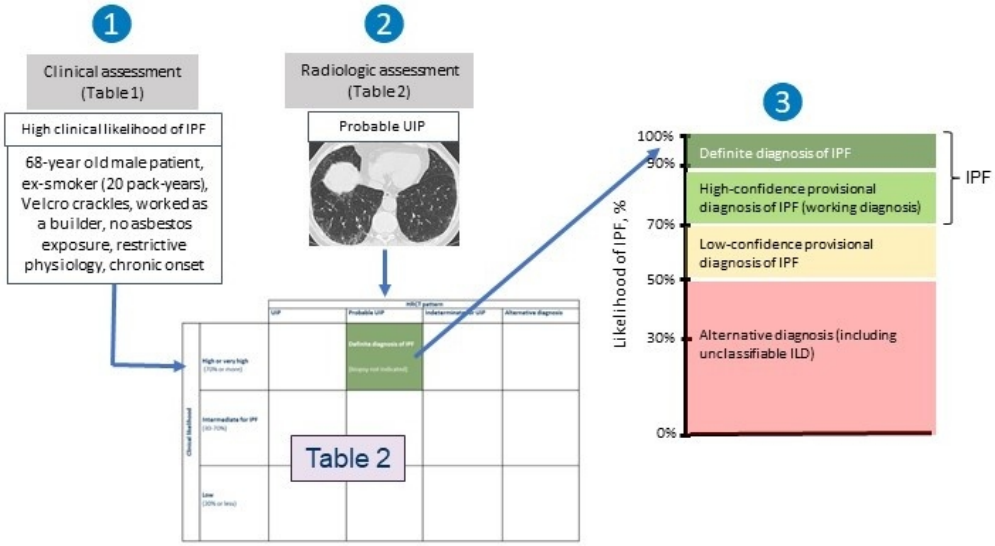

Figure 2. Schematic representation of probability of diagnosis at each step of the evaluation.
Figure 2a. Example 1: patient with high clinical likelihood of IPF and probable UIP at HRCT. A high-confidence diagnosis of IPF was made; biopsy was not necessary.

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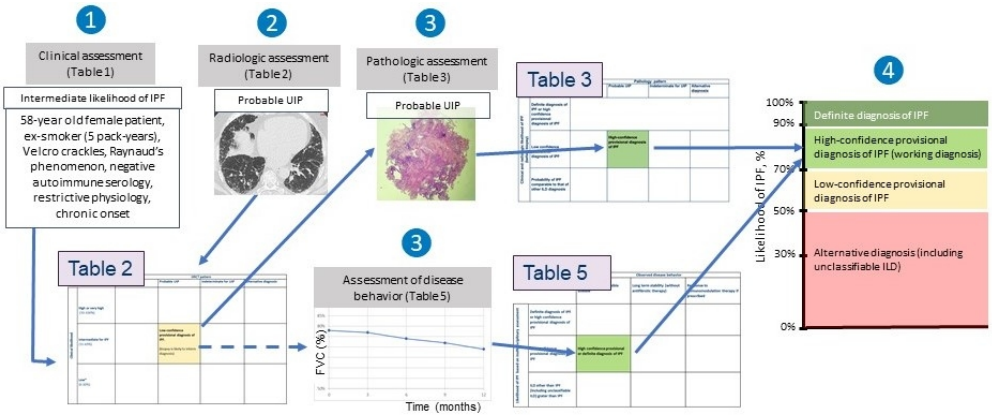

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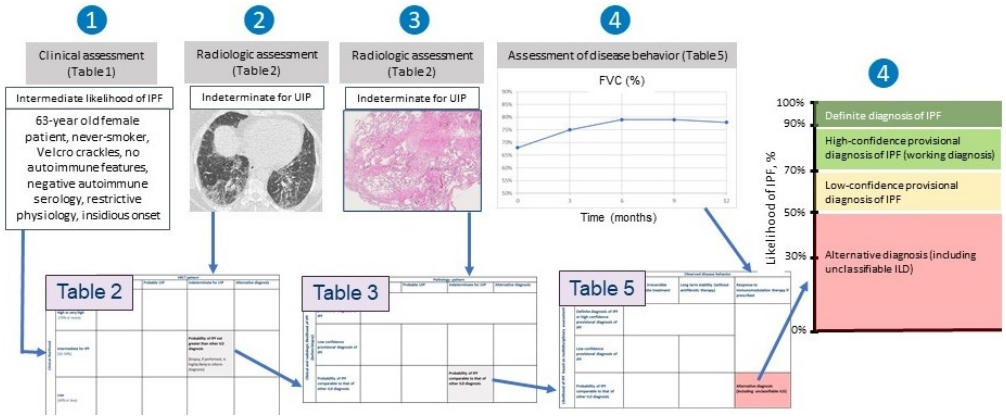

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Supplementary Material

Integrating Clinical Probability into the Diagnostic Approach to Idiopathic Pulmonary Fibrosis: An International Working Group Perspective

Table of content:

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Figure S1. Votes of the expert committee to populate Table 1.

Bars indicate the percentage of respondents who voted that each factor was a major or minor factor influencing the likelihood of IPF.

Figure S2. Votes of the expert committee to populate Table 2.

The percentages superimposed on the colored bar indicate the proportion of respondents who voted for each of the categories of diagnostic probability. The "% agreement IPF" corresponds to the proportion of respondents who voted that the post-test probability in each situation corresponded to a diagnosis of IPF (definite diagnosis of IPF, or high-confidence diagnosis of IPF), as opposed to a low confidence provisional diagnosis of IPF or a probability of another diagnosis comparable to or greater than a diagnosis of IPF.

Figure S3. Votes of the expert committee to populate Table 3.

Bars indicate the percentage of respondents who voted that each factor was a major or minor factor influencing the likelihood of IPF.

Figure S4. Votes of the expert committee to populate Table 4.

The percentages superimposed on the colored bar indicate the proportion of respondents who voted for each of the categories of diagnostic probability. The "% agreement IPF" corresponds to the proportion of respondents who voted that the post-test probability in each situation corresponded to a diagnosis of IPF (definite diagnosis of IPF, or high-confidence diagnosis of IPF), as opposed to a low confidence provisional diagnosis of IPF or a probability of another diagnosis comparable to or greater than a diagnosis of IPF.

Figure S5. Votes of the expert committee to populate Table 5.

The percentages superimposed on the colored bar indicate the proportion of respondents who voted for each of the categories of diagnostic probability. The "% agreement IPF" corresponds to the proportion of respondents who voted that the post-test probability in each

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situation corresponded to a diagnosis of IPF (definite diagnosis of IPF, or high-confidence diagnosis of IPF), as opposed to a low confidence provisional diagnosis of IPF or a probability of another diagnosis comparable to or greater than a diagnosis of IPF.

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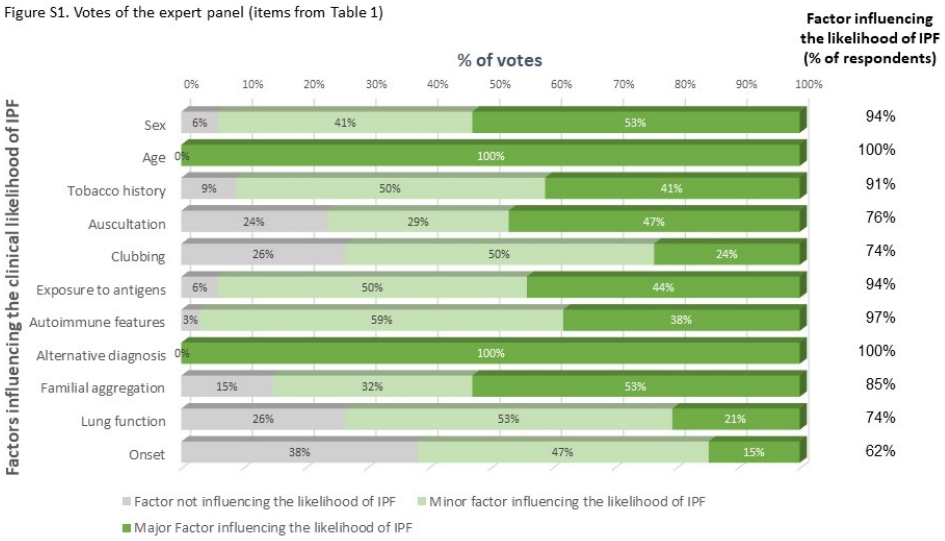

Figure S1. Votes of the expert committee to populate Table 1.

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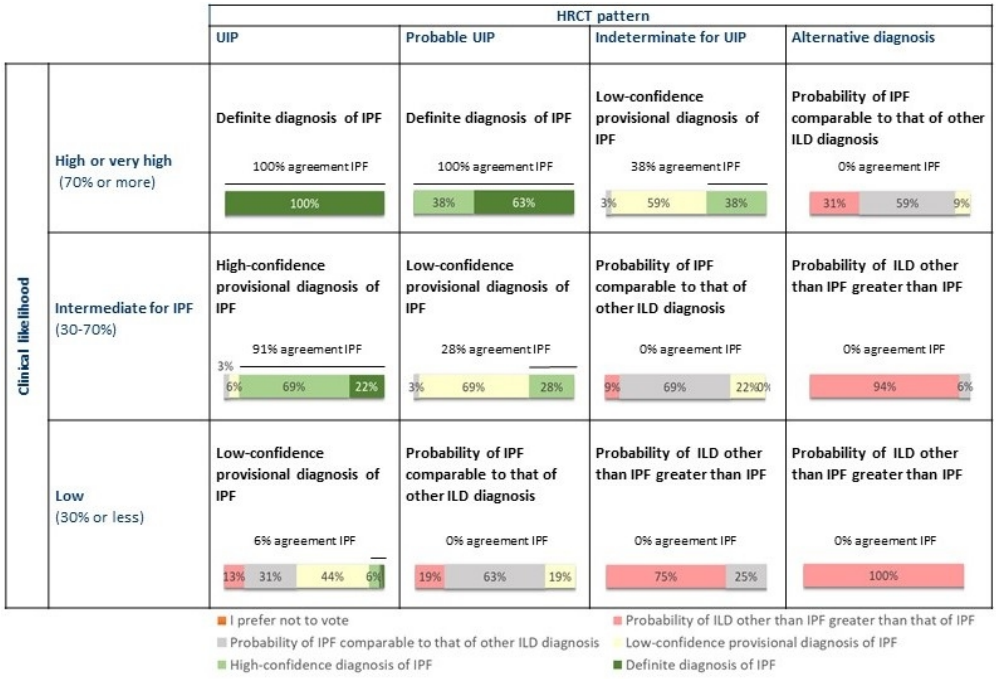

Figure S2. Votes of the expert committee to populate Table 2.

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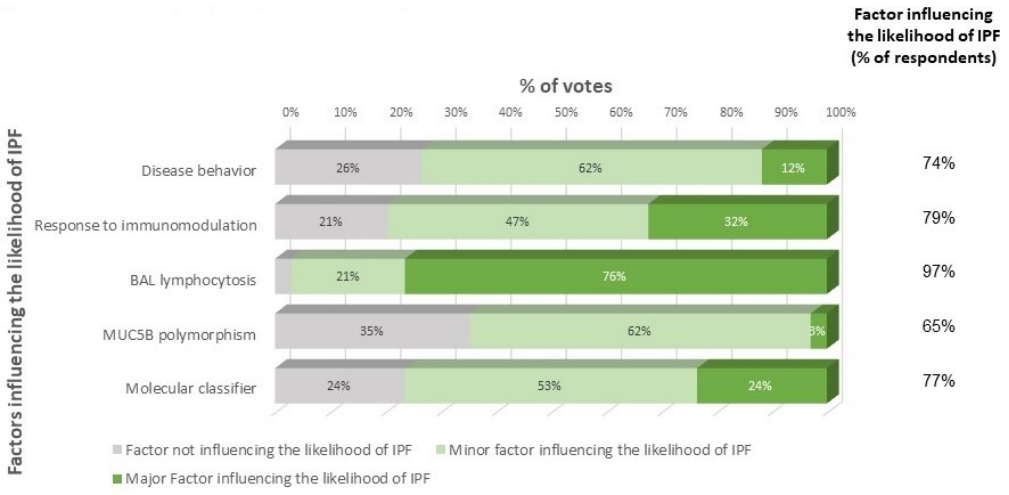

Figure S3. Votes of the expert committee to populate Table 3.

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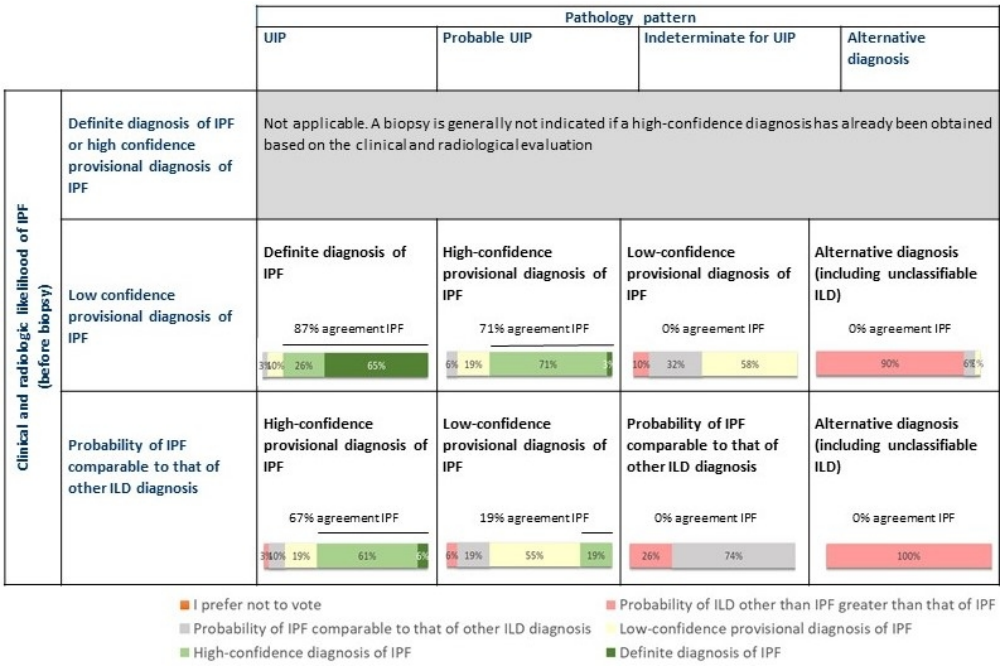

Figure S4. Votes of the expert committee to populate Table 4.

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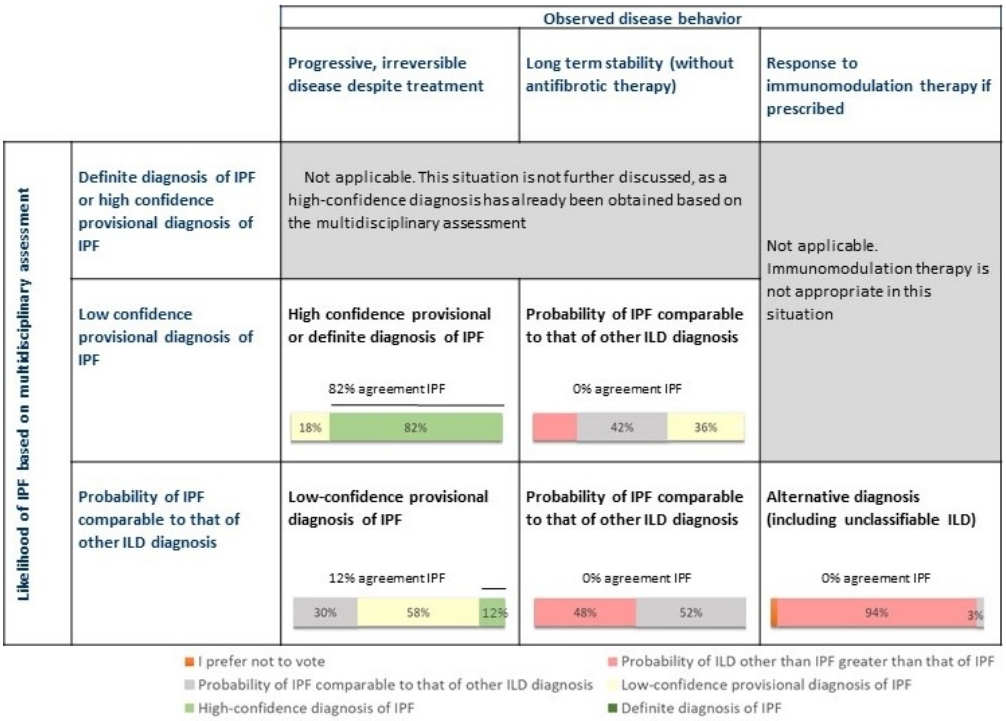

Figure S5. Votes of the expert committee to populate Table 5.

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