# *Idiopathic Pulmonary Fibrosis*

## *Why the Differential Diagnosis is Important*

## Needs Assessment

### *Gap Analysis Table*

| Gap | Learning Objective | Outcome |
|---|---|---|
| **Clinicians may not be aware that a targeted history and physical assessment can be performed specifically to identify clinically suspected IPF** | **Perform a targeted history and physical examination designed specifically to assess for clinically suspected IPF** | **The clinician will perform a targeted history and physical examination designed specifically to assess for clinically suspected IPF** |
| **Clinicians may not be aware that new diagnostic guidelines for IPF have been published in 2018, or of the implications of the revisions to the category labels** | **Describe the four categories of HRCT that help to determine the differential diagnosis of IPF vs. other ILDs** | **The clinician will match the HRCT image and clinical narrative to the appropriate diagnostic category** |
| **Clinicians may not be aware of the evidence-based superiority of multidisciplinary care over single provider care in many cases of clinically suspected IPF and/or new ILD** | **Formulate a plan of appropriate diagnostic tests and referrals based on nuanced case-scenarios involving patients with clinically suspected IPF** | **Upon clinical suspicion of IPF, the clinician will order appropriate tests while concomitantly facilitating appropriate referrals to a multidisciplinary ILD center** |

***Overview of Idiopathic Pulmonary Fibrosis***

Idiopathic pulmonary fibrosis (IPF), one of the 200+ interstitial lung diseases (ILDs), is characterized by an insidious and progressive fibrosis of the lung parenchyma, leading to non-productive cough, worsening dyspnea, decreased pulmonary function, disability, and death.[1] While several of the ILD diagnoses may involve lung fibrosis, IPF is one of the most common ILDs and has an especially poor prognosis. The cause of IPF is unknown, hence the disease is "idiopathic", and the diagnosis is achieved by ruling-out other diagnoses. The population with IPF consists mostly of middle-aged and elderly patients, with the majority aged 60 or above, although it can appear less commonly in the 40 to 60-year-old range, as with familial IPF. It is more common in males, and in people who have a history of cigarette smoking, even years after quitting.[2] Median survival is 3 to 5 years from time of diagnosis, and the prognosis has been called "worse than for most common malignancies." [2] The disease has an incidence rate range of 3 to 9 cases per 100,000 per year in North America, and apparently, incidence of idiopathic pulmonary fibrosis is increasing worldwide.[3,4,5]

The progressive course of IPF is variable and unpredictable; it can progress steadily and/or rapidly. Sometimes, the disease will progress more slowly than predicted, and sometimes a diagnosis will be changed as new signs present themselves. In some people, the disease may stabilize for a while but can quickly take a downturn, in what is called an "acute exacerbation of IPF" (AE- IPF). Occasionally, an acute exacerbation will be the first presenting sign of previously undiagnosed IPF. [6]

AE-IPF involves an acute worsening of symptoms within a 30-day period, with new radiologic changes[7], such as ground-glass opacities and/ or consolidation on top of the pattern of the pre-existing IPF, and after ruling out other diagnoses, including pulmonary embolism, infection, exposures, and cardiac conditions.[4] Four to 20% of IPF patients will have an acute exacerbation and patients experiencing an acute exacerbation have a median survival of about 3 months. [5]

In a 2018 article, IPF is described in terms of the "burden of illness" on national healthcare costs; annual per capita cost of patients with IPF in North America was estimated around US $20,000, which is "2.5-3.5 times higher than the national healthcare expenditure."[8] Also discussed is the significant negative effect that IPF has on patients, as per several studies looking at health-related quality of life (HRQoL) and healthcare resource use, with the authors calling the disease a "growing threat for public

health worldwide, with considerable impact to the patients and healthcare providers" [8] and "(as) with other respiratory conditions, the impact of IPF... has wider consequences for HRQoL, including physical (body weight loss, fatigue, clubbing) and social ones (recreational activities, relationships etc.)."[8]

Prior to the FDA approval of two antifibrotic medications in 2014, there were no medications effective in slowing, stopping, or reversing the fibrotic process of IPF. Transplant was and still is the only cure, with its own set of risks. In the typical patient with IPF, qualifying for and receiving a transplant is limited by advanced age, comorbidities, and the scarcity of organs. Care still must focus on symptom management as cure is not usually an option. However, in 2014, the FDA approved two antifibrotic medications for IPF, pirfenidone and nintedanib.

Antifibrotics have been found to slow the progression of fibrosis, but they are not able to completely halt or reverse the process. These medications have also been found to be more effective when initiated early.[9] Therefore, an early differential diagnosis is necessary to ensure the prompt initiation and optimal benefit of antifibrotic therapy, before extensive fibrosis has already occurred. However, a 2016 chart audit survey in Europe found that about 40% of the audited patients were not receiving antifibrotic treatment despite the recent drug approvals there and professional guidelines recommending that antifibrotics be offered to patients with IPF.[9] Indeed, patients with IPF described by their physicians as "mild" or "stable", were often left untreated with antifibrotics, reflecting a "watch and wait" approach.[9]

The study authors speculate that clinicians may hesitate to treat because, "Treatment requires a confident diagnosis of IPF, and it may be that a lack of awareness about IPF as a potential diagnosis and/or a lack of referral to specialist centers for (multidisciplinary) diagnostic assessment have an impact upon treatment practices." [9] The survey showed that a higher proportion of untreated patients had "suspected IPF" as compared to those who were treated, and a lower proportion of the untreated patients had received a multidisciplinary evaluation at diagnosis.[9]

**The INTENSITY Survey**

As in Europe, clinicians in the US have also been grappling with lack of clarity on how to proceed with diagnosing and treating suspected IPF. The Intensity study surveyed 600 adult patients living in the US with either an IPF or a non-IPF ILD diagnosis. The Intensity Survey looked at the diagnostic experiences of these 600 patients, and in early 2018, the authors of the study reported, "Current diagnostic guidelines define characteristic radiologic and histopathologic features that suggest a diagnosis of IPF however, high resolution computed tomography (HRCT) scans and lung biopsies frequently exhibit mixed or discordant patterns, and findings in patients with IPF and other ILDs are often marked by subtle differences.[10,11] Studies evaluating diagnostic agreement among pulmonologists, radiologists, and pathologists have reported only modest inter-observer agreement, even among expert observers." [10,12]

The complexity of making a diagnosis of IPF was underscored by the disheartening findings from the Intensity Study. The survey focused on the patients' experiences of being diagnosed; of the 600 participants, "55% reported ≥ 1 misdiagnosis and 38% reported ≥ 2 misdiagnoses prior to the current diagnosis. The most common misdiagnoses were asthma (13.5%), pneumonia (13.0%), and bronchitis (12.3%). The median time from symptom onset to current diagnosis was 7 months (range, 0–252 months), with 43% of respondents reporting a delay of ≥ 1 year and 19% reporting a delay of ≥ 3 years."[10]

The survey found that 61% of the patients had at least one invasive procedure, and that "on average, patients had six lung function tests, five chest X-rays, and two bronchoscopies before ending up with a correct diagnosis." [10] The report states that the patients' diagnostic experiences involved "considerable delays, frequent misdiagnosis, exposure to costly and invasive diagnostic procedures and substantial use of healthcare resources" [10]

The report discusses the multiple challenges that occur during the complex process of diagnosing an ILD; there are "delays related to scheduling and availability, interpretation of test results, and the need to repeat certain tests and procedures."[10] Patients may undergo '"multiple diagnostic tests and procedures, including spirometry, serology, chest x-ray, HRCT, bronchoscopy, exercise tests, and surgical lung biopsy."[10] In fact, 28% of the respondents reported that the "burden imposed by the diagnostic process" contributed to the decision to retire or apply for disability benefits, "suggesting a need for meaningful improvements in diagnostic methods, timeliness, and accuracy." [10]

Indeed, IPF can progress significantly in the time it takes to get a firm diagnosis. It has been shown that decreases in forced vital capacity (FVC) of only 5 to 10% over 6 months are associated with significant increase in death.[10,13] The delayed referral to specialty care is also associated with an increased risk of death in patients with IPF .[10,14]

A delay in diagnosis can also lead to delay in evaluation and possible loss of eligibility for lung transplant, due to worsening morbidity and increased age. The initial misdiagnosis of another pulmonary disease or of a cardiovascular disorder can also result in the patient being treated with medications that will not improve IPF and may even harm the patient. In fact, the Intensity Study found that one in five patients with diagnosed IPF reported previous treatment with corticosteroids, which was strongly recommended against in the diagnostic guidelines at the time. [10,15,,16]

The "diagnostic guidelines" referenced in the paragraph above were formulated in 2011 by an international group of respiratory specialists who come from four professional societies, including the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Latin American Thoracic Society (ALAT). In 2018, responding to the need for more diagnostic clarity, and also to new research that shines light on some of the more ambiguous or atypical radiologic pictures, the ATS/ERS/JRS/ALAT committee published updated diagnostic guidelines for IPF.

## Gap # 1: Clinicians may not be aware that a targeted history and physical assessment can be performed specifically to identify clinically suspected IPF

While the 2018 ATS/ERS/JRS/ALAT guidelines focus on HRCT patterns as the primary tool for the definitive diagnosis of IPF and the differentiation of ILDs in general, the authors also acknowledge the role of the general practitioner and general pulmonologist, and the primacy of a thorough and targeted history and physical exam as soon as a patient presents signs and symptoms suggestive of an ILD. They emphasize that it is usually the primary clinician who first sees the patient presenting with often vague, and even mild signs and symptoms. This practitioner is well-positioned to begin the honing-in process that will ideally become a multidisciplinary effort to achieve a diagnosis and/or to treat and support the patient. The committee implicates the essential role of the primary clinician in two "motherhood statements."[6]

**MOTHERHOOD STATEMENTS**

While the primary focus of the guidelines appears to be the refinement of the HRCT diagnostic categories, the committee makes two "motherhood statements" to which "there is no reasonable alternative to the recommended course of action. "[6] The first of these motherhood statements highlights the importance of a thorough medical history; in a patient with signs, symptoms, and risk factors suggestive of an ILD. The committee recommends "taking a detailed history of both medication use and environmental exposures at home, work, and other places the patient frequently visits, to exclude potential causes of ILD."[6] The search needs to move beyond the lungs, toward possible autoimmune, hypersensitivity, or other disease processes. Indeed, in an observational study looking at 1,084 patients with new ILD of unknown cause, 47% of the patients were diagnosed with hypersensitivity pneumonitis on detailed assessment, suggesting that "a cause can be found in many patients who present with ILD."[6]

The committee suggests using "questionnaires" designed to identify possible sources of exposure; "pertinent exposures include mold, birds, down feathers, animals, metal dusts (e.g., brass, lead, steel), wood dust (e.g., pine), vegetable dust, exposure to livestock, stone polishing and cutting, medications taken, current or recent occupations (e.g., hair dressing), and current or recent hobbies." [6]

The history can reveal factors or comorbid conditions which might influence the diagnosis and/ or the treatment path. In particular, gastroesophageal reflux and certain viral infections, such as Epstein-Barr virus and hepatitis, are risk factors associated with IPF. A family history of ILD suggests an epigenetic component, and in fact, "at least 30% of patients who have sporadic or familial pulmonary fibrosis have genetic predisposing factors that are known to increase the risk of pulmonary fibrosis." [6]

The diagnostic process should begin promptly when a patient presents with the following physical exam findings, and, "IPF should be considered in all adult patients with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and/or digital clubbing that occur without constitutional or other symptoms that suggest a multisystem disease," [6] according to the guidelines committee.

In regard to bibasilar crackles, in a 2018 article, Sgalla et al discuss "Velcro-type" crackles as "Historically... representative of established lung fibrosis" and that "quantitative analysis of crackles in ILD confirmed distinctive features as compared to those generated in other disorders such as chronic heart failure and pneumonia".[8] In fact, it was shown that bilateral crackles "most strongly predict the presence of a UIP pattern at HRCT." [8] The authors go on to describe the primary clinician's role in this "**point-of-care, low-**cost opportunity for detection of early disease and timely diagnostic work up." [8]

For patients presenting with a clinical picture suspicious for IPF or other ILDs, the history and physical exam should be followed by high-resolution computed tomography (HRCT).[6] HRCT is preferred over sequential CT because it can better detect subtle or focal abnormalities and is better able to analyze the characteristics and distribution of pulmonary lesions, which is important to the differential diagnosis of an ILD.[6]

## Gap #2: Clinicians may not be aware that new diagnostic guidelines for IPF have been published in 2018, or of the implications of the revisions to the category labels

As stated earlier, the ATS/ERS/JRS/ALAT 2018 guidelines focused on refining diagnostic categories based on HRCT patterns; these now consist of the following: usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, and alternative diagnosis.[6]

Usual interstitial pneumonia (UIP) is the defining category for IPF. Features of UIP include "honeycombing, traction bronchiectasis, and traction bronchiolectasis, which may be seen with the concurrent presence of ground-glass opacification and fine reticulation."[6] Honeycombing is an appropriately descriptive term for this pattern consisting of dilated, thick-walled cysts, often stacked, giving it the honeycomb appearance. Traction bronchiectasis/bronchiolectasis is deformity of these structures, which "ranges from subtle irregularity and nontapering of the bronchial/bronchiolar wall, to marked airway distortion and varicosity. It is usually peripheral/subpleural in UIP, often coexisting with honeycomb cysts, and may be best regarded as peripheral traction bronchiolectasis."[6]

Outside of the silo of an unambiguous UIP pattern are the configurations that were previously called "possible UIP"; in the 2011 guidelines, an HRCT pattern consisting of "subpleural, basal-predominant reticular abnormalities without honeycombing" was assigned to the HRCT diagnostic category of "possible UIP". This category was changed to "probable UIP" in 2018. The change was made after it was demonstrated that HRCT images of UIP are highly predictive of a confirmatory histopathologic diagnosis of UIP, with a predictive value "between 90% and 100%".[6] However, it has also been shown that "a significant minority of patients with histopathologic UIP do not fulfill HRCT criteria for UIP." [6] This finding confirms the redundancy of ordering invasive tests for most patients with UIP, and also suggests that the diagnosis of IPF still needs to be considered in patients with probable UIP on HRCT.

Raghu et al. note that "about 30%" of patients with atypical HRCT features show a histopathologic pattern of UIP/IPF, and that "the category 'indeterminate for UIP pattern' should be assigned when HRCT demonstrates features of fibrosis but does not meet UIP or probable UIP criteria and does not explicitly suggest an alternative diagnosis," and "This category includes a subset of patients with very limited subpleural ground-glass opacification or reticulation without obvious CT features of fibrosis, for whom there is a suspicion that early UIP or probable UIP is present." [10] Again, new knowledge linking an "indeterminate for UIP" pattern to early progressive fibrosis could mean that more people will receive antifibrotics when they are more efficacious, early in the disease."[6]

The final category defined in the 2018 ATS/ERS/JRS/ALAT guidelines is that of "alternative diagnosis." Indeed, even if the HRCT shows UIP, probable UIP or indeterminate for UIP," ancillary findings (may) suggest an alternative diagnosis."[6] This underscores the value of a thorough preliminary history and physical exam, as well as a multidisciplinary team, to explore all the diagnostic possibilities. To exclude or identify an "alternative diagnosis", the second motherhood statement says, "For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF, we recommend serological testing to aid in the exclusion of CTDs as a potential cause of the ILD " [6] For a patient with a new ILD or suspected IPF, it is important to rule out connective tissue diseases (CTD), as these can have a lung component, and also require a tailored treatment approach.

The guidelines address uncertainty about when and when not to order more invasive tests, to either confirm HRCT findings or to clarify an ambiguous HRCT pattern. Procedures were weighed for costs and benefits in relation to scenarios. The costs included potential harm that could result from an invasive procedure. For example, surgical lung biopsy (SLB) has a risk of death (1.7%; 95% CI, 0.8–3.5%) and the most common adverse consequence is respiratory infection (6.5%; 95% CI, 4.6– 9.0%).[6] SBL also increases

the risk of acute exacerbations, bleeding, prolonged air leak and delayed wound healing. The committee weighed these risks vs. benefits and concluded with the following recommendation: “For patients with a new ILD, suspected IPF, and clear UIP pattern on HRCT, the panel recommended that SLB not be performed. [6]

However, for patients with probable UIP, indeterminate for UIP or an alternative diagnosis, the committee concluded that the benefits of SLB outweigh the risks and made the conditional recommendation that SLB be considered in these cases. Note that the stipulation of “conditional” implies that there was not a unanimous agreement on this recommendation, and that this is a consensus statement with a minimum of 70% in agreement. As the authors state, “The conclusion was strengthened by the panel’s opinion that making a diagnosis provides additional unquantified benefits, such as more accurate estimates of prognosis, cessation of additional diagnostic testing, and the initiation of more specific treatment. However, it was mitigated by the panel’s low confidence in the estimated effects of SLB.”[6]

Cellular analysis of bronchial lavage (BAL) is also weighed in the 2018 ATS/ERS/JRS/ALAT guidelines. BAL may be “less invasive” than surgery but is not without risks. Like SLB, there were mixed opinions about the utility of BAL. Because of this, the panel recommended against BAL in patients with suspected IPF and clear UIP pattern. The procedure was conditionally recommended for those with probable UIP, indeterminate for UIP and an alternative diagnosis. The authors state that BAL is most useful when there is a suspected diagnosis of eosinophilic pneumonia, cryptogenic organizing pneumonia, sarcoidosis, or infection.[6]

The committee also considered transbronchial biopsy and the newer technique of cryobiopsy but were not able to reach a consensus on whether these should be used in cases of probable UIP, indeterminate for UIB, and alternative diagnosis. Because of the lack of consensus, they made no recommendations one way or another on the use of transbronchial biopsy and cryobiopsy for patients with probable UIP, indeterminate for UIB, and alternative diagnosis. In cases with an HRCT pattern of UIP, they recommend against these two procedures. They did acknowledge that these tests might have more utility at a specialty center where practitioners are very familiar with these procedures, and stated ”The panel concluded that it is reasonable for experienced centers and experts with a track record of performing the procedure safely to continue performing lung cryobiopsy in patients whose HRCT pattern is probable UIP, indeterminate for UIP, or an alternative diagnosis.“[6]

Finally, the committee discussed the use of several serum biomarkers to diagnose IPF, and state, ”For the time being, the guideline panel dismissed serum biomarker measurement as an approach to distinguishing IPF from other ILDs because of the high false-positive and false-negative result rates.”[6]

As one can see, diagnosing an ILD is often complicated and may require input not only from experienced pulmonologists, but from radiologists, rheumatologists, pathologists and general practitioners, in a “ dynamic, diagnostic, integrated process.” [11] In the 2018 ATS/ERS/JRS/ALAT guidelines, the authors state that the “accuracy of diagnosis is increased through multidisciplinary discussions by experienced experts at regional centres for interstitial lung disease. The panel also states that the multidisciplinary team is especially important in patients with probable UIP, indeterminate UIP and alternate diagnoses, or when “there exist discordant clinical, radiologic, and/or histologic data.”[6]

## Gap # 3: Clinicians may not be aware of the evidence showing the superiority of multidisciplinary care over single-provider care in many cases of clinically suspected IPF and/or new ILD

According to Maher et.al, the data from their chart audit in 2016 “suggest that referral to a non-specialist pulmonologist may be another barrier to diagnosis and treatment access.” [9] They also note that limited access to specialty centers was a factor in the delay of diagnoses. From the patient participants of the Intensity Study, “ 68% of respondents cited referral to a subspecialist with expertise in ILD as the most important contributing factor to obtaining a clear diagnosis.” [9,10]

The multidisciplinary team can provide the expertise to make a timely and accurate diagnosis, to start treatment, and to educate and inform patients, caregivers, other providers, and policy makers. The specialty center will have work flows in place which can buy valuable time for patients, and perhaps more importantly, provide a sense of caring and belonging for the patients and families. Services that are offered in comprehensive ILD treatment centers include all relevant medical and diagnostic specialties, as well as pulmonary rehabilitation and respiratory therapy, physical and occupational therapy, palliative care, mental health care, case management and social work. The specialty center should have a fine-tuned transplant protocol in place. It can also be the hub where patients connect with each other as well, “giving a clear reference to patients, who often feel alone with their disease.

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