Special REPORT

Identification and Evaluation of Idiopathic Pulmonary Fibrosis in Primary Care

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease of unknown or undetermined origin that primarily occurs in older adults. Its radiologic presentation is characterized by fibrosis of varying degree.[1] A diagnosis of IPF often is difficult to obtain and is best facilitated with the use of a multidisciplinary team of pulmonologists, radiologists, and pathologists, typically at a center specializing in detecting interstitial lung diseases (ILDs) and related lung disorders.[1] The diagnostic course often begins when patients suffering from a persistent cough, breathlessness and/or fatigue present for an evaluation in the office of their primary care physician (PCP).

As a first-line for disease identification, PCPs share a unique role in determining the possible causes of symptomology—including dyspnea upon exertion and bouts of nonproductive cough—that commonly present in older patients and those with nonrespiratory health conditions.[2] Often these symptoms are related to heart disease or more common lung diseases such chronic obstructive pulmonary disease (COPD), but in a subset of patients, these symptoms can be caused by ILD. IPF often is misdiagnosed as asthma, COPD, or congestive heart failure (Table 1).[3-5] Following confirmation from a team of pulmonary specialists, the diagnosis of IPF may be made.[1,5] ILDs, also known as diffuse parenchymal lung diseases (DPLD),[6] include over 200 related lung disorders grouped into multiple categories depending on disease etiology (ie, drug or environmental exposure, inherited conditions).[6,7] Unlike obstructive lung diseases such as COPD, ILDs generally comprise conditions and disorders of lung restriction whereby the ability of the lungs to expand when inhaling is reduced, as in IPF.[5]

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With appropriate testing and assessment, PCPs can begin the process of excluding asthma, COPD, and heart failure from the list of potential causes of the patients' symptoms. Listening for telltale 'crackling' during auscultation in patients with IPF, completing a thorough patient history that accounts for past working conditions, smoking behavior, and familial history of ILDs, as well as noting seemingly minor abnormalities on standard chest X-rays (CXR) are all key steps to determine if patients are suffering from another lung condition or should be referred to a specialist for suspected ILD.[5]

Misdiagnosis of ILDs at the primary care level can be common due to nonspecific symptoms in patients with risk factors for several different diseases, which is why careful attention must be paid to all older patients who present with exertional dyspnea.[5] The importance of early referral for patients with suspected IPF to pulmonary specialists cannot be overstated; the irreversible lung damage and progressive course associated with IPF necessitate early diagnosis and management for optimal long-term outcomes.[4] As IPF often is a fatal disorder, PCPs who identify potential symptoms of ILD and pair these symptoms with risk factors for the development of IPF gathered via comprehensive history and testing can quickly refer the patient to a pulmonologist to ensure early diagnosis and management of the disease.[4,5] Once the diagnosis of IPF is made, PCPs can continue to improve the patient's condition through treatment of symptoms and comorbid conditions, and disease education.

Table 1. Initial Diagnoses in Patients Eventually Diagnosed With Pulmonary Fibrosis[a]

Bronchitis (18.5%)
Asthma (14.1%)
COPD (7.5%)
Emphysema (6.6%)
Heart disease (5%)

[a] Data gathered from responses from 1,448 current patients or caregivers.

Based on reference 3.

This report will describe the integral role PCPs play in the diagnosis of IPF and measures clinicians can implement to ensure at-risk patients are evaluated properly.

IPF Prevalence, Survival, and Risk Factors

In general, IPF occurs more frequently in older patients, men, and those with a history of cigarette smoking. While the exact incidence and prevalence of IPF are unclear, estimates in the United States (US) range from 7 to 20 cases per 100,000 women and 10 to 40 cases per 100,000 men.[8,9] Two-thirds of these cases occur in patients older than age 60.[9] In a recent analysis of IPF among US Medicare recipients over 65 years of age, the incidence in this population was estimated at 93.7 cases per 100,000 person-years.[10] Although IPF is still considered to be a rare disease, this report found the prevalence to be increasing rapidly in this population, from 202.2 cases per 100,000 people in 2001 to 494.5 cases per 100,000 people in 2011.[10] As in other analyses, IPF in this population occurred most frequently in older patients and was more common in men.[10]

IPF is a progressive disease and is one of the most common causes of death due to progressive lung disease in the US.[11] The prognosis of IPF varies depending on the stage at which the disease is diagnosed, underlying comorbidities, and patient factors such as age and gender. According to the above-referenced analysis of IPF in the Medicare population, the median survival for all newly-diagnosed patients with IPF is 3.8 years. Survival in patients 66 to 69 years of age was higher than average at 8 years, although at 2.5 years, survival was lower than average in patients 80 years of age and older. Women with IPF survive an average of 1 year longer than their male counterparts.[10]

Unlike many other pulmonary disorders, the risk factors and causes of IPF are not fully characterized, and the natural history is poorly understood. Smoking and exposure to environmental and occupational hazards, such as metal and wood dust, solvents, fumes, and livestock are all known risk factors.[12,13] IPF also has been associated with infections, including the Epstein-Barr virus and certain types of human herpes viruses, several genetic mutations, and gastroesophageal reflux disease (GERD). However, direct causation has not been proven for any of these agents.[14-16] Up to 20% of patients with IPF have a family history of the disease. Familial IPF is clinically and histologically identical to sporadic IPF and is considered the same disease for diagnostic and treatment purposes. Potential underlying genetic aberrations resulting in familial IPF have not yet been fully elucidated.[17]

IPF Pathogenesis and Clinical Course

Although IPF once was hypothesized to be caused by an inflammatory process and to be best controlled by immunosuppressives,[18] research in the past decade has suggested other mechanisms with inflammation playing a less prominent role.[19] Rather than being driven by inflammation, fibroblast activation and aberrant signaling from alveolar epithelial cells are important aspects of the pathobiology of lung fibrosis.[20,21]

Although typically a normal component of the wound healing process,[22] in the IPF lung, activated fibroblasts initiate deposition of a fibrotic matrix comprising collagen, hyaluronic acid, and fibronectin, resulting in scarring that destroys the delicate lung structure and prevents normal lung function.[20,22] Fibroblast activation is a self-sustaining process, initiating an irreversible cascade which further promotes lung damage. Progressive fibrosis is correlated with declining pulmonary function and a poorer prognosis.[22]

Once the wound healing cascade underlying IPF has been initiated, there are typically three potential courses of disease which are currently unpredictable at the time of diagnosis (Figure 1).[1,19] Some patients experience a stable disease course, while other patients may experience accelerated disease progression and rapid decline; however, the majority of patients experience a slow yet steady disease progression.[1] Furthermore, some IPF patients experience an acute exacerbation possibly resulting from secondary complications, including pneumonia or cardiac failure, which results in an irreversible and rapid decline in lung function and possibly death.[1]

Importance of Early Diagnosis

An early and accurate diagnosis of IPF is critical as it has a direct impact on patient outcomes. Unfortunately, it often takes 2 or more years from onset of dyspnea until an accurate diagnosis is made and appropriate treatment initiated.[23] Patient response surveys also report that 55% of respondents are misdiagnosed and 61% visited their PCP more than twice before an accurate diagnosis of ILD or IPF was made. In the same survey, there was a median of 11 months before a correct diagnosis was made.[24] This lost treatment time is directly linked to poorer outcomes, as a longer delay between symptom onset and first clinical evaluation is associated with a higher mortality rate. For example, one study found that mortality rates associated with IPF increase by nearly 10% for each year of dyspnea prior to evaluation (Figure 2).[23]

"Now that there are new therapies for the disease which either slow the progression or stabilize the disease, and the earlier that we can catch patients, make the diagnosis, and get them started on appropriate treatment, the longer we may prevent the need for lung transplantation in the future," said S. Samuel Weigt, MD, assistant professor of medicine in the Lung and Heart-Lung Transplant Program, Division of Pulmonary, Critical Care, Allergy and Immunology at the David Geffen School of Medicine at UCLA in Los Angeles, California.

The nonspecific symptoms associated with IPF and the sheer number of diseases with similar symptoms and pathophysiology makes achieving an accurate diagnosis of IPF challenging. This difficulty in diagnosis is compounded by the fact that the underlying cause of IPF is unknown, and as such, IPF can only be diagnosed by ruling out all other ILDs. In older patients, exertional dyspnea is often attributed to aging; therefore, patients think that these types of increasing physical limitations are to be expected. For example, physicians often attribute complaints of breathlessness when using stairs or walking to the mailbox to deconditioning typical of aging.[2] An accurate diagnosis often occurs only when symptoms worsen with progressive fibrosis. These misdiagnoses delay appropriate treatment and, in some cases, result in patients receiving highly inappropriate or even harmful treatments.[5]

For example, a patient with ILD may be initially diagnosed with asthma and treated with bronchodilators and/or prednisone. These treatments are not beneficial in IPF and may even be harmful. According to results of the PANTHER-IPF trial, the combination of prednisone, azathioprine, and N-acetylcysteine showed no evidence of clinical benefit and resulted in statistically significant increases in hospitalization and death compared with placebo.[25] Indeed, prognosis and treatment for IPF differ significantly from other ILDs, requiring an accurate diagnosis to begin appropriate treatment.

"Often, prognosis is linked to an accurate diagnosis," said Gregory Cosgrove, MD, associate professor in the Department of Medicine, Pulmonary Division at National Jewish Health/University of Colorado–Denver in Denver, Colorado and chief medical officer of the Pulmonary Fibrosis Foundation in Chicago, Illinois. "It is very much the same as a clinician diagnosing someone with a 'cancer'; the next question becomes 'what kind of cancer is it?' If it is basal cell carcinoma and we can treat it early, the patient lives a completely normal life. But if it is melanoma and it is caught too late, the prognosis is significantly different. This works much the same in individuals with pulmonary fibrosis."

"If the diagnosis is IPF, this is a progressive disease. If the condition is asbestos-related lung disease, patients might not progress as frequently as those with IPF. It is not only that a confident diagnosis is beneficial for the physician, but also it helps he or she to know what to do, since different interstitial lung diseases may be treated differently. There are approved therapies for patients with IPF that have not been studied for other interstitial lung diseases," Dr. Cosgrove said.

Patient Evaluation in Primary Care

For the PCP evaluating a patient with unexplained chronic exertional dyspnea, three steps will help ensure that the suspicion of IPF is warranted and that referral to specialists is necessary: First, as mentioned previously, a thorough patient and family medical history will help eliminate exposure/environmental, hereditary, and drug-induced ILDs. Second, physical examination reveals a distinctive 'Velcro'-like crackling upon inhalation that persists beyond several breaths during auscultation. This is noted beyond the patient's presenting complaints.[5] Lastly, radiological and surgical assessment is necessary to rule out other conditions and verify suspicion of IPF. Assessments include a CXR, HRCT, and, in certain cases, surgical lung biopsy when HRCT is inconclusive for a pattern of lung scarring indicative of IPF.[1] However, consultation with a specialist before ordering more complex and invasive diagnostic studies beyond a PA and lateral CXR is recommended.

Medical and Familial History

The primary purpose of taking a comprehensive patient history in the diagnosis of IPF is to either rule out or identify

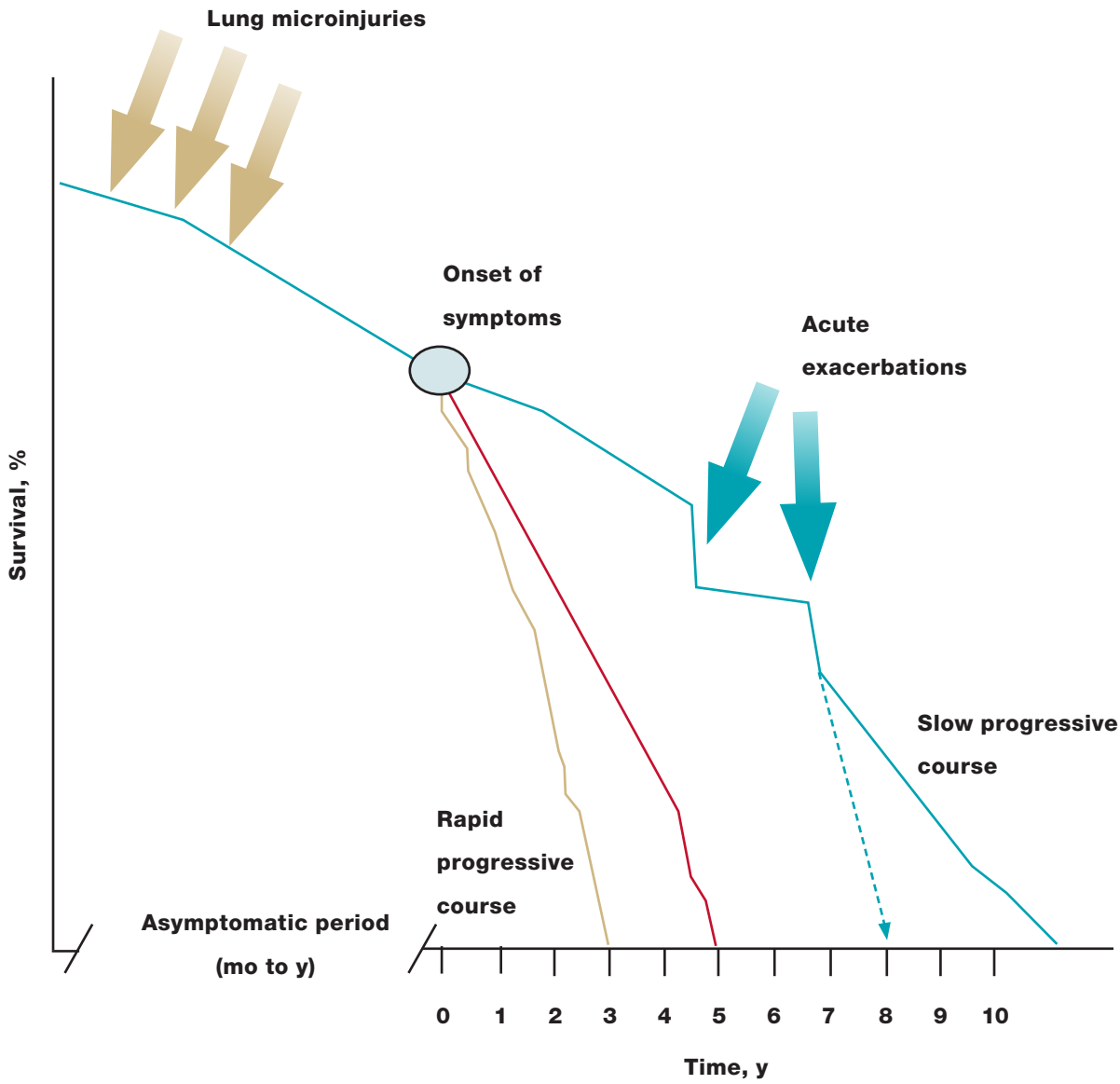

Figure 1. Clinical phenotypes of IPF.

The heterogeneous natural history pattern in patients with IPF: The disease has a long asymptomatic period, lasting for months or even years. Patients seek consult with their primary care physician when the severity of the lung lesions reaches a threshold that is enough to provoke symptoms. Most patients follow a relatively slow clinical and functional decline (slowly progressive) after diagnosis. About 10% of these patients present with episodes of acute clinical deterioration (acute exacerbations) that precede and possibly initiate the terminal phase of their disease. Some patients have a short duration of illness with a rapidly progressive clinical course. Heavy smokers might develop pulmonary fibrosis combined with emphysema, which predicts shorter survival compared with patients with IPF alone.

IPF, idiopathic pulmonary fibrosis

potential causes of ILD. The history should include past medical history, current and past drug exposures, work and environmental exposures, and social and family history. The American Thoracic Society advises that all clinicians use a standardized approach to gathering patient history when an ILD is suspected, and recommends a questionnaire published by The American College of Chest Physicians.[1,26]

Questions asked during patient history elicitation should be geared toward identifying non-idiopathic causes of ILD. For example, a PCP may ask patients if they are experiencing symptoms such as fatigue, joint pain, or stiffness which may indicate a connective tissue disease such as rheumatoid arthritis.[5] Questions about a patient's work duties and hobbies can identify exposure to agents that may cause ILD, including antigens from pet birds or significant mold intrusion, silicas, asbestos, metal dust, and fumes.[12] Questions focused on past medical history, including previous treatments and a thorough discussion of medication history, can identify medications known to cause ILD, such as chemotherapeutics, antimicrobial agents including nitrofurantoin, and certain treatments for cardiovascular disease, particularly if congestive heart failure also is suspected.[27] The patient should also be asked about family medical history, including family history of both autoimmune disorders and pulmonary fibrosis, or if they remember any relatives using supplemental oxygen.[28]

Taking a thorough patient history also will help determine if breathing complaints are related to past and/or current patient working conditions (including asbestos exposure, construction or farm work), hobbies, or environmental exposures. Discuss the patient's hobbies and living conditions to determine if they are exposed to mold or if they have pets in their home as this may cause exposure-related lung disease, most often hypersensitivity pneumonitis. While these patients still may have IPF, ILDs related to exposure should be considered as well.

Physical Examination

Similar to the patient history, the physical examination on a patient with suspected ILD serves both to identify traits characteristic of specific types of ILD and to rule out other causes of ILD. Because the symptoms related to IPF are the same as several other diseases, a careful physical examination aimed at identifying underlying causes of disease is essential before proceeding with further evaluation. The physical exam should, at a minimum, include a typical physical evaluation, careful evaluation for signs of connective tissue disease, and include auscultation. Lung capacity measures and basic serologic

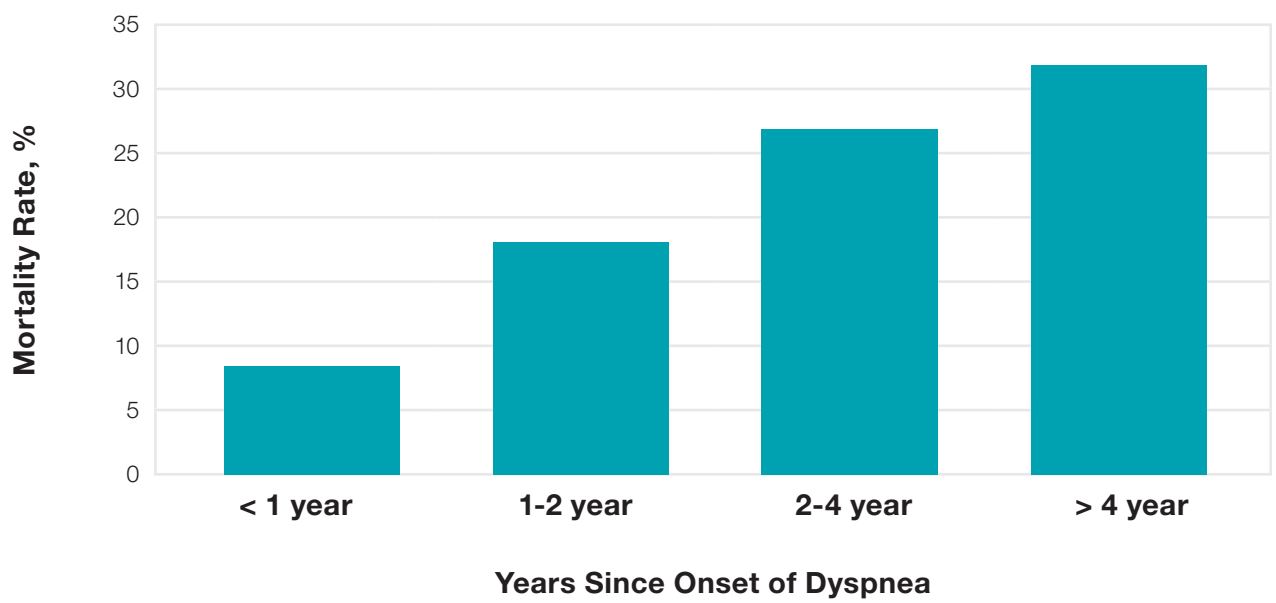

Figure 2. Delayed referral to subspecialty care center associated with higher mortality rates in patients with IPF.[a]

[a] Delay is defined as time from onset of dyspnea to time of initial evaluation at a tertiary care center.

IPF, idiopathic pulmonary fibrosis

Based on reference 23.

testing may be performed if the diagnosing team suspects an ILD. Identifying common causes of pulmonary dysfunction should be a major focus of this portion of the patient evaluation, particularly in younger patients or in patients presenting with additional unexplained symptoms not associated with IPF.[1,29] As dyspnea is an early symptom of IPF that drives patients to their PCP and is also present in heart failure, a cardiac evaluation may be necessary, particularly in an aging, male patient population.

In particular, connective tissue diseases such as systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, Sjögren's syndrome, and polymyositis-dermatomyositis often present with pulmonary symptoms similar to IPF and other ILDs in early stages, and thus must be confirmed through serologic testing, or eliminated if presenting symptoms do not indicate the presence of these disorders during evaluation.[29] Serological testing is of the utmost importance to exclude non-idiopathic causes of ILD, including pneumonia, rheumatoid arthritis and other connective tissue diseases, and should be performed even in the absence of any signs or symptoms of these diseases. Current guidelines recommend that serological analysis should include at minimum a rheumatoid factor, anti-cyclic citrullinated peptide (CCP), and antinuclear antibody (ANA) titer and pattern.[1]

Several other serological tests, including creatine kinase, antisynthetase antibodies, and scleroderma antibodies can further narrow the differential diagnosis in the appropriate clinical context.[1] The presence of anti-nuclear antibodies or rheumatoid factor can occur in up to 15% of patients with an ILD at low titers, and alone is not indicative of connective tissue disease.[1,30] These patients should undergo careful evaluation for signs and symptoms of connective tissue diseases, such as arthritis, Raynaud's disease, and skin changes.[28] If these changes are not present and antibody titers remain low, it is appropriate to continue assessing the patient for suspected IPF.

Look, Listen, Walk

A simple technique for physical evaluation of a patient with suspected ILD is commonly referred to as "Look, Listen, Walk." In this technique, the patient's skin and fingers are first checked for digital clubbing and other signs characteristic of pulmonary fibrosis or connective tissue disease, such as dermatomyositis or Raynaud's syndrome.[28] The PCP listens to the patient's breath sounds at both lung bases and along the mid-axillary lines, approximately halfway down the back, to identify crackling in the lungs. After auscultation, the patient undergoes what is commonly referred to as a 6-minute walk test (6MWT) whereby the patient's peripheral oxygen saturation (SpO_2) is measured before and after walking for 6 minutes or a period of time sufficient to elicit exertional dyspnea. A 3% drop in SpO_2 indicates exertional desaturation and often dictates the prescription of supplemental oxygen. Finally, the patient walks again with oxygen titration in an attempt to determine the oxygen flow required to prevent desaturation below 88%. The patient's total distance walked to this endpoint also is measured (Table 2).[28,31,32]

Breath sounds are perhaps the clearest physical indicator of IPF. Dry, end-inspiratory, 'Velcro' crackles are detected on chest auscultation in most patients with IPF. These are most commonly heard in the bases of the lung, but will extend toward upper lung regions as the disease progresses. Importantly, the crackles are present early in the disease course and should not be ignored, especially if they do not resolve over time.[33] According to Dr. Cosgrove, "When listening to patients with IPF, the PCP should hear crackles on their lung exam, which are abnormal and need to be investigated. In the setting of newly-recognized crackles, a differential diagnosis including atypical pneumonia, congestive heart failure, atelectasis, and interstitial lung disease should be considered. While crackles are often similar in sound, the clinical context is often quite different and one cause can readily be distinguished from another."

Also, if auscultation reveals squeaks, conditions including hypersensitivity pneumonitis or bronchiolitis should be considered in the diagnosis.[28]

Other physical signs of IPF include digital clubbing, which occurs in approximately 50% of patients, cyanosis, abnormal enlargement of the heart, an accentuated pulmonic second sound, right ventricular heave, and peripheral edema. However, these symptoms are particularly observed in the later stages of the disease and may not be observed in patients presenting with early disease.[34] Fatigue may be associated with ILD, but the presence of fever is indicative of an alternate diagnosis such as infection.[35]

Other clinical tests that may be appropriate for individual patients, depending on their symptoms, characteristics, and family history include a baseline metabolic panel, a complete myositis panel, HIV testing, urinalysis for signs of renal failure, and screening for anti-phospholipid antibodies and anti-RNA polymerase 3 antibodies.[28] Bronchoaveolar lavage can be used to identify patients suffering from hypersensitivity pneumonitis, typically identified as lymphocytosis of 50% or greater.[35]

Finally, a useful method both for identifying IPF and gauging the extent of the disease is lung function testing. This is most commonly done using spirometry, a procedure during which patients are asked to take a maximal inspiration and then forcefully expel air for as long and as quickly as possible. Measurements derived from this test include forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and the ratio of the 2 (FEV_1/FVC).[36] Calculation of FEV_1/FVC allows identification of airway obstruction or restriction.[27] Although spirometry is not diagnostic for IPF, it can be useful for eliminating the presence of obstruction and ruling out COPD. Full pulmonary function testing (PFT) includes measuring the diffusing capacity (DL_{CO}), partial pressure of oxygen in arterial blood (PaO_2), and SpO_2 which are also useful in diagnosis, as reduction in DL_{CO} often is one of the first lung function abnormalities to be noted in IPF and may adversely impact both PaO_2 and SpO_2, especially with exertion.[1]

Beyond their utility in the diagnosis of IPF, results from lung function tests also may be used to determine the severity and

potential prognosis of the disease. Oxygen desaturation during a 6MWT has been directly linked to survival in IPF,[37] as have end-of-exercise SpO_2, change in SpO_2 with exercise, walk distance, and walk velocity.[38]

Radiological and Surgical Assessment

If the PCP refers a patient early following symptom presentation, radiological testing typically occurs under the guidance of a multidisciplinary team at a specialty center. An HRCT scan should be ordered which allows for identification of the radiologic signs of usual interstitial pneumonia (UIP), which is the defining radiologic and histologic pattern of IPF. Radiologic UIP as interpreted by an expert thoracic radiologist is considered diagnostic in the presence of IPF symptoms once other causes of ILD have been eliminated.[1] According to American Thoracic Society guidelines, diagnosis of IPF requires the exclusion of other known causes of ILD (eg, environmental exposures, connective tissue disease, drug toxicity) and the presence of a UIP pattern on HRCT in patients who have not had a surgical lung biopsy, or specific combinations of HRCT and surgical lung biopsy patterns in patients subjected to surgical lung biopsy.[1]

Prior to referral, many PCPs may wish to obtain a CXR to verify exam findings (Figure 3). While CXRs are not diagnostic for IPF, they can identify a pattern of lung damage suggestive of IPF.[39] Importantly, while an abnormal CXR can provide additional evidence supporting a diagnosis of IPF,[39] a lack of abnormalities should not exclude the possibility of IPF. Further evaluation with HRCT and potentially surgical lung biopsy are the only definitive methods for diagnosing or excluding IPF.[1]

Diagnosing IPF

Distinguishing IPF from ILDs and Related Lung Disorders

ILDs include connective tissue diseases and autoimmune diseases that affect lung function, drug-induced lung diseases, infections, genetic disorders affecting the lung, lung damage caused by occupational or environmental hazards, and lung disorders of unknown etiology, including IPF.[6] Although the heterogeneity of ILDs can complicate the accuracy of prevalence data,[9] registry studies have estimated that ILDs, defined as pulmonary fibrosis and IPF, affect 30 out of 100,000 people per year, with a slightly higher incidence in men than in women.[9] Among ILD cases, 10% have been shown to be unclassifiable often due to inability to effectively assess lung tissue.[40]

Many of the pulmonary symptoms caused by these disorders are nonspecific at initial presentation and include a nonproductive cough and exertional dyspnea similar to infectious pneumonitis and other conditions,[41] which can lead to difficulty when making an early diagnosis.

Table 2. Six-Minute Walk Test (6MWT) Considerations

Patient Performance Measures			
Total distance walked by patient	Physical measure of functional lung capacity	Fatigue and dyspnea (measured by VAS or Borg scale)	Arterial oxygen saturation (if pulse oximetry is used)
Administration Guidelines			
Test should be administered by trained health care professional	Testing location should provide for rapid emergency response	Determine use of supplemental oxygen tank and pulse oximetry	Patient should wear comfortable clothing and footwear
Associated Patient Performance Factors			
Age	Height and stride length	Weight and amount of muscle mass	Gender
Presence of comorbidities (eg, arthritis, congestive heart failure)	Level of cognition and motivation	Test familiarity	Length of testing area (ie, number of turns during test)

Healthy patients' 6-minute walk tests range from 400 to 700 m.

IPF, idiopathic pulmonary fibrosis; **VAS,** visual analog scale

Based on references 31 and 32.

Despite presenting with the same symptoms of IPF, connective tissue diseases, including rheumatoid arthritis and systemic lupus erythematosus, can later be distinguished by the presence of a pleural effusion, rheumatoid nodules in the lungs, and other extrapulmonary symptoms such as joint pain and swelling.[41] Drug-induced lung diseases can cause nearly all types of histopathological patterns of interstitial pneumonia, but are characterized by spontaneous improvement of non-damaged lung tissue following medication cessation, emphasizing the importance of taking a careful history of the patients' past and current medications.[26,27] Complete patient evaluations (eg, blood cultures and urine analyses)[8] by clinicians should reveal the presence of infection, which should then be treated to provide symptom remission. If the cause for lung decline cannot be determined with standard testing and if symptoms persist despite intervention, the patient should be referred to a pulmonologist for suspected IPF, as this condition is the most common of the 7 known idiopathic interstitial pneumonias (IIPs; Table 3).[6,42]

Identifying Patients with IPF

Diagnosis of IPF is a complex, multistep process requiring careful collaboration between members of a multidisciplinary team including PCPs, pulmonologists, radiologists, and pathologists. An accurate diagnosis of IPF requires this process both to rule out non-idiopathic causes of ILD (eg, exposure or connective tissue disease) and to identify the signs and symptoms characteristic of IPF.[1] The diagnostic process typically involves a thorough medical history, physical evaluation, complete pulmonary function tests, CXR, high-resolution computed tomography (HRCT) scans, and, for patients who can sustain invasive assessment, surgical biopsy.[1]

This comprehensive diagnostic process requires the collaboration of the PCP with multiple specialists in order to arrive at an accurate diagnosis. The diagnostic process for IPF begins when a patient presents with general symptoms of pulmonary disease. In some ways, including ILD in the differential diagnosis for a patient presenting with chronic exertional dyspnea and a cough represents the largest hurdle to a patient receiving appropriate care.[4] As a less common and less well-understood disease, IPF typically is not considered early in the diagnostic process. More than 50% of patients with pulmonary fibrosis report a delay of more than a year between reporting of symptoms and a final diagnosis.[3]

"When a patient presents to a PCP's office with shortness of breath that has progressively worsened over time—especially if on the physical exam they may have crackles

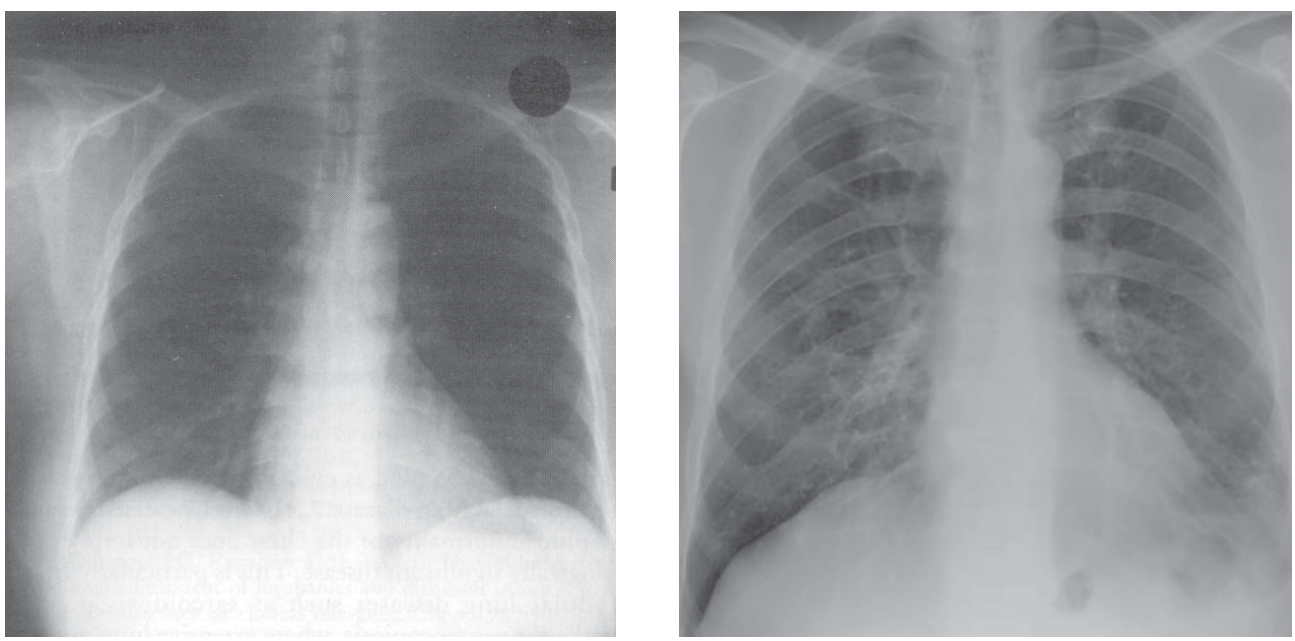

Figure 3. Normal CXR (left) and CXR showing ILD (right).

CXR, chest X-ray; **ILD,** interstitial lung disease

Images courtesy of Steven D. Nathan, MD, FCCP.

that are heard at the bases of their lungs—we should consider common causes, such as heart failure and COPD, but we should also consider less common causes, such as the interstitial lung diseases," said Mark Gotfried, MD, clinical professor of medicine at the University of Arizona in Phoenix, Arizona.

Role of HRCT and Lung Biopsy in the Diagnosis of IPF

While physical examination and medical history are essential tools to eliminate other potential causes of pulmonary dysfunction, the diagnosis of IPF cannot be made without an appropriate HRCT scan or lung biopsy in some cases. These tools are the gold standard for establishing a diagnosis of IPF, as the diagnosis cannot be rendered without conclusive results from at least one of these examinations.

High-Resolution Computed Tomography

HRCT is an integral part of the evaluation of patients with suspected IPF and many other ILDs, with an estimated predictive value of up to 90% in studies comparing HRCT to surgical lung biopsy for IPF.[43]

"If a clinician is concerned about an ILD or pulmonary fibrosis, the most sensitive diagnostic test would be HRCT," Dr. Cosgrove said. "The next hurdle after the clinician performs the scan is ensuring that a specialist with experience with interstitial lung disease interprets the HRCT scan. As with any rare disease, experience is important to identify subtle features that may distinguish different diseases from one another and provide the diagnostic guidance for the patient and ordering physician."

HRCT is the radiological imaging technique best suited to revealing changes in lung structure, providing the opportunity for global anatomic assessment of the lung and improving the sensitivity and specificity of the clinical diagnosis. HRCT provides the clearest radiologic picture for IPF because it allows improved assessment of the pattern, distribution, and extent of pulmonary abnormalities. Structures as small as 0.2 to 0.5 mm are identifiable on HRCT, and the resolution is greatly improved from traditional CT techniques.[44]

While there are several techniques for HRCT, all utilize thin slice images of less than 2 mm and high-resolution reconstruction algorithms to provide a large-scale, high-definition picture of the lung.[45] The 2 techniques most frequently used are volumetric acquisition and spaced axial imaging. Volumetric acquisition is the preferred technique for IPF imaging

Table 3. Features of 7 Known Idiopathic Interstitial Pneumonias

	IPF	LIP	NSIP	COP	DIP	RB-ILD	AIP
Histologic pattern	UIP	LIP	NSIP	Organizing pneumonia	DIP RB-ILD	DIP RB-ILD	Diffuse alveolar damage
Illness duration	Chronic (>12 mos)	Women: chronic (>12 mos)	Subacute to chronic (months to years)	Subacute (<3 mos)	Smokers: subacute (weeks to months)	Smokers: subacute (weeks to months)	Abrupt (1-2 weeks)
Prognosis	50% to 80% mortality in 5 y	Unknown	<10% mortality in 5 y	Mortality rare	5% mortality in 5 y	5% mortality in 5 y	60% mortality in <6 mos

AIP, acute interstitial pneumonia; **COP,** cryptogenic organizing pneumonia; **DIP,** desquamative interstitial pneumonia; **IPF,** idiopathic pulmonary fibrosis; **LIP,** lymphocytic interstitial pneumonia; **NSIP,** nonspecific interstitial pneumonia; **RB-ILD,** respiratory bronchiolitis–associated interstitial lung disease; **UIP,** usual interstitial pneumonia

Based on reference 6.

as it improves both the identification of lung nodules and characterization of patchy ILD, and allows for better differentiation between honeycombing and traction bronchiectasis, 2 key features of the radiologic UIP pattern (Figure 4).[46] The major drawback of volumetric acquisition is the higher dose of radiation associated with this technique.[46] For this reason, spaced axial imaging may be a better option for some patients, particularly if they are younger and at greater risk of developing long-term complications from radiation. Spaced axial imaging does not allow assessment of the entire lung, but can provide slightly better resolution and a lower radiation dose.[45]

When evaluating for IPF, the results from an HRCT scan can be divided into 3 possible categories: (a) UIP pattern, which together with clinical symptoms is diagnostic of IPF, (b) possible UIP pattern, which may require surgical evaluation to confirm diagnosis, and (c) inconsistent with UIP, which can indicate an alternate diagnosis.[1] Subpleural, basal honeycombing is the most specific feature of the UIP pattern and is crucial for an accurate diagnosis without surgical biopsy.[1] "Early on, the CT scan for IPF would show a basilar lower lobe predominance and peripheral predominance, reticular findings, and scarring at the edges of the lungs and the bases," Dr. Weigt said. "These findings would not be specific for IPF early on, but as the disease gets worse, the clinician often sees typical features such as honeycombing, which would be diagnostic."

On HRCT, honeycombing is characterized by clustered cystic air spaces of comparable diameters. Cyst diameters typically are <10 mm surrounded by well-defined walls.[47] Interestingly, the precise definition of honeycombing tends to vary between observers and, more specifically, between radiologists and pulmonologists, further emphasizing the need to have an experienced specialist interpret the HRCT scans when diagnosing IPF.[48] Having the scan performed by an experienced technician and read by a thoracic radiologist familiar with the specific abnormalities associated with ILD is essential in order to accurately interpret the results and provide the correct diagnosis. The characteristics of IPF may appear similar to other diseases or be entirely overlooked by the untrained eye.

A UIP pattern also is seen in other disorders such as connective tissue diseases, chronic hypersensitivity pneumonitis, asbestosis, familial ILD, sarcoidosis, vasculitis, and Hermansky-Pudlak syndrome.[6,29,30]

Surgical Lung Biopsy

Historically, surgical lung biopsy has been a major tool used for the diagnosis of IPF.[49] In recent years, use of biopsy as a first-line diagnostic tool has declined in favor of HRCT. According to American Thoracic Society guidelines, if a definitive diagnosis of IPF can be made using HRCT alone, surgical lung biopsy is not indicated.[1] It is only in those patients for whom HRCT findings are not clear or when a variety of diagnoses are suggested by the clinical and radiological findings that surgical lung biopsy is necessary.

"When thinking about a surgical lung biopsy, we want to make sure that the information that is gained from the procedure is going to affect the treatment of this patient," Dr. Gotfried said. "For example, if you have a patient with far advanced clinical disease with a limited life expectancy because of comorbidities, you may not want to proceed with a lung biopsy. The morbidity and mortality of surgical lung biopsies are acceptable in most elective cases, but clinicians know that the older a patient is, the more comorbidities are found, and the morbidity and mortality associated with a biopsy surgery can increase."

Surgical lung biopsy involves using open thoracotomy or video-assisted thoracoscopy to obtain tissue samples from the patient's lung. Because of the histological variability associated with UIP, biopsies must be taken from at least 2 lobes of the lung.[34,49] Biopsy is a highly invasive procedure and comes with its own set of potential complications, including death. The 30-day mortality rate following surgical lung biopsy for IPF ranges from 7% to 17% in published studies.[50,51] Importantly, these studies included all patients receiving surgical lung biopsy, including those considered 'high risk' due to age, comorbidities, the need for mechanical ventilation, or rapid deterioration of respiratory status prior to surgery. When these cases are excluded from analyses, the 30-day mortality rate drops to 1%, indicating that surgical lung biopsy is generally a safe procedure for non-high risk patients.[52] However, due to the high level of accuracy associated with HRCT and the ability to diagnose IPF using this technique in most patients,[43] the need for surgical lung biopsy as a diagnostic tool for IPF has declined and it is no longer used in all patients.

Most often, the current role of surgical lung biopsy is to confirm findings of a possible UIP pattern on HRCT. In patients whose HRCT does not demonstrate a UIP pattern, often due to the absence of honeycombing, surgical lung biopsy may demonstrate a UIP pattern and confirm diagnosis (Figure 5).[1,21] The defining characteristic of UIP on surgical lung biopsy is a heterogeneous appearance at low magnification in which areas of fibrosis with scarring and honeycombing alternate with areas of less affected or normal lung parenchyma.[49] Inflammation is mild and consists mostly of patchy interstitial infiltrates of lymphocytes and plasma cells. As seen in radiologic evaluations, the changes associated with a UIP pattern are commonly concentrated in the subpleural and paraseptal parenchyma.[1] As with HRCT, the histopathological evaluation for UIP must take into consideration other diseases that cause a UIP pattern, including connective tissue disorders and chronic hypersensitivity pneumonitis. The final diagnosis requires careful consideration of the clinical, radiological, and histopathological features of the disease.[1]

Role of the PCP in Care of the Patient with IPF

Although specialists at centers focused on IPF and ILD make the final diagnosis of IPF and will work with the patient to make decisions about treatment, the PCP is an essential component of the team whom ensures the well-being of the

patient throughout the course of his or her life. PCPs often play a front-line role in communication with their patients about all aspects of IPF, from explaining the diagnosis and setting expectations, to counseling on lifestyle changes and managing comorbidities. When discussing the diagnosis of IPF with patients, it is important for all members of the patient's medical team to provide realistic expectations and accurate information to the patient. One of the most important roles the PCP plays in the management of IPF is in educating patients about the disease and available treatment options. This is particularly important, as many patients diagnosed with IPF report feeling inadequately informed about the nature of the disease and their options for treatment and symptom control. In a survey of 1,251 patients with IPF and 197 caregivers of current patients, 64% of respondents indicated that they did not consider themselves adequately informed about the disease, and more than a third said they were unaware of the benefits of certain treatments including pulmonary rehabilitation.[3]

"You have to balance the need to be up-front and make sure the patient understands the implications of their disease, but at the same time this information can be depressing for patients and their caregivers, and you should also stress what we can do to help them," Dr. Weigt said.

Having treatments available for IPF has changed the outlook of the disease tremendously, and this is reflected in patient care. "IPF has been a frustrating disease to treat in the past and has led to a certain degree of nihilism—'There's nothing to do for these patients. You can't help them. They're hard to diagnose, but do we really need to because you can't treat them anyway'. Recent advances suggest that pharmacologic and nonpharmacologic treatments effect the course of the disease," Dr. Cosgrove said. "We can do a lot for patients in the absence of curing them of their disease. Healthier patients do better, especially those with chronic diseases."

Along with education, counseling patients about appropriate lifestyle changes is key. These changes may include improvements in nutrition, increased exercise, or weight loss. An important lifestyle change for patients with IPF is smoking cessation. Approximately 69% of patients with IPF are current or former smokers.[3] Although some studies have found an association between smoking and increased survival in patients with IPF, this relationship is not clear. It is suspected that smokers who develop IPF have longer survival simply because they are more likely to recognize disease symptoms and seek diagnosis and treatment earlier than their non-smoking counterparts.[53,54] Beyond any potential direct impact on IPF, smoking is a risk factor for several comorbidities, especially hypertension, that can adversely impact quality of life (QoL) and speed disease progression in patients with IPF.[53]

Another step PCPs can take to improve their patients' overall well-being is to diagnose and manage comorbidities that may affect patients with IPF. Managing comorbidities in these patients is important as they may lead to serious,

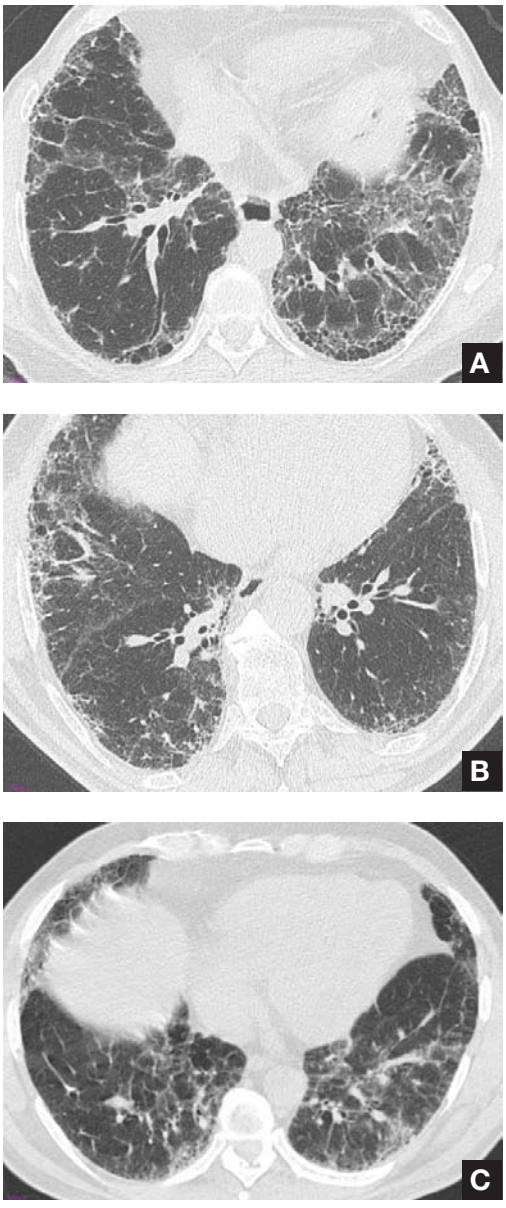

Figure 4. HRCT imaging showing UIP pattern.

(A) Definite UIP pattern. Axial HRCT image shows subpleural basal honeycombing (more evident in the left lung) with traction bronchiectasis and reticular and ground-glass opacities. **(B)** Biopsy-proven UIP with a possible UIP pattern on HRCT. The axial HRCT image through the lower lobes shows patchy and peripheral reticular opacities without obvious honeycombing. **(C)** Biopsy-proven UIP with an HRCT pattern inconsistent with UIP. There are some patchy ground-glass and peripheral reticular opacities, which are more suggestive of NSIP.

HRCT, high-resolution computed tomography; **NSIP,** nonspecific interstitial pneumonia; **UIP,** usual interstitial pneumonia

Adapted from reference 46.

life-threatening acute exacerbations. These comorbidities range from relatively benign illnesses, such as GERD,[55] to more serious complications like pulmonary hypertension.[34] The incidence of GERD is high in IPF and other ILDs, and studies have shown an association between the treatment of GERD and longer survival.[56,57] Concomitant pulmonary hypertension is associated with very poor prognosis and occurs frequently in IPF, with rates ranging from approximately 32% to 84% of patients.[58,59] The PCP should also help the patient take steps to avoid other comorbidities. Because patients with IPF are at increased risk for infection, they should receive seasonal influenza vaccines along with the pneumococcal and pertussis vaccines.[34] Patients should be counseled to avoid contact with people who are sick and be proactive about reporting any signs of illness.

Oxygen supplementation may improve QoL in some patients with IPF, particularly those experiencing extreme hypoxia.[1] Several studies have demonstrated the benefits of oxygen supplementation in other pulmonary diseases, including COPD, though there have not been studies thoroughly investigating its efficacy in IPF.[60,61] However, ambulatory oxygen is frequently used in IPF as in some cases, it may be able to improve exercise capacity, enhance mobility, and potentially allow the patient to participate in normal daily activities.

Finally, PCPs can improve the overall well-being of patients by recommending pulmonary rehabilitation. Current guidelines for IPF recommend pulmonary rehabilitation for the majority of patients with IPF,[1] Several small studies over the course of the past decade have demonstrated the efficacy of pulmonary rehabilitation in these patients. Pulmonary rehabilitation provides significant short-term improvements in functional exercise capacity, QoL, and perception of dyspnea. In addition, a continued program of exercise-based pulmonary rehabilitation results in increased oxygen uptake and improved physical conditioning, all of which can improve the overall health of patients with IPF (Figure 6).[62-65] Updates to the American Thoracic Society guidelines for the treatment of IPF that will include increased recommendations for pulmonary rehabilitation are underway.[55]

"We must take a holistic approach with our patients," Dr. Gotfried said. "We have to make sure that their nutrition is well managed. If the patient is smoking, we as physicians

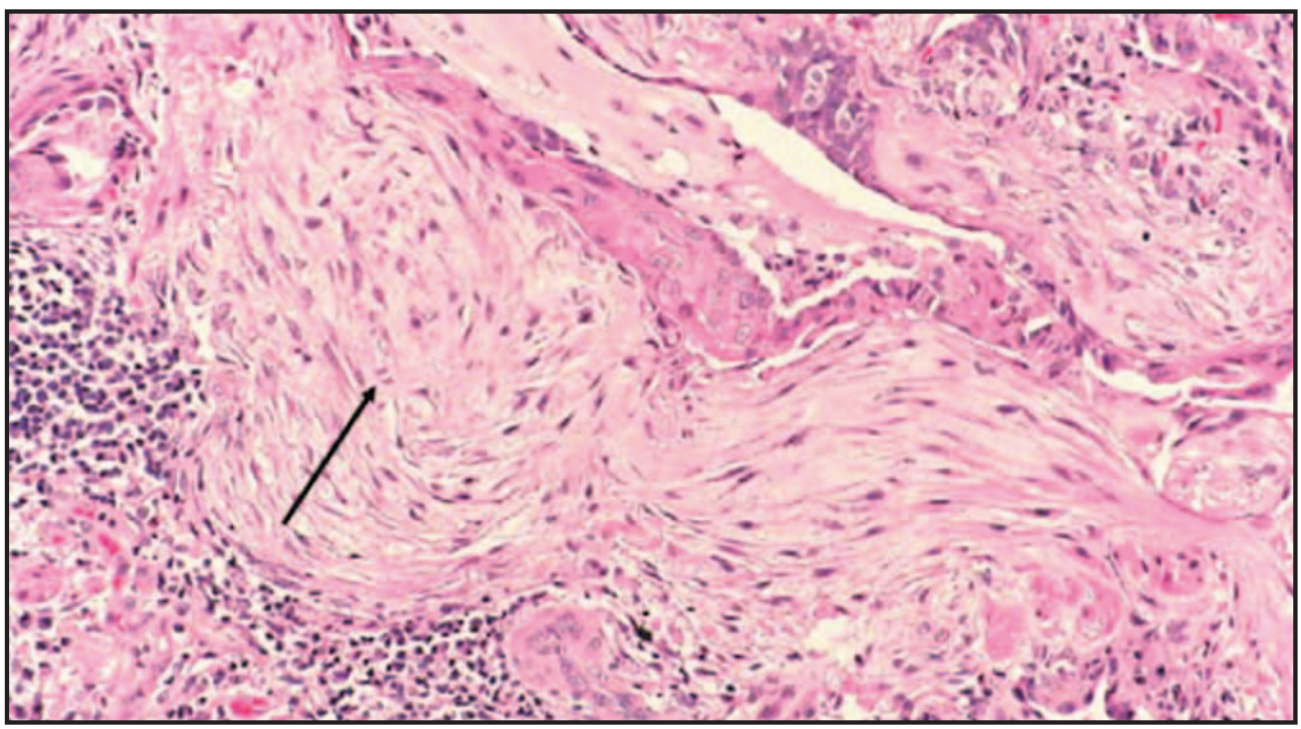

Figure 5. The photograph shows a large fibroblastic focus (arrow) in an area of interstitial chronic inflammation, located beneath epithelial cells that line the luminal surface (magnification ×200).

Reprinted with permission from reference 21.

need to try to intervene very vigorously because we know that cigarette smoking is a risk factor for pulmonary fibrosis, and the numbers show that 10% of patients with pulmonary fibrosis will die of lung cancer. We need to keep an eye on our patients' general health."

Overall, the PCP and a multidisciplinary team of specialists should work together with the patient to develop and provide a comprehensive management strategy that aims to slow disease progression, minimize the presence of comorbid conditions, and improve the patient's overall mental and physical well-being.

Conclusion

Early diagnosis provides the best chance to improve outcomes and prolong survival for patients with IPF.[4,5] As the front-line of diagnosis, PCPs should be aware of the symptoms of IPF and other ILDs, and be prepared to engage in the appropriate steps to achieve an accurate diagnosis.

In older patients presenting with a gradual onset of unexplained exertional dyspnea and a nonproductive cough, ILDs should be a major diagnostic consideration.[1] Appropriately, more common causes for pulmonary disease should be ruled out through a careful physical exam and thorough medical history before exploring a diagnosis of ILD. If ILD or IPF are suspected, patients should be referred to a pulmonologist for further evaluation and additional diagnostic studies including HRCT and surgical lung biopsy, if warranted. Although a multidisciplinary team led by a pulmonologist at an ILD specialty care center should make the final diagnosis and treatment decisions,[1] PCPs play a key role in the management of their patient's disease and should remain engaged in patient education, management of comorbidities and symptoms, and treatment recommendations.

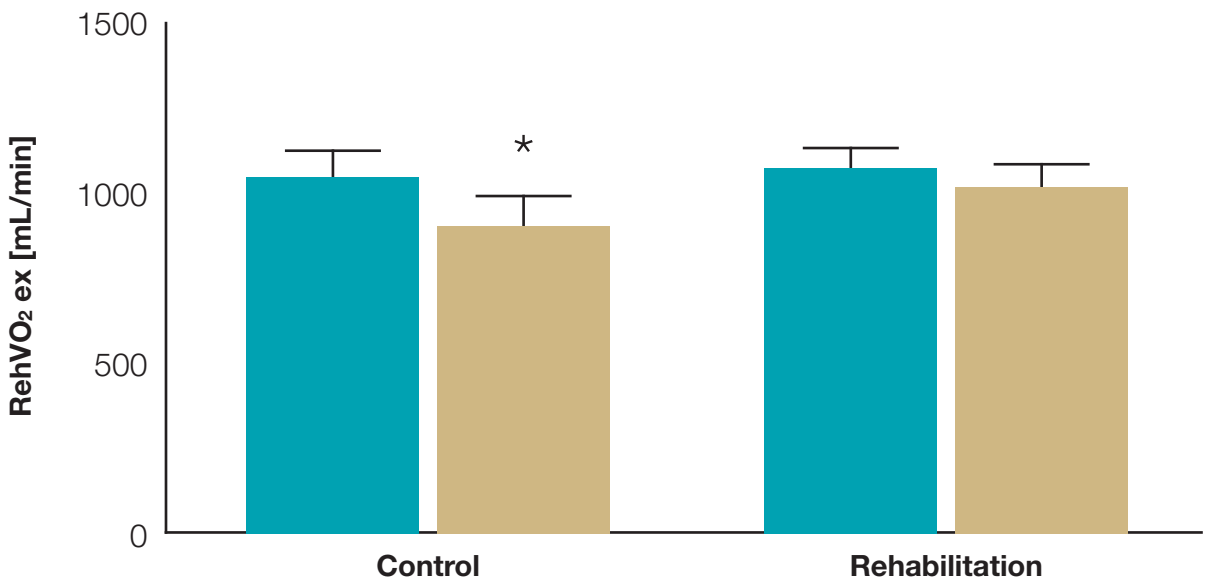

Figure 6. VO_2 during exercise among patients receiving pulmonary rehabilitation versus controls at 3 months.

Subjects in rehabilitation program maintained exercise VO_2 at baseline. We measured exercise oxygen uptake (exercise VO_2) during cycle ergometry exercise testing at baseline (solid gray bars) and again after 3 months (cross hatched bars) of rehabilitation (Rehabilitation) or observation (Control). Data shown are the mean ± SEM exercise oxygen consumption (mL/min) measurements in the rehabilitation and control groups at baseline and at 3 months. Exercise VO_2 did not change over 3 months in the rehabilitation group, while it decreased significantly in controls; $^*P<0.05$.

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