

# 2 0 0 5 PILOT™

Pulmonary Fibrosis Identification:  
Lessons for Optimizing Treatment

FALL 2005

## PILOT™ MISSION STATEMENT

PILOT™ is a national education initiative designed to provide physicians with a comprehensive continuing medical education program that focuses on the early and accurate diagnosis of idiopathic pulmonary fibrosis (IPF), while addressing educational objectives critical to optimizing disease intervention and management.

## FAMILIAL IDIOPATHIC PULMONARY FIBROSIS

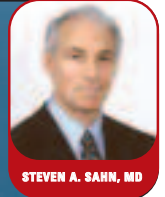
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Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial lung disease. While there has been significant progress in deciphering the cellular and molecular events involved in IPF, a complete understanding of its cause and pathogenesis remains elusive. The existence of familial IPF, however, suggests a role for inherited genetic factors and provides an opportunity to gain important insights into the etiology and pathogenesis of IPF. Indeed, the familial and sporadic forms of IPF are clinically (with a possible exception of a younger age in the familial form) and histologically indistinguishable, suggesting that the same signaling pathways may be affected in both forms of the disease. By discovering genetic defects in familial IPF, investigators might be able to identify genetic defects predisposing to the sporadic form.<sup>1</sup>

Familial idiopathic pulmonary fibrosis (FIPF) has been defined as the occurrence of idiopathic pulmonary fibrosis in two or more first-degree relatives. While the precise incidence and prevalence of IPF are unknown, its incidence has been estimated at 7 to 11 per 100,000 in the general population, while the prevalence has been estimated at 13 to 20 per 100,000.<sup>2</sup> It is unknown what proportion of IPF is familial; however, recent studies have estimated that 0.5% to 3.7% of cases have a genetic basis.<sup>1,3</sup>

In a study of FIPF in the United Kingdom, Marshall and colleagues identified a cohort of 25 families comprising 67 cases classified as IPF on the basis of high resolution computed tomography (HRCT) and/or histologic findings. The prevalence of FIPF was estimated at 1.34 cases per million,

accounting for 0.5% to 2.2% of cases of IPF in the UK.<sup>3</sup>

In a nationwide epidemiological study in Finland, hospital and pulmonary clinics were screened for patients diagnosed under the disease code ICD-10 ("alveolitis fibroticans idiopathica"). Patients meeting this criterion were thoroughly examined to identify both sporadic and familial IPF cases. Based on this methodology, the prevalence of FIPF was calculated at 5.9 per million, accounting for 3.3% to 3.7% of all Finnish cases of IPF. Additionally, the authors reported that there was evidence of geographical clustering of multiplex families, suggesting a recent founder effect in patients with FIPF.<sup>1</sup>

Finally, in a large study of FIPF currently being conducted in the United States, 75 families with two or more affected individuals have been identified. In 56 of these, detailed phenotyping has revealed uniform IPF in 25 families, while the remaining 31 exhibited phenotypic heterogeneity. Importantly, the existence of different forms of idiopathic interstitial

pneumonia within the same family suggests that environmental exposures or other diseases may initiate common pathogenic mechanisms among individuals who are genetically predisposed. A detailed linkage analysis aimed at identifying a common gene or genes among these families is currently underway. Identification of such a gene(s) will provide a critical target for subsequent research aimed at advancing the current state of knowledge regarding the pathogenesis of pulmonary fibrosis.<sup>4,5</sup>

As noted previously, FIPF is clinically indistinguishable from the sporadic form. While some studies have suggested an earlier age of onset among patients with FIPF, it is unclear whether this represents a true earlier onset, a more rapid progression to clinically evident illness, or perhaps a heightened awareness within families affected by the disease. Lee and colleagues recently reported the results of a retrospective analysis of clinical, radiologic, and pathologic data from a consecutive series of patients with FIPF who were seen at the Mayo Clinic between 1992 and 2002.<sup>6</sup> The investigators identified 27 patients from 15 families in whom the

**TABLE 1.**  
**COMPARISON OF CHARACTERISTICS IN FAMILIAL AND SPORADIC IPF<sup>6-8</sup>**

	Familial IPF	Sporadic IPF
<b>Age of onset</b>	59.4 years	63–66 years
<b>Mean age of death</b>	61 years	
<b>Survival</b>	2.41 years	2.78 years
<b>Gender</b>	2 male: 1 female	2 male: 1 female
<b>Clubbing</b>	30%	50–65%
<b>History of smoking</b>	51%	60–70%

No notable differences in radiologic, pathologic, or clinical presentation have been observed.

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complete clinical course was monitored. Compared to a well-characterized cohort of patients with sporadic IPF, patients with familial IPF did not demonstrate any notable differences in clinical, radiologic, or pathologic features (see Table 1).<sup>6,8</sup> Moreover, patients with FIPF had a statistically similar outcome to patients with sporadic IPF; median survival time for FIPF patients was 2.41 years, while that for sporadic IPF patients was 2.78 years. Interestingly, however, the authors noted a statistically significant correlation between the total number of affected members within a family and the risk of mortality among patients with FIPF ( $P = 0.016$ ; hazard ratio = 1.43 for every increase of one affected family member). By contrast, analysis of FVC and DLCO did not reveal any significant differences that were related to the number of affected persons in these families.

### Genetic Counseling

The mode of inheritance of FIPF is most consistent with an autosomal dominant inheritance with reduced penetrance. Most individuals diagnosed with FIPF have an affected parent, although the disease may appear to have skipped a generation because of reduced penetrance. The risk to the siblings of a proband depends on the genetic status of the proband's parents; if the parent is affected or known to have a disease-causing mutation, the risk to the siblings of being affected is as high as 50% (depending upon penetrance). Each child of a proband, in turn, has a 50% chance of inheriting the disorder.<sup>7</sup>

While genetic testing for IPF has not yet been established, the prudent clinical screening of unaffected family members, the avoidance of injurious inhalational agents (eg, tobacco smoke), and periodic monitoring appear to be justified. Asymptomatic first-degree relatives who are older than 50 years of age should undergo pulmonary function testing (including a 6 minute walk test), an HRCT, and a standardized questionnaire to assess the presence of respiratory symptoms at least every five years.<sup>7</sup> Recent studies suggest that up to 50% of unaffected family members have a positive screen and require further evaluation.<sup>7</sup>

Finally, because it is likely that testing methodology and our understanding of molecular genetics will improve in the future, consideration should also be given to banking DNA of affected individuals.<sup>7</sup> A directory of laboratories that offers this service can be located at [www.genetests.org](http://www.genetests.org).<sup>9</sup>

Genetic studies have identified several candidate genes that may be involved in the pathogenesis of pulmonary fibrosis, including genes encoding surfactant protein C, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), transforming growth factor- $\beta$  1 (TGF- $\beta$ 1), and interleukin-1 receptor antagonist. None of these associations, however, have been replicated.<sup>5</sup> Ultimately, susceptibility to IPF probably involves a combination of polymorphisms related to epithelial cell injury and abnormal wound healing. When combined with the appropriate environmental or cellular triggers,

these abnormalities may trigger signaling pathways that result in the phenotypic expression of disease. In the future, careful screening of family members of individuals with IPF and genetic analysis of large pedigrees of autosomal transmitted FIPF will be necessary to further define the pathways that result in pulmonary fibrosis and develop new targets for therapeutic intervention.

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## PILOT™ RESOURCE HUB RECOMMENDED READINGS

### Management and Treatment

Bajwa EK, Ayas NT, Schulzer M, Mak E, Ryu JH, Malhotra A. Interferon-gamma 1b therapy in idiopathic pulmonary fibrosis: a metaanalysis. *Chest*. 2005;128:203-206.

Pereira CA, Malheiros T, Coletta EM, et al. Survival in idiopathic pulmonary fibrosis-cytotoxic agents compared to corticosteroids. *Respir Med*. 2005;[Epub ahead of print].

Whelan TP, Dunitz JM, Kelly RF, et al. Effect of preoperative pulmonary artery pressure on early survival after lung transplantation for idiopathic pulmonary fibrosis. *J Heart Lung Transplant*. 2005;24:1269-1274.

### Diagnosis and Prognosis

Lynch DA, Godwin JD, Safrin S, et al. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. *Am J Respir Crit Care Med*. 2005;172:488-493.

McLoud TC. Role of high-resolution computed tomography in idiopathic pulmonary fibrosis: the final word? *Am J Respir Crit Care Med*. 2005;172:408-409.

### Pathogenesis

Noble PW, Homer RJ. Back to the future: historical perspective on the pathogenesis of idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2005;33:113-120.

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[www.PILOTforIPF.org](http://www.PILOTforIPF.org)

## NONPHARMACOLOGICAL THERAPIES FOR IDIOPATHIC PULMONARY FIBROSIS

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Idiopathic pulmonary fibrosis (IPF) is a poorly understood disease with devastating consequences to those afflicted. IPF is a specific form of chronic fibrosing interstitial pneumonia of unknown etiology and is associated with the histological pattern of usual interstitial pneumonia (UIP). Patients diagnosed with well-established IPF have a mean survival rate of 2.8 years,<sup>1</sup> and treatment options are limited. In fact, there is insufficient evidence to suggest that any current pharmacological treatment can improve survival or stop the progression of the disease. In part, this is due to the limited number of well-designed, controlled studies conducted in the past, limited number of patients, and the continually evolving and unknown pathogenesis of the disease. However, several large clinical trials are currently underway that may offer more hope in the near future.

In the meantime, nonpharmacological management of IPF plays an important role in maintaining or improving the patient's quality of life, as well as preparing the patient and their families with ways to cope with this disease. Pulmonary rehabilitation, supplemental oxygen, education and support, and lung transplantation are a few of the more effective management strategies for IPF patients. Pulmonary rehabilitation and oxygen supplementation may offer patients some relief from their respiratory symptoms, while lung transplantation may prolong survival.

Comprehensive pulmonary rehabilitation programs, which include physical and respiratory care instruction, education, psychosocial support, and supervised exercise training, are one of the more effective nonpharmacological treatment options that help IPF patients cope with their daily respiratory symptoms. In a randomized clinical trial, 119 stable patients with chronic obstructive pulmonary disease were randomly assigned to either an 8-week comprehensive pulmonary rehabilitation program or to an 8-week education program. The study concluded that the comprehensive pulmonary rehabilitation program significantly improved exercise performance and symptoms, and these benefits were seen for at least 1 year.<sup>2</sup> Since physical health and

perception of independence are key issues for most IPF patients, greater exercise capacity and the ability to cope with the respiratory symptoms in IPF improve the quality of life.<sup>3</sup>

Intervention with oxygen therapy has been proven to be beneficial in patients with advanced lung disease allowing patients to remain physically active and preventing the presence of pulmonary hypertension. Long-term oxygen therapy is largely used in the management of severe hypoxemia in patients with lung disease. It has been demonstrated that long-term oxygen

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therapy prolongs life (depending on the degree of airway obstruction), prevents progression of hypoxic pulmonary hypertension, controls polycythemia, and improves cognitive functions and emotional status. There is some evidence suggesting that it also improves quality of life.<sup>4</sup> Since the fibrotic process in IPF will continue unabated and destroy larger regions of the lung that cannot be repaired, oxygen therapy plays an important role in management as the condition progresses and respiratory insufficiency increases.

While there is a great deal of support for the role of oxygen supplementation, the use of oxygen should be considered for each individual carefully, since some studies have suggested that oxygen supplementation may have limited effects on a patient's quality of life. Chang and colleagues found that IPF patients treated with supplemental oxygen had lower health related quality of life (HRQL) scores than non-users.<sup>5,6</sup> Conversely, the

study by DeVries and colleagues found no significant difference between IPF patients using supplemental oxygen and patients not using supplemental oxygen, demonstrating that although oxygen saturation may improve, the quality of life for the patients may not be affected, or worse—adversely affected.<sup>5,6</sup> It was also found that patients with IPF appear to have impairments in HRQL equal to those with chronic obstructive pulmonary disease.<sup>7</sup> While it is true that having to use oxygen may adversely affect the quality of life of patients—after all no one likes to carry an overt sign of their impairment and admit their disease is progressing—its use has proven to be beneficial in advanced lung disease and we should encourage its prescription and use where indicated.

Lung transplantation is the only therapeutic intervention shown to prolong life in patients with advanced lung disease who have failed medical therapies. This option should seriously be considered for each IPF patient for it has been found to improve survival and halt disease progression. Early referral is critical to avoid the high risk of death (30–35%) on the waiting list. It is recommended that patients with IPF be referred for transplantation at the time of diagnosis or when vital capacity is below 50–60%. The survival benefit of lung transplantation is well established in studies in the United States.<sup>8,9</sup> Although, Abdelaziz and colleagues found that 50% of IPF patients with lung transplantation died by 3.4 years, lung transplantation can bring about an immediate improvement in pulmonary function and daily activities, and quality of life may return to near normal levels.<sup>10</sup>

Unfortunately, this is not a lasting solution and lung rejection often results in death after transplantation.<sup>9</sup> Thabut and colleagues studied 46 patients referred to a transplant center with the diagnosis of IPF over a 12-year period. Of these 46 patients, 27 patients received a single lung transplant (SLT), and 1 received a bilateral lung transplant (BLT), 16 died while on the transplant list, and 2 remained on the list at end of study. Survival rates were 79.4% after 1-year

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posttransplant, 63.5% after 2 years, and 39% after 5 years for IPF. This is comparable to results of patients undergoing transplantation for other indications. In this same article, Thabut et al noted a 75% reduction in risk of death for patients with IPF undergoing lung transplantation. Graft failure, rejection, and heart failure were listed as causes of early death after transplantation. Bronchiolitis obliterans, infection, and cancer are the main causes of later death. Of the patients awaiting lung transplantation, the death rates are highest in those with IPF, suggesting that many IPF patients are referred late for transplantation.<sup>9</sup>

A limited window of opportunity exists to refer IPF patients for lung transplantation who have the highest mortality rate while awaiting transplantation.<sup>9</sup> In the United States, transplantation guidelines and new lung allocation systems are being implemented, which are based on the estimated transplant benefit (survival after 1 year) and the estimated mortality at 1 year without transplant.<sup>9</sup> Previously, IPF patients in the United States were given a 3-month waiting advantage compared to patients with emphysema to mitigate the high mortality rate on the waiting list.<sup>11</sup> The timing for referral for transplantation should be carefully evaluated based upon the progression of disease, age, and prognosis. In previous studies, poor survival was associated with male sex, older age, non-response to steroids, and reduced pulmonary function at presentation. Patients should be placed on the lung transplant list at an early stage, soon after initial diagnosis of IPF. Due to the lack of available donors, waiting for the disease to progress decreases the outlook for transplantation to occur.

Obesity is another variable to consider in patients with IPF. Its restrictive nature affects the patient's ability to exercise, and is a relative contraindication for lung transplantation. A weight management program was formed at a transplant center to help obese patients with lung disease lose weight and maintain their goal weight, with the hope of decreasing their waiting time to be listed for transplantation and their incidence of weight-related complications. Some patients even experienced symptomatic improvement, which delayed their need for lung transplantation.<sup>12</sup>

An often neglected aspect of therapy is the need for education and support of patients and family members of individuals dealing with chronic illness. The validation that the experiential knowledge gained by patients as they live with their disease is important in enhancing self-care and optimizing outcomes. This has not been fully

recognized by physicians dealing with patients with IPF. The editorial and article by Winkelman clearly extol the benefits of such a practice. Providing reliable and quality information to patients with diseases that are difficult to understand and manage, such as IPF, increases their knowledge and improves their self-care, decision-making and health outcomes. Many authors argue that "information is as important to a patient's health as any drug, medical test, or surgery" and as such it should be prescribed just as any other treatment. Provision of "prescription-strength information" requires fulfillment of certain criteria.<sup>13,14</sup>

Significant progress has been made in the area of IPF, particularly in diagnosis: a stricter case definition has been outlined by consensus among international experts. Insights into the pathophysiology have revealed novel areas for therapeutic intervention. These advances have helped clarify diagnostic and therapeutic intervention in this disease.<sup>15</sup> An effective regimen is yet to be determined, however, new insights into the natural course and monitoring of disease progression has provided appropriate endpoints to test the safety and efficacy of new regimens. It is hoped that ongoing molecular and genetic studies and results of clinical trials will improve the outcome of patients and families affected with IPF in the near future.<sup>16</sup> In the meantime, nonpharmacological treatments are important adjuncts in the management of IPF patients.

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## UPCOMING CME EVENTS

### PILOT™ CME DINNER MEETINGS: EMERGING PERSPECTIVES ON IPF: PRACTICAL STRATEGIES FOR DISEASE MANAGEMENT

#### October 18, 2005

Farmington Hills, MI	James H. Dauber, MD
Philadelphia, PA	Steven D. Nathan, MD
McLean, VA	Steven A. Sahn, MD

#### October 19, 2005

Ontario, CA	David A. Zisman, MD
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#### November 8, 2005

Richmond, VA	Steven A. Sahn, MD
Boston, MA	Marvin I. Schwarz, MD
Leola, PA	Francis C. Cordova, MD, FCCP

#### November 9, 2005

Farmington, CT	Marvin I. Schwarz, MD
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#### November 10, 2005

Fairfield, CT	Marvin I. Schwarz, MD
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#### November 15, 2005

Eagle, ID	Ganesh Raghu, MD, FCCP, FACP
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#### November 16, 2005

Sioux Falls, SD	David A. Lynch, MD
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#### December 1, 2005

Omaha, NE	Anthony A. Floreani, MD
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#### December 12, 2005

Seattle, WA	Ganesh Raghu, MD, FCCP, FACP
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