Review of current literature on the diagnosis and treatment of idiopathic pulmonary fibrosis

Burley, Sarah Victoria

http://hdl.handle.net/2144/19208
Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

REVIEW OF CURRENT LITERATURE ON THE DIAGNOSIS
AND TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

by

SARAH V. BURLEY
B.A., University of Chicago, 2014

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
2016
Approved by

First Reader

Helen Hollingsworth, M.D.
Associate Professor of Medicine

Second Reader

Hee-Young Park, Ph.D.
Professor of Medical Sciences & Education and Dermatology
ACKNOWLEDGMENTS

I would like to thank my kind readers who provided helpful comments and suggestions during the preparation of this thesis. I deeply appreciate the substantive and stylistic comments and medical insight provided by Dr. Hollingsworth, and I value the support Dr. Park has provided me on this effort and throughout the MAMS program. I could not have completed this journey without you both. I would also like to thank my grandfather, Dr. David Byrne, as he was the one who inspired me to write about this particular topic. Thank you all.
REVIEW OF CURRENT LITERATURE ON THE DIAGNOSIS
AND TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

SARAH V. BURLEY

ABSTRACT

This thesis reviews the current literature on idiopathic pulmonary fibrosis (IPF), a progressive, scarring lung condition largely affecting older adults that is experiencing an increasing incidence in the U.S. and abroad. Two troubling clinical aspects of IPF are the difficulty of timely diagnosis and uncertain progression once diagnosed. The need for early detection is driven by the condition’s median survival rate post-diagnosis of about 3 years. Environmental and familial risk factors are important predictors of IPF, but cannot alone determine who is at risk for the condition. High-resolution computed tomography is currently the best non-invasive diagnostic tool, but many efforts are now underway to identify biological markers, which may aid not only in diagnosis, but illuminate both susceptibility and progression of the disease. Although the pathogenesis of IPF remains unclear, a compelling correlation has surfaced between the mechanics of IPF and herpes virus infection, which also may lead to a biological marker for the condition. Likewise, some genetic factors have shown promise in revealing pathogenesis and possible diagnosis. The only treatment currently available to ameliorate IPF is lung transplantation, but it is a last resort effort. In terms of pharmaceutical treatment, the most significant development has been the recent approval and use of two anti-fibrotic drugs, pirfenidone and
nintedanib, that appear to slow the progression of the disease, but do not eliminate the fibrotic condition that impairs patients’ breathing. As efforts progress in addressing affirmative treatments for IPF, there is consensus that not enough is being done to address palliative and psychological needs of IPF. In sum, a review of the current literature suggests tremendous accomplishments have made in treating what remains a fatal condition, but much work remains to truly understand how and why IPF occurs, and whether, short of lung transplantation, there are treatments that can improve, not just maintain, patients’ health.
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<tr>
<td>6MWD</td>
<td>6 Mile Walking Distance</td>
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<tr>
<td>ALAT</td>
<td>Latin American Thoracic Association</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<td>BLT</td>
<td>Bilateral Lung Transplant</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CRP</td>
<td>Clinical, Radiological and Physiological</td>
</tr>
<tr>
<td>D_{LCO}</td>
<td>Diffusing Capacity of Carbon Monoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr Virus</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked Immunosorbet Assay</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>FF</td>
<td>Fibroblastic Foci</td>
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<td>FVC</td>
<td>Forced Vital Capacity</td>
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<td>GAP</td>
<td>Gender/Age/Physiology</td>
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<td>HCRT</td>
<td>High Resolution Computed Tomography</td>
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<td>HHV</td>
<td>Human Herpesvirus</td>
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<tr>
<td>HSP70</td>
<td>Anti-heat Shock Protein 70</td>
</tr>
<tr>
<td>IIP</td>
<td>Idiopathic Interstitial Pneumonia</td>
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<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
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ILD ................................................................................ Interstitial Lung Disease
IPF ................................................................................ Idiopathic Pulmonary Fibrosis
JRS ............................................................................... Japanese Respiratory Society
KL-6 .............................................................................. Glycoprotein Krebs von den Lungen-6
LTx ................................................................................. Lung Transplant
miRNA ........................................................................ MicroRNA
MV ................................................................................ Mechanically Invasive Ventilation
NA ................................................................................ Not Applicable
NIH ............................................................................... National Institutes of Health
NIMV ............................................................................. Non-Invasive Mechanical Ventilation
OR ................................................................................ Odds Risk
RNA ................................................................................ Ribonucleic Acid
TGF ................................................................................. Transforming Growth Factor
UIP ................................................................................ Usual Interstitial Pneumonia
INTRODUCTION

The goal of this thesis is to examine the current literature on Idiopathic Pulmonary Fibrosis (IPF) with regard to its diagnosis, treatment and effects in the context of prior views of the disease. While taking a holistic view of IPF, this thesis aims to highlight emerging diagnostic tools and newly-introduced treatments that provide earlier diagnosis and treatment, both fundamental in extending the lives of those with IPF.

IPF is a so-called “orphan” disease occurring in a small, but growing, population of older persons. It impairs lung function, often rapidly, resulting in death within several years of diagnosis, although the disease progresses differently depending on the patient. Despite this, there have been recent efforts to provide more clinical certainty around the staging of the disease in order to aid in its treatment.

Long-held views that IPF was triggered by inflammation of uncertain origin have given way to agreement that alveolar micro-injuries resulting in excessive fibrotic growth is the mechanism at play in this condition. Pharmaceutical treatments targeting this fibrotic growth have been recently introduced in an effort to delay progression, but currently only lung transplants have shown to be effective in improving patients’ lives (so much so, that patients with IPF are now the largest group of recipients of North American lung transplants).
It has been suggested that there may be genetic or viral factors affecting individuals’ susceptibility to IPF, as well as related biomarkers that might be able to be used to aid in diagnosing the condition or managing its care. However, for the present, IPF is best diagnosed through attention to distinctive auditory cues during auscultation and confirmed through radiological, spirometric, and/or histological examination. Finally, there is a need for improved patient education regarding the treatment of IPF and its impact on them, as the current paucity of information may contribute to depression and resignation. Nevertheless, prospects for patients with IPF are much better than they were as recently as ten years ago.
**PUBLISHED STUDIES**

**Epidemiology of IPF**

IPF is the most common type of idiopathic interstitial pneumonia (IIP) (Abe, 2016). It is a fatal condition of relatively short duration that tends to affect individuals over 65 years of age (Raghu, 2014). The median duration of a patient’s life, once diagnosed with IPF, is approximately 3 years (Sampson, 2015). During 2014, IPF resulted in deaths estimated to number from 28,000 to 65,000 in Europe and from 13,000 to 17,000 in the United States (Hutchinson, 2014). Incidence of the disease is reported to be akin to that of cancers of the stomach, liver, testes, and cervix (Hutchinson, 2015). IPF skews toward older, male patients (Kuwano 2016), who are also are reported as having a worse prognosis in some, but not all, studies of IPF (Raghu, 2011).

IPF occurs worldwide with no predilection for ethnicity or race (Morrisey, 2003). Conservative estimates of incidence in North America and Europe are between 3 and 9 cases annually per 100,000 persons, based on a review of published studies since 2000 (Hutchinson, 2015). Mortality rates of IPF continue to increase steadily worldwide (Hutchinson, 2014). Presumably, this can in part be attributed to wider familiarity with the condition (and thus its diagnosis) and greater consensus on the mechanics of such diagnosis. Another factor that is likely contributing is simply the fact that people are living longer now than ever before, and this disease is one that presents in an older population. However, the incidence and prevalence of IPF varies globally, which is likely attributable to local differences in diagnosing the condition, as well as the sample size, methods.
and statistics used in the studies from which such conclusions are drawn (Nalysnyk, 2012).

Nonetheless, the upward trend in IPF globally over time is evident in the literature. For example, in a review of a large health insurance claims database in the U.S. over the period 1996-2000, annual incidence was reported as 6.8 per 100,000 applying a comparatively narrow IPF diagnostic standard, and 16.3 per 100,000 under a broader test, while prevalence was 14.0 per 100,000 under the stringent standard and 42.7 per 100,000 under the broader criterion (Raghu, 2006). In a more recent review of patient files between 2006–2012 in the HealthCore Integrated Research Database -- employing a newly-developed screening algorithm for U.S. adults (limited in application to patients older than 50 years of age) -- produced an estimated incidence (for the population, not just the 50+ cohort) of 14.6 per 100,000, while prevalence was 58.7 per 100,000 (Esposito, 2015). In Europe, estimated annual incidence/prevalence per 100,000 was 0.22/1.25 in Belgium, 0.93/3.38 in Greece, 0.94/6.5-12.1 in the Czech Republic, 2.17/NA in Denmark, 3.0/NA in Spain, 4.3/23.4 in Norway, and 7.94/NA in the United Kingdom (Kuwano, 2016). In Japan, one study determined incidence/prevalence is 2.23/10.0 per 100,000 (Kuwano, 2016).

As the name indicates, IPF is of uncertain etiology but is thought to be associated with a variety of risk factors, including occupation, cigarette smoking and viral infections (Baumgartner, 2000). Exposure to inhalation agents remains the most common aggregate risk factor, with prolonged, repetitive injury to the lungs potentially contributing to the fibrotic processes (Kuwano, 2016). IPF has
also been observed to occur in a familial pattern (affecting two or more members of an immediate family), although the occurrence of such familial cases varies in studies between 2% and 25% of all IPF cases (Tang, 2003). However, one study concluded that among all risk factors associated with IPF, having a parent or sibling with IPF was the highest single risk factor (odds risk ($OR = 6.1$))(Garcia-Sancho, 2011).

Outside of the environmental and genetic factors noted above, there are several medical conditions that tend to present alongside IPF. A literature review that considered 126 studies from 1990 to 2015, determined significant comorbidities associated with IPF. The respiratory comorbidities were as follows: pulmonary hypertension (34%), chronic obstructive pulmonary disease (18%), lung cancer (15%), obstructive sleep apnea (6%), and pulmonary embolism (2%). The non-respiratory comorbidities included cardiovascular disease (27%), metabolic disease (24%), and gastro-esophageal reflux disease (18%) (Raghu, 2015). The nature of these associations, whether they are causal or share common risk factors (e.g., age), has not been determined.

Gastroesophageal reflux (GER) is often associated with IPF, suggesting that these patients have an enhanced risk of aspiration of oropharyngeal or gastric contents into the larynx and lower respiratory tract and that recurrent aspiration contributes in some way to lung injury (Lee, 2010). What makes it even more mysterious is that one study of comorbidities associated with IPF found that GER represented enhanced survival rates (Kreuter, 2016). The 2015 clinical guidance issued by the ATS/ERS/JRS/ALAT Committee on Treatment of
IPF suggests that clinicians use regular anti-acid treatment for patients with IPF, but notes that the committee has very low confidence in estimates of effect (Raghu, Rochwerg 2015). Despite the cautious position, use of anti-acid treatment in IPF cases has been found to be associated with lowered instances of fibrosis as well as longer survival and smaller decreases in FVC (Daccord, 2016). Nevertheless, there has been no confirmation that GER plays a causative role in IPF, indicating that further study is needed to review the efficacy of anti-acid treatment (Daccord 2016).

**Current Knowledge of Pathology**

IPF is characterized by the distortion of lung structure and resulting loss of respiratory function (Konigshoff, 2008). It is a chronic progressive condition associated with initial injury to alveolar epithelial cells followed by abnormal repair (Kuwano, 2016). The abnormal repair is characterized by increased fibroblastic proliferation and extracellular matrix remodeling (Morrisey, 2003). The proliferative fibrotic response results in hyperplastic, hypertrophic, and metaplastic epithelium, cystic honeycomb change, septal expansion, and variable inflammation (Meuten, 2012). The distorted lung architecture, associated with alveolar epithelial cell injury and myofibroblast activation (Konigshoff, 2008), and the loss of gas exchanging surface area produce the symptoms patients experience associated with IPF (e.g., breathlessness, decreased exercise tolerance).
It should be noted that, in general, fibrosis represents the innate and adaptive immune response to pathogen (Thannickal, 2014). Both fibroblasts and myofibroblasts participate in host defense by containing pathogens to either eliminate them or prevent their spread (Thannickal, 2014). However, other types of lung inflammation and injury can also lead to fibrosis, such as that caused by allergens, chemicals, radiation and environmental particulates (Coultas, 1994).

For a long time, the etiology of IPF was presumed to involve inflammation of the lungs. According to a 2001 literature review of studies published between 1965 and 2000, the then-prevailing hypothesis was that the fibrosis associated with IPF resulted from a chronic inflammatory process preceding the disease, in turn injuring the lung and triggering lung fibrogenesis that produced the end-stage fibrotic scar (Selman, 2001). This hypothesis was disproved through the review, which found no empirical evidence that inflammation was the triggering factor in the onset of the condition. Conversely, the review demonstrated that epithelial injury in the absence of inflammation could still stimulate fibrosis (Selman, 2001). Rather than inflammation, the literature review identified an emerging view that IPF involves “abnormal wound healing in response to multiple, microscopic sites of ongoing alveolar epithelial injury and activation associated with the formation of patchy fibroblast-myofibroblast foci, which evolve to fibrosis” (Selman, 2001). A separate study in 2001 reached the same conclusion, finding that “the critical pathway to end-stage fibrosis is not ‘alveolitis’ but rather the ongoing epithelial damage and repair process associated with persistent
fibroblastic proliferation. Controlling these processes, rather than stopping inflammation, appears most important in preventing progressive disease and the fatal outcome common in IPF” (King, 2001). This remains the prevailing view today (Kuwano, 2016).

As noted above, fibrosis typically constitutes a response to infection. However, the same cellular and molecular mechanisms in humans that are genetically programmed to produce defensive fibrotic responses to infectious pathogens may have been co-opted to respond to noninfectious stressors in our modern environment (Thannickal, 2014). In other words, our immune system has not had sufficient evolutionary time to allow it to discriminate effectively between the hostile and the non-hostile (Thannickal, 2014). Meta-analysis of several IPF studies has indicated a wide range of risk factors associated with environmental and occupational influences: Smoking (OR=1.58); Agricultural/Farming (OR=1.65); Livestock (OR=2.17); Wood Dust (OR=1.94); Metal Dust (OR=2.44); and Stone/Sand (OR=1.97) (Kuwano, 2016). In short, chronic, repeated exposure to both industrial and rural inhalants may represent triggers for micro-injuries that some individuals’ lungs simply are unprepared to deal with, leading to an uncontrolled and inappropriate fibrotic response.

As the scientific community strives to define the pathology of IPF, an interesting relationship between herpesviruses and the occurrence of IPF has been observed and is being considered as a potential contributing factor of disease progression. This association was best demonstrated by a 2003 study that found the DNA of Epstein-Barr virus (EBV), cytomegalovirus (CMV), or
human herpesviruses (HHV-7 or HHV-8) were present in lung tissues of 97% of patients with IPF, compared with 36% of control patients (Tang, 2003). In addition, two or more herpesviruses (CMV, EBV, and HHV-8) were identified in 57% of patients with IPF compared to 8% of controls (Tang, 2003).

Further evidence in favor of a contributory role for such infections in IPF comes from a study of gammaherpesvirus-68. In this study, the virus appeared to exacerbate already-existing pulmonary fibrosis through the up-regulation of chemokines, followed by recruitment of pulmonary fibrocytes and in turn fibrosis (McMillan, 2008). This effect may be more pronounced depending on patient age. In a subsequent study, young and old populations of mice were infected with gammaherpesvirus-68. Compared to respective controls, the older populations, but not the younger, experienced significant increases in collagen content and fibrosis (Naik, 2011). Enzyme-linked immunosorbent assay (ELISA) testing showed a higher level of transforming growth factor-β in whole lung homogenates from the infected aged mice (Naik, 2011). Another study suggested possible therapeutic or prophylactic measures for IPF, in that depletion of CD8+ T-cells during the course of murine herpesvirus infection served to prevent the development of fibrotic lung disease in such mice. The study suggests that viral matrix M1-induced CD8+ T-cells are mediators of fibrotic disease-inducing inflammation and altered cellular recruitment to the lung results in immunopathology and fibrosis (O'Flaherty, 2015). It has been concluded, based on both human post-mortem and in vivo murine studies that
herpesvirus infection may “act as a second hit that precipitates or worsens lung fibrosis” (Kropski, 2012).

Despite the evidence of exacerbation, it remains unclear whether such viruses serve to contribute to the initial occurrence of IPF, or are merely an example of opportunistic infection following the onset of IPF (Kuwano 2016). However, recent research supports those advocating a causative role. The DNA of Herpesvirus saimiri (endemic but non-pathogenic in squirrel monkeys) was found in the regenerating epithelial cells of 21 of 21 IPF cases, with none found in the 21 control subjects. Reverse transcription polymerase chain reaction testing demonstrated that the source of the cyclin D RNA in active IPF was Herpesvirus saimiri and not human (Folcik, 2014). This suggests an etiological role for Herpesvirus saimiri in human IPF and is consistent with the studies of murine gammaherpes-68, which is closely related to Herpesvirus saimiri (Folcik, 2014).

As the data showed that IPF, and no other types of pulmonary fibrosis, is associated with Herpesvirus saimiri, it has been suggested that this particular virus may prove to be a valuable diagnostic tool to identify IPF among patients with unspecified pulmonary fibrosis (Folcik, 2014). In other words, the strength of the association with the virus (100% effective in the study) means that despite doubt over the causative sequences, the presence of such viral evidence offers clinicians a potentially powerful tool to rule IPF in, or out, in suspected cases of IPF. Though the exact relationship between the two has yet to be confirmed, the
above research suggests a strong linkage between the mechanics of IPF and herpesvirus infection that demands further study.

**Diagnosis of IPF**

**Symptoms**

Typically, the first indication that a person has IPF is the gradual onset of shortness of breath (dyspnea) upon exertion. In light of the tendency of the condition to present in older patients, this could be initially attributed to aging in general or to other medical conditions such as emphysema, heart disease or a respiratory tract infection. Because of the symptom overlap, diagnosis of IPF can be delayed several months after its symptomatic onset (Loveman, 2015). Other symptoms of IPF include a non-productive (dry) cough, reduced exercise tolerance and increased anxiety, while less frequent symptoms may include fatigue, depression and chest pain (Loveman, 2015). One study suggests that there may also be cognitive aspects of IPF presented to clinicians: applying a battery of tests to a control group and to patients with either severe or mild IPF, it found that those with more severe IPF demonstrated worse cognitive function than the other subjects (Bors, 2015). This confirmed, without referencing it, a 2009 published report (to date uncited in the IPF literature) that found that patients with IPF appeared to have a cognitive function deficit on a test that requires sustained visual attention (Sprunger, 2009). Both reports suggested the
need for additional studies to explain the differences and to tailor treatments to address them.

**International Standards**

Diagnosis of IPF has proven challenging for clinicians, as its symptoms are so often similar to those of other conditions (see below). In 2002, the American Thoracic Society (ATS)/European Respiratory Society (ERS) advocated a multi-disciplinary approach for diagnosing all instances of IIP, including IPF, calling for diagnostic interaction among clinicians, radiologists, and pathologists (Abe, 2016). In 2011, ATS and ERS issued revised the definition of IPF and provided further diagnostic guidance with the Japanese Respiratory Society and the Latin American Thoracic Association (Abe, 2016).

Under the current 2011 standard, IPF is defined as a “specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of [Usual Interstitial Pneumonia (UIP)].” (Raghu, 2011). These standards provide that a diagnosis of IPF may only be made with the following (Raghu, 2011):

<table>
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<th>Table 1 - 2011 International Standards for Diagnosis of Idiopathic Pulmonary Fibrosis</th>
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<tr>
<td>• Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).</td>
</tr>
<tr>
<td>• The presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy.</td>
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Clinical Examination

While much of the research today centers around identifying biomarkers of IPF, the initial presentation of IPF is most likely to be detected though routine examination. This is because upon clinical examination, more than 90% of those experiencing IPF will exhibit inspiratory crackles (described as “Velcro®-like crackles”) typically heard at the lung bases posteriorly (Behr, 2012). Crackles may be a good early indicator of IPF (Oldham, 2014). A French academic practitioner argues that, for patients over 60, the presence of crackles that persist after several deep breaths in successive examinations conducted several weeks’ apart should strongly raise a suspicion of IPF and be followed by diagnostic HRCT to confirm (Cottin, 2012). In addition to crackles that can be identified easily in the clinical setting, up to 50% of patients with IPF will display finger clubbing, although this tends to be associated with more advanced disease (Oldham, 2014).

HRCT

As reflected by the international diagnostic standards, HRCT plays a vital role in the identification of IPF in those patients suspected of having the condition. A 2005 international study considered the efficacy of use of HRCT by community-based physicians and found (based on blind review by a panel of
three independent radiologists in the study) that two reviewers reached consensus that confirmed the prior physician’s HRCT-based diagnosis of IPF in 81.3% of cases (Lynch, 2005). The most prevalent physiological condition evident in the HRCT and observed by reviewers in confirming the earlier diagnosis of disease was honeycombing (Lynch, 2005).

Biopsy

In view of its comparatively intrusive nature, subjecting patients to a lung biopsy has long been viewed as appropriate only where clinical and/or radiological examination in diagnosing IPF is uncertain or otherwise inconclusive (Hunninghake, 2001). A study of all patients who underwent surgical lung biopsies in connection with possible interstitial lung diseases between 2000 and 2011 found that the in-hospital mortality rate following such biopsies was 6.4% (Hutchinson, Fogarty, 2015). However, the efficacy of surgical lung biopsies may justify the risk. A 1999 study concluded that among newly-diagnosed patients with IPF, the diagnosis would have been missed in one-third of patients had a biopsy for histological review not been performed (Raghu, 1999). Whether technological advancements in HRCT since 1999 might obviate the need for biopsies is unclear, but worthy of study.

A new, less invasive method of biopsy has been shown to be effective in yielding sufficient lung tissue samples for examination for IPF (Tomassetti, 2016). Bronchoscopic lung cryobiopsy involves the use of compressed gas delivered by a cryoprobe to chill lung parenchyma, allowing a tissue sample to be collected.
(Patel, 2016). Provided that the same level of histological information is available, in a recent one-center study, this technique yielded diagnostic results comparable to that of surgical lung biopsy (Tomassetti, 2016). However, a recent editorial notes that this study is of limited utility because it does not consider accuracy but rather consensus of findings, because it involves only one site, and because of a lack of demonstration of the safety and yield of bronchoscopic lung cyrobiopsies (Patel, 2016). Of particular concern, one-third of patients undergoing bronchoscopic lung cyrobiopsies suffered pneumothorax (Patel, 2016). Nevertheless, in view of the substantial probative value that lung biopsies can bring to the diagnosis of IPF, and the potentially lower morbidity relative to surgical lung biopsies, there are sound reasons for expanding consideration of this new technique to augment existing surgical biopsy options.

The histopathologic features of IPF seen on lung biopsy include a heterogeneity with patchy areas of interstitial inflammation, fibroblast foci, and honeycombing interspersed among areas of normal lung. Fibroblast foci (FF) are small aggregates of proliferating myofibroblasts and fibroblasts (Raghu, 2011). A 2001 retrospective study of 87 biopsy-diagnosed patients with IPF employed four pathologists to assess the presence of various histological patterns relative to the patients’ survival. It found that the extent of FF alone was predictive of mortality (King, 2001). Conversely, the observed degree of alveolar space cellularity, alveolar wall fibrosis, and cellularity were found to be unrelated to mortality. A 2002 retrospective study of 53 patients subjected to biopsies considered the
presence of four histological features (FF, interstitial mononuclear cell infiltrate, established fibrosis, and intra-alveolar macrophages). It found the strongest correlation between an increasing extent of FF and mortality (Nicholson, 2002). 

**Lung Capacity (FVC)**

It has been observed that a measured decline in forced vital capacity (FVC) is consistent with disease progression while also being predictive of reduced survival time (Richeldi, 2014). A retrospective study reviewed FVC results within one month of HRCT-based diagnosis and again as recorded at 6 months (±3 months) following diagnosis. Patients were placed in one of three groups based on relative change in FVC percent over the study period: stable (decline <5%), marginal decline (decline ≥5% but <10%), or significant decline (decline ≥10%) (Reichmann, 2015). The study showed the more FVC declined in the first 6 months after the initial IPF diagnosis, the worse the clinical outcome and the likelihood of increased IPF-related health resources utilization. The study’s author argues that the incremental burden of the decline in FVC on patients and the healthcare system illustrates the importance of physicians’ seeking to preserve lung function in patients with IPF (Reichmann, 2015). This suggests aggressive use of the pharmaceutical anti-fibrotics, as discussed below. Moreover, as illustrated below, FVC, and change in FVC, have both been employed in a comprehensive model of IPF progression.
**Diagnostic and Treatment Biomarkers**

While research continues on IPF pathogenesis and treatment, IPF survival rates remain largely unchanged, demonstrating the urgent need for identifying biomarkers associated with IPF (Fernandez, 2012). Biomarkers can play several roles: screening for susceptibility to IPF; diagnosing IPF; evaluating progression of IPF, including the potential for acute exacerbation (discussed below). Efforts to apply genetic testing to early IPF detection are underway, but have not yet produced results. However, genome linkage analysis has identified a variant on the short arm of chromosome 11 in the promoter region of the mucin 5b gene is strongly associated with IPF (Putman, 2014). However, the search for potential markers remains in the early stages (Ley, 2014). NIH researchers, working under the “Precision Medicine” initiative, have identified a number of ongoing clinical trials that may result in the development of IPF biomarkers (Brownell, 2016).

Serological biomarkers would be preferred as they do not require patient effort, are reproducible and are less invasive than pulmonary function testing or bronchoalveolar lavage (Chiba, 2016). There are prospects for broader use of biomarkers, such as surfactant protein-A, surfactant protein-D and glycoprotein Krebs von den Lungen-6 (KL-6) for managing IPF (Chiba, 2016). KL-6 may prove to be a significant tool for predicting the progression of IPF when tested at initial diagnosis. A 2006 retrospective study among Japanese patients found that,
when measured against a benchmark of 1000 units/ml, those patients with initial KL-6 levels below this threshold experienced a median survival greater than 36 months, while those with KL-6 levels above had a median survival of only 18 months (Yokoyama, 2006). In a later study on German patients, a benchmark of 1300 units/ml was applied to account for genetic differences between Japanese and Caucasian subjects. It confirmed that baseline serum KL-6 level is a sensitive predictor for the onset of “acute exacerbation” of IPF (see below) for this population (Ohshimo, 2014).

As noted above, the presence of Herpesvirus saimiri correlates strongly to IPF and not to other types of pulmonary fibrosis. Thus, DNA testing for Herpesvirus saimiri in particular (as contrasted with other related viruses) may also prove to be an important diagnostic biomarker (Folcik, 2014).

There may be other viable prospects for serum-based testing. One study has found that patients with IPF testing positively via Western Blot or ELISA for heat shock protein 70 (HSP70) IgG autoantibodies in the serum are more likely to experience near-term lung function deterioration and mortality (Kahloon, 2013). This suggests both the possibility of effective testing for the presence of such autoantibodies in serum to predict the progression of previously-diagnosed disease while also illustrating that IPF progression may be linked with antigen-specific autoimmunity. If humoral autoimmunity has a pathogenic role in IPF progression, then effective treatment could be developed to target these autoantibodies (Kahloon, 2013). Another study considering HSP70 suggests that
genetic variation in observed in certain HSP70-related genes, as determined by serum testing, may influence the likelihood of developing IPF (at least in the study’s Mexican population) (Aquino-Galvez, 2015).

Elevated levels of Immunoglobulin A (IgA) in patients with IPF correlate with greater risk of mortality from the disease (ten Klooster, van Moorsel, 2015). IgA production is regulated by transforming growth factor (TGF)-β, a cytokine that is associated with the development of pulmonary fibrosis. While TGF-β is up-regulated in patients with IPF, it is reported to be difficult to use as a biomarker. Instead, it may prove possible to use serum IgA as a proxy (Ten Klooster, van Moorsel, 2015).

Another potential biomarker related to TGF-β is the presence of certain microRNAs in patients with IPF’ blood serum. MicroRNAs (miRNAs) are small RNA molecules involved in tissue development and differentiation, cellular proliferation, and tissue repair (Yang, 2015). A key study determined that nearly 10% of the miRNAs found in the lungs of patients with IPF had experienced significant changes. Many of these implicated miRNAs are regulated by transforming growth factor β1 (TGF-β1) (one of the TGF-β family), but also regulate the TGF-β1 pathway. Aberrant expression of miRNA results in a release of inhibitions affecting the TGF-β1 pathway and to the creation of feed-forward loops (Pandit, 2011). Studies have identified microRNAs that alter proliferative and migratory properties of fibroblasts, and induce phenotypic changes in epithelial cells (Pandit 2015). It has been suggested that imbalance between
profibrotic miRNAs and antifibrotic miRNAs may be closely associated to IPF progression (Rho, 2015). By shifting focus from presence of miRNAs in the lungs to those in serum, a study in China evaluated a relative small sample of patients and found that a significant number of serum miRNA molecules were altered in patients with IPF, raising the prospect that differentially expressed miRNAs in serum may play a role in the disease’s progression (Yang, 2015).

To summarize, the following table identifies the prospective biomarkers and their respective roles relative to IPF:

<table>
<thead>
<tr>
<th>Table 2 - Possible Biomarkers for IPF</th>
</tr>
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<tbody>
<tr>
<td><strong>Genetic</strong></td>
</tr>
<tr>
<td>Chromosome 11 Mucin 5b (diagnosis)</td>
</tr>
<tr>
<td><strong>Serological</strong></td>
</tr>
<tr>
<td>Surfactant protein-A (diagnosis)</td>
</tr>
<tr>
<td>Surfactant protein-D (diagnosis)</td>
</tr>
<tr>
<td>KL-6 (acute exacerbation)</td>
</tr>
<tr>
<td><em>Herpesvirus saimiri</em> (diagnosis)</td>
</tr>
<tr>
<td>HSP70 (acute exacerbation and possible susceptibility)</td>
</tr>
<tr>
<td>IgA (mortality)</td>
</tr>
<tr>
<td>MicroRNA (mortality)</td>
</tr>
</tbody>
</table>
Progression of the Disease

Extensive heterogeneity has been observed among individual patients with IPF, with the disease’s clinical course proving difficult to anticipate with confidence (Hambly, 2015). The 2011 international standards indicate that the natural history of IPF is variable and unpredictable, with most patients experiencing “a gradual worsening of lung function over years” (Raghu, 2011). In some cases, patients experience significant functional impairment and death within months of diagnosis (Hambly, 2015). Others may encounter a sudden decline (termed “acute exacerbation”) only after an otherwise long period of previous stability (Raghu, 2011). Acute exacerbation is associated with a mortality rate as high as 85% and mean survival periods of between 3 to 13 days (Juarez, 2015).

This varying set of responses to the disease mean that normal approaches to fibrotic diseases – assigning risk based on clinically observed variables (i.e., history and physical examination, pulmonary function, exercise testing, radiographic findings, and histological examination) – are “poorly reflective of disease pathogenesis and provide insufficient power to accurately predict clinical outcome” (Hambly, 2015). Difficulty in anticipating the course of IPF necessarily complicates the clinical determination of how best to treat the disease.

For years, there was no standardized test to distinguish among mild, moderate, and severe instances of IPF, although those conducting clinical trials
generally employed two different lung physiology variables to establish a segmenting test to differentiate between mild-to-moderate patients from those with severe IPF: a FVC threshold of 50–55% predicted and a diffusing capacity of carbon monoxide ($D_{LCO}$) threshold of 35–40% (Kolb, 2014). An early longitudinal model based on seven factors (dyspnea, chest radiograph, spirometry, lung volume, diffusion capacity, resting alveolar-arterial $P_{O_2}$, and exercise $O_2$ saturation) resulted in a clinical, radiological and physiological (CRP) scoring system that predicted, with some confidence, survival IPF rates based on observations over a six-month period (Watters, 1986). However, given the imprecision of IPF diagnosis at that time, the value of these conclusions today is unclear.

In 2012 a streamlined model of disease staging was developed using only four baseline variables: gender, age and the two lung physiology factors noted above (FVC and $D_{LCO}$). This approach, termed “GAP” (Gender/Age/Physiology), resulted in both a three-stage scoring system, which provides as a quick screening tool for use in the clinical setting, as well as a more specialized risk calculator for calibrating treatment in previously-diagnosed patients (Ley, 2012). Its discriminatory power was validated in studies in Korea (although the 3-year mortality projection could not be confirmed) (Kim, 2015). However, over a 2-year period, patients’ GAP stage was not associated with differences in yearly lung function decline in an international study involving over 600 patients (Salisbury, 2016). These predictive failings of GAP may be addressed by a new model,
Longitudinal GAP, which, like the CRP score, takes account of changes over time (in this instance, the patient’s history of respiratory hospitalization and 24-week change in FVC (Ley, 2015). Given its novelty, there are no studies on the discriminatory and predictive powers of the Longitudinal GAP model, but presumably there are ongoing studies testing it.

**Treatment of IPF**

IPF remains a major cause of illness and mortality and thus reflects a largely unmet medical need (Spagnolo, 2015). However, over the past five years, new pharmaceutical treatments have made significant strides to ameliorate the impact of IPF on patients. Despite these advances, it should be noted that surgical intervention through lung transplantation (LTx) remains the sole therapy that can effectively remove the cause of IPF related dyspnea (but this treatment is a last resort).

**Pharmaceutical Treatment**

Because inflammation was long thought to be associated with the development of IPF, glucocorticoids or immunosuppressive agents represented the conventional approach to the treatment of patients, especially those with milder cases of the disease (Bando, 2016). However, the 2011 ATS/ERS/JRS/ALAT guidance recommended that IPF not be treated with corticosteroid monotherapy, cyclosporine A therapy, or the combination of corticosteroid with immunosuppressant (azathioprine or cyclophosphamide)
Underlying the emergence of this new thinking was a 2012 study that found that a triple anti-inflammatory treatment regime using N-acetyl cysteine, prednisone, and azathioprine was, in fact, significantly harmful to patients with IPF. The trial was abandoned when it was found to have resulted in a 10% increase in mortality – largely due to respiratory causes – and a material (>300%) increase in hospitalization and adverse effects (Raghu, 2012).

Rather than immunosuppressant agents, since October, 2014, mild-to-moderate IPF is now treated with either of two recently FDA-approved oral antifibrotics: pirfenidone and nintedanib. However, their efficacy in severe IPF and the optimal length of therapy remain unknown, given their relatively recent introduction. Neither has yet been recommended in international IPF guidelines (Handa, 2016).

Pirfenidone, a pyridone, is believed to act via anti-inflammatory and antifibrotic chemical pathways, although its exact mechanism is unknown (Karimi-Shah, 2016). It is thought to attenuate TGF-β production and effect (Fernandez, 2012). Meta-analysis of three European/Japanese trials of pirfenidone showed a reduction the proportion of patients experiencing a greater than 10% predicted decline in FVC in nearly 44% in the pirfenidone group compared with placebo (Noble, 2016). Similarly, An FDA-mandated study prior to U.S. approval found a relative reduction of 50% in the proportion of patients who had such a decline in predicted FVC (Aravena, 2015). It has been observed that
Pirfenidone in trials produced more favorable mortality rates than did nintedanib, but this may be due to differently structured trials (Wells, 2016).

Nintedanib is a tyrosine kinase inhibitor first used to treat IPF in Japan. It has been shown to have a broad inhibitory activity on the downstream signaling cascades of fibroblasts and myofibroblasts (Wollin, 2015). Nintedanib was found to reduce the decline in FVC while also delaying the onset of acute exacerbation (Richeldi, 2014). The number of deaths in the nintedanib group was consistent those in the placebo group, but the study may not have been powered to demonstrate a mortality benefit.

It must be noted these newly-introduced oral therapies (pirfenidone and nintedanib) do not reverse the fibrosis; they merely delay patients' functional decline (O'Flaherty, 2015). Moreover, one recent study has concluded that using both drugs in combination, rather than either alone, demonstrates greater efficacy in reducing in vitro proliferation of fibroblastic cells (Lehtonen, 2016). This was presaged by a 2015 editorial that succinctly noted that “[c]ombination therapy is the IPF treatment of the future (Wells, 2015). The challenge in structuring combined or successive uses of different treatments, according to Drs. Kolb, Jenkins and Richeldi, is that with “IPF, we still do not know how to define treatment failure. The decline of lung function over a definite period of time...has been widely used to assess disease progression and risk of death in IPF, but its value has been questioned...and it does not necessarily reflect the effect of therapy on an individual and hence can't define treatment failure.” (Kolb, 2016).
They argue that more controlled studies, not merely retrospective data reviews, on the combined use of both drugs must be pursued in an effort to balance “individual needs with community sustainability”. (Kolb, 2016).

According to clinicaltrials.gov, a number of potential therapies are under investigation, including antiviral therapy targeting herpesvirus. As noted above, a potential linkage between herpesvirus and IPF has been identified (Kropski, 2012).

**Oxygen Therapy and Ventilation**

Unsurprisingly, given the universal dyspnea suffered by patients with IPF, ambulatory oxygen therapy is often used in the treatment of patients with hypoxemia due to IPF. Despite the passage of time, as of 2013, no clinical trials have evaluated the functional outcomes or survival of patients with IPF based on either short or long-term oxygen therapy (Criner, 2013). A Mayo Clinic retrospective statistical study of patients in the mid-1990s concluded that patients with IPF treated with oxygen fared worse than those not receiving this treatment (Douglas, 2000). This study could not, however, determine whether the use of oxygen therapy correlated with severity of disease or in fact reflected a lower incidence of survival resulting from the oxygen therapy (Douglas, 2000).

Similarly, a 2005 review of HRCT use found, without further comment, that the supplemental use of oxygen was a significant risk factor for mortality of patients with IPF (Lynch, 2005). Despite the lack of clinical trials and the results of the reviews linking use and mortality, most physicians treating patients with
IPF reportedly believe that supplemental oxygen treatment is appropriate for use when resting, exercise, or nocturnal peripheral oxygen saturation falls below 89% (Holland, 2014). “This belief is likely driven by clinicians’ unwillingness to leave uncorrected something…that can be remedied when so many other aspects of the disease are untreatable.” (Holland, 2014). Thus, oxygen therapy remains a key palliative component in the management of patients with IPF, as it appears to improve symptoms and overall quality of life (Criner, 2015).

Mechanical ventilation is sometimes used for patients with IPF suffering acute exacerbation resulting in hospitalization. Acute exacerbation affects a significant minority of patients with IPF, but is associated with high mortality. A comprehensive review of medical records of over 17,000 patients with IPF between 2006 and 2012 considered the comparative use of mechanically invasive ventilation (MV) (endotracheal or tracheostomy tube) and noninvasive mechanical ventilation (NIMV). The overall mortality for the entire cohort of patients with IPF was 11.3%. MV patients experienced higher mortality (51.6% vs. 30.9%), were younger (66.3 years vs. 70.2 years), and had longer hospital stays (13.3 days vs. 6.5 days) than those receiving NIMV (Rush, 2016). Perhaps confirming the benign impact of patients’ use of ambulatory oxygen therapy, such use by those in the study had no impact on the mortality between the MV and NIMV cohorts (Rush, 2016). It must be noted that the severity of condition that likely prompted the use of MV over NIMV in the first instance makes comparisons between the impact of these modalities of care difficult.
Pulmonary Rehabilitation

Many studies have found a benefit from pulmonary rehabilitation, although there is no accepted standard on the type, intensity or duration of such treatment (Puglisi, 2016). In a review of such studies, pulmonary rehabilitation was found, perhaps unsurprisingly, to result in "improvement in exercise tolerance, particularly a transient increase in the distance travelled in the walk test or a decrease in heart rate". (Puglisi, 2016).

Yet, there is doubt regarding the long-term benefit of such treatment. For example, a 2015 report found that in comparing patients with IPF in Israel who underwent a 12-week course of pulmonary rehabilitation with a control group that did not, the findings with respect to survival and cardio-respiratory-related hospitalizations showed no significant differences (Vainshelboim, 2015). In a sense, then, pulmonary rehabilitation may be viewed akin to palliative care – allowing improvements in quality of life (or end of life) without delivering improvements in arresting or reversing the underlying condition. However, there can be no doubt that patients with IPF are in acute need of improvement of their psychological and emotional conditions.

Lung Transplant

As a general rule, patients with IPF qualify for LTx when post-transplant life expectancy exceeds their current life expectancy without the transplant (George, 2015). Because of the severity of the disease and the efficacy of the treatment, IPF is currently the most common indication for which United Network
for Organ Sharing allocates lungs for transplant, having increased from 15% in 2000 to 37% in 2009 (George, 2015). In addition to the narrow classes of absolute surgical contraindications, the following relative contraindications have been observed for IPF (George, 2015):

<table>
<thead>
<tr>
<th>Table 3 - Relative Contraindications for Lung Transplant Procedure for Treatment of IPF</th>
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<tbody>
<tr>
<td>• Recipient older than 65 years.</td>
</tr>
<tr>
<td>• Unstable clinical condition (e.g., shock or ventilator dependence).</td>
</tr>
<tr>
<td>• Limited functional status with poor rehabilitation potential.</td>
</tr>
<tr>
<td>• Body mass index (calculated as weight in kilograms divided by height in meters squared) of greater than 30</td>
</tr>
</tbody>
</table>

In view of challenges in predicting the relative mortality of patients with IPF, current LTx waiting list guidelines recommend early referral of all patients with histologic or radiographic evidence of IPF in the following order (George, 2015):

<table>
<thead>
<tr>
<th>Table 4 - Lung Transplant Waiting List Criteria for Interstitial Lung Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Histologic or radiographic evidence of [UIP] and 1 or more of the following: ([D_{LCO}]) of less than 39% predicted; decrease in ([FVC]) by 10% during a 6-month period; decrease in pulse oximetry to less than 88% during ([6 \text{ minute walking distance (6MWD)}]); and pulmonary fibrosis score of greater than 2 on computed tomography.</td>
</tr>
<tr>
<td>• Histologic evidence of nonspecific interstitial pneumonia and 1 or more of the following: ([D_{LCO}]) of less than 35% predicted; decrease in ([FVC]) by 10% during a 6-month period; and decrease in ([D_{LCO}]) of 15% during a 6-month period.</td>
</tr>
</tbody>
</table>
Interestingly, the factor having the most predictive value of mortality of those on a waiting list is lower 6MWD score. It was strongly and independently associated with an increased mortality rate for wait-listed patients with IPF, and was a better predictor of death at six months on the waiting list than was FVC predicted (Lederer, 2006). In particular, patients who cannot walk more than 207 meters in six minutes have a high mortality rate in the absence of LTx (Lederer, 2006).

Many patients with IPF receiving a LTx can be expected to survive for years beyond the procedure. Recently, the results of a retrospective study on all Dutch patients with IPF who were registered for LTx between 1989 and 2001 were released. Of these 98 patients, 30% died waiting for a LTx, while 52 patients received a LTx with a median survival post-surgery of 10 years. Of those who died on the waiting list, 21.9% were deemed high-urgency based on the prevailing European transplant standards, while 38.6% were elective patients (ten Klooster, Nossent, 2015). In the end stage of IPF in older patients, bilateral lung transplantation (BLT) is the preferred course to single lung transplantation, as it has a significantly improved survival rate (Gulack, 2015). Nevertheless, in the Dutch study, those patients with IPF slated for BLT appear to have an increased risk of pre-transplant mortality (ten Klooster, Nossent, 2015). Presumably, they were judged, rightly, as having a more acute need for LTx than others on the list, although the higher mortality may simply be attributable to relative scarcity of double lungs for transplant.
Palliative

As compared with patients with cancers, palliative care and hospice are typically much less used by those with other types of chronic lung diseases (Gilbert, 2009). For example, in a study of 277 deceased patients with IPF seen in a Pittsburgh hospital between 2000 and 2012 whose location of death could be determined, 57% died in the hospital, with only 13.7% receiving a formal palliative care referral, with nearly a quarter of those receiving such referral within 1 month of their death (Lindell, 2015). One recent article summed up the situation: “Despite the recognized need, efforts to provide effective palliation often fall short for patients and families living with chronic respiratory disease….The situation is even worse for patients living and dying with pulmonary fibrosis, who have received scant attention until recently.” (Rocker, 2015).

Psychological

With a condition with a prognosis as uniformly grim as IPF, and in light of the frequent delay in its diagnosis from the outset of symptoms, and the uncertainty over the progression of the disease in individual patients, it seems reasonable to expect many patients with IPF to struggle emotionally and psychologically with their diagnosis. A qualitative survey of a group of 17 patients in England between 2007 and 2012 confirmed that patients reported “struggling to get a diagnosis and coping with a life-limiting, rapidly progressive illness with no good treatment and few support structures” (Duck, 2015). It
should be noted that during the pertinent period, neither pirfenidone nor nintedanib was yet available. During the European trials for pirfenidone, a similar qualitative survey was undertaken of 71 patients with IPF receiving the drug. They also reported similar difficulties with diagnosis and the impact of the condition on their quality of life (Russell, 2016). However, they also related that pirfenidone had given them a measure of hope despite concerns over side effects (nausea and photosensitivity), but those using supplemental oxygen reported less hope, mainly because its use limited their activities and identified them publicly as other than healthy (Russell, 2016).

An Internet-based survey using the Patient-Reported Outcomes Measurement Information System® (PROMIS®) conducted twice with 220 patients with IPF during an undisclosed period of time (thus making consideration of the impact of pharmaceutical treatments impossible) found that depression scores of patients with IPF were comparable to those seen in individuals with major depressive disorders (Yount, 2016). This study also found that those receiving supplemental oxygen therapy were more impaired than non-users in fatigue, physical function, and social role participation (Yount, 2016).
DISCUSSION

It is axiomatic that the resources, both intellectual and financial, to research all medical conditions is limited. Yet surprisingly, the phrase “managed research” appears in resources indexed by Web of Science only 20 times, while “managed care” is employed 15,117 times. This begs the question: how does our society prioritize efforts to deepen our understanding of medical conditions such as IPF? This is not a new problem. In 2003, a seminal report asserted that “systematic flaws exist in the production of scientific evidence, in part because there is no consistent effort to conduct clinical trials designed to meet the needs of decision makers. (Tunis, 2003).

As seen above, there is currently a wide range of IPF-related research underway, some to validate the efficacy of the newly-introduced pharmaceutical treatments, others to explore the potential genetic underpinnings of IPF, while more seek biomarkers to aid in quicker and more effective diagnosis relative to scanning or biopsies. To which efforts should priority be given? In some sense there is an acute need to understand whether pirfenidone and nintedanib (alone or together) have the prospect of doing more than just delaying death, if only to validate the projected cost of nearly $100,000 annually being spent on such drugs for each American IPF patient taking them (Morrow, 2015).

Yet, as we consider the issue more broadly, there are strong arguments for focusing efforts around the goal of identifying strongly predictive biomarkers for IPF. This is especially the case if such biomarkers do more than merely
diagnose the condition but give clinicians the ability to tailor their care for patients. Considering such personalized medicine efforts more generally, it has been argued that “[i]f successfully implemented, these biomarker diagnostics would potentially save the health care system billions of dollars and prevent needless patient burden due to futile interventions.” (Hey, 2015). Thus, it could be argued that more focus should be placed on intensifying the search for IPF diagnostic and treatment biomarkers – especially to identify earlier in life those susceptible to IPF – with a view to delaying or avoiding the onset of the disease. In addition, with the emergence of effective pharmaceutical treatment, biomarkers might be able to provide insight in terms of when and how to utilize nintedanib and/or pirfenidone. It is an exciting possibility that perhaps certain biomarkers could enhance personalized treatment, in that their presence or absence could indicate which patients with IPF are more likely to respond to nintedanib or pirfenidone, or neither. This information would be invaluable in terms of slowing disease progression.

But, paradoxically, even with such biomarkers, science today lacks confidence in determining what triggers IPF, so even with a means of identifying an at-risk set of individuals, there is no targeted means of eliminating risk factors. All that can be offered is advice to shun particulates and cigarette smoke that are thought to be associated with the micro injuries to the lungs that are associated with IPF. However, as noted above, familial occurrence of IPF has been found to be a stronger associated factor than environmental conditions. This suggests
more research is needed to explore this apparent strong genetic element (or the need for new research to better control for environmental co-factors). Thus, until there is a better understanding of the mechanism by which the cellular damage is triggered, it makes more sense to focus on biomarkers that confirm the presence of IPF. Improved confidence in diagnosis – without having to resort to biopsies and HRCT – would reduce costs and save months of delay seen today in confirming the condition. Work on specifying the mechanics of cell injury and prophylactic measures to protect at-risk persons should be pursued, and the cost-benefit of pirfenidone and nintedanib use must be validated. Because LTx is currently so relied upon as a last resort treatment for advanced IPF, efforts to examine how to improve the results of such treatment for IPF and all other conditions are needed. For example, chronic lung allograft dysfunction, specifically bronchiolitis obliterans, affects “50% of [all lung transplant] patients within 5 years after the transplant procedure and [causes] up to 30% of late mortality between 3 and 5 years after transplantation” (Verleden, 2014). Finally, in a development that may expand the hopes of patients with IPF needing LTx, it has been suggested recently that single LTx, rather than double LTx, is as effective and should be pursued in order to make donor lungs more widely available to patients with IPF (Chauhan, 2016).
CONCLUSION AND SUGGESTIONS FOR FURTHER RESEARCH

Great strides have been made in the diagnosis and treatment of IPF in the 21st Century. However, despite this progress, it remains a fatal disease. The literature suggests the following areas as opportunities for further research to broaden the understanding of the disease, its risk factors, progression and treatment:

• Etiology: Given the wide variety of reported incidence of familial cases of IPF, and the growing evidence of genetic factors related to susceptibility, a more concentrated effort to examine the true risk of familial IPF is needed.

• Etiology: In view of the international variation in reported incidence and prevalence, it would be helpful to better understand whether there are variations in the populations or in diagnostic measures that are driving this observed variation.

• Etiology: Given the evidence of a potential viral nexus, further efforts are needed to explore the contribution of Herpesvirus saimiri and other viral agents

• Impact: Further examination of cognitive impairment reported in one study should be undertaken.

• Diagnostic: Are surgical biopsies still necessary to effectively diagnose IPF, or is the less-invasive cryoprobe alternative sufficient?
• Diagnostic: Serum-based biomarkers are needed to diagnose IPF, monitor response to treatment, and aid in predicting its prognosis. Thus, this should be a primary focus of research activity.

• Diagnostic: In light of the familiarity of the GAP elements, steps should be taken to validate the efficacy of Longitudinal GAP in predicting the disease’s progression.

• Diagnostic: A better understanding of the predictive and diagnostic power of the 6MWD test is needed as it relates to progression and mortality.

• Treatment: Broader studies of pirfenidone and nintedanib over a longer period of time should be undertaken, with particular attention to combined usage and the potential improvement in effect.

• Treatment: The optimal role of ambulatory oxygen therapy and pulmonary rehabilitation should be better characterized in patients with IPF.

• Treatment: Seek efforts to improve survival of all LTx recipients, IPF and otherwise
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CURRICULUM VITAE

Sarah V. Burley
svburley@yahoo.com
DoB: November 10, 1991
614-256-1219

Permanent Address:
2209 Ivor Lane
Alexandria, VA 22304

School Address:
1340 Commonwealth Ave.
Apt. 5
Boston, MA 02134

EDUCATION

Boston University School of Medicine
Master of Science in Medical Sciences
Cumulative GPA: 3.42/4.00

(Coursework in Biochemistry and Cell Biology, Human Medical Physiology, Cellular Organization of Tissues (Histology), Biomedical Information, and Biostatistics)

The University of Chicago
Bachelor of Arts in Biological Sciences
Cumulative GPA: 3.14/4.00

RESEARCH

Research Internship, Herman B. Wells Center for Pediatric Research at Indiana University School of Medicine
June-August 2012

HONORS

Dean’s List, The University of Chicago 2010-2011
College Board AP Scholar with Distinction 2009-2010
Wendy’s Heisman Award 2009-2010
National Field Hockey Coaches Association National Academic Squad 2009-2010
U.S. Lacrosse Academic All-American 2009-2010
Williams College Book Award 2008-2009