Key Sessions on IPF Pathogenesis, Diagnosis, and Management From PFF Summit 2017

A CME/CE-certified supplement to CHEST® Physician
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The Promise of Genetics and Personalized Medicine in Pulmonary Fibrosis

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This plenary session focused on the long-term goals of genetic research and personalized medicine in pulmonary fibrosis. Researchers studying the genetics of familial and sporadic idiopathic pulmonary fibrosis (IPF) have learned about a number of important mechanisms of the disease process, including changes in telomere length and changes in surfactant protein C, and hope to learn about additional disease mechanisms in other patient subpopulations. Future studies will identify potential novel targets for therapy and biomarkers for measuring response to treatment.

National Heart, Lung, and Blood Institute Support for Personalized Therapy in Lung Disease

James Kiley, PhD, of the National Heart, Lung, and Blood Institute (NHLBI) described the Institute’s support for genetics and personalized medicine in IPF. Personalized medicine refers to the process of understanding and targeting the underlying genetic and molecular mechanisms of disease within a given patient. Patients with pulmonary fibrosis present with similar clinical symptoms, and physicians treat them the same way. But patients respond differently to treatment, suggesting that the underlying disease processes are heterogeneous. The current goal of research is to identify subpopulations of patients with pulmonary fibrosis who share molecular and genetic characteristics and develop treatment specifically for them. Ideally, we could predict which patients would respond to particular treatments, and their response could be measured at the molecular level using biomarkers.

As examples of personalized medicine, Dr Kiley described recent work in asthma and pulmonary hypertension. In asthma, a subpopulation has been identified that has high levels of eosinophils, a marker of airway inflammation. Other subpopulations have been identified that have high or low type 2 helper T cell (Th2) response. The high Th2 response correlated with the production of periostin in airway epithelial cells. The levels of eosinophils and periostin predicted the patients who would respond to lebrikizumab, an anti-interleukin (IL)-13 monoclonal antibody, in a clinical trial.

In pulmonary hypertension, a patient’s response to an endothelin receptor antagonist is determined by genetic variations in the endothelin receptor. Further studies should help to identify the optimal first-line therapy for patients with pulmonary hypertension.

Dr Kiley noted some important studies in IPF that were funded by the NHLBI. One study found that sildenafil improved dyspnea and quality of life, but no benefit was seen in the primary outcome, 6-minute walk distance. Another study found that warfarin treatment did not benefit patients with pulmonary fibrosis. Similarly, a widely used combination treatment of prednisone, azathioprine, and N-acetylcysteine (NAC) was compared with NAC monotherapy. The combination treatment increased risks of death and hospitalization in patients with IPF, but it did benefit IPF patients carrying a specific polymorphism in the TOLLIP gene. This finding, a difference in response among patients with a specific molecular characteristic, is the first step toward personalized medicine.

Other studies have found differences among patients with IPF at the molecular level. One study has found an association between shorter telomere length and higher mortality in three IPF cohorts. Another found that a promoter polymorphism in the MUC5B gene, which plays a role in mucus clearance, is associated with improved survival. Last year, a 52-gene expression signature in peripheral blood was found to predict mortality and transplant-free survival in patients with IPF.

Dr Kiley also described NHLBI-funded genomics resources in pulmonary fibrosis, including:
- TOPMed Program, which consists of 1,500 peripheral blood DNA samples from patients with idiopathic and familial pulmonary fibrosis prioritized for whole genome sequencing
- Lung Tissue Research Consortium, which provides human lung tissues, blood, and extensive phenotypic data (primarily from IPF and chronic obstructive pulmonary disease [COPD] donors) to researchers
- Lung Genomics Research Consortium, with five centers with open-access genomic and clinical IPF data

In concluding, Dr Kiley called for a proactive pulmonary fibrosis community to foster the partnerships and collaboration that will be necessary to move forward.

State-of-the-Art Approaches to Genetic Discovery in Complex Disease

Jeffrey M. Trent, PhD, spoke about state-of-the-art approaches associated with genomic discovery. He heads the Translational Genomic Research Institute (TGen), a nonprofit biomedical research institute that focuses on generating and analyzing genomic information with the goal of using this information to improve treatment.

Cancer treatment today is highly personalized, and the genomes of tumors can be analyzed to determine the best course of treatment. TGen has collaborated with many leading researchers on precision medicine trials in cancer. They also work on many idiopathic diseases, particularly those that arise in children.

Dr Trent described a cancer initiative with many similarities to IPF. The Multiple Myeloma Research Foundation worked with TGen to develop a Data Bank with genomic and clinical information that is available to all researchers. The data can be used to identify new targets, pathways, and biomarkers, as well as to generate hypotheses for clinical trials and explore new ways of treating myeloma. Within the past 10 years, they have conducted 70 clinical trials. Ten new treatments for multiple myeloma have received US Food and Drug Administration (FDA) approval, and life expectancy for patients with multiple myeloma has more than tripled.

Leaders in the IPF community are beginning to discuss how to develop such a precision medicine model for patients with IPF. Work would begin with genetic data, imaging data, and investigations in the clinic. For IPF, it will require better ways of understanding and automating analysis of changes taking place at the cellular level, facilitated by novel technology such as single-cell RNA sequencing. Dr Trent encouraged the IPF community to collaborate on this initiative to improve patient treatment.
Current Status of Clinical Genetic Testing in Interstitial Lung Disease

James Loyd, MD, summarized current knowledge of the genes that play a role in pulmonary fibrosis. He explained that approximately 20% of patients have a family history of pulmonary fibrosis. Some patients are not aware of their family history until they query family members after their own diagnosis. Others discover that their pulmonary fibrosis is familial when another member of the family is diagnosed years later.

Genetic testing is available and is usually covered by insurers, with results available within a few months. Educating and counseling the patient about the testing is more difficult, as is the patient’s decision to receive the results and discuss them with the rest of the family. The Genetics Home Reference from the National Library of Medicine (https://ghr.nlm.nih.gov/) is an excellent resource for patients and their families.

Studies of familial pulmonary fibrosis have identified two major pathways in the development of the disease: the telomerase pathway genes and the surfactant pathway genes. Most of the genes in these pathways show dominant inheritance.

About 20% of families with inherited pulmonary fibrosis have mutations in the telomerase pathway. The most common are TERT, RTEL1, and PARN. Mutations in nTR/TERC, DKC1, TINF2, and CTC1 are less common, accounting for about 1% of families each, and more will probably be discovered. Genes in the surfactant pathway include SFTPc, SFTPA1, and SFTPA2. They only account for about 1% of families, but their discovery was scientifically notable because it identified the important role of surfactant protein C and the alveolar epithelial cells in pulmonary fibrosis.

In addition to the major pathways, additional genes have been identified in families with pulmonary fibrosis, including ABCA3, the adenosine triphosphate-binding cassette subfamily A, member 3. Another variant is the 4-fold increase in the MUC5B gene.

Families with telomerase pathway mutations experience additional disorders at a greater frequency than expected, including nonspecific interstitial pneumonitis, cryptogenic organizing pneumonia, pneumonitis, and dyskeratosis congenita. Those with dyskeratosis congenita often have premature gray hair, as well as liver and bone marrow diseases.

Anyone in the family may be at risk for disease if they have chromosomes with short telomeres, even if they have not inherited a telomerase mutation. This can be confusing in genetic counseling because the disease does not segregate like a mutant gene. Telomere length can now be measured clinically, with results available in about 2 weeks. White blood cell telomere length has been shown to correlate with IPF survival.

A family with a mutation in surfactant protein C was reported in 2002. Pulmonary fibrosis in patients with mutations in this pathway has a distinct phenotype. It can present at any age, even in childhood, as early as age 1 or 2 years. It may be triggered in children by viral infection, influenza, or respiratory syncytial virus. It can have a long course; one person in the original family developed symptoms at age 5 years and died of interstitial lung disease (ILD) at age 55 years.

Genetically, patients with IPF can be divided into four categories:

• Sporadic with a negative family history
• Familial with two or more patients with no specific phenotype
• Familial with features of surfactant pathway
• Familial with features of telomerase pathway

A Genetic Counselor’s Perspective: Impact of Genetic Information for Patients and Families

Janet Talbert, MS, spoke of pulmonary fibrosis from the perspective of a genetics counselor. She explained that approximately 80% of cases of IPF are sporadic. Pulmonary fibrosis is considered familial if there are two or more relatives with IPF, but there can be many more cases occurring over multiple generations. A detailed family history can give clues to the type of mutation that might exist and the type of testing that should be done. Does the pattern of inheritance suggest a dominant or recessive gene, or an X-linked gene? Do the clinical features suggest a mutation in the telomerase pathway, with cases of dyskeratosis congenita, liver cirrhosis, or bone marrow disorders in the family? Or does it suggest a surfactant mutation with cases of early onset?

Test results can be complex and difficult to interpret. If the variant is likely to be pathogenic, other family members should be tested. This may be the case if the mutation is a truncating mutation, a frame shift, or a large deletion. For a variant whose significance is truly unknown, no change in clinical management is recommended and no testing of family members should be done.

For patients with a mutation in the telomerase pathway, it would be wise to monitor liver function and do hematologic monitoring. Other mutations, including MUC5B and TOLLIP, can provide survival information. Perhaps in the future, there will be therapies based on genotype.

Patients are usually concerned about the risk their relatives face. Family members do have an increased risk of disease. The common gene variants show Mendelian inheritance as autosomal dominants. There are no established guidelines for testing or monitoring family members, but it has been demonstrated that unaffected first-degree relatives may show interstitial changes on computed tomography (CT) scan and have abnormal biopsies. Ms Talbert encouraged unaffected family members to discuss their risk with their doctors and possibly have baseline screening and work on minimizing their risk by maintaining a healthy lifestyle and avoiding exposures.

Patients and their families also ask about the possibility of discrimination based on their genetic risk. Federal law (Genetic Information Nondiscrimination Act) prohibits discrimination in health insurance and employment. It does not mandate coverage for tests or treatment, nor does it apply to life or disability insurance. It only applies to the use of genetic information indicating risk for disease, but the presence of the disease itself may be used in insurance determinations.

Dealing with genetic information may have psychosocial effects on patients and family members. Health care providers should be alert for symptoms of depression and anxiety. On the other hand, many family members want this information and will take preventive steps to avoid the disease themselves and in their future children.

Good resources for patients include the Pulmonary Fibrosis Foundation, www.pulmonaryfibrosis.org; for clinical trial information, see www.clinicaltrials.gov, and for information on genetic discrimination (GINA information), see www.ginahelp.org.
Key Takeaways

- The current goal of research in personalized medicine for patients with IPF is to identify subpopulations of patients who share molecular and genetic characteristics and develop treatment specifically for them.
- Studies of familial pulmonary fibrosis have identified two major pathways in the development of the disease, the telomerase pathway genes and the surfactant pathway genes.
- Genetic testing is available for patients with IPF and their families, but test results can be complex and difficult to interpret.
- Dealing with genetic information may have psychosocial effects on patients and family members. Health care providers should be alert for symptoms of depression and anxiety.

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Environmental Influences

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Abnormal Gastroesophageal Reflux Disease and Idiopathic Pulmonary Fibrosis

Ganesh Raghu, MD, FACP, FCCP, described the current paradigm of IPF pathogenesis: Exogenous and endogenous stimuli (eg, dust, fumes, autoimmune conditions) cause ongoing microscopic lung injury in the context of genetic predisposition. Over time, fibroblasts proliferate, with excess collagen and extracellular matrix deposition, and this aberrant wound healing results in IPF. Dr Raghu thinks that microaspiration of gastric acid is a form of lung injury that causes IPF.

The reflux of gastric contents to the lower esophagus in small amounts is a normal phenomenon. Damage depends on several factors:

- Duration and extent of reflux
- Characteristics of the refluxed fluid (acidity, pepsin, bile)
- Number of reflux episodes/unit of time
- Esophageal peristalsis
- Salivary neutralization

Many observations support the hypothesis that microaspiration may play a role in the pathophysiology of IPF. The prevalence of gastroesophageal reflux (GER) is higher in patients with IPF compared with patients with lung diseases other than IPF.1 Most of the patients with IPF who have GER do not have typical symptoms, but the GER tends to occur at night and often extends to the proximal esophagus.2 Another study confirmed this observation.3 Hiatal hernia, a risk factor for GER, is more common in IPF compared to asthma and COPD.4 Microaspiration may precipitate an acute exacerbation of IPF. In one recent case, an autopsy of a patient with an acute exacerbation found cells from the gastric lining in the lung.

Although still controversial, observational data suggest that treatment of GER may slow the progression of IPF. In one study, patients with IPF who were taking a proton pump inhibitor/histamine H2 blocker (PPI/H2B) had a slower decline in forced vital capacity (FVC) compared to patients who were not taking a PPI/H2B. In addition, patients with IPF taking a PPI/H2B did not manifest episodes of adjudicated acute exacerbations during the study period.5 Prospective randomized clinical trials studying the impact of GER treatment on IPF are needed to address this question. One National Institutes of Health–sponsored trial, WRAP-IPF (NCT01982968), will address this issue by testing whether laparoscopic anti-reflux surgery will slow the progression of IPF.
Sleep Apnea in Idiopathic Pulmonary Fibrosis
Lisa H. Lancaster, MD, FCCP, explained that patients with IPF tend to have poor sleep quality, characterized by sympathetic nervous system activation and fragmented sleep with nocturnal cough, reflux, shortness of breath, hypoxia, and obstructive sleep apnea (OSA). Sleep architecture tends to be abnormal with increased stage 1 and 2 sleep and decreased deeper sleep. Patients with IPF tend to have rapid, shallow breathing during sleep and while awake.

In OSA, when the upper airway is blocked, but attempts to breathe continue, there is an increased negative pressure in the chest, resulting in a transdiaphragmatic differential pressure. Stomach juices can be refluxed and may be aspirated into the lung. Patients with IPF have a risk of gastroesophageal reflux disease (GERD) greater than patients with other lung diseases.

OSA is common in patients with IPF. A study of outpatients with stable disease found that 88% had OSA. Treatment of OSA in patients with IPF may be associated with improved survival.

What is the relationship between OSA and IPF? According to one hypothesis, there are two components driving this interaction. First, in patients with IPF, there is reduced caudal traction of the upper airway causing increased collapsibility. Second, increased ventilatory control system instability may be causative. These factors lead to a cycle of overventilation and hypocapnia/apnea.

Other studies have found that lung volumes can be reduced by the pressure of abdominal fat with recumbent posture, which may reduce caudal traction of the upper airway surfaces and increase the thickness of the lateral pharyngeal walls. An interesting study examined the effect of increased lung volume on sleep-disordered breathing. A negative-pressure ventilator was used to manipulate lung volume in patients with OSA treated with continuous positive airway pressure (CPAP) therapy. As lung volume increased, there was a decline in obstructive apnea events and hypopneas due to upper airway occlusion.

Studies also show that inspiratory resistive breathing is proinflammatory, with increased cytokine markers and translocation of neutrophils into the lung. CPAP therapy can produce a decrease in oxidative stress biomarkers.

Another hypothesis suggests that recurrent, tractional injury to the periphery of the aging lung contributes to IPF in genetically predisposed individuals. The damage occurs over many years to the epithelial-mesenchymal interface, especially at the outer edges of the basilar lung lobules where tractional stress is high during inspiration, compliance is relatively low, and there is a greater tendency for alveolar collapse during inspiration. Inherited or acquired surfactant abnormalities may contribute to this process.

The fact that OSA is more common in IPF and that it is associated with risk factors and comorbid disorders of IPF suggests that this may be a particular phenotype of IPF. Research would be needed to see if this phenotype is linked to a specific genotype. For clinicians, the data suggest that patients with IPF should be considered for sleep studies to detect possible OSA.

Key Takeaways
• The prevalence of GER is higher in patients with IPF compared with patients with other lung diseases. One study showed that patients treated with PPI/H2B had a slower decline in FVC.
• It has been hypothesized that microaspiration may be a source of lung injury causing or exacerbating IPF.
• Obstructive sleep apnea is common in patients with IPF and is associated with risk factors and comorbid disorders of IPF. The data suggest that patients with IPF should be considered for sleep studies.

References
Researchers have previously found IPF has a substantial genetic component. The genes that have been identified through family studies, in surfactant protein and in telomerase, account for a portion of the overall population genetic risk. Less common variants have larger effect sizes and taken together, they account for a larger subset of genetic risk in the IPF population.

So far, they have sequenced the genomes of 2,283 patients with IPF to identify rare variants (defined as present in less than 1% of the population) associated with this disease.

In telomerase genes, they found that rare variants in TERT, TERC, and RTEL1 are enriched in patients with IPF relative to controls.

They also did a genetic modifier screen to better understand the MUC5B risk allele. This allele is present in about 40% of patients with IPF, but 60% of patients with IPF do not have it. They discovered that a rare variation in TERT is enriched in patients with IPF who have no MUC5B risk allele.

It is well known that patients with IPF have shorter telomeres than age-matched controls with other chronic diseases. It has also been established that rare coding variants in TERT, TERC, and RTEL1 are more common in patients with IPF.

Research plans include looking at genome-wide studies for rare and common variations associated with disease progression and pirfenidone treatment response, as well as further investigation of MUC5B polymorphism carriers.

**Key Takeaways**
- Information from the human genome can be used to discover and verify candidate biomarkers, to understand disease pathogenesis and heterogeneity, and to discover new drug targets.
- Whole genome sequencing can identify rare variants that, taken together, account for more of the genetic risk in the pulmonary fibrosis population than the common variants.

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**The Role of Aging and Senescence in Idiopathic Pulmonary Fibrosis**

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Victor Thannickal, MD, FCCP, discussed IPF as a disease caused by the loss of cellular homeostasis associated with aging and senescence.

It has been argued that the molecular and cellular mechanisms that give rise to fibrosis may develop as an aberrant healing process in response to environmental exposures. In the presence of environmental challenges, genetic susceptibilities, epigenetic alterations, and aging-related cellular changes, failure of evolutionarily conserved healing processes drives specific cell phenotypes that give rise to IPF. Some of these cellular processes, such as senescence, may have evolved to be protective in early life and during specific biologic processes. After reproductive age, they may contribute to diseases of aging including, perhaps, IPF. Hallmarks of aging that may contribute to IPF include telomere attrition, genomic instability, epigenetic changes, loss of proteostasis, mitochondrial dysfunction, altered intercellular communication, and stem cell exhaustion.

Dr Thannickal went on to describe some of the molecular and enzymatic pathways involved in senescence. Although there are a number of upstream activators and regulators of senescence, they all appear to work through either the p53-p21 pathway or the p16 pathway. Both pathways have downstream effects on cyclins and cyclin-dependent kinases and the retinal blastoma gene, leading to senescence reprogramming within a cell.

Dr Thannickal described enzyme pathways that his laboratory and others have been studying. The NADPH oxidase (Nox) family of enzymes regulate redox-dependent signaling pathways and are critically involved in immunity, cell differentiation, and proliferation. Nox4 is important in fibrosis of the lung in animal models, as well as in the liver, heart, and kidney. His laboratory has shown that Nox4 may contribute to the redox imbalance that drives some of the age-related phenotypes.

Dr Thannickal’s laboratory has studied the role of Nox4 in young mice and older mice. In young mice injured with bleomycin, there is a self-limited fibrotic response that resolves over several weeks. This response is associated with an upregulation of Nox4, as well as a compensatory response of the NRF2 antioxidant that leads to a self-limited senescence. In older mice, they observed upregulation of Nox4 without the compensatory response of the NRF2 antioxidant. This action resulted in myofibroblasts with a sustained senescent phenotype. In older mice, the fibrosis is not resolved; the myofibroblasts do not undergo programmed cell death and clearance. In more recent work, Nox4 inhibition was found to reverse established fibrosis in aged mice. Relevance of these pathways to IPF was established by showing IPF lungs stained for p16, a marker of senescence, demonstrating that p16 was present in the epithelium and fibroblastic foci. Furthermore, IPF fibroblasts were found to express Nox4 and have decreased expression of NRF2.

Dr Thannickal also described data on the AMP-activated protein kinase (AMPK) pathway. The data have shown that there is deficient activation of AMPK in lungs with IPF, which may lead to altered turnover of collagen and mitochondrial dysfunction. Restitution of AMPK activation may be a potential strategy to improve the resolution capacity of fibrosis in response to bleomycin. Finally, they have shown that metformin is antifibrotic in bleomycin-injured mice, suggesting a possible future treatment.

**Key Takeaways**
- Cell senescence may contribute to diseases of aging including, perhaps, IPF. Upstream activators and regulators of senescence all appear to work through either the p53-p21 pathway or the p16 pathway. Both pathways have downstream effects on cyclins and cyclin-dependent kinases and the retinal blastoma gene, leading to senescence reprogramming within a cell.
- The NADPH oxidase family of enzymes regulate redox-dependent signaling. Nox4 is important in fibrosis of the lung in animal models, as well as in the liver, heart, and kidney. Nox4 inhibition was found to reverse established fibrosis in aged mice.
- The AMPK pathway may also play a role in IPF. There is deficient activation of AMPK in IPF lungs, which may lead to altered turnover of collagen and mitochondrial dysfunction.
Maximizing the Impact of Available Therapies in Idiopathic Pulmonary Fibrosis

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KEYNOTE: A Translational Science Platform to Foster a Learning Health Care System Within the Vanderbilt University Medical Center

The keynote speaker, Gordon R. Bernard, MD, FCCP, discussed the process at Vanderbilt University Medical Center for conducting clinical research during routine treatment of patients. This process allows for faster testing of interventions than the usual clinical trial. Once a study is complete, the results are published and indicated changes are incorporated into hospital practice.

In a standard clinical trial, screening and enrolling patients is time-consuming. Federal regulations require a lengthy consent process, but in certain circumstances, that process can be waived. This approach can be used when the interventions are of minimal risk, the waiver does not adversely affect the rights and welfare of the participants, consent is impracticable, and all participants are provided information about the results after participating.

Dr. Bernard described seven examples of research projects conducted at Vanderbilt using this process. The first compared washing patients daily with soap or chlorhexidine to see if chlorhexidine would reduce infection rates. The trial was conducted in five intensive care units (ICUs) at Vanderbilt over the course of a year and included about 9,000 patients. The ICUs varied the intervention by month. The Institutional Review Board approved the trial with a waiver of consent. The primary outcome was a composite rate of health care–associated infections: central line-associated bloodstream infections, catheter-associated urinary tract infections, *Clostridium difficile* infection, colon infection, and ventilator-associated pneumonia. The data were collected from hospital medical records and were adjudicated by an infection control service, which reviews infections as part of the hospital’s normal practice. The results of the study did not support daily bathing of critically ill patients with chlorhexidine. Another study compared two intravenous fluids, saline vs lactated Ringer’s solution, in critically ill patients (N=15,802) in the five ICUs. Researchers also did a similar study in noncritically ill patients (N=13,347) in the emergency department. The primary outcome was a combination of doubling creatinine at hospital discharge, new need for renal dialysis, or mortality. The effect was small but clinically significant in favor of Ringer’s in both cohorts. The difference in mortality was only 0.7%, but if saline were replaced with Ringer’s in all the hospitals in the United States, roughly 300,000 lives would be saved. Other study found that a new video laryngoscopy system was no better than direct laryngoscopy for intubating a patient. There was no difference in success at the first attempt and no difference in the time needed. They have also studied the effect of post-discharge follow-up telephone calls on hospital readmissions. Results of this study are not yet published.

While conducting these studies, they have developed standard procedures, which include an institutional and regulatory policy, master protocols, clinical decision support, clinical registries, real-time electronic health record data capture coupled with REDCap database support, and more. They can provide services and support for any researcher who wants to study important clinical questions.

PFF Care Center Network and PFF Patient Registry Update

Kevin R. Flaherty, MD, MS, FCCP, reviewed two activities of the Pulmonary Fibrosis Foundation (PFF): the Care Center Network and the Patient Registry.

The Care Center Network (CCN) is a group of treatment centers that provide excellent care for patients with fibrotic lung diseases while participating in research to move the field forward. By 2015, 40 treatment centers across the United States belonged to the network, and there are plans to expand again in 2018. Criteria for care centers include:

- Provision of excellent patient care
- Having an established fibrotic or interstitial lung disease program
- Access to multidisciplinary care for patients and families, including rheumatology, gastrointestinal (GI) services, specialized diagnostic testing, social work support, palliative care support, pulmonary rehabilitation services, sleep medicine, and a lung transplant program
- Provision of training for health care providers and researchers
- Ongoing research
- Affiliated support groups
- Ability to participate in the PFF programs

Working groups from the CCN are collaborating to determine how best to train residents and fellows. Another working group of radiologists and pulmonologists is determining standards for high-resolution CT scanning. A third working group is discussing how to conduct future research on environmental risk factors for ILD. Others are determining how to provide care to patients who live far from care centers.

The PFF has also developed a patient registry. The registry collects information on patients with broad types of fibrotic lung disease. Patients who are included in the registry will receive their usual care at one of the care centers that belong to the CCN; with their consent, information about the patients...
such as their demographic information and medical history, their care, their CT scans, and the course of their disease will be shared with the registry. Researchers will be able to look for patterns in patient care and outcomes and develop hypotheses for clinical research. Patients also have the option of being informed of clinical trials they may be eligible to participate in.

The inclusion criteria are broad. A patient must be 18 years or older and give informed consent. The patient must have a primary pulmonary diagnosis of ILD or fibrotic lung disease that is made at a care center and is based on a history and physical exam, pulmonary function testing, and a CT scan at a minimum.

Patients will have the option of providing a blood sample when they enroll. Researchers will be able to use those samples in their research. The pairing of clinical data and biological samples for thousands of patients will be a powerful tool for the research community.

As of October 2017, 1,500 patients had enrolled in the registry, with a final goal of 2,000. Nearly 60% have a diagnosis of IPF, and almost 90% had provided a blood sample. Information about the registry is available online at www.pfpatientregistry.org.

The first research projects using the registry have gotten under way. Researchers interested in submitting a proposal should check the Pulmonary Fibrosis Foundation website for further information.

Key Takeaways

- Researchers at Vanderbilt have developed a fast method of conducting large trials of clinical interventions in a hospital setting. They developed standard procedures, including institutional and regulatory policy, master protocols, clinical decision support, clinical registries, and real-time EHR data capture coupled with REDCap database support. They can provide services and support for any researcher interested in studying important clinical questions.

- The Pulmonary Fibrosis Foundation is planning to expand the Care Center Network (CCN) beyond the current 40 members in 2018. Working groups from the CCN are discussing training for residents and fellows, standards for high-resolution CT scanning, future research on environmental risk factors, and providing care to patients who live far from care centers.

- Patients treated at centers belonging to the CCN have been recruited to join a patient registry. Researchers will be able to look for patterns in patient care and outcomes and develop hypotheses for clinical research.

References


The Diagnosis of Idiopathic Pulmonary Fibrosis

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Advances in HRCT Imaging and Quantitative HRCT Imaging in IPF Trials and Clinical Care

Jonathan Goldin, MD, PhD, discussed the role of high-resolution computed tomography (HRCT) in the diagnosis of IPF and its use in clinical trials. He noted that although HRCT is integral to the diagnosis of IPF, heterogeneity in scanning technique and evaluation has limited its utility. However, recent advances in HRCT promise benefits to patients. Higher slice systems enable an entire lung scan with less than 3 seconds of breath-hold, which permits greater image area coverage and reduced radiation exposure. Detector technology using microelectronic circuits has improved resolution and reduced noise in images. Additionally, greater computer processing power allows for iterative reconstruction, which reduces artifacts and clarifies images with lower doses of radiation. Currently, a diagnosis of IPF can be based on HRCT images in about half of the cases, eliminating the need for surgical biopsy. But the classification systems for distinguishing among usual interstitial pneumonia (UIP)—which is the clinical correlate of IPF—probable UIP, possible UIP, and unlikely UIP are evolving; scientific societies are working to develop a new standard.1,2 Follow-up scans are not routine in clinical practice but may be useful in acute exacerbation.

Requirements for HRCT scans that will correlate with the pattern of UIP have been published.3 Some important issues include optimizing image quality, obtaining scans at correct breath-holds (total lung capacity and residual volume), using standardized patient positioning including prone positions, and thin section (<2 mm) acquisition and reconstruction (0.625-1.5 mm). Volumetric multidetector computed tomography is a new standard in that these contiguous images offer more information and should facilitate more accurate and complete assessment of abnormalities.

Clinical progression in IPF is unpredictable. The rate of progression varies widely and may occur in patients with stable symptoms. Hence, tests of lung function are imperfect indicators of clinical course and response to therapy. The use of HRCT may also have a role in the future as an indicator of progression and response to treatment, replacing FVC, single-breath transfer, and the 6-minute walk test. In addition, HRCT is used in clinical trials to assess in vivo the morphologic response to treatment, although usually for exploratory or post hoc analysis. Furthermore, HRCT has advantages in predicting
and measuring change: It is technically easier than spirometry, it allows direct visualization and assessment of the relative contributions of IPF and other pathologic abnormalities, and the extent of CT involvement correlates with patient mortality and functional impairment.4

Several groups of researchers are developing software to quantitatively evaluate HRCT scans to detect features not visible by eye. These methods could enable the use of HRCT as an efficacy or safety endpoint in clinical trials. Dr Goldin showed data from the research group at UCLA on quantitative lung fibrosis demonstrating its potential in clinical trials, as a predictor of prognosis, and for patient follow-up.5,6 The use of HRCT is likely to expand into clinical trials and patient care as imaging and its analysis improve.

Utility and Options for Lung Biopsy: Emerging Utility of Bronchoscopic Cryobiopsy

Fabien Maldonado, MD, FCCP, made the case for cryobiopsy as a safe and effective alternative to surgical lung biopsy (SLB). The use of SLB for the diagnosis of ILD is common in the United States—about 12,000 cases per year. In the ASCEND and INPULSIS 1 and 2 trials of pifemidone and nintedanib, 20% to 30% of patients had SLB.7,8 Biopsies for the diagnosis of IPF have declined with the rise of HRCT as a diagnostic tool. Some of this decline may also be due to greater awareness of the mortality associated with SLB. One retrospective cohort study of US mortality rates associated with SLB from 2001 to 2011 found that inhospital mortality was 1.7% for elective procedures but significantly higher, 16%, for nonselective procedures.9

Transbronchial biopsies during bronchoscopy are not a reasonable alternative to SLB. When combined with other data, they provide enough information for a diagnosis in only about 20% to 30% of patients with ILD.10 The samples are small, and they get crushed during the procedure. An ideal diagnostic tool would have a minimally invasive approach (preferably imaging-based, but if not, a flexible bronchoscopic approach); provide large biopsy specimens, with multiple specimens from different lobes; have a minimal crush artifact; and have a safety profile like that of conventional bronchoscopy.

Bronchoscopic cryobiopsy fulfills these criteria. A cryoprobe has a cannula that releases compressed gas at the tip, resulting in rapid gas expansion that freezes the tip to -70°C to -90°C. The tissue is frozen and pulled out. The main risk is bleeding, which is mitigated by using an Arndt endobronchial blocker.

Since 2009, 31 studies have been published on this procedure. One of the best studies found that transbronchial cryobiopsy increased diagnostic confidence and interobserver agreement almost as well as SLB.11 Dr Maldonado reported that typical specimens at Vanderbilt are 5 mm to 7 mm, which is sufficient for diagnosis.

Safety is still a concern. One academic medical center closed its cryobiopsy program after finding a high rate of complications in the first 25 patients.12 Safety results from others have been reported, but unfortunately, the literature is uneven, with no standard methods of reporting complications or diagnostic yield. Best practices for cryobiopsy have been standardized; however, the American College of Chest Physicians is developing evidence-based recommendations for cryobiopsies, which at the earliest will be available in late 2018. Meanwhile, recommendations from an international group of experts have recently been published.13

Preclinical Interstitial Lung Disease: Early Pulmonary Fibrosis Detection

G. Matthew Hunninghake, MD, presented a summary of work done by his group and their collaborators. Their goal is to identify interstitial lung abnormalities (ILA) present in early disease so a diagnosis can be made earlier than is possible today, and ultimately to prevent progression to advanced stages of fibrosis. Much of the work is based on reading about 22,000 CT scans on patients from several different research cohorts.

About 7% to 9% of the adult population over age 50 years have abnormal densities suggestive of ILD. Studies on their research participants have found that people with ILA are more likely to report respiratory symptoms, but most do not. People with ILA, particularly those measured by CT, have reduced total lung capacity. This population also shows reduced diffusion capacity and reduced exercise capacity.

Dr Hunninghake’s group and their collaborators have reviewed histopathologic specimens from lung nodule resections from patients with stage 1 adenocarcinomas or benign lesions. They demonstrated that subpleural reticular changes on imaging were most likely associated with subpleural fibrosis and fibroblastic foci.14 They also characterized serial chest CT images in about 1,700 people for whom serial measurements of pulmonary function were available. They found that, over time, disease progression observed by imaging is associated with an accelerated loss of FVC.15

By examining data from four research cohorts, they have also demonstrated that people who have early ILA have higher mortality rates than people who do not. Cause of death data were available for one subpopulation and showed that people with ILA were more likely to die of respiratory failure.16 In another cohort, they found that the increased excess rate of mortality that occurred 4 years after serial chest CTs appeared to be best explained by ILA progression.15

Risk factors for the interstitial changes observed in these cohorts include smoking and genetic abnormalities. The MUC5B promoter variant is associated with an increased risk for ILA, more rapid ILA progression, and increased risk for having definite fibrosis by CT.15,17 In addition, they found that the MUC5B promoter variant was associated with specific radiologic subtypes of ILA.18 They plan to develop a comprehensive characterization of common and rare genetic variants associated with ILA. They would like to combine all the data to characterize the comprehensive phenotype that is most likely to develop ILA and to progress over time in order to identify patient groups that would benefit most from further screening. They also have plans to study the relationship between genetic patterns and outcomes in patients with IPF. Then they plan to do comprehensive testing of first-degree relatives of these patients. In initial tests, they are finding many relatives with ILA and possible IPF.

Natural History of Interstitial Lung Disease: Lessons From an At-Risk Cohort

Timothy S. Blackwell, MD, discussed his research on the natural history of ILD and ongoing work on an at-risk cohort study. Many studies have shown that the median survival time after the onset of symptoms in patients with IPF is 3 to 5 years. Much less is known about the course of disease prior to symptom onset and diagnosis. Dr Blackwell and his collaborators are working to identify the abnormalities in the lung that may give rise to IPF because earlier identification and treatment of patients with IPF may improve outcomes.
The early, presymptomatic period of IPF is difficult to study in the general population because the prevalence of disease is so low. But up to 20% of patients with IPF have a family history of ILD. The clinical, radiographic, and pathologic features of familial and “sporadic” cases are quite similar. Family history of IPF is the strongest risk factor for IPF, so the first-degree relatives of patients with familial IPF have a markedly increased risk for disease. Research on 100 families published in 2005 showed that one in eight of these at-risk people had radiographic abnormalities.\(^9\)

Dr Blackwell and his colleagues launched their early IPF study in 2009, enrolling siblings and children of patients with IPF. Participants are ages 40 to 70 years at enrollment, or 5 years younger than the youngest patient in the family. People with other chronic lung diseases are excluded, along with people with substantial dyspnea. The main objectives are to define the natural history of IPF, develop risk-prediction models for the onset of IPF, determine approaches to early diagnosis, and define genotype/phenotype relationships.

So far, 284 participants from 135 families have enrolled in the study. The age of participants at enrollment is 52.3 years, about 13 years younger than the average age of onset of clinical disease in these families. The smoking rate is 26.7%, which is about the average rate of smoking in this region. Their HRCT scans show abnormalities consistent with ILD in 23% of this group, with higher rates in older participants and smokers. Biopsies on the first 71 participants found 26 (36%) participants had abnormalities, and many of these lesions had not been detected on HRCT scans. At-risk participants also tend to have short telomeres in type II alveolar epithelial cells. Herpesvirus DNA (Epstein-Barr virus and cytomegalovirus) is higher in bronchoalveolar lavage (BAL) fluid from these at-risk subjects compared with normal subjects, but the levels are lower than those observed in patients with IPF. A screen of 30 plasma biomarkers found four that were elevated in the at-risk group compared with age-matched controls: matrix metalloproteinase-7 (MMP-7), surfactant protein-D (SP-D), endothelin-1, and TIMP-2. Of all these possible risk factors, the greatest predictors of HRCT abnormalities in the at-risk subjects were telomere length, smoking, age, MMP-7, and SP-D.\(^7\)

So far, 57 participants have had 5-year follow-up HRCT scans. The researchers estimate that HRCT abnormalities precede clinical diagnosis by at least 8 years.

### Key Takeaways
- HRCT is expected to improve in the coming years with higher slice systems, better detector technology, and greater computer processing power. This will lead to improved resolution, fewer artifacts, and lower doses of radiation. It is hoped that more patients will be diagnosed by HRCT, reducing the need for surgical lung biopsy. HRCT may also have a role in the future as an indicator of progression and response to treatment.
- Bronchoscopic cryobiopsy is an alternative to surgical lung biopsy. Evidence-based recommendations for cryobiopsies are under development, which should reduce concerns about bleeding risk.
- Researchers are studying people at risk for developing pulmonary fibrosis to identify methods for earlier diagnosis and prevention of disease progression. They have found that the greatest predictors of HRCT abnormalities in the at-risk subjects were telomere length, smoking, age, and the biomarkers MMP-7 and SP-D. The researchers estimate that HRCT abnormalities precede clinical diagnosis by at least 8 years.

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Therapeutics

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Drug Development in Idiopathic Pulmonary Fibrosis: What Is on the Horizon?

Andrew H. Limper, MD, FCCP, described the increase in knowledge about the pathophysiology of IPF since 2001, particularly about genetic susceptibility and the role of aging and senescence. This development has suggested many possible targets for intervention.

A recent review described agents being tested in IPF clinical trials. Pirfenidone and nintedanib have been approved for use in IPF. Eight agents have had negative results in phase 3 trials, with one more trial in progress. Seven agents have had positive results in phase 2, with six additional trials in progress. A list of selected agents, with additional commentary, is also available.

The prevalence of IPF among Medicare beneficiaries appears to have more than doubled between 2001 and 2011, but the incidence has remained stable. It is not clear if this represents improved survival or earlier diagnosis, but that does match the period in which HRCT became more widely used. Prevalence increases with age and is more common in men.

Genetic susceptibility in IPF is complex. There are at least 10 genes and, for certain genes, there may be up to 100 different mutations.

One future approach to treatment may rely on removing senescent cells or blocking their effects. In a recent study, IPF lung tissue samples were stained for biomarkers of senescence, with p16 expression increasing with disease severity. Expression of the collagens and the matrix genes increased with IPF severity, but many of the senescence-associated pathways also were activated and correlated with severity. The secretome of senescent fibroblasts was shown to be fibrogenic, but senescent fibroblasts were selectively killed by a combination of dasatinib and quercetin. In bleomycin-treated mice, dasatinib plus quercetin improved pulmonary function and physical health. New classes of therapeutics are being developed that kill senescent cells, modulate their phenotype, block their secretome, or enhance immune function to increase their detection and elimination.

Other approaches to new therapeutics include mitochondrial-targeted therapies, stem cell therapies, telomerase reactivation, activation of proteostasis, and agents that target the epigenome. Eventually, perhaps some of these approaches will be used as combination treatment.

Dr Limper’s research group has been screening potential therapeutics by culturing fibroblasts with cytokines, testing, and looking for matrix generation. Their testing found unexpected drugs with antifibrotic activity, including someazole antifungal drugs, cyclooxygenase inhibitors, glucocorticoids, and vardenafil.

Large data analytics will be another tool for identifying novel pathways and targets, as well as a means of monitoring safety and efficacy. Gene expression analysis and mutational analysis can be coupled with artificial intelligence and supercomputing to select new pathways as targets for drug development.

Personalized Medicine in Idiopathic Pulmonary Fibrosis: Integrating Genetics in Clinical Trials

Imre Noth, MD, noted that personalized medicine refers to tailoring treatment for the individual patient. This approach is the foundation of therapy in oncology, for example, in which molecular markers on tumors determine which therapy should be used.

Precision or personalized medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. Applied to IPF, this approach may lead to the discovery of mechanisms and targets, identify individuals at risk for developing IPF, predict prognosis, and match treatments with patient characteristics. For example, telomeres and other markers identify patients who are likely to progress, and genome-wide association study has been used to identify variants associated with IPF susceptibility and mortality.

Some trials of personalized medicine in IPF include the WRAP-IPF trial and the CleanUp-IPF trial. The WRAP-IPF trial was based on data showing that patients with IPF have a higher rate of sliding hiatal hernias, which predisposes them to esophageal reflux. Information from retrospective databases suggested that treating reflux in patients with IPF might be beneficial. In the WRAP-IPF randomized trial, only patients with increased acid were enrolled and treated with Nissen fundoplication to prevent reflux of gastric juices. This approach is a form of personalized medicine in that the treatment was not offered to all patients, but only to patients exhibiting a specific symptom.

The CleanUp-IPF trial was based on earlier findings that showed patients with IPF who had a higher bacterial load had poorer outcomes, and antibiotic treatment might be beneficial. In the CleanUp-IPF trial, all patients receiving usual treatment were randomized to antibiotic treatment or no additional treatment. In addition, swabs of the oropharynx were examined to determine if the treatment should be personalized, that is, confined to a subset of patients with a high bacterial load.

The PANTHER-IPF Study, which compared the widely used regimen of prednisone, azathioprine, and N-acetylcysteine (NAC) with NAC alone and with placebo, found that the combination treatment was harmful. The study was continued with the remaining two arms, but it found no difference between the two groups. In a retrospective analysis, the researchers found, however, a significant interaction between response to NAC treatment and the single-nucleotide polymorphism (SNP) rs3750920 (TOLLIP), P=0.001 compared with placebo. Patients who were homozygous for the rs3750920 (TOLLIP) CC genotype had more hospitalizations, but patients who were homozygous for the rs3750920 (TOLLIP) TT genotype benefitted from NAC treatment across all outcome measures. This finding suggests that NAC may be effective therapy for one in four patients with IPF. The findings were confirmed in a large combined cohort.

This approach will be tested in a prospective trial with patients selected by genotype. The PRECISIONS Trial is a double-blind, randomized, placebo-controlled trial of 200 subjects with the TOLLIP rs3750920 TT genotype who will receive NAC or placebo for a 2-year duration. Background therapy with pirfenidone or nintedanib will be allowed. The primary endpoint will be categorical decline in the FVC or diffusing capacity of the lungs for carbon monoxide, first-time respiratory nonelective hospitalization, transplant, or death. To find 200 patients with this genotype, 800 to 1,000 patients will have to be screened. Researchers will screen...
The Role of Biomarkers in the Diagnosis and Treatment of Pulmonary Fibrosis—
A Call for Action

Naftali Kaminski, MD, reviewed recent progress on biomarkers and their use in diagnosis and predicting mortality. He went on to discuss what needs to be done for biomarkers to have a clinical impact.

A biomarker is a variable that is objectively measured and indicates a normal or pathogenic process. Biomarkers can be indicators of predisposition, like genetic markers. Other biomarkers are used in diagnosis or as prognostic indicators. Biomarkers should be simple, technically accurate, broadly reproducible in multiple cohorts, standardized, and have an acceptably risk. Ideally, biomarkers should reflect the pathophysiology of the disease.

A number of circulating biomarkers have been identified in patients with IPF: SP-A, SP-D, MMP-7, KL-6, MUC1, CCL18, YKL-40, anti-HSP70, CXCL13, SPP1, COMP, VCAM-1, peristin, MMP-1, LOXL2, matrix neoeptipotes, free mitochondrial DNA, microRNAs, and cancer markers (CA125 and CA19-9).

Dr Kaminski’s group has worked on MMP-7, a small protease that degrades casein, proteoglycans, and fibronectin and promotes epithelial cell migration and apoptosis. In patients with IPF, MMP-7 is highly expressed in epithelial cells in the lung, and MMP-7 blood levels are increased. Increased MMP-7 levels at presentation are associated with increased mortality. MMP-7 levels can also distinguish between patients with stable disease and those with an accelerated course. This relationship has been confirmed in cohorts around the world. Furthermore, MMP-7 may also be an indicator of early disease.

It is important to note that there have been no prospective studies on biomarkers in IPF. Ultimately, the challenge will be to standardize the procedure, but this biomarker is robust and reproducible, especially in combination with KL-6 and SP-D.

Another biomarker consists of 52 genes whose expression profiles in peripheral blood mononuclear cells are associated with transplant-free survival in patients with IPF. The 52-gene signature was used to classify patients from six cohorts into low-risk or high-risk groups with significant differences in mortality or transplant-free survival in each of the six cohorts. For most patients, the gene risk profiles were stable over 4 to 6 years of follow-up, but some treated patients showed a change in gene expression indicative of lower risk; this finding coincided with an improvement in FVC and may indicate response to therapy.

In other studies, Dr Kaminski’s group has found that BAL gene expression and lung gene expression are each indicative of mortality. In addition, lung gene expression may be diagnostic.

The blood biomarkers, as well as telomere length and the 52-gene signature, have been better validated. Change over time and in response to therapy is being studied. Some information is available about diagnosis, but it is not comparable to current clinical information. No biomarkers indicate disease burden or provide information about molecular pathways.

Biomarkers are not used clinically in IPF. Dr Kaminski suggested the creation of a partnership among industry, academia, and patient advocacy representatives to fund the generation, standardization, and performance of a basic IPF panel that would be part of the initial evaluation of every patient. He also encouraged patients to ask to be tested and to be informed of the results.

Finally, he asked scientists to move to more novel technologies to profile every cell in the lungs of patients with IPF, to better identify biomarkers that reflect the pathophysiology of the disease in individual patients and to apply precision medicine approaches.

Key Takeaways

- Future approaches to treatment may include removing senescent cells or blocking their effects. Other approaches to new therapeutics include mitochondrial-targeted therapies, stem cell therapies, telomerase reactivation, activation of proteostasis, and agents that target the epigenome.
- MMP-7, a small protease, is being studied as a potential biomarker. In IPF, it is highly expressed in epithelial cells in the lung, and MMP-7 blood levels are increased. Increased MMP-7 levels at presentation are associated with increased mortality. MMP-7 levels can also distinguish between patients with stable disease and those with an accelerated course, and it may also be an indicator of early disease. This biomarker is robust and reproducible, especially in combination with the biomarkers KL-6 and SP-D.
- Another biomarker consists of 52 genes whose expression profiles in peripheral blood mononuclear cells are associated with transplant-free survival in patients with IPF.
Mechanoregulation of Matrix Deposition and Fibrosis Progression

Daniel Tschumperlin, PhD, discussed his group’s studies on mechanical signaling between the matrix and fibroblasts in the propagation and progression of pulmonary fibrosis.

In a fibrotic remodeling lung, persistent activation of fibroblasts results in excessive deposition of extracellular matrix, which is an essential part of fibrosis. As the matrix becomes deposited, it changes the mechanical environment in the lung. His group developed a technique for sectioning lung tissue and measuring tissue stiffness by an atomic force microscopy microindentation method. In bleomycin-treated mouse lung and in tissue from humans with IPF, they measure a 6- to 10-fold change in the mechanical properties of the extracellular matrix in mature scar in the fibrotic lung.

His group and others have found that both normal fibroblasts and fibroblasts from patients with IPF in tissue culture can change their morphology, migratory capacity, and cytoskeleton, depending on the stiffness of the underlying matrix. On a soft matrix, the cells are quiescent and will undergo apoptosis if deprived of nutrients. On a stiff matrix, they organize the cytoskeleton to contract the matrix, produce much more extracellular matrix, and are more proliferative and more resistant to undergoing apoptosis.

Dr Tschumperlin described two pathways that mediate this process. One transcription factor that responds to matrix changes is myocardin-related transcription factor (MRTF) or MRTF1. On a soft matrix, MRTF staining in cells is diffuse, but if the cells are moved to a stiff matrix, MRTF accumulates in the nucleus. The canonical marker of a myofibroblast, α-smooth muscle actin (SMA), is upregulated on a stiff matrix but not on a soft matrix. A mechanotransduction pathway was defined involving Rho/Rho kinase, actin cytoskeletal remodeling, and MRTF, which coordinately regulate myofibroblast differentiation and survival. Animals deficient in MRTF did not develop α-SMA-positive cells or a robust fibrotic response with bleomycin treatment.

Other transcription factors, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), are key matrix stiffness-regulated coordinators of fibroblast activation and matrix synthesis. They translocate to the nucleus on a stiff matrix in fibroblast cell lines and in fibroblasts from patients with IPF. When both YAP and TAZ were knocked down in fibroblasts using an siRNA approach, all of the features of activated fibroblasts were attenuated. The intervention had little effect on cells on a soft matrix. Activating mutations in YAP and TAZ introduced into cells showed accumulation in the cell nucleus even when the cells were on a soft matrix. When these mutations were introduced into a mouse model, the lungs quickly filled with activated cells laying down extracellular matrix. Other groups have shown that YAP and TAZ are important in fibrosis in other organs, including the liver, kidney, and skin.

Dr Tschumperlin’s group also tried introducing siRNA to YAP and TAZ into bleomycin-treated animals but found that it resulted in more lung injury and more collagen. Apparently, YAP and TAZ are important in wound healing in other cells. An approach that specifically targets YAP and TAZ in fibroblasts in the lung may be more effective.
Epithelial-Mesenchymal Interactions in Pulmonary Fibrosis
Kevin Kim, MD, explained that much of what is known about epithelial-mesenchymal interactions in the lung is derived from the studies of lung development. Major pathways whose role in development have been elucidated include: the fibroblast growth factor (FGF) family, Wnt/β-catenin, Shh/Gli (Hedgehog), TGF-β superfamily (including bone morphogenetic protein [BMP] and activins), and the extracellular matrix (ECM)-integrin pathway.

Dr Kim’s group has focused on how epithelial cell dysfunction can cause pulmonary fibrosis. Activated epithelial cells secrete profibrotic factors leading to mesenchymal cell activation and proliferation. New research on three important pathways challenges the previous dogma regarding epithelial-mesenchymal interactions in fibrosis: TGF-β signaling, Hedgehog, and growth factor receptor tyrosine kinase.

Both epithelial cells and mesenchymal cells are required for TGF-β activation during fibrosis. TGF-β is secreted in an inactive form by epithelial cells and by many other cell types. It binds to the extracellular matrix through a specific binding protein. When it is activated by integrins, it can bind to its receptor on its target cells (mainly fibroblasts), resulting in fibroblast activation and fibrosis. The integrin initially described, αvβ6, is only expressed in the lung in epithelial cells, so this seemed to be a straightforward process of epithelial cells as the site of TGF-β activation and fibroblasts as the main site of response to TGF-β. More recent research has found that this process may be more complicated because several other integrins, expressed on many cell types, can lead to TGF-β activation. In addition, it is now thought that TGF-β binding to a stiff matrix on one side and a contractile force on the other side leads to greater TGF-β activation.

Hedgehog, produced by epithelial cells, leads to mesenchymal proliferation through the Smoothened/GLI signaling pathway during lung development. After injury there is upregulation of GLI, indicating an upregulation of Hedgehog, suggesting that Hedgehog has a role in mesenchymal cell proliferation and accumulation during fibrosis. More recently, it has been shown that Hedgehog and GLI are present at high levels in uninjured lung, and that Hedgehog suppresses mesenchymal proliferation, an unexpected result.

The growth factor receptor tyrosine kinase pathway is complex. The fibroblast growth factor family includes 20 different ligands and four different receptors that all signal in different ways. The pathway has profibrotic activities, including fibroblast growth and fibroblast activation, but some of the FGF pathways are now known to be antifibrotic.

Finally, Dr Kim discussed some recent research on the epithelial-mesenchymal transition (EMT), the ability of epithelial cells to become mesenchymal-like with inhibition of some epithelial features and acquisition of some mesenchymal features such as migration, invasion, and production of fibrotic matrix. Several groups have studied if EMT occurs during fibrosis using fate-mapping strategies, with conflicting results. Dr Kim’s group has shown that atypical epithelial cells can express procollagen, a hallmark of an activated myofibroblast. Single-cell RNA sequencing also showed that one type of epithelial cell had marked upregulation of type I collagen. Dr Kim’s group deleted the gene for type I collagen in a transgenic mouse and found marked reduction of bleomycin-induced pulmonary fibrosis, demonstrating an important role for epithelial cell-derived type I collagen in this model.

Immune and Inflammatory Cells in Idiopathic Pulmonary Fibrosis
Erica Herzog, MD, PhD, described some concepts about adaptive and innate immunity in the context of IPF.

About 10 years ago, a study was published showing that relative to control patients, IPF patients had fewer regulatory T (Treg) cells, defined by certain intracellular and surface markers, in their peripheral blood and BAL fluid. Further, the Tregs in IPF patients showed functional impairment that correlated with disease severity. Dr Herzog’s group found an abnormal Treg population that was associated with reduced event-free survival. When these cells were injected into mice, the mice developed mild IPF. When an antibody-mediated method was used to remove Tregs in mice, there was an increase in proinflammatory mediators as well as augmented lung remodeling and collagen accumulation. Other studies found abnormally activated, hyperstimulated, somewhat senescent helper T cells in the blood of patients with progressive IPF. However, attempts to treat IPF with agents that suppress the adaptive immune system have not been successful.

The innate immune system includes macrophages, monocytes, mast cells, dendritic cells, and others. Innate immune cells are driven by activation of pattern recognition receptors. They respond to either pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). PAMPs are repeating patterns that are found in bacteria, like lipopolysaccharides or certain sugars found in gram-positive bacteria, or unmethylated CpG islands in bacterial DNA. DAMPs are either intracellular substances that are released after necrosis or cleaved extracellular matrix. Dr Herzog’s group found that mitochondrial DNA, which functions as a DAMP, is released with cell injury and increased in the blood of patients with rapidly progressive IPF. Patients with higher concentrations of mitochondrial DNA have poorer outcomes.

Dr Herzog’s team studied the immune system response to these ligands. They found that in patients with IPF, monocytes and macrophages at baseline are hypermigratory. Compared with cells from healthy controls, they are also abnormally activated and express markers of alternative activation. These cells are also profibrotic and found in higher concentrations in patients with progressive IPF compared with patients with stable IPF.

In a culture system, they found that adding the activated macrophages resulted in accumulation of fibroblasts. They had similar results in a bleomycin mouse model, in which they observed an increase in accumulation of proliferative fibroblasts, which they characterized as immortal. In these studies, macrophages did not participate in the specification of the fibroblast cell fate.

In summary, cells of the innate immune system may be critical regulators of IPF by orchestrating existing fibrotic responses. They may be useful targets for future drug development.

Key Takeaways
- Young adults with certain subtypes of the rare genetic disease Hermansky-Pudlak syndrome develop pulmonary fibrosis. Studies in these patients and in mice have explored the roles of oxidative stress, increased TGF-β pathway activation, and the secretory factor MCP1 in the development of pulmonary fibrosis
• Both normal fibroblasts and fibroblasts from patients with IPF in tissue culture can change their morphology, migratory capacity, and cytoskeleton depending on the stiffness of the underlying extracellular matrix. Two pathways mediate this process. One consists of Rho/Rho kinase, actin cytoskeletal remodeling, and MRTF, which coordinately regulate myofibroblast differentiation and survival. The other consists of the transcription factors, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), which are key matrix stiffness-regulated coordinators of fibroblast activation and matrix synthesis.

• Studies of lung development have elucidated its major pathways: the fibroblast growth factor family, Wnt/β-catenin, Shh/Gli (Hedgehog), TGF-β superfamily (including BMP and activins), and the extracellular matrix (ECM)-integrin pathway. These also play roles in epithelial-mesenchymal interactions in pulmonary fibrosis.

• In patients with IPF, abnormally activated monocytes and macrophages are hypermigratory, profibrotic, and found in higher concentrations in patients with progressive IPF compared with patients with stable IPF. These cells may be useful targets for future drug development.

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Treating Idiopathic Pulmonary Fibrosis: Information for Patients and Caregivers

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Patients and caregivers attending PFF Summit 2017 comprised a lively, well-informed, and deeply interested group determined to learn and share at the meeting. Attendees heard advice from practicing clinicians on interpreting symptoms, concomitant conditions, and the benefits of pharmacologic therapy and nonpharmacologic therapies, including oxygen therapy, pulmonary rehabilitation, and palliative and advanced care. At every scientific session, as well as several intimate roundtables, patients and caregivers were invited to ask questions and share their opinions.

A clear theme emerging from the Summit was the need for improved communication and information sharing, both within the PF community and out to the general medical community; a recent survey reflected this need.1 Patients agreed that PFF should provide significantly more channels for information about pulmonary fibrosis to family physicians, particularly those in rural locations, and newly diagnosed patients and their caregivers.

Many patients reported having waited years before receiving an accurate diagnosis or finding a knowledgeable practitioner. Self-education about pulmonary fibrosis, determination, and creativity in finding and maintaining appropriate medical care were prominent issues among attendees; some had found their physician by researching published papers, others by seeking out academic centers. At least one patient reported traveling 4 hours for her care at the nearest PFF Care Center Network site. The PFF plans to designate additional Care Center Network sites around the United States in 2018.
Practical Aspects of Pharmacotherapy

Three speakers shared basic information and best practices from their centers on using medication for ILD, including managing side effects and getting help to pay for treatment. Joyce Lee, MD, gave an overview of the treatment of ILD. First, it is critical to get an accurate multidisciplinary diagnosis. Once that is established, all patients should receive education in self-management strategies. They should be referred for pulmonary rehabilitation and be prescribed oxygen therapy if needed. The next step is treatment with “disease-targeted therapy.” This approach includes management of symptoms, such as cough or breathlessness; identification and management of important comorbid disorders; prevention, such as getting vaccinations; pharmacologic therapy; and participation in a clinical trial.

An accurate diagnosis is the first step to selecting the appropriate medication for the disease. Treatment of hypersensitivity pneumonitis begins with finding and removing the antigen and perhaps treating with immunosuppressants; lymphangioleiomyomatosis is often treated with sirolimus; and IPF may be treated with pirfenidone or nintedanib. As suggested, there is no single medication for patients with interstitial lung disease or pulmonary fibrosis. Therapy is specific to the underlying disease process.

Treatment guidelines published in 2015 review several medications that should and should not be used, based on prior investigations. Nintedanib and pirfenidone have conditional recommendations for use in IPF.

Dr Lee reviewed the safety and efficacy data from the clinical trials for both nintedanib and pirfenidone, noting that they are roughly equivalent in efficacy, but have different tolerability profiles. While these therapies are not curative, they slow the progression of IPF as measured by change in FVC.

Wendi R. Mason, ACNP-BC, discussed safety and managing the side effects of nintedanib and pirfenidone. For nintedanib, the most common side effects related to the drug were diarrhea, nausea, and reduced appetite. For diarrhea, she suggested that patients stay hydrated and use antidiarrheal medications, if necessary. Dose adjustment and titration of medication may also improve tolerability. For nausea and other GI complaints, she suggested antiemetics and proton pump inhibitors. Other important side effects observed in the nintedanib clinical trials include bleeding and elevated liver enzymes. In practice, bleeding is rare, probably because anticoagulants are avoided, but patients should alert their doctors if they have pink urine or black, tarry stools. Liver enzymes must be monitored regularly. Nintedanib may interact with other drugs, so any new medications should be discussed.

Ms Mason also discussed safety and tolerability data from the pirfenidone RECAP trial, a long-term, open-label study. Nausea and GI complaints were common side effects, followed by diarrhea and rash. Noteworthy side effects include elevated liver enzymes, so regular monitoring is necessary.

Nausea can be prevented by taking the medication as directed, three times per day with a meal. Taking the medication with too little food may be the source of the GI distress. Again, dose reduction and slow titration up to the full dose is another possible solution, as is using a proton pump inhibitor or antiemetics. Patients taking pirfenidone may develop a rash if they have too much exposure to sunlight. They should use sunblock and protective clothing. If the rash is severe, a drug holiday may be appropriate.

Drug interactions are also a concern. An important drug to avoid is high-dose ciprofloxacin, due to its effect on the metabolism of pirfenidone.

At every visit, patients should discuss any side effects they are having. Many side effects can be managed. In addition, many side effects occur at treatment initiation or when the dose is increased and may resolve over time. If side effects remain a problem, there is always the possibility of switching drugs.

Another concern with both medications is their cost. Anne Turner, RN, BSN, explained that financial assistance is available for some people. Commercial insurance policies commonly cover a significant portion of the cost of the medication, as do Medicare and Medicaid. Each patient should discuss his or her prescription coverage when pursuing treatment with either pirfenidone or nintedanib.

Private foundations, such as PSI Inc and the HealthWell Foundation, offer grants to help patients. Both drug manufacturers also have programs for assisting patients: the Genentech Access to Care Foundation and the Boehringer Ingelheim Cares Foundation Patient Assistance Program. The drug manufacturers also have programs to assist people with commercial insurance with their co-pays.

Each program has an income limit. In general, if the household adjusted gross income is over $150,000 per year, there is a chance the patient is not going to be able to find any assistance unless special financial circumstances can be explained. Each physician’s office has a different process for referring patients for assistance. It is important for patients to find out who is responsible for doing the referrals, what the steps in the process will be, and how long each step will take.

If there is no insurance, the doctor will refer the patient to the manufacturer’s program. Most people have some pharmacy benefit insurance. In that case, the doctor’s office must request prior authorization from the insurance company. Usually these are approved, but if not, the physician may appeal. Once the authorization is approved, the pulmonologist’s office sends the prescription to a specialty pharmacy because these medications are handled by only a select group of pharmacies. The pharmacy files a test claim with the insurance company, which will inform them of the co-pay. The pharmacy will contact the patient with this information. Co-pays can range from $48 per month to $4,800 per month or more. If the co-pay is high, the pharmacy will refer the patient to the manufacturer’s co-pay card program or to one of the private foundation programs.

Some advice for patients: Do not be shy. On the phone, always ask for the caller’s name, what their role is, what the next steps are, and when you should expect to hear from them. Be available by phone or at least have a working voicemail that you check regularly. If the patient doesn’t respond to requests for information, the process will stop. Complete forms and submit them promptly. Keep information organized and near the telephone. Keep in touch with the person in the doctor’s office who manages this process, and keep a list of contact information for that person, the pharmacy, and the foundations. If you don’t get a response, don’t wait. Call them. Don’t be afraid to be a squeaky wheel.
Oxygen, Pulmonary Rehabilitation, and Symptom Management

Susan Jacobs, RN, MS, described the use of oxygen therapy. She explained that the thickening of the interstitial wall impairs oxygen uptake in the lungs. Using oxygen can decrease or prevent shortness of breath, decrease the stress on the heart, lower pulmonary hypertension, and, in some patients, improve sleep quality. Oxygen is prescribed for patients whose oxygen levels are low. Being short of breath may mean that breathing requires exertion, but it does not necessarily mean that oxygen levels are low. Patients are tested in three conditions: at rest, with activity, and during sleep; they also may sometimes be tested at altitude. There may be different prescriptions for each condition.

Different types of oxygen systems exist. Ms Jacobs recommended the Pulmonary Paper, which publishes an annual review of oxygen concentrators (www.pulmonarypaper.org). She also recommended using Oxymizer cannulas when higher flow rates are required. The Supplemental Oxygen Guide, published by the LAM Foundation and the COPD Foundation, has excellent information for patients newly on oxygen.

Pulmonary rehabilitation includes disease education, exercise training, and behavior change. Trina Limberg, BS, RRT, explained that the goals of rehabilitation are to help the patient control and alleviate the symptoms, improve activity levels and exercise tolerance, and encourage self-reliance and independence. Generally, physicians refer patients to rehabilitation when they are short of breath, have symptoms that are challenging to manage, and experience loss of activity.

Pulmonary rehabilitation has regional variations, but it usually runs for 6 to 12 weeks and may include physical therapy and exercise physiology. It may include a therapist to help with stress reduction, coping, and behavior changes. Supervised exercise helps patients learn about and improve their capabilities in a supportive setting. Oxygen assessment is an important component; about 60% of patients have modifications to their oxygen prescription after a thorough evaluation in rehabilitation. As exercise abilities improve, oxygen prescriptions are changed to match.

Mary Strek, MD, FCCP, discussed three common symptoms: cough, shortness of breath, and fatigue. Cough impairs quality of life, but it is not necessarily correlated with the severity of the underlying disease. Common triggers include talking, laughing, eating, exertion, and taking a deep breath. Known causes include rhinitis or sinusitis in the upper airway; asthma, bronchitis, or emphysema in the lower airway; increased mucus; GERD; and infection. Each of these can be evaluated and treated.

Shortness of breath worsens as IPF progresses and is a marker of worsening outcome. The many possible causes include inability to exchange oxygen, anemia, increased work of breathing, muscle weakness, blood clot, anxiety/depression, and pulmonary hypertension. Careful evaluation and treatment are critical.

Fatigue is common in IPF. It may be due to an associated condition such as low thyroid function, sleep apnea, coronary artery disease, anxiety, or depression. It may also be a side effect of an antifibrotic medication, particularly if it started with medication initiation. These underlying causes should be evaluated and treated. Exercise and pulmonary rehabilitation may help, as well as psychotherapy and support groups for anxiety and depression.

Cough, dyspnea, and fatigue are common in patients with IPF. They may be caused by IPF or by an associated condition. A stepwise approach to evaluation and treatment should be taken and supportive therapies, including pulmonary rehabilitation, should be added early.

Key Takeaways

• It is critical to get an accurate multidisciplinary diagnosis. All patients should also receive education in self-management strategies. They should be referred for pulmonary rehabilitation and be prescribed oxygen therapy if needed.

• Disease-targeted therapy includes management of symptoms, such as cough or breathlessness, identification and management of comorbid disorders, pharmacologic therapy, and participation in clinical trials.

• The 2015 treatment guidelines provide conditional recommendations for nintedanib and pirfenidone, which are equivalent in efficacy but have different tolerability profiles. Both drugs are expensive. Financial assistance is available through private foundations and the drug manufacturers, but the process can be complicated. Patients must be persistent.

References


POST-TEST CME/CE QUESTIONS

1. A serious complication associated with bronchoscopic cryobiopsy is
   A. Bleeding
   B. Opportunistic infection
   C. Pulmonary embolism
   D. Septic shock

2. Approximately what percentage of patients have a family history of pulmonary fibrosis?
   A. 10%
   B. 20%
   C. 30%
   D. 40%

3. Telomerase pathway mutations are associated with
   A. Fibroblast apoptosis
   B. Lower rates of comorbid disorders
   C. Premature gray hair
   D. Recessive inheritance

4. The PANTHER-IPF trial was a randomized, placebo-controlled trial comparing combination treatment with prednisone, azathioprine, and N-acetylcysteine (NAC) vs NAC monotherapy in patients with IPF.
   What were the results of this trial?
   A. NAC monotherapy was beneficial for patients with IPF, but combination treatment was not
   B. Combination treatment was beneficial for patients with IPF, but NAC monotherapy was not
   C. Both monotherapy and the combination treatment were beneficial for patients with IPF
   D. Neither monotherapy nor combination treatment were beneficial for patients with IPF

5. The Genetic Information Nondiscrimination Act
   A. Mandates coverage for genetic testing in patients with IPF
   B. Prohibits discrimination in health insurance
   C. Prohibits discrimination in life insurance
   D. Prohibits discrimination in disability insurance

6. Which of these is associated with improved survival in patients with IPF?
   A. Abnormally activated Treg cells
   B. Combination treatment with prednisone, azathioprine, and N-acetylcysteine
   C. A promoter polymorphism in the MUC15 gene
   D. Shorter telomere length in white blood cells

7. In what percentage of cases can a diagnosis of IPF be based on high-resolution computed tomography?
   A. <15%
   B. 10%
   C. 50%
   D. >90%

8. Which drug is associated with rash on exposure to sunlight?
   A. Nintedanib
   B. Omeprazole
   C. Pirfenidone
   D. Prednisone

9. Clinical trials of nintedanib and pirfenidone have demonstrated that
   A. Both drugs reverse lung fibrosis in patients with IPF
   B. Both drugs slow progression of IPF
   C. Nintedanib is more efficacious than pirfenidone
   D. Elevated liver enzymes were observed in the nintedanib trials but not in the pirfenidone trials

10. When should patients be referred for pulmonary rehabilitation?
    A. All patients with IPF should be referred for pulmonary rehabilitation at the time of diagnosis
    B. Referral to pulmonary rehabilitation should be deferred until patients are placed on the waiting list for lung transplantation
    C. Pulmonary rehabilitation is appropriate for patients who experience a functional decline
    D. Pulmonary rehabilitation is only appropriate for patients who require more than 2 liters of oxygen at rest

Overall, the program met my expectations.

The information presented will help me improve patient care/my job performance.

The information presented increased my awareness/understanding of the subject.

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

__________________________________________________________________________________

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

__________________________________________________________________________________

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

__________________________________________________________________________________

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?

Yes. E-mail address: ____________________________

No. ____________________________

I don’t plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what system barriers are (eg, institutional systems, lack of resources, etc).

__________________________________________________________________________________

EVALUATION FORM Please indicate your profession/background: (check one)

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APRN/NP ☐ PharmD/RPh ☐ Resident/Fellow Researcher ☐ Administrator ☐ Student ☐ Other: __________

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

__________________________________________________________________________________

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?

Yes. E-mail address: ____________________________

No. ____________________________

I don’t plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what system barriers are (eg, institutional systems, lack of resources, etc).

__________________________________________________________________________________

LEARNING OBJECTIONS: Having completed this activity, you are better able to:

StrONGLY AGREE AGREE SOMEWHAT AGREE DISAGREE STRONGLY DISAGREE

Describe the role of personalized medicine in the treatment of pulmonary fibrosis.

Demonstrate an understanding of the impact of genetic mutations on the course of idiopathic pulmonary fibrosis (IPF) and the risk of IPF in first-degree relatives.

Describe recent advances in pulmonary fibrosis pathogenesis, including research in aging and senescence, oxidative stress, matrix stiffness, biomarkers, and the innate immune system.

Engage a multidisciplinary care team to treat patients with IPF, by referral or collaboration.

Appropriately manage common symptoms of patients with IPF.

Appropriately refer patients with IPF for nonpharmacologic therapy.

Identify patients with IPF and their relatives who should be considered for referral for genetic counseling.

Select patients with IPF for referral for treatment of gastroesophageal reflux and obstructive sleep apnea.

Evaluate clinical trial data supporting the efficacy and safety of pirfenidone and nintedanib.

Select pharmacologic therapy for patients with IPF.

OVERALL EVALUATION The information presented increased my awareness/understanding of the subject.

The information presented will influence how I practice/do my job.

The information presented will help me improve patient care/my job performance.

The program was educationally sound and scientifically balanced.

Overall, the program met my expectations.

I would recommend this program to my colleagues.

Mary Armanios, MD

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Timothy S. Blackwell, MD

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Gregory P. Cosgrove, MD, FCCP

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Kevin R. Flaherty, MD, MS, FCCP

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Naftali Kaminski, MD

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Lisa H. Lancaster, MD, FCCP

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Jeffrey M. Trent, PhD

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Paul Wolters, MD

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

Lisa Young, MD

Author demonstrated current knowledge of the topic.

Author was organized in the written materials.

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

Please provide additional comments pertaining to this activity and any suggestions for improvement.