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Disease Management and Effective Clinician-Patient Partnering

This continuing medical education (CME/CE) supplement was developed from faculty presentations at the PFF Summit 2015: From Bench to Bedside, November 12-14, 2015, in Washington, DC.

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The opinions expressed are those of the faculty and do not necessarily reflect the views of the accredited provider, supporter, or the Publisher.
Idiopathic pulmonary fibrosis (IPF) is the most common and lethal of the idiopathic interstitial pneumonias. Although rare enough to be considered an orphan disease, IPF still accounts for 15,000 to 40,000 deaths per year in the United States—and the incidence and mortality of IPF are increasing. The disease is characterized by insidious onset and progressive decline in lung function due to fibrosis of the lung parenchyma. Despite the recent approval of two new drugs (pirfenidone and nintedanib), each shown to slow the decline in lung function, there remains no cure for IPF. Indeed, the prognosis of IPF is poor, with median survival estimates of 3.8 years or less. The only treatment shown to improve survival is lung transplantation. The availability of new therapies shown to slow disease progression highlights the need for earlier diagnosis and intervention in IPF. It has been suggested that a “window of opportunity” may exist during which treatment can promote optimal outcomes. Furthermore, delays in diagnosis may limit treatment options, as well as increase costs, reduce patient quality of life, and impact survival.

Learning Objectives
After reading and studying this journal supplement, participants should be better able to:
- Employ a multidisciplinary care team approach for IPF to enhance patient outcomes
- Review clinical trial data supporting the efficacy and safety of pirfenidone and nintedanib
- Select appropriate pharmacologic therapy for patients with IPF
- Communicate with patients with IPF and provide effective disease-state education

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Patients with PF remain burdened by considerable unmet needs—in particular, the need for therapy that reverses disease progression. This is a hopeful time, however, because academia and industry are engaged, patients and advocates recognize areas where they can participate, and the FDA is providing guidance on improving efficiency and patient-centered outcomes.

Reference


## Lung Transplantation: Nuts and Bolts or...This Is Nuts, I Am Going to Bolt

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Lung transplantation remains a potentially life-saving therapy for patients with end-stage lung disease, and anecdotal evidence suggests excellent results in many patients. Patients who have done well experienced improved dyspnea and gas exchange. Over the last decade in the United States, lung transplantation procedures increased from 1,200 to 2,000 per year, and nearly all of this growth involved patients with interstitial lung disease (ILD).1

A shortage of donor lungs has required the creation of a waiting list. Patients are listed using a lung allocation method that rates them according to need based on a lung allocation score. Only a small fraction of patients with idiopathic pulmonary fibrosis (IPF) are treated with lung transplantation; there are an estimated 100,000 to 200,000 patients with IPF in the United States, but only about 1,000 adults with ILD undergo lung transplantation each year.

Transplantation is considered suitable for patients with a <50% risk of death (within 2 years without lung transplant), who are otherwise surgically fit, and with a high likelihood of 5-year survival.2 Immediate referral for transplant is recommended for patients with ILD who have a forced vital capacity (FVC) <80% or any oxygen requirement, among other criteria. However, referral does not mean immediate placement on a waiting list; referred patients may wait 6 months to a year or longer before being listed.

Bilateral transplants have demonstrated improved outcomes compared with single-lung transplants in IPF,3 but patients who placed themselves on the “bilateral-only” list risked waiting longer for surgery.4 A higher percentage of patients die awaiting bilateral transplants. Finally, a trend toward performing transplants in older and sicker patients may lead to worse outcomes in the coming years.
Dr Brown began by reviewing the last 2 decades of clinical trials in pulmonary fibrosis. Pioneering clinical trials may not have shown benefit, and in some cases even caused harm, but they established the possibility of overcoming the many barriers to working on this severe and rare disease. There has been much progress. In 1995, there were no companies with drug discovery programs in IPF and no drugs in development. By 2015, there were 41 companies with programs in IPF and 54 agents in development. The May 29, 2014, issue of The New England Journal of Medicine contained three articles reporting on clinical trials in IPF.\(^5\)\(^7\)

Today, researchers have recognized the problem, described and defined it, and even slowed its progression with new therapies. But, as Dr Brown noted, “We’ve got a lot of work in front of us.”

Previous clinical trials used either the surrogate marker FVC or a composite endpoint of hospitalization and mortality. Stakeholders are allied in recognizing the need for new endpoints that directly assess benefit to patients while permitting adequately powered clinical studies. The result is broad alignment on patient-reported outcomes (PROs). However, PROs have not yet been as sensitive to treatment effect as FVC. It is essential to identify an outcome that is sensitive to treatment effect and supports innovative research.

Dr Woodcock concisely summarized the issue: “How do you move forward from the drugs we have, to the next generation of studies where PROs are the endpoint, and get regulatory approval?” The FDA is focused on benefit to the patient, which means improving how the patient feels, functions, or survives. In past studies, FVC was considered similar enough to breathing to serve as a surrogate endpoint, but FVC does not directly measure benefit to the patient. Patients with pulmonary fibrosis cited convulsive cough as one of the most troubling symptoms, and Dr Woodcock noted that it might be possible to measure cough using a wearable device. In this scheme, quantifying the frequency and severity of cough could serve as an effective PRO. Bruce Snyder, a patient with pulmonary fibrosis, confirmed that cough, along with shortness of breath and quality of life, are the most important issues for him. PROs hold another advantage—they may demonstrate treatment effects more quickly than FVC, which can take months to change.

Certainly, the FDA will accept PROs, but these endpoints must be validated to ensure that measurements are meaningful for the treatment of the disease and the patient. The development of validated PROs is costly; the National Institutes of Health does not fund non-discovery research, and pharmaceutical companies do not want to bear the burden of PRO validation costs. The advocacy community may be able to help in this regard by initiating and funding the research to validate PROs for use in clinical trials.

Recruiting patients with rare diseases poses a challenge because such patients are few and are widely distributed throughout the country. Dr Montgomery noted that 1% of all patients may choose to participate in clinical trials, so if there are 80,000 new cases diagnosed per year, that provides enough patients for two trials. How can clinical trial enrollment be increased in pulmonary fibrosis? The Cystic Fibrosis Foundation created a network of 150 care centers that supports clinical trials in cystic fibrosis. Patient enrollment is only the first step in supporting trials. Clinical care at different sites must be consistent for the trial results to be meaningful. Recognizing the many sacrifices of patients who participate in trials, the physicians applauded them as heroes for putting their health and even their lives at risk to benefit the IPF community.

The presence of new drugs in the pipeline raised the issues of combining agents in trials and whether or not it is ethical to have a placebo group. Dr Montgomery noted that clinical trials of new agents for patients with cystic fibrosis allow background medications in the treatment and placebo groups. Another important consideration, however, is that using multiple agents increases the likelihood of adverse events. One strategy is to perform smaller trials of 30 to 40 participants to evaluate the tolerability of combination therapies and to learn how to manage side effects before launching a large trial. Other concerns likely to affect future trials include sharing negative outcome data and preventing the costly pitfalls of data dredging.

Patients remain concerned about the difficulty of obtaining a quick and accurate diagnosis. There is a great need for physician education to improve detection of this rare disease. Clinician scientists are engaged in trying to develop more accurate and simple ways to achieve diagnosis, and the Pulmonary Fibrosis Foundation is focused on outreach and education.

References

An Overview of Personalized Medicine for Pulmonary Fibrosis

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Personalized medicine (also called precision medicine) aims to integrate genomics into patient care. This process has been made possible, in part, because of the increased capacity and speed of genomic sequencing. Many countries, including the United States, the United Kingdom, and China, have formal initiatives to sequence the genomes of up to one million people in different clinical domains. The long-term goal is to document genomic data in each patient's electronic medical record.

Employing personalized medicine in idiopathic pulmonary fibrosis (IPF) may improve patient care in numerous ways. First, identifying a reliable molecular biomarker would aid diagnosis, which remains a clinical challenge in IPF. Biomarkers also contribute to tracking drug efficacy in clinical trials. Second, genomics may provide specific molecular signatures for IPF that would help in patient stratification for different treatments and predict response to therapy or the likelihood of adverse events. Finally, genetic markers may identify at-risk patients prior to the onset of disease and allow surveillance and intervention. The discovery of many pertinent gene variants has led to increased insight into the disease mechanism. Further, understanding which patients have a poor prognosis will also allow the prioritization of lung transplant candidates.

To realize the full benefits of genomics will require the collection and organization of genomic, phenotypic, and clinical data. Indeed, studies of the genes involved in IPF have thus far depended on patients who are willing to share both clinical and personal data. Four institutions currently have programs that use precision medicine for the early detection and prevention of IPF. These teams use a multidisciplinary strategy that integrates molecular medicine and clinical practice to guide individualized patient care. Continued development and broader dissemination of these strategies will improve the outlook for patients with IPF and their families.

Genetics of Pulmonary Fibrosis

Genetics can illuminate the pathogenesis of disease, identify people who are protected or at risk, and even uncover how individual patients might respond to a specific therapy. Emerging genetic methods, such as personal genome next-generation sequencing and genome-wide association studies, have revealed more than 100 gene variants involved in IPF. Common gene variants include MUC5B, which codes for a mucin glycoprotein; DSP, which is involved in cell-cell interaction and maintaining the integrity of the lung epithelium; and TOLLIP, a ubiquitin-binding protein and an important regulator of the innate immune response. Research into these genes and their products points to important pathophysiological mechanisms in IPF. The fact that some people with IPF do not have genetic factors associated with IPF suggests that other genes or mechanisms of disease have not yet been identified.

Rare gene variants have been identified in kindred studies and through investigation of familial disease. For example, whole exome sequencing and analysis was performed on genomic DNA samples from 99 probands with familial pulmonary fibrosis of unknown genetic cause. Rare genes discovered in this process included two that code for surfactant proteins (SFTPA2, SFTPC) and two related to telomere length (TERT, TERC). These gene variants are autosomal dominant, and the patients are more likely to be male. However, even within the same family, the disease course may differ.

Recent research has implicated two genes related to telomere function in IPF, RTEL1 and PARN. In searching for the new genes, researchers expected the frequency of these genes to be rare, less than 1 per 100,000 people with IPF. The investigators used exome sequencing to examine novel genes by looking for loss-of-function mutations that would decrease protein activity. RTEL1 and PARN emerged from this screen. The RTEL1 gene product maintains telomere length, whereas PARN plays a role in silencing maternal gene expression during oocyte maturation. PARN had not previously been linked to disease, but since this report it has been linked with dyskeratosis congenita.

There are now six different telomere-related genes that predict IPF in families, with high penetrance. And telomere length may be a biomarker that is relevant to underlying pathogenesis and survival in patients with IPF.

Molecular and Cellular Biomarkers of Pulmonary Fibrosis

Biomarkers are clinical variables that may predict disease development, improve diagnosis, or predict response to therapy. Optimally, a biomarker is simple to use, noninvasive, reproducible and accurate, and reflective of disease pathogenesis. Advances in pulmonary fibrosis genetics in the last decade may soon identify biomarkers that are suitable for improving IPF diagnosis, but biomarkers that demonstrate treatment response (prognostic biomarkers) in IPF have been elusive.

The pathogenesis of IPF involves lung epithelial cell dysfunction, fibroblast and matrix accumulation in the lungs, and immune dysregulation. Although all of these biological processes may yield biomarkers, circulating biomarkers are the most convenient because they are easily accessible in the blood. Among potential circulating biomarkers, matrix metalloproteinase-7 (MMP7) is currently the most validated, although MMP7 levels do not change dramatically during disease progression or following treatment.

Matrix remodeling involves the degradation of collagen and release of collagen degradation products (CDPs). CDPs have been measured in prospectively collected serum samples by using antibodies that recognize novel MMP-degraded protein epitopes. In the Prospective Study of Fibrosis In the Lung Endpoints (PROFILE), some CDPs differentiated between healthy controls and patients with IPF and between patients with stable versus progressive disease. Although promising, this new technology requires further validation and standardization.

More recently, gene expression profiles in peripheral blood mononuclear cells have been studied using microarray technology. Using this method, 52 genes were associated with transplant-free survival in five cohorts. Of these genes, 41 were significantly correlated with changes in forced...
vital capacity ($P<0.05$). Extending the microarray method to bronchoalveolar lavage samples also yielded prognostic gene profiles. Additionally, combining this genomic signature with a patient’s GAP score (which uses gender [G], age [A], and two physiologic parameters [P] to score prognosis) improved prognostic accuracy over either indicator alone. Even formalin-fixed lung biopsy samples can now be used to generate gene expression data.

Currently, researchers have characterized outcome-related changes in proteins, cells, and genes that predict prognosis in patients with IPF. Building on these results may provide biomarkers that improve diagnosis and can be used to measure responses to therapy.

**References**


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**Improved Understanding of Pulmonary Fibrosis Pathogenesis: Highlighting Recent Advances in Basic Science Research**

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For the PFF Summit 2015, Drs Andrew Tager and Erica Herzog convened a session to highlight recent advances in understanding the pathogenesis of pulmonary fibrosis entitled “Basic Science: Lung Remodeling and Regeneration.” The session drew attention to three areas of biology that are increasingly appreciated as key drivers or modulators of pulmonary fibrosis: (1) the role of aging in general, and mitochondrial dysfunction in particular; (2) the role of the abnormal mechanical characteristics of fibrotic tissues, such as increased tissue stiffness, as contributors to, rather than simply consequences of, fibrosis; and (3) the role of cells of the innate immune system, such as macrophages, in orchestrating fibrotic responses to tissue injury.

**Fibrosis as a Disease of Aging and Mitochondrial Dysfunction**

Drs Ana Mora and Marta Bueno recently discovered subcellular clues that suggest why some people develop chronic diseases as they age. Their research found that mitochondria are sensitive to aging and stress and are more likely to be affected in cells with high energy requirements, such as neurons (eg, Parkinson’s disease), heart, and the type II alveolar epithelial cells (AECs) affected in idiopathic pulmonary fibrosis (IPF). AECs consume large amounts of energy and contain about half of all mitochondria in lung tissues. The new research demonstrated that the AECs in fibrotic areas of IPF lung tissue accumulate dysfunctional mitochondria and that these organelles are in the same cells that have endoplasmic reticulum (ER) stress. Although the stressed cells initiated autophagy—a process that clears dysfunctional mitochondria—clearance was impaired in the AECs, resulting in mitochondrial accumulation. Together, aging and ER stress compromise mitochondrial function and clearance. Such stressed AECs were found to be deficient in PINK1 (phosphatase and tensin homolog protein–induced putative kinase 1), a mediator of mitochondrial homeostasis.

Analysis of lung expression libraries from patients with IPF and healthy age-matched controls revealed that PINK1 expression was significantly reduced in IPF lung tissue. Study of isolated human lung cells confirmed this finding and also revealed that decreased PINK1 in IPF reflected decreased expression in AECs, not fibroblasts. Extending the studies to mice, the investigators found that PINK1-knockout mice exhibited many of the features of IPF: They had abnormal mitochondria and increased collagen deposition around airways, impaired mitochondrial activity, reduced turnover of damaged mitochondria, increased AEC apoptosis, and increased levels of transforming growth factor β (TGFβ). Discovering the link between PINK1, loss of mitochondrial function, and induction of inflammation suggests therapeutic opportunities to improve mitochondrial function.

**Mechanotransduction and the Role of Tissue Stiffness in Fibrosis**

Activated fibroblasts are the architects of fibrosis in IPF. Their dominant role requires differentiation to a myofibroblastic phenotype, a step requiring both a mechanical signal and activated TGFβ. Until now, the mechanism by which fibroblasts sense mechanical signals has been elusive. New research implicates the transient receptor potential vanilloid 4 (TRPV4), a channel-forming membrane receptor. Cells as diverse as neurons and endothelial cells express TRPV4, which functions as an osmosensor and mediator of differentiation. The present study identified a new role for TRPV4: mechanosensing.

The Olman laboratory used several methods to demonstrate the role of TRPV4 in myofibroblast differentiation. In studies using cultured human lung fibroblasts, investigators “knocked down” the expression of TRPV4 by treating the cells with TRPV4 small interfering RNA (siRNA), a technique that targets specific gene messages for degradation. The RNA knockdown decreased TGFβ-induced myoblast differentiation by more than 50%, whereas the control test (scrambled siRNA) had no effect. The absence of TRPV4 in the fibroblasts reduced cell differentiation. By culturing lung fibroblasts from TRPV4-knockout mice, investigators confirmed the finding. When treated with TGFβ in cell culture, the differentiation of fibroblasts without TRPV4 was reduced by 60% relative to fibroblasts from wild-type mice. The effect was specifically reversible by restoring TRPV4 using a viral expression system. TRPV4 is a calcium-dependent ion channel. In lung fibroblasts isolated from patients with IPF, channel activity is increased compared with cells from healthy donors, though the amount of TRPV4 protein is
unchanged. Together with other findings, this result suggests that the effect of TRPV4 on normal and differentiated fibroblasts may differ. When fibroblasts from healthy donors were treated with a TRPV4 inhibitor, differentiation to the myofibroblast phenotype was reduced by 25%. In contrast, treatment of fibroblasts from patients with IPF resulted in a 50% reduction in differentiation. In other words, fibroblasts from patients with IPF may have a greater dependence on TRPV4 activity than normal fibroblasts.

TRPV4 signals through the phosphatidylinositol 4,5-bisphosphate 3-kinase gamma, or PI3-kinase γ, pathway. Studies of small-molecule inhibitors of the PI3 pathway are already under way in other diseases in which TRPV4 has been implicated, including inflammatory pain and pulmonary edema. Some TRPV4 inhibitors have been tested for toxicity in rodent models and will soon be available for further investigation.

The Role of Macrophages in Fibrosis

Injured and hypoxic cells release adenosine, a signal that recruits inflammatory cells such as alternatively activated macrophages (AAMs). In fact, bronchial lavage from patients with IPF has elevated levels of both adenosine and AAMs. Although adenosine normally mediates wound healing, in IPF it may promote inflammation. AAMs contribute to the pathogenesis of IPF, and preventing their activation may provide therapeutic benefit.

Adenosine acts by binding to cell surface receptors. Investigators in the Blackburn laboratory reasoned that adenosine signaling on AAMs might mediate the aberrant AAM activation in IPF. They tested this hypothesis in a mouse model of IPF called bleomycin-induced fibrosis. Mice with bleomycin-induced fibrosis that were treated with a specific adenosine-receptor inhibitor (CVT-6883) had 50% less fibrosis compared with untreated mice. This finding implicated the adenosine type 2b receptor (ADORA2B), which is specifically inhibited by CVT-6883. Further evidence for a role of the ADORA2B was derived from experiments in knockout mice, in which conditional deletion of the ADORA2B in myeloid cells also attenuated bleomycin-induced fibrosis. Further, the ADORA2B−/− mice had improved lung function and no evidence of pulmonary hypertension compared with control mice.

Because preventing AAM activation reduced fibrosis, the findings implicated activated AAMs in the pathogenesis of IPF. The inflammatory cytokine interleukin (IL)-6 is a prime suspect. Indeed, subsequent experiments showed that one effect of bleomycin was increased IL-6 production, and this increase was mediated by the ADORA2B receptor. The findings suggested that adenosine-mediated activation of macrophage-ADORA2B plays an active role in the pathogenesis of lung fibrosis. Human lung macrophages isolated from patients with IPF also exhibited increased IL-6 when treated with an agonist specific for the ADORA2B, 5′-N-ethylcarboxamide-adenosine (NECA). Finally, when the cells were treated with an ADORA2B antagonist (GS-6201), both the baseline and the NECA-stimulated IL-6 production were reduced. Thus, the adenosine ADORA2B receptor drives IL-6 production in humans, and receptor antagonists may prevent fibrosis. Additionally, NECA-dependent production of IL-6 may provide an excellent biomarker, identifying patients who would respond to ADORA2B-antagonist therapy.

Summary

Despite the recent availability of medications able to slow the progression of idiopathic pulmonary fibrosis, the morbidity and mortality of this and other devastating forms of pulmonary fibrosis remain unacceptably high, and new therapeutic strategies remain desperately needed. The development of effective new therapies for these diseases will require better understanding of the biological processes that drive the development and progression of pulmonary fibrosis, and better identification of the molecules that mediate these processes. Improving our understanding of the roles of aging, mechanical forces, and innate immunity, as the investigators who shared their recent research at this session at the PFF Summit 2015 are doing, should identify a rich new set of therapeutic targets for future development of effective antifibrotic drugs.

References


How to Build a Patient-Reported Outcome

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Patient-reported outcomes (PROs) measure disease progression over time. The 2009 guidance from the US Food and Drug Administration defined a PRO as any report coming directly from the patient without interpretation by a third party about how the patient feels or functions in relation to a health condition and a given intervention.1 The COPD Assessment Test is an example of a PRO that was developed specifically for use in the clinical environment. The eight-item test is a validated measure of how chronic obstructive pulmonary disease affects the patient. To be validated and useful in a research context, PROs must survive a rigorous development and evaluation process.

Two principles inform the development of PROs. First, changes in score must be clearly defined and supported with ample clinical research; investigators need to know exactly what changes in score mean. Second, it is important to engage patients early on and often. Because patients are experts on the experience of living with their disease, they provide an essential perspective to the PRO development team. During initial stages, in concept solicitation interviews, patients identify what is important to them. Later, in cognitive interviews, they help distinguish whether the test content is understandable...
and culturally appropriate. Patients who can speak about their experience, and who are engaged in the community with other patients, are ideal. There are many good resources for finding patients who might be interested in partnering for development of PROs, including the Pulmonary Fibrosis Foundation’s PFF Ambassador program and the National Patient-Centered Clinical Research Network (PCORnet).

PRO development is a stepwise process. The first step is to determine the goals of measurement (e.g., a specific symptom such as cough or a more general assessment of quality of life) and whether there is an existing or adaptable tool available. If a new tool is needed, a concept solicitation interview begins, as described above. Researchers may also examine patient support group literature to glean the topics that patients are talking about. These findings are collected and used to create a draft item pool, which is then evaluated for cultural validation. Patients are enlisted to examine the items before a test is created and then again in pilot testing. This process is iterative and requires testing, revising, and retesting to arrive at the key items to include in a final version.

Next, the psychometric properties of draft instruments are evaluated in populations of 150 to 200 patients, depending on patient heterogeneity. Quantitative studies, evaluating new instruments, may also be done in the context of phase II trials; these studies measure numerous parameters such as reliability and construct validity. Reliability encompasses both internal consistency and reproducibility, which are defined by achieving specific values in quantitative tests (Cronbach α < 0.70; interclass correlation coefficient, < 0.70). PROs should also demonstrate moderate to high correlation with similar constructs and/or low correlation with distant constructs, and the scale score should differ significantly among groups in which there is a known change in the concepts of interest. The scale must be able to identify clinically relevant change.

Regulatory organizations expect researchers to be able to identify thresholds of change that are clinically meaningful. Capturing patient voice, establishing a rationale for a new or revised measure, and demonstrating that the content has validity are other important considerations. However, different regulatory agencies have different requirements and areas of focus for PROs.

Optimal patient assessment tools may have multiple components, including objective markers of disease development, PROs, and/or wearable devices. In these cases, it is important to consider how a PRO will integrate with the other markers. PROs must also create minimal burden and have a high impact. Developing PROs begins and ends with patients, because developing assessment tools is an ongoing process.

### Measuring Function: Beyond the 6-Minute Walk Test

Functional status matters to patients. Performing basic activities and participating in life situations is what life is about. Measures of functional status could also be essential in clinical trials, provided they are quantitative and have acceptable psychometric qualities.

In the past, the 6-minute walk test (6MWT) and the cardiopulmonary exercise test (CPET) have been used to measure functional capacity in patients with idiopathic pulmonary fibrosis. Although both of these tests measure patient function, they have little to do with the activities of daily living (ADL). An ideal tool would be one that measures physiological capacity, performance, and psychosocial factors in relation to the ADL.

In an update on the quest for viable tools, Olson and colleagues evaluated the continuous-scale physical function performance test (CS-PFP). The CS-PFP encompasses physical capacity and performance based on ADL but performed in a clinical environment. Defined physical tasks such as lifting and carrying a pot, sitting on and rising from the floor, climbing stairs, and carrying groceries measure physical parameters such as upper body strength, balance, coordination, and endurance. The test has been widely applied in healthy elderly people and in patients with Parkinson’s disease, congestive heart failure, and chronic obstructive pulmonary disease. In these populations, the CS-PFP displayed excellent psychometric characteristics. The test-retest correlation ranged from 0.84 to 0.97, and there was high internal consistency among domains, with a Cronbach α value ranging from 0.74 to 0.97 (in both measures, values < 0.70 are acceptable). In comparison, the 6MWT and CPET administered in the same population had low sensitivity.

Olson’s group applied the CS-PFP in 16 participants with IPF who ranged in disease severity. Study subjects had a mean age of 69.3 years, an average forced vital capacity (FVC) of 65%, and 68.8% used supplemental oxygen with activity. Patients were tested, then retested within 1 week, yielding a superlative test-retest correlation with an intraclass correlation coefficient of 0.84 (well above the acceptable value of 0.70). The CS-PFP also had exceptional internal consistency in this population, with a Cronbach α value of 0.91. The investigators, who knew the patients from clinical practice, found it “eye-opening” to obtain an objective measure of their functional status. Prior to the CS-PFP results, the clinicians believed the patients to be high functioning, but when viewed through the lens of the objective CS-PFP, deficits were obvious.

When compared with age-matched healthy subjects, patients with IPF had significantly lower scores in the domains of lower body strength, endurance, and total score. The CS-PFP correlated with tests more closely related to physiology, such as the 6MWT and FVC, but CS-PFP measured more variables and revealed more about each patient’s functional status. The CS-PFP also correlated with quality of life tools. These findings support the validity of the CS-PFP as a measure of functional status in patients with IPF. The next steps in developing the CS-PFP include setting up an on-site laboratory where these tests can be administered to a larger population of patients.

### References


Collaborative Networks as Tools for Improving Clinical Care

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The Pulmonary Fibrosis Foundation’s PFF Care Center Network (CCN) is a growing group of medical centers throughout the United States. The CCN expanded from 9 to 40 centers between 2013 and 2015. An overarching goal of the CCN is to change the clinical landscape, care, and quality and quantity of life for patients with pulmonary fibrosis (PF). This will be done through a partnership of specialized centers, local physicians, and patients/caregivers.

CCN sites were selected by demonstrating ability to provide—and are charged with providing—multispecialty care, education, patient support groups, and research. Even with 40 centers, it is clear that there are non-CCN practices that deliver excellent care, as well as patients without easy access to specialty care. Moving forward, the PFF aims to add new sites and increase the influence of current sites. One model is for sites to serve as hubs, aiding local physicians in the care of patients and providing specialized services, eg, lung transplantation, when needed.

As a relatively rare and presently fatal disease, PF poses many challenges to drug development. Potential therapeutic agents must be evaluated in clinical trials, but populating trials remains difficult. The PFF CCN can help identify patients who are suitable for trials and educate them regarding the value and possible benefit of participating in a clinical trial. In her keynote address, Pat Furlong, the CEO of the Parent Project Muscular Dystrophy (PPMD), described instances in which the PPMD recruited 150 patients in 3 weeks due to their own CCN and patient engagement.

A key initiative of the the PFF CCN is the development of a Patient Registry. The PFF Patient Registry will enroll at least 2,000 participants with both idiopathic pulmonary fibrosis as well as non-IPF fibrotic lung diseases such as hypersensitivity pneumonia or connective tissue disease–related PE. A Registry documents patient characteristics in a real-world setting. One advantage lies in observing a wider breadth of the patient population than in a clinical trial, for which specific patients are often chosen and the care is protocolized. Analysis of care patterns across the country will hopefully allow investigators to identify and subsequently disseminate “best practices” for patients with PF.

Evaluating biomarkers is another focus of the CCN. Patient participation is similarly essential in developing a patient-reported outcome (PRO), a useful measure of disease activity that can be used in drug development. Clinical trials must evaluate drugs for benefit and risk, and a PRO can be an important measure, especially in the absence of a validated biomarker. As patients enroll in the Registry, they will begin to document their symptoms, such as cough, fatigue, and shortness of breath—information that may contribute to the development of a PRO that can be used in clinical trials.

The CCN infrastructure, as well as the data and biosamples from the Registry and biorepository, are important resources that are available to aid in the goals of improving the quality and quantity of life for patients with PF. These goals can be realized through the collaboration of multiple stakeholders, including patients, caregivers, government agencies, industry, investigators, and local physicians.

Toward an Improved Quality of Life: Starring Oxygen Therapy and Pulmonary Rehab

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Dyspnea and cough are the chief contributors to reduced quality of life (QOL) in patients with idiopathic pulmonary fibrosis (IPF). Other nonspecific symptoms may include fatigue, weight loss, depression, anxiety, and poor sleep. In addition, nonsomatic issues commonly encountered include lack of good-quality and consistent information, financial burden, and impact on relationships. Patients also reported factors that enhanced QOL, such as honesty about prognosis and access to centers of excellence.

Although medical treatments for IPF have made tremendous advances, these therapies have not been found to improve QOL in patients with IPF. However, supportive therapies, such as pulmonary rehabilitation and oxygen therapy, can significantly improve QOL.

Pulmonary rehabilitation encompasses exercise training, education, and behavior change goals in a program that is tailored to each patient’s needs. Ideal programs incorporate two visits per week for 10 weeks, with 30 minutes of aerobic exercise per visit. Patients in such programs experienced significant improvement in dyspnea, physical activity, and QOL.1 Exploring patients’ wishes
future, or mistaken expectations about existing therapies, contrib-

patients with IPF repeatedly requested honest information about
QOL. Regarding the education process pertaining to their disease,
Therefore, both oxygen and pulmonary rehabilitation can improve
QOL. Regarding the education process pertaining to their disease,
patients with IPF repeatedly requested honest information about
their prognosis. Patients reported that uncertainty about their future,
or mistaken expectations about existing therapies, contrib-
uted to a reduced QOL. Therefore, providing accurate information
regarding disease progression and prognosis may contribute to a
patient’s QOL.

Palliative Care and Hospice: Losing or Retaking Control
A notable presentation by Kathleen O. Lindell, PhD, RN, which explores
misconceptions patients with PF and their families hold about palliative care
and proposes instead a positive, evidence-based perspective.

A diagnosis of IPF often triggers an initial response of denial, especially
in patients who have otherwise been healthy. This was brought home to
clinicians who heard comments from caregivers such as, “No one told
me he was going to die.”

Effective patient education has the potential to help patients prepare
for adverse outcomes and can guide them to consider palliative care.
However, patient and clinician confusion about palliative care and the
typical 2-year delay in referral to specialty services may deprive many
patients of optimal care and the opportunity to make conscious, inten-
tional end-of-life choices.

Palliative care differs from hospice care. Appropriate for any serious
illness, regardless of projected lifespan, palliative care aims to manage
symptoms and thereby improve QOL. Aggressive medical care and
palliative care may be provided concurrently, and palliative care is
appropriate at any disease stage. Conversely, hospice care is typically
provided for patients whose projected lifespan is 6 months or less or
those who have refused aggressive medical therapy.

Patients with serious illnesses who receive palliative care live longer and
retain a better QOL. In a study of patients with non-small cell lung
cancer, patients who received palliative care scored higher on measures
of QOL, had fewer depressive symptoms, and survived longer (11.6 vs
8.9 months; \( P=0.02 \)). A Cochrane review comparing palliative and
usual care produced similar results: Patients experienced fewer symp-
toms and were twice as likely to die at home as in a hospital.

Educating patients about the inability to predict acute decline and the
benefits of palliative care has the potential to help manage symptoms,
improve QOL, and facilitate advance care planning.

References
1. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung
2. Holland AE, Fiore JF Jr, Goh N. Be honest and help me prepare for the future:
What people with interstitial lung disease want from education in pulmonary
ences and needs of patients with idiopathic pulmonary fibrosis. J Adv Nursing.
4. Temel JS, Greer JA, Muzikansky A. Early palliative care for patients with metastatic
5. Gomes B, Calanzani N, Higginson IJ. Benefits and costs of home palliative care
compared with usual care for patients with advanced illness and their family caregivers.

The 2014 PFF Patient
and Caregiver Survey
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The Pulmonary Fibrosis Foundation (PFF) conducted the
national PFF Patient and Caregiver Survey between August 6
and November 25, 2014, to gather patient-specific information
on several important criteria: how patients and caregivers are managing
the disease and taking care of themselves; the nature of patient-
physician interaction; and attitudes toward participation in clinical
trials for new treatments for pulmonary fibrosis (PF).

As of the PFF Summit 2015, 1,068 people had participated in the
survey, results from which have been used to educate US Food and
Drug Administration regulators about patients with PF, their unique
requirements, and the urgent need for new PF therapies. Such
education is crucial because idiopathic pulmonary fibrosis (IPF)
is not a well-known condition; it is considered an orphan disease,
affecting a small number of people every year. In the United States,
the estimated prevalence of IPF is 14 to 43 per 100,000 people, and
there are 7 to 16 new cases per 100,000 people each year. The esti-
imated burden of disease is likely underestimated in prior studies,
reflecting both a limited awareness of IPF and the difficulty of ef-
ciently and accurately diagnosing patients with the disease. The risk
for developing IPF increases with age; the median age at diagnosis
is approximately 63 years.
Disability Due to PF
The survey has yielded some important new information about how patients characterize their disability due to PF. For example, when asked to assess the degree to which they have been disabled by PF,

- 72% of patients interviewed say they experience at least some limitations
- 43% report a “slight disability” and are able to manage their own affairs without assistance but are “unable to carry out all previous activities”
- 29% describe their disability as “moderate,” requiring “some help, but able to walk unassisted”

Patients under 65 years are more likely than older patients to describe their symptoms as “moderate” (35% vs 23%); more women than men say the same (34% vs 23%).

Clinical Trials and Patients With PF
Clinical trials of new medicines and devices are crucial for advancing the management of PF. Part of the national survey was aimed at learning more about why patients choose whether or not to participate in studies of new treatment approaches. Patients with PF and their caregivers are savvy about the benefits of trial participation. Although patients understand that trial participation can help them and will pave the way for advances that can help future patients with PF, many still choose not to participate. The most common reason for rejecting participation is concern over receiving a placebo instead of the active medicine.

The survey produced several key findings in this area:
- Although three out of four patients with PF reported reading or hearing about clinical trials, only slightly more than half—55%—of those individuals said their PF healthcare provider had discussed such trials with them
- About one in four patients with PF reported participating in clinical trials. This is significantly higher than the participation rate for those with other important chronic illnesses. The participation rate for cancer trials, for example, is 1% to 2%
- The most common reasons reported by patients for non-participation were concern about receiving placebo vs active treatment and not being informed about trials by their doctors
- Women were more likely than men (42% vs 28%) to report that their doctors’ lack of recommendation was “very important” in their decision not to participate in clinical trials. They also reported a much greater concern than men about unknown side effects (41% vs 21%)
- Among patients who live alone, 50% said they chose not to participate in trials because of concern about disease progression if placed in a placebo group. But only 40% of those who live with others expressed the same concern
- Patients under 65 years of age were more inclined to report that they did not participate in trials because of an inability to travel to the trial center (28%) compared with patients 65 years and older (18%)

Patient-Centered Research: The Promise of Registries
Patients with PF are eager to contribute to systems or programs that will help enable treatment advances. One such program is the PFF Patient Registry. A Patient Registry is an organized system that compiles information about patients living with a specific illness, the effect of treatments, and ways to measure the benefit of those treatments. Registries are important because they offer researchers a database within which smaller subgroups of people living with a disease can be identified and studied. For example, people with different genetic or racial makeup, different concomitant conditions, and from different regions may manifest symptoms of PF differently. A Registry helps researchers study subgroups of patients with PF by gathering information from all over the United States. In contrast, research that is limited to patients in individual centers may not be able to enroll the numbers required to adequately study PF and PF subgroups.

The PFF Patient Registry is a recent development, having begun in 2015. The 40 centers that comprise the PFF Care Center Network (CCN) and PFF Patient Registry are contributing data on 2,000 patients. As the number of patients with PF participating in the Registry accrues, the quality and accuracy of the Registry’s research will increase. The new Registry will help move therapy forward and improve patients’ quality and length of life by:
- Better defining the numbers of new and total cases of PF in the United States each year
- Helping establish known subgroups of patients with PF for diagnosis, research, and follow-up
- Generating better information on the natural progression of PF and how well specific treatment approaches work for patients in the various subgroups
- Supporting clinical trials and biological research, specifically:
  — Shortening clinical trials and cutting their cost by providing lists of patients qualified to join particular studies. Clinical trials are often delayed because they have trouble finding qualified patients
  — Defining diagnostic criteria for specific patient subgroups
- Helping gain a better understanding of the real costs of PF treatment

Leveraging the PFF Care Center Network
The PFF CCN is a growing group of medical centers across the United States that have the specific experience and expertise necessary to diagnose and treat patients with fibrotic lung diseases. The CCN includes 40 centers geographically dispersed throughout the United States. All centers share a dedication to improving the clinical care of those living with the disease. As the principal coordinating entity for PF in the United States, the CCN is designed to act as the intermediary between patients and caregivers, government, academic researchers, and industry.

Because CCN sites provide multidisciplinary expert care for each patient, they are able to fully manage each patient’s disease. In addition to care, CCN sites offer education for patients and caregivers to improve their understanding of exactly what is happening over the course of the disease. CCN sites also provide organized support groups
and other opportunities for patients to connect with others who share this rare disease. Once enrolled in a CCN site, patients will be followed for life.

The most common PF symptoms patients experience every day are shortness of breath (90%), cough (73%-86%), anxiety/depression (23%-27%), and fatigue (40%-45%). Social isolation often increases over time, because the progression of PF symptoms may make it more difficult for patients to engage with others as symptoms progress. Research emanating from the CCN consortium will help determine the best treatments for these common symptoms and provide guidance on how therapy should be tailored for each subgroup of patients with PF. Patients depend on clear communication from healthcare professionals about how to deal with their daily struggle, but many at the meeting expressed dissatisfaction with communications related to symptom management, especially when oxygen therapy, for shortness of breath, is introduced and implemented.

Patients and caregivers at the PFF Summit 2015 were especially vocal about the importance of emotional, psychological, and social support for those living with PF. Such support is especially important for patients living on their own because they tend to be more isolated as time passes and may not have a caregiver to rely on. Sharing experiences with other patients provides a sense of community and hope. Looking back, many patients said they wished they had been pointed to a support group at the time of diagnosis.

**Fibroblast-Specific FGF Signaling in Bleomycin-Induced Pulmonary Fibrosis**

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mple evidence supports a role for fibroblast growth factor (FGF) in the pathogenesis of idiopathic pulmonary fibrosis (IPF). For instance, in the bleomycin model of fibrosis, if FGF is blocked or absent, the development of fibrosis is reduced. Both pharmacologic agents approved for the treatment of IPF modulate the FGF pathway: pirfenidone inhibits an increase in FGF2, interferon-γ, and transforming growth factor (TGF)-β1; and nintedanib is a receptor tyrosine kinase (RTK) inhibitor that blocks signaling in the FGF pathway. However, FGF actions are complex and involve several different cell types in the lungs, and the precise mechanism of action and specific cell target involved in IPF pathogenesis have remained elusive until now.

Using molecular methods, Guzy and colleagues deleted the three FGF receptors (FGFR1, 2, and 3) from fibroblasts in mouse lung cells. When these mice, which lacked FGF receptors, were treated with bleomycin, they had significantly decreased histologic fibrosis and collagen-I production in the lungs. These findings suggested that FGF receptors mediate fibrosis through activity in myofibroblasts. The inflammatory cytokine interleukin (IL)-6 was present in lung extracts of both wild type and FGF receptor–deficient mice, suggesting a similar degree of lung injury. However, phosphorylation of signaling molecules in the FGF pathway was also reduced in receptor-deleted mice, suggesting that removal of the receptor prevented downstream signaling.

Removing the three FGF receptors from fibroblasts specifically reduced fibrosis in the bleomycin model of fibrosis, supporting research into therapeutics that target fibroblast-specific FGF signaling.

**TOLLIP, MUC5, and the Response to N-Acetylcysteine Among Individuals With Idiopathic Pulmonary Fibrosis**

The genes TOLLIP and MUC5 code for proteins critical in lung host defense, which is an immune process influenced by oxidative signaling. In 2013, investigators showed that single-nucleotide polymorphisms (SNPs) in these genes were associated with disease susceptibility and clinical outcomes in IPF. Encouraged by these findings, Oldham and colleagues wondered whether TOLLIP and MUC5 variants may have affected treatment response to N-acetylcysteine (NAC) therapy in the PANTHER (Evaluating the Effectiveness of Prednisone, Azathioprine, and N-Acetylcysteine in Patients With Idiopathic Pulmonary Fibrosis) trial.

**Pulmonary Fibrosis Foundation Support Group Resources**

Are you interested in starting a pulmonary fibrosis support group? The Pulmonary Fibrosis Foundation (PFF) has many resources to provide you with all the information you will need to develop and run your support group. The PFF can assist in promoting your group to our members, provide you with PFF educational materials, and connect you with other support group leaders through the PFF Support Group Leader Network. You can also apply for grants to start a new pulmonary fibrosis support group and to develop a current group.

For further information on how to start a new PF support group or to get involved with a support group near you, please contact the PFF Patient Communication Center at 844.TalkPFF (844.825.5733) or pcc@pulmonaryfibrosis.org. Additional information is available at pulmonaryfibrosis.org.
In the original PANTHER trial, 60 weeks of treatment with NAC showed no significant improvement in forced vital capacity compared with placebo; the study was halted because of potential harm to patients. In a recent study, genetic analysis of blood samples revealed five SNPs within TOLLIP and MUC5. Correlating clinical findings with the genetic analyses uncovered significant interaction between three of the gene variants and treatment with NAC, and no interaction with the prednisone/azathioprine/NAC group. The new results revealed that, depending on genotype, NAC therapy was associated with three different treatment outcomes. Subjects with the TT genotype had a significant reduction in composite endpoint risk; harm (primarily increased hospitalizations) was associated with the CC genotype, and no treatment effects were observed in patients with the CT genotype. Therefore, NAC therapy may be beneficial for patients with IPF and the rs3750920 (TOLLIP) TT genotype, which represents about one-quarter of the patients with IPF. However, NAC therapy may be harmful for patients with the rs3750920 (TOLLIP) CC genotype. Although NAC may be beneficial, recommendations regarding therapy with NAC await prospective, genotype-stratified clinical trials.

The Mechanosensitive Transient Receptor Potential Vanilloid 4 Ion Channel Mediates the Pro-Resolution/Anti-Fibrotic Macrophage Response to Endotoxin (Lipopolysaccharide)

Repair of lung injury depends on the ability of macrophages to phagocytose foreign organisms and cellular debris. Cell surface receptors and factors within the extracellular matrix regulate phagocytosis, which also depends on cues from particles targeted for engulfment. Scheraga and colleagues reasoned that the transient receptor potential vanilloid 4 (TRPV4), a channel-forming membrane receptor and mechano-sensor, might integrate matrix and other cues controlling phagocytosis in lung macrophages. To study these cell behaviors, Scheraga’s group cultured bone marrow–derived macrophages (BMDMs) and alveolar macrophages from mice on fibronectin-coated hydrogels of varying thickness. Phagocytosis was measured by documenting the uptake of fluorescently labeled bacteria or IgG-coated latex beads. Macrophages engulfed the bacteria and latex beads. When a pharmacologic inhibitor of TRPV4 was added to the culture, phagocytosis stopped. Knockdown of TRPV4 with small interfering RNA or use of cells from a mouse null for TRPV4 had the same effect, suggesting a role for TRPV4 in mediating phagocytosis by macrophages. In the lungs of live mice that were null for TRPV4, phagocytosis of marked beads or bacteria was blocked. The findings suggest that TRPV4 integrates cues from the extracellular matrix and those from bacteria that promote phagocytosis in macrophages. These cellular behaviors may contribute to resolving inflammation and fibrosis.

References

Pulmonary Fibrosis Foundation Educational Materials
The Pulmonary Fibrosis Foundation (PFF) has educational resources available for patients with pulmonary fibrosis and their caregivers, including the Patient Information Guide, Physician Notepad, and Disease Awareness Poster. There is also a new ILD Pocket Guide for health care professionals. You can order hard copies of PFF educational resources for your clinic at no cost by calling the PFF Patient Communication Center at 844.TalkPFF (844.825.5733) or pcc@pulmonaryfibrosis.org. Or you can download materials straight from the PFF website at www.pulmonaryfibrosis.org.
POST-TEST CME/CE QUESTIONS

1. Which of the following treatments have been shown to significantly improve quality of life in patients with idiopathic pulmonary fibrosis?
   A. Nintedanib
   B. Pirfenidone
   C. N-acetylcysteine
   D. Pulmonary rehabilitation

2. In the PANTHER trial, treatment with N-acetylcysteine resulted in a significant reduction in the composite endpoint in participants with:
   A. MUC5 variants
   B. The CC genotype in the TOLLIP gene
   C. The CT genotype in the TOLLIP gene
   D. The TT genotype in the TOLLIP gene

3. The Pulmonary Fibrosis Foundation Patient Registry will:
   A. Gather clinical data only
   B. Collect blood and sputum samples
   C. Amass patient information in one location
   D. Store clinical data, biological samples, and up to three CT scans for each patient

4. Deleting fibroblast growth factor (FGF) receptors from fibroblasts in mouse lung and then treating with bleomycin to induce fibrosis resulted in:
   A. Increased fibrosis
   B. Increased FGF production
   C. Increased FGF receptor signaling
   D. Decreased fibrosis and type I collagen production

5. Surveys of patients with idiopathic pulmonary fibrosis revealed that patients were concerned about all of the following issues EXCEPT:
   A. Cough
   B. Dietary restrictions
   C. Shortness of breath
   D. Decline in quality of life
   E. Loss of the activities of daily living

6. All of the following genes have been implicated in the pathogenesis of pulmonary fibrosis, EXCEPT:
   A. MUC5B, coding for a mucin protein
   B. SFTPA2, coding for a surfactant protein
   C. TOLLIP, coding for a ubiquitin binding protein
   D. CASR, coding for the calcium-sensing receptor

7. According to the current understanding of the pathogenesis of pulmonary fibrosis, all of the following are potential targets for drug development EXCEPT:
   A. Telomerase
   B. Blood clotting
   C. Interleukins 4 and 13
   D. The adenosine A2BR receptor
   E. The transient receptor potential vanilloid 4 (TRPV4)

8. Which of the following statements is true of palliative care?
   A. Palliative care does not manage disease symptoms.
   B. Palliative care is only appropriate for patients in the end-stage of disease.
   C. Palliative care often results in a longer lifespan and improved quality of life.
   D. Palliative care and aggressive medical treatment are not provided concurrently.

9. Approximately how many patients with interstitial lung disease undergo lung transplantation per year?
   A. 750
   B. 1,000
   C. 1,500
   D. 2,000

10. Compared with physicians’ impressions from clinic visits, an objective measure of functional status in patients with idiopathic pulmonary fibrosis revealed that:
    A. Patients were lower functioning than expected
    B. Patients were higher functioning than expected
    C. Patients were much lower functioning than expected
    D. Patients had about the same deficit level as expected by their physician
Disease Management and Effective Clinician-Patient Partnering: Highlights of the PFF Summit 2015 Evaluation Form

Original Release Date: May 2016 • Most Recent Review Date: May 2016
Expiration Date: April 30, 2017 • Estimated Time to Complete Activity: 1.25 hours

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: http://tinyurl.com/PFFsupp15.

Please indicate your profession/background:

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Resident/Fellow Researcher ☐ Administrator ☐ Student
☐ Other; specify ________________________________

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


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

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)

☐ Implement a change in my practice/workplace.
☐ Seek additional information on this topic.
☐ Do nothing differently as the content was not convincing.
☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

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 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 the system barriers are (eg. institutional systems, lack of resources, etc).

OVERALL EVALUATION

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

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

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

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

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

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

The program was educationally sound and scientifically balanced.

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

Overall, the program met my expectations.

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

I would recommend this program to my colleagues.

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

Author demonstrated current knowledge of the topic.

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

Author was organized in the written materials.

☐ Strongly Agree ☐ Agree ☐ Somewhat Agree ☐ Disagree ☐ Strongly Disagree

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.

__________________________________________________________________
__________________________________________________________________
__________________________________________________________________

The Postgraduate Institute for Medicine thanks you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.

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