REPORT

Strategies to Manage Costs in Idiopathic Pulmonary Fibrosis

Gary M. Owens, MD

Idiopathic pulmonary fibrosis (IPF) is a complex, progressive disease, challenging to diagnose, due to the need to exclude alternative diagnoses, and challenging to manage.[1,2] While it has a histopathologic pattern of usual interstitial pneumonia (UIP)—characterized by diffuse fibrosis and scarring of the interstitium—its etiology is unknown and its natural history is variable and unpredictable. IPF is characterized by worsening dyspnea, declining lung function, nonspecific respiratory symptoms, a wide array of associated multiple comorbidities, and a varied clinical course randomly punctuated by episodes of acute exacerbations.[1,2] In most patients, the disease progresses with a gradual worsening of lung function over years. However, a minority of patients may remain stable or decline rapidly, with some experiencing episodes of acute respiratory worsening despite previous stability.[1]

IPF primarily impacts middle-aged to older adults, most with a history of cigarette smoking.[1] The disease is typically fatal, with median survival estimated at 3 to 5 years from the initial diagnosis.[3] However, male gender is associated with a higher incidence of disease, higher mortality, and shorter survival time after diagnosis. It is interesting to note that among newly diagnosed patients with Medicare, the majority tend to be white (91%) and female (54%).[4,5] These data, compared with previous studies, showed an unusually higher proportion of female patients. This may be due to limitations in coding in the Medicare database. Over the past decade, Medicare data and death certificate data have also shown a trend toward increasing prevalence of IPF among Americans older than 65 years, with increasing survival.[2,4,6] This trend may be partly attributed to the aging population, increased awareness of the disease, and improved guidelines in defining and diagnosing the disease.[1,5-8]

The rise in incidence is coupled with the usual high cost of treating chronic conditions and the comorbidities that follow, along with the typical health concerns that go along with aging. In the case of IPF, the complexity of reaching a confirmed diagnosis and the need for managing complications and concomitant comorbidities makes managing patients with IPF cost intensive and resource intensive.[9,10] Additionally, IPH has 2 costly treatment options: lung transplant or a choice of 2 recently approved pharmacologic treatments for

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a diagnostically challenging disease. Clinicians are faced with the need to exclude alternative diagnoses, limited treatment and management guidelines, and few treatment options. Patients with IPF have significantly increased healthcare usage compared with similar patients without the disease. Medicare estimates for this disease are as high as $3 billion, not including cost of treatment. The disease, characterized by worsening dyspnea, declining lung function, nonspecific respiratory symptoms, and a varied clinical course randomly punctuated by episodes of acute exacerbations, is also accompanied by a host of comorbid conditions that contribute significantly to increased healthcare usage and cost. The comorbidities, which increase impairment and disability, and compromise patient quality of life and survival, include pulmonary and cardiac conditions, sleep apnea, gastroesophageal reflux disease, depression and anxiety, and lung cancer. Until recently, palliative care and lung transplant were the only options for management of IPF. Without a lung transplant, the median survival was estimated at 3 to 5 years from the initial diagnosis. Newer treatments, pirfenidone and nintedanib, demonstrate a modest effect on slowing decline in lung function in patients with IPF. Both were approved for the treatment of IPF in 2014. As potentially effective therapies emerge, attention should be given to healthcare resource usage and healthcare processes that ensure patient-centered management with sustainable, cost-effective, and quality care. As such, it is imperative that a structured, comprehensive, multidisciplinary management approach is used in the treatment and management of IPF and its associated comorbidities to limit costs and provide effective and quality healthcare.

Am J Manag Care. 2017;23:S191-S196

For author information and disclosures, see end of text.

IPF.[1,11] As such, it is important to understand the economic burden associated with the disease and understand the impact on budgets from the only approved pharmacologic treatments, with no generic substitutions available.

Cost of Care

An examination of health resource usage and costs indicates that patients with IPF have significantly increased healthcare usage compared with demographically matched controls and incur substantial costs to payers both before and after the time of diagnosis. As determined through administrative claims, the cost of managing the 158,000 patients with IPF covered by Medicare in 2011 was estimated at almost $3 billion, not including cost of drug treatment; $1.8 billion specifically was attributed to IPF and its associated comorbidities.[9] Between 2000 and 2011, patients with IPF used hospitals and emergency departments almost twice as often with an 82% higher risk of hospitalization (28.8% vs 15.8%) and an 82% greater chance of an emergency department visit (23.9% vs 13.1%). Similarly, total healthcare costs were 72% higher ($10,124 vs $5888) compared with matched controls. One year after initial diagnosis, patients with IPF had a 134% higher risk of hospitalization (48.7% vs 20.8%) and a 126% higher chance of an emergency department visit (39.6% vs 17.5%), compared with the control group. The cost difference between the 2 groups nearly doubled in the first year after diagnosis, with patients with IPF incurring 134% higher total healthcare usage costs ($20,887 vs $8932), not including medication costs.[9] Inpatient services accounted for half of the medical costs in patients with IFP, and these costs doubled in the first year after a diagnosis of IPF was confirmed.[12] Similar results were found using US claims databases, with direct annual costs, not including medication costs, totaling $26,378 per patient with IPF compared with $12,124 per control patient.[10]

Another recent retrospective analysis looked at claims incurred between 2006 and 2011 from a national commercial claims database of 1735 patients with IPF. The analysis confirmed the need for appropriate management of episodes of IPF acute exacerbations to help slow disease progression, reduce associated morbidity and mortality, and mitigate costs.[13] Based on the claims data, 38.6% of patients with IPF had at least 1 all-cause hospitalization, 10.8% had IPF-related hospitalizations, and 72.1% had suspected IPF exacerbations leading to urgent outpatient visits during the first year after an IPF diagnosis. The average cost per IPF-related hospitalization was $16,812, and the average cost per exacerbation requiring hospitalization was $14,731. Furthermore, the cumulative risk of each event occurring increased over time. In this group of patients, costs of exacerbations requiring hospitalization, amounting to $1.5 million per year, accounted for almost 46% of the total exacerbation-associated costs. However, the costs of exacerbation not requiring hospitalization, at $444 per event, totaled to 54% for a $1.7 million cost per year because of the high rate of exacerbation and occurrence. These data show the significant need to effectively define and identify acute exacerbations in IPF, and to distinguish these exacerbations from IPF-associated comorbidities to curtail the associated high cost of healthcare usage.[13]

Contributors to Cost

Several comorbidities are associated with IPF, and most patients with IPF will have at least 1 secondary complication that will increase their impairment and disability, resulting in further compromise to their quality of life and potentially impacting survival.[14] A claims data study of Medicare beneficiaries (5%, 3.7 million people) from 2000 to 2011 found that, in the 1 year before diagnosis, patients with IPF (n = 7855) were more likely to suffer from other pulmonary conditions, such as chronic obstructive pulmonary disease (COPD) (41.0% vs 13.5%) and respiratory infections (33.1% vs 13.3%), compared with control patients (n = 38,856).[9] In fact, all selected comorbidities were more common in the IPF group than in the control group (P <.01). Comorbidities with the highest comparative prevalence ratio (PR) included pulmonary hypertension (PR = 4.9), pneumonia (PR = 3.7), pulmonary embolism (PR = 3.1), COPD (PR = 3.0), lung cancer (PR = 2.8), sleep apnea (PR = 2.7), and congestive heart failure (CHF) (PR = 2.2).[9]

Some comorbidities, such as pneumonia, CHF, and pulmonary embolism, may present acutely and are often difficult to distinguish from an acute exacerbation of the disease.[15] An acute exacerbation of IPF is an unexplained, sudden acceleration of the underlying fibrotic disease and unpredictable deterioration. Identifiable causes of deterioration, such as infection, pulmonary embolism, or heart failure, must be excluded.[16] The exact frequency of exacerbations is unknown because of the lack of consensus in definitions and diagnostic criteria for these exacerbations. It is estimated that exacerbations occur in 5% to 15% of patients per year.[17] One predictor of exacerbations in these patients is declining forced vital capacity (FVC). Also, acute infections may cause respiratory decline in patients with IPF that behaves similarly to an exacerbation. It is agreed that patients with acute exacerbations have an especially poor prognosis, with retrospective intensive care unit studies reporting mortality rates as high as 85%.[13,15,18] The most commonly reported cause of mortality in patients with IPF is respiratory complications, usually because of an acute exacerbation.[19]

Other significant comorbidities associated with IPF include gastroesophageal reflux disease (GERD), present in up to 90% of patients with IPF, which is associated with a worsening or exacerbation of IPF.[20] Depression and anxiety are observed in about a quarter of patients with IPF and are associated with increased dyspnea and pain, poor sleep quality, and reduced FVC. The use of antidepressants in this patient population is therefore widespread.[21,22] Obstructive sleep apnea is reported in up to 88% of these patients.[23]

Patients with IPF have a 7-fold increase in the risk of developing lung cancer, with squamous cell carcinoma and adenocarcinoma being most common.[22,24,25] Finally, venous thromboembolism occurs at an incidence 34% higher than in the general population and higher than disease-matched controls, with emphysema or lung cancer necessitating the use of anticoagulants and other medications to prevent or treat thromboembolic events.[26] Other common comorbidities include pulmonary infection, bronchitis, asthma, heart disease (including heart failure, myocardial infarction, atrial fibrillation, and coronary artery disease), and cerebrovascular disease, among others. These comorbid conditions, along with cough and dyspnea, the most prominent symptoms of IPF, contribute significantly to the impairment and disability in patients with IPF, further compromising their survival and quality of life, and ultimately increasing the cost of treatment and care.[14]

Treatment of these comorbid conditions has not been well studied.[14] However, appropriate identification and treatment of comorbidities may help result in improved survival and quality of life for selected comorbid conditions such as GERD. Unfortunately, there are limited data and guidance available on the management of comorbidities in patients with IPF. Because of the varied course of the disease and the presence of comorbidities and periods of adverse events that may necessitate aggressive treatment, there is no single central IPF treatment strategy. Often, the combination of comorbid conditions and patient health status requires an individualized approach to management.[27] The high prevalence of comorbidities associated with IPF suggests that comorbidities are important contributors to the increased healthcare usage and cost associated with an IPF diagnosis. IPF management needs to continually evolve over the course of the disease to slow down disease progression and maximize quality of life and health status.

Cost-Effective Treatment

Until 2014, the only available treatment for IPF, apart from a lung transplant, was palliative care and management of comorbidities to improve patient quality of life.[11] In 2014, the US Food and Drug Administration (FDA) approved pirfenidone and nintedanib for IPF, each at a cost of almost $100,000 per patient per year.[1,11] Additionally, treatments such as *N*-acetylcysteine are known to be used off-label in clinical practice.[28] The efficacy of all 3 of these treatments was evaluated based on a systemic review of phase 2 and 3 randomized controlled trials in adults with IPF.[28] Based on the 9 studies included in this meta-analysis, pirfenidone and nintedanib demonstrated greater effectiveness in slowing the decline in FVC compared with placebo after 1 year of treatment (pirfenidone vs placebo: difference = 0.12 liter (L), 95% confidence interval [CI], 0.03-0.21 L; nintedanib vs placebo: difference = 0.11 L, 95% CI, 0.00-0.22 L). *N*-acetylcysteine did not demonstrate any significant efficacy compared with placebo. Furthermore, treatment with pirfenidone demonstrated a lower risk of decline in percent predicted FVC of ≥10% over 1 year (odds ratio [OR],0.58; 95% CI, 0.40-0.88). All-cause mortality was reduced with pirfenidone compared with placebo over 1 year (hazard ratio [HR], 0.52; 95% CI, 0.28-0.92). A survival advantage in comparison to placebo was not seen with nintedanib (HR, 0.70; 95% CI, 0.32-1.55), or *N*-acetylcysteine (HR, 2.00; 95% CI, 0.46-8.62).[28] Treatment with pirfenidone has been suggested to improve life expectancy in patients with IPF compared with best supportive care (BSC).[29] A sub-analysis of data from 2 randomized clinical studies (ASCEND and CAPACITY), an open-label extension study (RECAP), and the Inova Fairfax Hospital database calculated the mean life expectancy for patients with IPF being treated with pirfenidone at 8.72 (95% CI, 7.65-10.15) years compared with 6.24 (5.38-7.18) years with BSC. This was an improvement in life expectancy of 2.47 (1.26-4.17) with pirfenidone compared with BSC.[29]

Both FDA-approved agents have demonstrated a modest effect on slowing decline in lung function in patients with IPF.[30,31] In contrast, the PANTHER trial showed that combination therapy with prednisone, azathioprine, and *N*-acetylcysteine results in harm with increased mortality and increased hospitalizations. However, because the agents are relatively new, there is an absence of consensus on when to initiate treatment and a dearth of long-term health outcomes data to support the steep cost associated with treatment. In the absence of these long-term outcomes data treatment guidelines, it is imperative that healthcare providers take all the factors involved in the management of IPF into account, including the cost of treating declining symptoms and the cost of comorbidities.[32]

Optimizing patient care requires a thorough understanding of the role of new pharmacologic treatments and how they can change the management of patients and the health-economic assessment of IPF. One recent trial demonstrated that nintedanib slowed the decline in lung function independent of the degree of FVC impairment at baseline. In the study, patients with IPF and preserved lung volume (FVC >90% predicted) had the same rate of FVC decline over the following year and received the same benefit from nintedanib as patients with more impaired lung volume.[33] Treatment with nintedanib slowed the annual rate of decline in FVC in patients with IPF regardless of predicted FVC. Low or worsening FVC has been shown to be a risk factor for acute exacerbations, and these patients may be more likely to receive treatment.[34] There is evidence that patients with less severe impairment in FVC are not as likely to receive treatment.[35] However, there is some rationale to early treatment initiation, regardless of FVC. The first is that early treatment initiation can help preserve lung function, potentially delay disease progression, and potentially increase quality of life. The second is that FVC percent predicted is not an absolute indicator of functional lung tissue. In fact, the presence of emphysema increases FVC by modifying the impact of fibrosis on respiration.[33,36] These

findings of the nintedanib study support the concept of initiating treatment in patients with IPF with preserved lung volumes at the time of diagnosis, rather than waiting for symptoms of progression.

Optimizing Patient Care

As diagnostic criteria become more refined and accurate and potentially effective therapies emerge, attention should be given to healthcare resource usage and healthcare processes that ensure patient-centered management with sustainable, cost-effective, and quality care. As such, it is important to implement a structured, comprehensive, multidisciplinary management approach for the treatment and management of IPF and its associated comorbidities. This may help limit costs and provide effective and quality healthcare. In the case of a chronic condition such as IPF, this includes:

- Structured communication between healthcare professionals and the patient
- Initiation of care management programs that incorporate patient counseling and professional support

Importance of Communication

The realization of an IPF diagnosis is daunting, and the complexity of the process leading up to the diagnosis is likely to place significant stress on an already difficult situation. Before a diagnosis, approximately 40% of patients with IPF have already consulted 3 or more medical professionals.[37] The rapid disease progression may require that patients make decisions about care management, such as whether to opt for lung transplantation versus medical therapy. Unlike cancer or diabetes, educational support for IPF is lacking, and patients are often completely dependent on their healthcare team for support, advice, and disease education. As such, effective communication between the healthcare team and the patient is critical for patient support and effective treatment of this complex disease. This communication is greatly improved when the healthcare provider not only has a thorough understanding of IPF (including its etiology, associated comorbidities, and treatment options), but also an understanding of how the course of the disease impacts the patient on a day-to-day level. A patient-centered care approach includes informed, activated, participatory patient and family; an accessible, well-organized, responsive healthcare system; and a patient-centered communicative clinician who work together to improve communications that lead to improved health outcomes.[37] These factors will ensure that health outcomes are improved through responding to emotions, exchanging information, managing uncertainty, enabling patient self-management, fostering healing relationships, and making decisions together.

Care Management Programs

Care management programs are patient centered and are designed to improve the health outcomes and reduce cost due to disease-related complications; this is accomplished through coordinated healthcare interventions and communications for patients with a specific medical condition.[38,39] These programs do so by focusing on a target population and select factors that contribute to decreased functional status in patients with chronic diseases.[40] Most programs center around the idea that patient education is critical to self-management and overall treatment success.[39] Overall, targeted care management programs for people with rare chronic diseases support a partnership between healthcare professionals and patients, and develop a plan of care that focuses on prevention of exacerbations and complications. The plan aims at empowering the patient and includes[39]:

- ***Population identification*** processes based on demographic characteristics and healthcare usage
- ***Evidence-based practice guidelines*** to ensure consistency in diagnosis and treatment
- ***Collaborative practice models*** using a multidisciplinary team that includes healthcare professionals and support-service providers to educate patients on disease management
- ***Patient education,*** goal setting, and self-management support through patient counseling. Patient education is focused on prevention of exacerbations and the importance of treatment adherence, and uses behavior modification programs and supplemental services, including home visits, counseling, and appointment reminders
- ***Process and outcomes measurement*** using patient satisfaction, and health and economic outcomes to evaluate the success or failure of a plan. Outcomes monitored include drug use and treatment-related adverse events to maximize therapeutic efficacy and patient outcomes while minimizing drug-related adverse events and cost
- ***Routine reporting*** and feedback from patients, healthcare professionals, health plan administrators, and ancillary providers

Through patient education, care management programs can also help to facilitate preventive care, which is critically important in the management of chronic conditions including IPF. Examples of preventive care strategies include support for smoking cessation and incentives for yearly influenza vaccination and 5-yearly pneumococcal vaccination. Another example of how a care management program can help patients overcome hurdles is seen in a single center observational study of 40 patients with IPF.[41] In an attempt to understand low treatment adherence, the study evaluated the before and after effects of the following patient counseling measures with regard to pirfenidone: (1) slow dose titration to a target regimen and the use of prokinetic agents to lessen gastrointestinal-related intolerance; and (2) the use of sunscreen, sunlight avoidance, and dose interruption and reintroduction to minimize skin-related adverse events. Before the counseling measures, 15% of patients discontinued treatment within the first 6 months and more than half

experienced drug-related adverse reactions. Nearly 1 year later that number dropped to zero after clinician-initiated interventions were introduced.[41] The study demonstrated that improved adherence and compliance can be achieved by specialist nurse and clinician review, support, and education of the patient. Other common strategies used by care management programs to improve medication adherence include proactively and retroactively monitoring refill rates and educating patients and/or caregivers about drug administration and handling, adverse effects, and the potential for drug interactions.[42] Considering that pirfenidone and nintedanib are metabolized by enzymes of the cytochrome P-450 system, screening for drug interactions and communicating this information to patients has the potential to reduce adverse drug-related events and improve patient quality of life.

Care management programs are particularly important in the management of chronic conditions such as IPF, where patients have identified a dearth of clear and understandable disease education, comprehensive support, and counseling programs.[43] Compliance and adherence are key to the management of these conditions. Forty-six percent of people with chronic conditions do not believe that they receive the treatment they need, and 74% have difficulty obtaining prescription medications.[43] Studies have shown that up to 50% of patients with chronic conditions fail to adhere to their prescribed medications despite the effectiveness of the medication on their condition and their quality of life.

Conclusion

IPF is a high-cost disease, and optimizing cost efficiency requires an awareness of the evolving treatment landscape for IPF. Currently, nintedanib and pirfenidone are the only 2 prescription medications approved for treatment of IPF, each at a cost of almost $100,000 per patient per year.[44,45] It is highly likely that patients with IPF will be prescribed numerous different drugs in addition to these novel treatments to manage symptoms and comorbidities. This polypharmacy will further increase their prescription costs, adding to the already substantial economic burden associated with IPF. These treatment costs will continue to increase as novel therapeutics are approved and the population ages. It is important for payers to recognize the growing complexity of the management and drug treatment issues surrounding this condition. Care management programs using a team of individuals, such as case managers, clinical pharmacists, and specialty pharmacists, can play a vital role in managing these patients. Frequent contact with the care team and the patient may be useful to monitor for comorbidities and exacerbations, and result in interventions that can decrease emergency department use and hospitalizations. Likewise, medication therapy management programs to help patients with compliance, adherence, and the management of a multidrug regimen can provide essential support to these patients. As the treatment for this complex disease evolves, payers and treating physicians need to find ways to work in concert to improve outcomes.

Author affiliation: President, Gary Owens Associates, Ocean View, Delaware

Funding source: This activity is supported by educational grants from Genentech and Boehringer Ingelheim Pharmaceuticals, Inc.

Author disclosure: Dr Owens has no relevant financial relationships with commercial interests to disclose.

Authorship information: Concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and supervision.

Address correspondence to: gowens99@comcast.net.

Acknowledgment: Priya H. Karkhanis, MS, provided medical writing and editorial support for this manuscript.

REFERENCES

1. Raghu G, Collard H, Egan J, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183(6):788-824. doi: 10.1164/rccm.2009-040GL.
2. Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. *Clin Epidemiol.* 2013;5:483-492. doi: 10.2147/CLEP.S54815.
3. Frankel SK, Schwarz MI. Update in idiopathic pulmonary fibrosis. *Curr Opin Pulm Med.* 2009;15(5):463-469. doi: 10.1097/MCP.0b013e32832ea4b3.
4. Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11 [erratum in *Lancet Respir Med*. 2014;2(7):e12]. *Lancet Respir Med*. 2014;2(7):566-572. doi: 10.1016/S2213-2600(14)70101-8.
5. Nalysnyk L, Cid-Rufaza J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. *Eur Respir Rev.* 2012;21(126):355-361. doi: 10.1183/09059180.00002512.
6. Olson AL, Swigris JJ, Lezotte DC, Norris JM, Wilson CG, Brown KK. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. *Am J Respir Crit Care Med.* 2007;176(3):277-284. doi: 10.1164/rccm.200701-044OC.
7. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2011;183(4):431-440. doi: 10.1164/rccm.201006-0894CI.
8. Mannino DM, Etzel RA, Parrish RG. Pulmonary fibrosis deaths in the United States, 1979-1991. an analysis of multiple-cause mortality data. *Am J Respir Crit Care Med.* 1996;153(5):1548-1552. doi: 10.1164/ajrccm.153.5.8630600.
9. Collard HR, Chen SY, Yeh WS, et al. Health care utilization and costs of idiopathic pulmonary fibrosis in U.S. Medicare beneficiaries aged 65 years and older. *Ann Am Thorac Soc*. 2015;12(7):981-987. doi: 10.1513/AnnalsATS.201412-553OC.
10. Collard HR, Ward AJ, Lanes S, Courtney Hayflinger D, Rosenberg DM, Hunsche E. Burden of illness in idiopathic pulmonary fibrosis. *J Med Econ.* 2012;15(5):829-835. doi: 10.3111/13696998.2012.680553.
11. De Guzman J. FDA approves two drugs (Esbriet, Ofev) for treating fatal lung disease. *Capital OTC*. October 16, 2014. www.capitalotc.com/fda-approves-two-drugs-esbriet-ofev-for-treating-fatal-lung-disease/24307/. Accessed May 17, 2017.
12. Chen SY, Collard HR, Yeh WS, et al. An analysis of US Medicare beneficiaries: burden of direct medical costs in patients with idiopathic pulmonary fibrosis. PRS26. Presented at ISPOR 17th Annual European Congress Research Abstracts. November 8-12, 2014, Amsterdam, The Netherlands. www.ispor.org/awards/17Euro/PRS26-IPF-Medicare-Costs-EU-ISPOR_2014_FINAL.pdf. Accessed May 17, 2017.
13. Yu YF, Wu N, Chuang CC, et al. Patterns and economic burden of hospitalizations and exacerbations among patients diagnosed with idiopathic pulmonary fibrosis. *J Manag Care Spec Pharm.* 2016;22(4):414-423. doi: 10.18553/jmcp.2016.22.4.414.
14. Lee AS, Mira-Avendano I, Ryu JH, Daniels CE. The burden of idiopathic pulmonary fibrosis: an unmet public health need. *Respir Med*. 2014;108(7):955-967. doi: 10.1016/j.rmed.2014.03.015.
15. Juarez MM, Chan AL, Norris AG, Morrissey BM, Albertson TE. Acute exacerbation of idiopathic pulmonary fibrosis—a review of current and novel pharmacotherapies. *J Thorac Dis*. 2015;7(3):499-519. doi: 10.3978/j.issn.2072-1439.2015.01.17.
16. Agarwal R, Jindal SK. Acute exacerbation of idiopathic pulmonary fibrosis: a systematic review. *Eur J Intern Med*. 2008;19(4):227-235. doi: 10.1016/j.ejim.2007.04.024.
17. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J*. 2011;37(2):356-363. doi: 10.1183/09031936.00159709.
18. Mollica C, Paone G, Conti V, et al. Mechanical ventilation in patients with end-stage idiopathic pulmonary fibrosis. *Respiration.* 2010;79(3):209-215. doi: 10.1159/000225932.
19. Daniels C, Yi ES, Ryu JH. Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. *Eur Respir J.* 2008;32(1):170-174. doi: 10.1183/09031936.00176307.
20. Pashinsky YY, Jaffin BW, Litle VR. Gastroesophageal reflux disease and idiopathic pulmonary fibrosis. *Mt Sinai J Med.* 2009;76(1):24-29. doi: 10.1002/msj.20088.
21. Ryerson CJ, Arean PA, Berkeley J, et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. *Respirology.* 2012;17(3):525-532. doi: 10.1111/j.1440-1843.2011.02122.x.
22. King C, Nathan SD. Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. *Curr Opin Pulm Med.* 2013;19(5):466-473. doi: 10.1097/MCP.0b013e328363f460.
23. Lancaster LH, Mason WR, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest.* 2009;136(3):772-778. doi: 10.1378/chest.08-2776.

24. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. a population-based cohort study. *Am J Respir Crit Care Med.* 2000;161(1):5-8. doi: 10.1164/ajrccm.161.1.9906062.
25. Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. *Chest*. 2015;147(1):157-164. doi: 10.1378/chest.14-0359.
26. Sprunger DB, Olson AL, Huie TJ, et al. Pulmonary fibrosis is associated with an elevated risk of thromboembolic disease. *Eur Respir J.* 2012;39(1):125-132. doi: 10.1183/09031936.00041411.
27. Fulton BG, Ryerson CJ. Managing comorbidities in idiopathic pulmonary fibrosis. *Int J Gen Med*. 2015;8:309-318. doi: 10.2147/IJGM.S74880.
28. Fleetwood K, McCool R, Glanville J, et al. Systematic review and network meta-analysis of idiopathic pulmonary fibrosis treatments. *J Manag Care Spec Pharm*. 2017;23(3-b suppl):S5-S16. doi: 10.18553/jmcp.2017.23.3-b.s5.
29. Fisher M, Nathan SD, Hill C, et al. Predicting life expectancy for pirfenidone in idiopathic pulmonary fibrosis. *J Manag Care Spec Pharm*. 2017;23(3-b suppl):S17-S24. doi: 10.18553/jmcp.2017.23.3-b.s17.
30. Ofev [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2017.
31. Esbriet [prescribing information]. South San Francisco, CA: Genentech, Inc; 2017.
32. Idiopathic Pulmonary Fibrosis Clinical Research Network; Raghu G, Anstrom KJ, et al. Prednisone, azathioprine, and *N*-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012;366(21):1968-1977. doi: 10.1056/NEJMoa1113354.
33. Kolb M, Richeldi L, Behr J, Anstrom KJ, Glazer C; IPFnet investigators. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax*. 2017;72(4):340-346. doi: 10.1136/thoraxjnl-2016-208710.
34. Collard HR, Yow E, Richeldi L, Anstrom KJ, Glazer C; IPFnet Investigators. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respir Res.* 2013;14:73. doi: 10.1186/1465-9921-14-73.
35. Behr J, Kreuter M, Hoeper MM, et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *Eur Respir J.* 2015;46(1):186-196. doi: 10.1183/09031936.00217614.
36. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. *Chest.* 2013;144(1):234-240. doi: 10.1378/chest.12-2403.
37. Wuyts WA, Peccatori FA, Russell AM. Patient-centred management in idiopathic pulmonary fibrosis: similar themes in three communication models. *Eur Respir Rev*. 2014;23(132):231-238. doi: 10.1183/09059180.00001614.
38. Annis AM, Holtrop JS, Tao M, Chang HC, Luo Z. Comparison of provider and plan-based targeting strategies for disease management. *Am J Manag Care.* 2015;21(5):344-351.
39. Disease Management Programs: Improving health while reducing costs? Georgetown University Health Policy Institute. Issue Brief 4. January 2004. hpi.georgetown.edu/agingsociety/pubhtml/management/management.html#2.
40. Duck A, Pigram L, Errhalt P, Ahmed D, Chaudhuri N. IPF Care: a support program for patients with idiopathic pulmonary fibrosis treated with pirfenidone in Europe. *Adv Ther*. 2015;32(2):87-107. doi: 10.1007/s12325-015-0183-7.
41. Chaudhuri N, Duck A, Frank R, Holme J, Leonard C. Real world experiences: pirfenidone is well tolerated in patients with idiopathic pulmonary fibrosis. *Respir Med*. 2014;108(1):224-226. doi: 10.1016/j.rmed.2013.11.005.
42. Patel BN, Audet PR. A review of approaches for the management of specialty pharmaceuticals in the United States. *Pharmacoeconomics*. 2014;32(11):1105-1114. doi: 10.1007/s40273-014-0196-0.
43. Chronic Conditions: Making the case for ongoing care. September 2004 update. Johns Hopkins University, Partnership for Solutions. www.partnershipforsolutions.org/DMS/files/chronicbook2004.pdf. Accessed May 17, 2017.
44. Drugs.com. Esbriet Prices, Coupons and Patient Assistance Programs. www.drugs.com/price-guide/esbriet. Accessed May 8, 2017.
45. Drugs.com. Ofev Prices, Coupons and Patient Assistance Programs. www.drugs.com/price-guide/ofev. Accessed May 8, 2017.