

Idiopathic Pulmonary Fibrosis: The Role of the Pharmacy Benefit Manager in Providing Access to Effective, High-Value Care

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It primarily affects individuals aged 60 and older, with an annual incidence in a Medicare population between 78.7 and 93.2 per 100,000 person-years. As patients with IPF live longer, the prevalence has increased, from 202.2 cases per 100,000 in 2001 to 494.5 cases per 100,000 in 2011.¹

The condition, although rare, is growing in incidence because of the aging population in the United States. IPF is generally fatal with a median survival of 3 years or less after diagnosis unless patients undergo lung transplantation. Even then, the mortality rate is high.²

Until recently, there were no approved pharmacologic treatments for IPF. Instead, national guidelines from the American Thoracic Society (ATS) and the European Respiratory Society recommended pulmonary rehabilitation, long-term oxygen therapy, lung transplantation, and enrollment in clinical trials.² However, a new update to the guidelines from the ATS released in 2015 recommends conditional use of 2 recently approved drugs: nintedanib and pirfenidone.³

High-Cost Disease

The chronic nature of IPF, coupled with high rates of comorbidities, puts a substantial financial burden on payers, particularly Medicare. A 2015 analysis of a commercial claims database and a Medicare supplemental insurance database found that patients with IPF are twice as likely to be hospitalized and require outpatient medical visits as compared to those without, resulting in direct medical costs twice as high (\$26,378 in 2008 dollars vs \$12,124). That translates into an additional cost of \$1 billion per year. Inpatient mortality for patients with IPF was also 3-fold higher than that of controls (52.5 deaths per 1000 persons/year vs 14.8 per 1000 persons/year [rate ratio = 3.64; 95% CI, 3.12-

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause that primarily affects individuals aged 60 and older. The economic costs of the disease are significant, with patients twice as likely to be hospitalized and twice as likely to require outpatient medical care as compared with those without IPF, resulting in an additional annual cost to the Medicare system of \$1 billion. The first pharmacologic treatments for IPF, nintedanib and pirfenidone, were approved in 2014 for conditional use. Their use is expected to significantly increase the cost of care for this population, given that patients will likely continue to take the medication until their death. The use of these medications requires that payers implement innovative opportunities to manage their utilization and cost, as well as other medical costs related to the disease. Pharmacy benefit managers have an important role to play in managing the cost and appropriate utilization of these new treatments through disease management programs, negotiated discounts and rebates, improved adherence to treatment recommendations, and benefit design to optimize patient care.

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For author information and disclosures, see end of text.

Table 1. Direct Medical Costs of IPF per Person/Year (2008; Dollars)⁴

	IPF	Control
Outpatient medications	\$6565	\$3033
Inpatient services	\$9100	\$5120
Outpatient services	\$10,713	\$6100
Total	\$26,378	\$14,254

IPF indicates idiopathic pulmonary fibrosis.

Adapted from Collard HR, Chen SY, Yeh WS, et al. *Ann Am Thorac Soc.* 2015;12(7):981-987.

4.25)].⁴ **Table 1**⁴ compares medical costs for patients with IPF versus controls.

Another analysis of data from Medicare beneficiaries from 2000 to 2011 revealed that direct medical costs were significantly higher in patients with IPF than in matched controls, even before their diagnosis (\$10,124 vs \$5,888), and nearly 3-fold higher in the year following diagnosis (\$20,887 vs \$8,932). Half of those costs were related to inpatient admissions compared with 43% of costs for inpatient admissions in the control group; inpatient costs doubled after diagnosis, reflecting the rather rapid progression of this disease as well as the historically poor prognosis of the disease.⁵ Costs reflect the seriousness of this disease; patients with IPF also have higher rates of comorbidities than matched controls, including pulmonary hypertension, chronic obstructive pulmonary disease, pulmonary embolism, and pulmonary infection.⁴

The overall cost of this disease is expected to increase substantially with the addition of pirfenidone and nintedanib, the first FDA-approved therapies for IPF, which have an annual cost of \$94,000 and \$98,000, respectively. Unlike patients receiving other high-priced drugs that have received significant attention in the media, such as those for hepatitis C or cancer, patients with IPF will likely remain on these medications until they either receive a lung transplant or die.⁶

Since there were previously no approved therapies for IPF, pirfenidone and nintedanib were approved based on placebo-controlled studies. Although the trials differed in their design and end points, the results were significant enough to allow approval.

Neither drug has been studied against the other, in conjunction with the other, or for other currently used (off-label) pharmacologic and lifestyle therapies. Thus, it remains unclear which patients should receive which treatment. It is also not clear if they should be used simultaneously.⁷ A meta-analysis of trials of the 2 drugs and indirect comparisons between nintedanib

and pirfenidone showed a slower decline in forced vital capacity (FVC) for patients treated with nintedanib compared with patients treated with pirfenidone. There was no difference in mortality rates between the 2 cohorts. Both drugs were better at reducing the rate of decline in FVC than placebo. Analysis of the pooled data suggests a reduction in the rate of acute exacerbations with nintedanib, with a decrease of overall mortality and respiratory-related mortality with pirfenidone.⁸

Other concerns center on the design of the clinical trials, which enrolled patients with mild to moderate IPF and without significant comorbidities. Most trials used FVC as a primary end point. Although FVC is correlated with disease progression, it is not clear that treatment-related changes in FVC correlate with clinically meaningful changes, such as survival.⁹ Instead, it has been suggested that progression-free survival, overall survival, hospitalization, and patient-reported outcomes are better end points.¹⁰⁻¹³ Another concern is that the FDA approved the 2 drugs for use in all patients with IPF, even though the studies were conducted only in those with mild to moderate IPF.^{14,15}

Sales of the drugs are already robust. In the first half of 2015, the manufacturer of pirfenidone reported sales of \$234 million. Nintedanib's manufacturer is privately held and does not publically report sales figures. Overall sales of both drugs are predicted to top \$500 million in 2015.^{16,17}

As with other high-cost specialty drugs, the approvals of pirfenidone and nintedanib will require that payers implement innovative strategies to manage their utilization and cost, as well as other medical costs related to the disease.

Cost Effectiveness of Pirfenidone and Nintedanib

First, we must preface any comparison of cost in other countries with the reality that for a variety of reasons, the cost of these drugs in other countries may not reflect the cost in the United States. However, because there is

scant literature from US-based studies, it is at least worth considering some of the findings from other nations.

A group of British researchers conducted a systematic review of the clinical and cost effectiveness of current treatments for IPF. Fourteen studies—13 randomized, controlled clinical trials (RCTs) and 1 controlled clinical trial from various countries—were selected from 905 references.¹⁸

At an assumed cost of £39,388 a year (US \$61,581 in 2015), the authors' analysis indicated that nintedanib must cost less than £736 a month (US \$1150 in 2015) to be considered cost-effective compared with best supportive care at a willingness-to-pay (WTP) threshold of £30,000 (\$46,904 per quality-adjusted life year). Pirfenidone at an assumed cost of £70,118 (\$109,627) was also not cost-effective at a WTP of £30,000. The authors identified inhaled N-acetylcysteine as the most clinically and cost-effective option at a WTP threshold of £30,000, but noted that its treatment effect was not statistically significant in the 1 reviewed RCT, and that larger studies are required to demonstrate the level of statistical significance required in the clinic.¹⁸ However, there are many additional factors to consider when evaluating cost-effectiveness of therapies.

Managers and Specialty Drugs

Specialty drugs, such as pirfenidone and nintedanib, have accounted for an ever-increasing percentage of overall drug spending. In 2014, specialty drugs accounted for one-third of all pharmaceutical spending in the United States, which is an increase from 23% in 2009. In addition, the \$54 billion the United States spent on specialty drugs over the past 5 years has contributed to 73% of the overall growth in spending on pharmaceuticals.¹⁹ That trend shows no sign of slowing. In 2014, 19 of the 41 new molecular entities the FDA approved (46.3%) fit the definition of a “specialty” drug.²⁰

Pharmacy benefit managers (PBMs) have an important role to play in managing the costs and appropriate utilization of specialty drugs, including those for IPF. Currently, an estimated 95% of insured Americans have prescription drug coverage through a PBM.²¹

Although PBMs initially provided third-party administrative management of pharmacy claims, their role has grown exponentially over the past 20 years. Today, they act as intermediaries between payers and pharmaceutical companies, leveraging volume to elicit rebates and discounts from drug manufacturers and pharmacies. PBMs develop and maintain drug formularies, negotiate directly with drug manufacturers and pharmacies, identify and implement cost-savings programs, provide medication

therapy management, run mail order and specialty pharmacies, and interact with patients to improve adherence and outcomes.^{22,23} Given their role in developing tiered drug formularies, PBMs exert tremendous influence over drug prescribing.

A 2011 report from the Pharmaceutical Care Management Association predicted that PBMs would save plans and consumers about one-third of drug costs (nearly \$2 trillion) between 2012 and 2021 and up to half of the total costs for plans that complied with all PBM recommendations and tools.²⁴ In a 2014 survey of more than 80 large Midwest employers representing 1.5 million employees, 51% of respondents agreed or strongly agreed that their PBM did a “good job” managing specialty drug costs. However, 90% agreed or strongly agreed that new and innovative solutions were required.²⁵

Opportunities to Manage Costs and Utilization

PBMs have many options available to manage high-cost drugs and diseases. These include negotiating rebates and discounts with drug manufacturers, directing patients to generic alternatives, providing disease management programs, increasing medication adherence, encouraging the use of mail order and/or specialty pharmacies, and managing utilization through prior authorization, benefit design, step therapy, and refill limits. Through their specialty pharmacies, they can also help patients find financial assistance to pay for their medication.²⁴

Table 2²⁶ depicts the most commonly used strategies to manage specialty drug utilization based on a 2014 survey of 366 employers covering an estimated 23.5 million enrollees.²⁶

Rebates and Discounts

Rebates are most beneficial when there are several effective treatments available in the same class. However, given the lack of head-to-head clinical trials between pirfenidone and nintedanib and the fact that trials for each demonstrated similar outcomes, PBMs may want to consider negotiating deep discounts in exchange for exclusivity. A good example is hepatitis C, for which 4 new drugs have entered the market in the past 18 months, all with prices nearing \$100,000 for a 12-week treatment. With 4 similarly effective drugs available, PBMs are negotiating deep discounts with manufacturers in exchange for formulary exclusivity.²⁷

Disease Management Programs

PBMs also use disease management programs to improve access and reduce costs for patients to add value to

Table 2. Commonly Used Strategies to Manage Specialty Drug Utilization²⁶

	Pharmacy Benefit				Medical Benefit ^a	
	2011 ^b (n = 122)	2012 ^c (n = 306)	2013 ^d (n = 335)	2014 ^e (n = 300)	2013 (n = 214)	2014 (n = 195)
Prior authorization	82%	84%	90% ^e	86%	68%	72%
Clinical care management programs	81%	74%	82% ^e	76%	55%	61%
Step therapy	60%	68%	74% ^b	68%	43%	51%

Strategies are ranked by their use rate in the pharmacy benefit in 2014. No significant comparisons of 2013 with 2014 in the medical benefit. Tests of comparisons across benefits not performed.

^aBase: Respondents who cover at least one specialty drug under the medical benefit.

^{b,c,d,e}Significantly higher than group indicated by superscripted letter. Groups are identified in the column header.

Strategies are ranked by their use rate in the pharmacy benefit in 2014. No significant comparisons of 2013 with 2014 in the medical benefit. Tests of comparisons across benefits not performed.

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their core PBM functions. These programs identify patients with a specific medical condition, monitor drug use and effects, and encourage adherence and preventive care.²⁸ Disease management programs can also increase the rate of smoking cessation, which is particularly important with a respiratory disease like IPF, improve the delivery of care for related comorbidities, and improve patient quality of life.²⁹

A disease management program is particularly important in a disease like IPF, in which patients experience an overwhelming lack of psychosocial support, educational resources, and information regarding treatment options, supplemental oxygen, pulmonary rehabilitation, and transplantation.³⁰⁻³² In an industry-sponsored survey of 100 patients with IPF and 100 caregivers, 72% of respondents agreed that better disease management could improve their overall well-being.³³

There are 2 published studies on disease management programs for IPF. The IPF Care Patient Support Program (IPF Care), developed and supported by the manufacturer of pirfenidone together with healthcare specialists throughout Europe and the United Kingdom, is designed to support patients taking pirfenidone as they adjust to their diagnosis and treatment, provide patient education, support, and empowerment, including counseling about living with their condition and managing adverse events, and facilitating and enhancing communication between patients and their healthcare teams. The program begins when the patient is prescribed pirfenidone, and it involves phone calls and patient-tailored information booklets. In some countries, the program also involves face-to-face visits with nurses.³⁴

Results from IPF Care in the United Kingdom demonstrated low rates of discontinuation over 18 months. Of

the 465 patients enrolled in the program, 71% remained after 18 months. Sixteen percent discontinued the drug, mostly due to adverse events (8%) and worsening symptoms (3%), and 11% died. A survey sent to 100 patients who completed the program (44 of the 100 patients responded) suggested that IPF care improved patient self-efficacy about their disease, and patients generally agreed that they remained on pirfenidone longer because of the program than they would have otherwise.

The Program to Reduce Idiopathic Pulmonary Fibrosis Symptoms and Improve Management (PRISM), another disease management intervention, was a small pilot study designed to assess the impact of the program on patient and caregiver stress, evaluate how patient health-related quality of life (HRQOL) was affected, help improve symptom control, and encourage end-of-life decision making.³⁴

Researchers randomized 42 patients and their caregivers to either the intervention group or usual care. All patients completed baseline screening to measure anxiety, depression, perceived stress, HRQOL, and dyspnea.³⁵ The intervention consisted of six 2-hour weekly group sessions for patients and their caregivers. Participants received education about the pathophysiology, symptoms, and treatment of IPF; the basic principles of cognitive behavior and distorted cognitive thinking; the interrelationships between illness, depression, and anxiety; living with a terminal condition; and the day-to-day realities of living with IPF. Patients receiving usual care saw their regular clinicians every 3 to 6 months and could call a clinical nurse specialist with questions.³⁵

The researchers found that patients in the intervention group had lower HRQOL scores after the intervention than before, although their caregivers

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reported less stress. There were no statistically significant differences in scores measuring dyspnea, perceived stress, or depression for patients.³⁵ However, patients and caregivers participating in PRISM told researchers that they felt less isolated, had a more balanced view of their illness, and received personal satisfaction from participating in research. The researchers suggest that the decline in HRQOL scores and increased anxiety were due to patients confronting many difficult topics in the training, particularly end-of-life issues, and note that the study was underpowered to detect differences between the 2 groups.

Improving Adherence to Treatment Recommendations

A seminal analysis from the World Health Organization revealed that patients with chronic conditions adhere to long-term medication, including specialty medications, only about half the time.³⁶ Adherence to medications in pulmonary diseases is also low, with results from one study in patients with cystic fibrosis finding an average adherence rate of 48%.³⁷

An analysis of 41 studies of adherence to medications for a variety of pulmonary diseases found an average adherence rate of 68.6%.³⁸ Several factors contribute to nonadherence, many of which can be targeted through disease management programs. These include patient understanding of their disease, the importance of the medication, the perception that the medication is ineffective, and lack of professional and/or family support. Other barriers that can be addressed through case management include various social and economic issues and the complexity of the dose regimen.^{39,40} These kinds of barriers may be particularly relevant with a disease such as IPF, which progresses despite treatment.

To reduce nonadherence due to adverse effects, a panel of European experts in pulmonology, gastroenterology, and dermatology developed recommendations for the use of pirfenidone (nintedanib had not yet been approved in Europe at the time of publication).⁴¹ Recommendations include taking each of the 3 capsules throughout a meal, rather than at one time (ie, 1 at the beginning, 1 in the middle, 1 at the end) to help prevent the drug from slowing gastric motility; slowing titration to the full dose from 2 weeks to 4 weeks; reducing the dose to 1 or 2 capsules 2 to 3 times a day and matching the reduced dose to the time of day when the nausea was most severe; and using prokinetic agents such as domperidone, mosapride, and metoclopramide or proton pump inhibitors to manage gastrointestinal-related adverse effects.

To reduce skin-related adverse events, the panel recommended educating patients to avoid UV-A and UV-B light (including sunlamps), intense artificial light sources, and indirect sunlight for several hours after taking a dose; to use a sunscreen effective against both; and to wear clothing that blocks sunlight, a broad-brimmed hat, and gloves when in the sun. Other options include dose reduction, perhaps dose interruption and reintroduction. The panel also recommended that caregivers receive education about the medication from the entire healthcare team.

Most of the recommendations came from a published report on 40 patients with IPF treated with pirfenidone between September 2011 and January 2013. More than half (58%) experienced adverse effects, primarily gastrointestinal, and 15% discontinued the treatment within the first 6 months; however, that number dropped to zero 10 months later, after the clinicians initiated the interventions described in the panel's recommendations.⁴² Specialty pharmacies have numerous patient support functions, many of which are unique to specialty pharmacy. They can also improve patient adherence by proactively and retrospectively monitoring refill rates and reminding patients of refills with phone calls, as well as cards and text messages; the former is common to specialty pharmacies, with the latter being done by both retail and specialty pharmacies.

A regression model found that pharmacy type was the strongest predictor of medication refill adherence, with those using a retail pharmacy having a medication refill adherence rate that was 16% lower than those using a specialty pharmacy when controlling for reimbursement/payment type, copayment/payment amount per prescription, age, sex, and ethnicity.⁴³

Managing Utilization

PBMs have managed utilization of specialty drugs with benefit design, prior authorization, step therapy, and partial fills. Step therapy is highly unlikely with pirfenidone and nintedanib because there are no other approved options. Additional options for utilization management are described below.

Benefit Design

All PBMs use tiered formularies as an integrated part of benefit design, and health plans that have added pirfenidone and nintedanib to their formularies are placing them on the highest tier. This involves significant cost-shifting to patients, with coinsurance often as high as 30%.^{25,44} Manufacturers override those high out-of-pocket

payments, however, with coupons and other discounts, which countermands the intended effect of shifting more costs to patients.⁴⁵ In addition, there are no lower cost alternatives for IPF, so placing the drug on a higher tier and passing more cost to patients will not drive them to lower-cost alternatives. High out-of-pocket payments can also backfire, with numerous studies finding that rates of drug abandonment and nonadherence increase as out-of-pocket payments increase.⁴⁶⁻⁴⁸

Prior Authorization

Prior authorizations are also commonly used for specialty and other high-cost drugs.⁴⁴ Evidence related to their cost savings is mixed, however, with some studies finding little economic benefit given the cost of managing the program, the fact that 80% of requests are approved, and the potential for increased healthcare utilization if patients do not have access to the right medication.⁴⁹⁻⁵² The question, notes the American Society of Consultant Pharmacists, is whether utilization tools, such as prior authorization, provide value. In other words, do savings in drug costs, if any occur, offset other medical costs?⁵³ This question will need to be addressed with regard to the new treatments for IPF.

Partial Fill

Partial fill, in which patients may only receive a half-month supply, is another way to control costs and reduce waste by ensuring patients can tolerate the medication before providing a full supply. A 2015 report on specialty drugs involving a survey of 70 commercial payers found that half reported savings of 1% to 6% from a partial fill, whereas 16% reported greater savings.⁵⁴ Partial fill may be a good option for pirfenidone and nintedanib in the first 3 to 6 months of treatment because of the drugs' adverse effects.

Current Coverage of Pirfenidone and Nintedanib

To date, it appears that most plans have put pirfenidone and nintedanib on tiers 4 and 5, even tier 6 in some instances. Some require prior authorization, limit patients to a 30-day prescription, prohibit their concurrent use, require that patients have a clinically documented diagnosis of IPF and be under the care of a pulmonologist, or obtain the drugs only through a specialty pharmacy.⁵⁵⁻⁶⁰

Not all plans are covering the drugs. Citing a lack of clinical experience and utilization, Kaiser Permanente of the Mid-Atlantic States' Pharmacy and Therapeutics Committee voted in April and May 2015, respectively,

not to add pirfenidone or nintedanib to its commercial formularies or to formularies for its Medicaid managed care programs in Maryland and Virginia.^{55,61} Both are tier-5 drugs on the plan's Part D formularies.

Conclusion

How PBMs manage utilization and costs associated with pirfenidone and nintedanib, which patients will require for the rest of their lives, presents many challenges. The disease is fatal, and even a lung transplant can only delay death due to IPF. There are no other approved therapies indicated for IPF; other drugs are currently used off-label and are poorly studied.

With 2 newly approved therapies, however, PBMs will eventually be able to use data to determine which might be more cost-effective. In addition, nondrug options, including the development of IPF-specific mobile apps and wearable devices, home-monitoring devices, and virtual health assistants might provide PBMs with additional tools and data sources to manage IPF and other diseases.

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