Pulmonary Arterial Hypertension: Progress and Challenges in the Modern Treatment Era

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Abstract

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease with an estimated incidence of 2 cases per million individuals per year and a prevalence of approximately 10 to 15 cases per million individuals. PAH is more common in certain groups of patients, such as those with connective tissue disease and congenital heart disease, and is often overlooked in patients with these comorbidities. Treatment options in the United States have expanded to include 12 PAH-specific therapies, 3 of which were approved in 2013. As a result of treatment advancements, PAH patients are living longer. However, many challenges remain. Resource utilization in PAH, a primary driver of which is hospitalization, imposes a major economic burden on patients, payers, and society. Because change in 6-minute walk distance and other historical measures do not correlate well with the risk of hospitalization, guidelines favor more rigorous composite assessments of efficacy that take into account clinical worsening, including mortality and hospitalization. Stakeholders, including providers and payers, are tasked with selecting treatments with the best evidence of clinical benefit. Managing adherence to those therapies remains an important priority in improving clinical outcomes and reducing the overall clinical and economic burden of PAH. Future research that includes patient-reported outcomes, particularly those that reflect health-related quality of life, may be of particular relevance in this complex disease.

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For author information and disclosures, see end of text.

Pulmonary arterial hypertension (PAH) is a rare, chronic, and progressive disease characterized by an increased pulmonary vascular resistance (PVR) leading to right ventricular overload, hypertrophy, and eventually to right ventricular failure and death.[1,2] Data from a French national registry of 674 patients diagnosed with PAH provide conservative estimates for an annual incidence of 2.4 new cases per million individuals (2002-2003) and prevalence of 15.0 cases per million individuals.[3] An analysis of data involving 55 US centers from the largest PAH registry in the world, REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management), for study subjects matched to the French registry requirements, similarly showed an annual incidence of 2.0 cases per million individuals and a prevalence of 10.6 cases per million.[4]

The past 2 decades mark the modern treatment era for PAH, which began with the approval of Flolan (epoprostenol sodium) for continuous intravenous (IV) infusion in 1995.[5] Prior to this, traditional treatments included calcium channel blockers, diuretics, and anticoagulants.[6] Epoprostenol was the first agent approved specifically for the treatment of PAH and was the first such agent to demonstrate a survival benefit among patients with severe idiopathic PAH in an open label, prospective, randomized clinical trial.[5,7-10] Treatment has evolved considerably since that time, and now includes various mechanisms of action and methods of administration. Three identified signaling pathways with FDA-approved therapies exist—the prostacyclin pathway, the endothelin pathway, and the nitric oxide pathway.[6] Currently, there are 12 FDA-approved drugs for PAH available in the United States, targeting 1 of these 3 pathways. They include oral, inhaled, and parental therapies.[11-22] Three of these agents are oral therapies approved in 2013: the endothelial receptor antagonist (ERA) macitentan, the soluble guanylate cyclase (sGC) stimulator riociguat, and the oral form of the prostacyclin analogue treprostinil.[23-26] Advanced PAH-specific therapies are now the mainstay of treatment for PAH and may be used with supportive therapies (eg, diuretics, anticoagulants, digitalis, and oxygen).[6,10]

An examination of historical and more recent registry data suggest that survival in PAH has improved since PAH-specific therapies first entered the market. An analysis published by D'Alonzo et al used data from the National Institutes of Health registry for 194 patients who were diagnosed with PAH between July 1981 and December 1985 and followed until 1988. The analysis indicated that the survival rates at that time were approximately 68% at 1 year, 48% at 3 years, and 34% at 5 years.[27] More recent data from the REVEAL registry, which included 2635 incident and prevalent patients with PAH enrolled from March 2006 to December 2009, showed a survival rate among individuals with PAH of 85% at 1 year, 68% at 3 years, and 57% at 5 years.[28] Despite treatment advancements, mortality remains high, particularly in higher-risk populations such as in patients with connective tissue disease (CTD). A separate analysis of 484 consecutive patients treated at a single clinic between 1995 and 2004 showed a 1-year mortality rate of 32% among patients with PAH and CTD, while patients with idiopathic PAH had a 15% mortality rate after 1 year.[29]

PAH remains a complex disease with many challenges, including late diagnosis, suboptimal treatment adherence, variability in clinical trial designs, and limited morbidity, mortality, and economic outcomes data. Future research and programs that focus on improvements in these areas will provide relevant information to assist healthcare providers and payers in their decision making.

Delayed Diagnosis

The most recent data from the REVEAL registry demonstrate that patients with PAH are living longer. As with any chronic, progressive disease, early diagnosis is an essential component of optimizing health outcomes.[30,31] However, late diagnosis is common in PAH, occurring in about three-fourths of patients. The nonspecific nature of PAH symptoms (eg, shortness of breath, fatigue, weakness) and the insufficient specificity and sensitivity of the available screening tools contribute to the difficulties in diagnosing PAH, especially at an early stage.[30] Data from both the REVEAL and French national registries show that diagnosis typically occurs late in the disease process, as indicated by the percentage of patients with New York Heart Association (NYHA) functional class (FC) III or IV PAH in each registry (75% of patients in the French registry study, and 72% of patients in the REVEAL registry study).[3,4]

Moreover, the time from symptom onset to a confirmed diagnosis remains virtually unchanged from what it was in the late 1980s, with estimates ranging from 2.0 to 2.8 years.[30,31] Further, as reflected in data from the REVEAL registry, in certain high-risk groups, such as patients with CTD or congenital heart disease, PAH is often overlooked. More than half of patients in each of these subgroups receive a late-stage diagnosis (World Health Organization [WHO] FC III or IV).[32]

Experts participating in successive WHO World Symposia on Pulmonary Hypertension (WSPH) have long emphasized the importance of early screening for patients with CTD. In the 5th WSPH, held in Nice, France, in 2013, an expert working group developed a consensus statement in support of WHO PAH 2009 guidelines, which recommended annual screening of patients with CTD.[33-35] Additionally, it was recognized that various other groups of patients may be considered at high risk for development of PAH and ought to be candidates for early detection.[33,35,36] These include patients with congenital heart disease, chronic liver disease, and human immunodeficiency virus.[33] Educating healthcare professionals on recognizing the characteristics of PAH is important, particularly rheumatologists who treat patients with CTD and cardiologists who treat patients with congenital heart disease.

Data from the EARLY study, in which mildly symptomatic patients (FC II) with PAH were treated with an ERA, suggest that early diagnosis and treatment can improve outcomes; the placebo-controlled study found that treatment with an ERA was associated with a 22.6% reduction in PVR (P <.0001) and a nonsignificant treatment effect of 19.1 meters improvement in 6-minute walk distance (6MWD) compared with placebo. Bosentan treatment was associated with a lower incidence of worsening functional class compared with placebo (3 patients [3.4%] vs 12 patients [13.2%]; P = .0285). There was also a delay in time to clinical worsening in the bosentan-treated group compared with the placebo group (hazard ratio [HR] 0.227 (95% CI 0.065-0.798; P = .0114).[37] Furthermore, the EARLY extension phase results showed improvements in functional class in 18.4% of patients and high rates of event-free survival (79.5%) after 3.6 years of follow-up.[38] Promoting early diagnosis and early treatment is a critical component of delaying progression of the disease, which ultimately results in costly complications and hospitalizations.

Economic Burden of PAH-Related Hospitalization

PAH, particularly late-stage disease, imposes a heavy

economic burden on patients, payers, and society. Recent data indicate that one of the major drivers of PAH-associated costs is hospitalization. In a recent analysis using the REVEAL database, patients (n = 862) newly diagnosed with PAH were evaluated for first-time hospitalizations, categorized as PAH-related or non–PAH-related. A total of 56.8% of patients with PAH had 1 or more hospitalizations, of which 52.4% were specifically PAH-related. The analysis showed that PAH-related hospitalization was associated with a greater risk of rehospitalization and worse survival at 3 years compared with non–PAH-related hospitalization.[39] In addition, patients with PAH-related hospitalizations were more likely to be on parenteral therapy and to be in functional classes III or IV prior to being hospitalized.

Another recent analysis was presented by Lacey et al at the 2013 Academy of Managed Care Pharmacy Nexus meeting. The investigators examined the cost of hospitalizations among patients with PAH using a large claims database that included both Medicare Advantage and commercially insured patients in the United States. All-cause hospitalizations (n = 5582) incurred a mean cost of $34,123 (SD, $107,005) per hospitalization, with a mean length of stay (LOS) of 11.68 days (SD, 20.8 days).[40] By comparison, for patients with a principal diagnosis of PAH (n = 243), the corresponding means were $73,880 (SD, $188,354) per hospitalization and 16.21 days (SD, 27.1 days) for LOS.

In a separate analysis using the same database, Lacey et al assessed the impact of rehospitalization in driving high healthcare costs for patients with PAH. The investigators reviewed medical and pharmacy claims data (2007-2011) for 1203 patients with 1 or more rehospitalizations for PAH following the initial hospitalization. Approximately 1 in 5 (21.2%) patients with PAH were rehospitalized within 30 days after discharge from their initial hospitalization while 79.1% were readmitted within 1 year of their initial hospitalization and discharge. A substantial proportion (39.2%) of patients in this sample had multiple PAH-related rehospitalizations during the year that followed their initial hospitalization. The mean cumulative cost per patient of all PAH-related rehospitalizations during the first year after the initial hospitalization was $71,622 (SD, $189,433). For this cohort of patients, the mean cost of initial hospitalization was $30,286 (SD, $78,140) and the total cumulative mean for all hospitalizations was $101,908. These studies highlight the high morbidity and cost of PAH.[41]

Treatment Options and the Role of Combination Therapy

The complexity of the treatment algorithm for PAH has progressively increased since the second WSPH in 1998. At that time, therapeutic options in PAH were mainly restricted to 2 options: calcium channel blockers (for vasoreactive patients) and the only treatment specifically approved for PAH—epoprostenol for continuous IV infusion.[10]

Following the 5th 2013 World Symposium, experts published the current treatment algorithm, which is divided into 3 main areas: 1) general measures and supportive therapy; 2) initial therapy; and 3) with inadequate response to initial therapy, the recommendation and role of combination therapy and additional interventional procedures, such as balloon atrial septostomy and lung transplant.[10]

The WSPH algorithm changes over time also reflect the increased use of combination therapy in practice and clinical trials. In 2003, the year of the 3rd WSPH, combination therapy was considered experimental. Following the 4th WSPH, at Dana Point, California, in 2008, an expert consensus document was developed that included a PAH treatment algorithm with consideration of combination therapy when therapeutic goals were not met.[42] In the 2013 Nice proceedings, the experts recommended combination therapy when treatment goals are not achieved.[10]

Combination therapy is common in current practice, as reflected in the most recent REVEAL registry data showing the practice patterns of PAH centers in the United States for 2525 adults who met the criteria for PAH—46% of patients were being treated with dual agents and 9% were on triple therapy.[43] Payers have reported these trends in combination therapy as well. In a 2010 claims analysis by Angalakuditi et al, 28% of patients taking the ERA bosentan and 13% of patients receiving the phosphodiesterase type 5 (PDE5) inhibitor sildenafil were taking at least 1 other specific medication for PAH in the first 90 days following the index date (ie, the date of first PAH treatment claim).[44] The combination was usually an ERA plus a PDE5 inhibitor.

Strength of Evidence in PAH-Specific Drugs

In addition to the clinical efficacy and safety data submitted for regulatory review and approval, formulary and treatment decisions should take into consideration the strength of the available evidence and the complexity of the treatment regimen, which can impact the safety, tolerability, patient and caregiver burden,

Table 1. Definitions for Recommendation Class and Levels of Evidence[10]

Weight of evidence in favor of a given treatment in terms of safety/efficacy	
Class I	Evidence or general agreement that given treatment/procedure is beneficial, useful, or effective
Class II	Conflicting evidence/divergence of opinion
Class IIa	Weight of evidence favors usefulness or efficacy of treatment
Class IIb	Less well established based on evidence or opinion
Class III	Not useful, not effective, may be harmful
Type of evidence to support use of a given treatment	
A	Multiple RCTs/meta-analyses
B	One RCT or several uncontrolled studies or large nonrandomized studies
C	Consensus of expert opinion, small studies, retrospective studies, registries

RCT indicates randomized controlled trial.
Adapted with permission from Elsevier. Galie N et al. *J Am Coll Cardiol.* Updated treatment algorithm of pulmonary arterial hypertension. 2013;62(25, suppl D):D60-D72.

medication persistence, and the overall cost-effectiveness of treatment. The current treatment recommendations published following the 5th WSPH include an algorithm organized by recommendation class, evidence level, and WHO functional classification (see Tables 1 and 2).[10] According to the algorithm, in WHO FC II disease, level A or B evidence supports a Class I recommendation for the use of the ERAs, the PDE5 inhibitors, and the sGC stimulator. In WHO FC III disease, level A or B evidence also supports a Class I recommendation for the use of the ERAs, PDE5 inhibitors, and SGCs, as well as inhaled and parenteral prostanoids. Epoprostenol IV and macitentan were the only PAH-specific agents highlighted in this 2013 algorithm as either 1) having morbidity and mortality designated as a primary end point in a randomized controlled trial, or 2) demonstrating a reduction in prospectively defined all-cause mortality.[10]

The variability in the strength of evidence supporting the use of PAH-specific drugs is due in part to the variation in clinical trial designs—particularly with regard to study duration and the primary end point. Recently, there has been a transition from short trials (12-16 weeks) to longer trials that can assess disease progression and also from use of the traditional end point (change in 6MWD) to more rigorous and/or composite assessments such as time to clinical worsening (TTCW)/morbidity and mortality.[45,46] Stemming from the 2013 5th WSPH, the Nice Task Force on New Trial Designs and Potential

Table 2. Class I or IIa Recommendations for Initial Therapy With Approved Drugs in Nonvasoreactive PAH[10]

WHO Functional Class	Class I With Type A or B Evidence	Class IIa With Type C Evidence
II	Ambrisentan Bosentan Macitentan[a] Riociguat Sildenafil Tadalafil	
III	Ambrisentan Bosentan Epoprostenol IV[a] Iloprost inhaled Macitentan[a] Riociguat Sildenafil Tadalafil Treprostinil SC/inhaled	Iloprost IV Treprostinil IV
IV	Epoprostenol IV[a]	Ambrisentan Bosentan Iloprost IV/inhaled Macitentan[a] Riociguat Sildenafil Tadalafil Treprostinil IV/SC/inhaled

[a]Medication supported by a morbidity/mortality end point in RCTs or prospectively defined end point indicating a reduction in all-cause mortality.
IV indicates intravenous; PAH, pulmonary arterial hypertension; RCT, randomized controlled trial; SC, subcutaneous; WHO, World Health Organization.
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Table 3. Route, Dosing, and Registration Trial Primary End Point for PAH-Specific Medications[10-22,47,48]

Medication	Route	Dosing/Administration	Primary End Point (length of trial)
Ambrisentan tablets	Oral	Once daily	6MWD (12 weeks)
Bosentan tablets	Oral	Twice daily	6MWD (12-16 weeks)
Epoprostenol injection (Flolan, Veletri)[a]	IV	Continuous IV infusion	6MWD (12-16 weeks)
Iloprost inhalation	Inhaled	Inhalation sessions 6× to 9× daily	Combined clinical end point: 6MWD, improvement in FC, and lack of clinical deterioration or death (12 weeks)
Macitentan tablets	Oral	Once daily	Time to first morbidity/mortality event (median 115 weeks)
Riociguat tablets	Oral	3× daily	6MWD (12 weeks)
Sildenafil tablets	Oral	3× daily	6MWD (12 weeks)
Tadalafil tablets	Oral	Once daily	6MWD (16 weeks)
Treprostinil extended-release tablets	Oral	Twice daily to 3× daily	6MWD (16 weeks)
Treprostinil injection	SC/IV	Continuous subcutaneous infusion or (if diluted) continuous IV infusion	6MWD (12 weeks)
Treprostinil inhalation solution	Inhaled	Inhalation sessions 4× daily	6MWD (12 weeks)

6MWD indicates 6-minute walk distance; FC, functional class; IV, intravenous; PAH, pulmonary arterial hypertension; QOL, quality of life; RT, room temperature; SC, subcutaneous; TTCW, time to clinical worsening.
[a]Two formulations of epoprostenol exist, and differ in refrigeration requirements and the frequency with which infusion pumps must be replenished.

Therapies for PAH recommended that the primary end point for a registration trial of a PAH therapeutic agent be clinically meaningful and reflect disease progression (eg, worsening of function, worsening of PAH symptoms, a need for hospitalization or lung transplantation, or death).[45] To date, most PAH medications have been approved utilizing change in 6MWD as a primary end point (see Table 3).[10-22,47,48]

The clinical relevance of change in 6MWD data has been questioned, as the 6MWD test has been shown to correlate poorly with markers of PAH disease progression.[49-51] Gabler et al analyzed data from 10 trials with a total of 2404 patients with PAH. The authors reported that 6MWD explained 22% of disease progression in these patients and that this metric may not be useful in patients with higher baseline 6MWD values.[50] According to the analysis by Savarese et al of data from 22 trials including 3112 patients, correlations between changes in 6MWD and composite outcomes, all-cause death, hospitalization/transplantation, and PAH rescue therapy were all nonsignificant, with *P* values ranging from .097 to .499. The study found no relationship between changes in 6MWD and clinical outcomes.[51] The move toward conducting longer trials and the use of composite end points, which more accurately reflect progression of the disease, is evidenced in some of the more recent PAH studies. For example, in the recently completed trial of the novel ERA macitentan (SERAPHIN), in which a total of 742 patients with PAH were treated daily with either 3 mg or 10 mg of active drug or placebo, the median duration of treatment was 115 weeks (2.2 years), and the median follow-up was 129 weeks (2.5 years).[48] In the GRIPHON trial, evaluating the selective prostacyclin receptor agonist selexipag, a total of 1156 patients with PAH were treated for periods up to 4.3 years.[52] The AMBITION trial of newly diagnosed, treatment-naïve PAH patients receiving ambrisentan and tadalafil combination therapy had a mean treatment exposure of more than 500 days.[53,54] All 3 of these studies employed event-driven trial designs.

While these more recent studies contribute to the advancement of clinical knowledge by providing long-term outcomes data in PAH, the shift in trial designs (eg, change in 6MWD vs long-term outcomes) creates a complication in the evaluation of these agents by practitioners and payers. Until clinical protocols for multi-year studies using more comprehensive outcome parameters become more standardized, payers are forced to develop new methods to evaluate agents for formulary management

Key Areas for Improving Care in PAH

- Improved screening: pulmonary arterial hypertension (PAH) is often overlooked, even in high-risk groups, such as patients with connective tissue disease and congenital heart disease.
- Earlier diagnosis and treatment: diagnosis often occurs at a late stage of the disease (New York Heart Association functional class III or IV).
- Standardization of clinical trial design: payers are forced to make decisions using non-comparable end points (6-minute walk distance vs composite end points that reflect clinical worsening).
- Greater use of patient-reported outcomes (PROs): the complexities involved in the management of PAH, including the need for frequent dosing and monitoring and a wide variety of options for administration, may lend a particular relevance to capturing PROs.
- Improving adherence: adherence issues identified in the management of PAH include complex dosing regimens, laboratory testing, device management, aseptic technique for infused therapies, continued need for support, and side effects.

decision making using non-comparable end points. Also, because the basis of approval of most PAH-specific medications—change in 6MWD—correlates poorly with clinical outcomes, such as hospitalization, there are limited data with regard to the impact of treatment on resource utilization.[51] The pivotal trial for the recently approved drug macitentan included a pharmacoeconomic composite end point examining PAH-related deaths or hospitalizations. The risk of PAH-related death or hospitalization was 50% lower for the group treated with the approved dose of macitentan (10 mg daily) than for the placebo group (33.6% vs 20.7%; P <.0001).[15,48] In a post hoc analysis of hospitalizations and days of hospitalization, treatment with macitentan (10 mg daily) for PAH reduced rates of hospitalization by 55% (average of 27 hospitalizations per 100 patient-years with placebo treatment compared with an average of 12 hospitalizations per 100 patient-years with macitentan; P = .0002) and the LOS by 55% (average of 5.5 hospital days with placebo compared with 2.7 days with macitentan treatment; P = .0416).[55]

Future Directions for Outcomes Research

Due to a lack of well-validated PAH-specific assessment tools, much of the knowledge regarding quality of life (QOL) in PAH has been based on data from tools designed to assess health-related QOL (HRQOL) for related conditions (ie, cardiovascular and respiratory). The complexities involved in the management of PAH, including the need for frequent dosing and monitoring and a wide variety of options for administration (ie, oral, inhaled, subcutaneous injection, and continuous IV infusion), may lend a particular relevance to capturing patient-reported outcomes (PROs), particularly those that reflect the HRQOL of patients with PAH. To date, HRQOL in PAH has been studied only as an exploratory end point or secondary outcome in PAH clinical trials. Many of the measures used were based on those used in other disease states, and may not accurately reflect the QOL of a patient with PAH. However, reflecting recognition of the importance of QOL, the first pulmonary hypertension–specific questionnaire, CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review), was developed in 2006 and has been used in some PAH clinical trials.[54,56,57]

The use of PROs has increased over time, and this trend may continue given the recent treatment advancements in PAH and the greater overall emphasis being placed on patient-centered care. Future research that includes HRQOL outcomes measures designed specifically for PAH will provide additional information beyond traditional clinical data that can assist healthcare providers and payers in evaluating treatment options.[57]

Adherence and Persistence

As in other chronic disease states, medication adherence and treatment persistence are of importance to clinicians, healthcare systems, payers, and other stakeholders. Evidence shows that nonadherence is associated with adverse outcomes and higher costs of care, including increases in outpatient visits, hospital admissions, and emergency department visits.[58,59] Medication adherence data in PAH are limited; however, adherence is often quoted as ranging from 40% to 60% in other chronic diseases.[60,61]

Adherence issues identified in the management of PAH include complex dosing regimens, laboratory testing, device management, aseptic technique for infused therapies, continued need for support, and side effects. For example, continuous-infusion prostacyclin therapies have been associated with side effects that include

headaches, nausea, diarrhea, foot or leg pain, and subcutaneous site pain.[61] The need for programs to improve medication/therapy adherence in healthcare has been recognized. For instance, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has established a Medication Adherence and Persistence Special Interest Group. The ISPOR group has examined factors associated with adherence, the impact of interventions, the cost of medication nonadherence, and methods for integrating compliance and persistence in pharmacoeconomic evaluations.[62-64] Programs aimed at adherence in PAH may include disease state education, medication counseling, adherence education, and identification of barriers to therapy.

PAH treatment regimens require a unique collaboration among manufacturers, prescribers, specialty pharmacy staff, and patients, as the majority of the drugs are only available through specialty pharmacies.[42] This allows for support through high-touch, high-management interventions. As a result, specialty pharmacies may be in a unique position to promote compliance. At least 1 large specialty pharmacy organization has partnered with a manufacturer and is currently involved in a project to increase medication compliance and persistence in PAH patients.[59]

Conclusion

The modern era, since the first PAH-specific drug was approved in 1995, has seen much progress in the management of PAH due to more advanced PAH-specific therapeutic options, with respect to both mechanisms of action (targets) and methods of administration. Currently, 12 PAH-specific drugs are available in the United States, 3 of which are oral therapies approved in 2013. Regularly updated guidance documents are drafted by internationally renowned experts and issued under the auspices of the WSPH. Experts at the most recent WSPH, in 2013, recommended sequential combination therapy and the promotion of increasingly rigorous clinical trial designs incorporating critical outcomes–related end points. However, despite these therapeutic and clinical advances that include improvements in survival, PAH remains a disease with serious morbidities that is ultimately fatal. Early detection and diagnosis is crucial, especially with regard to some high-risk groups, such as patients with CTD and congenital heart disease. Other ongoing challenges include optimizing disease management and therapeutic regimens, promoting treatment adherence and persistency, and standardizing the design and conduct of study protocols to better reflect disease progression. In addition, there is a need for more research that satisfactorily addresses HRQOL/PRO parameters and pharmacoeconomic outcomes.[40]

Novel agents may provide additional clinical benefit. However, for the foreseeable future, PAH will remain a costly disease with no known cure, involving high-touch, high-management interventions, and costly specialty drugs. Given the low incidence and prevalence of PAH, payers are unlikely to have large numbers of members with this disease. Nonetheless, managed care is faced with making population-based decisions that will impact all their members as they allocate resources. This article has detailed some of the advancements and gaps in PAH knowledge in order to better inform these decisions.

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Notes