

# Overview of Idiopathic Pulmonary Fibrosis (IPF) and Evidence-Based Guidelines

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## ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive form of interstitial lung disease (ILD), characterized by fibrosis and worsening lung function, that primarily occurs in those 50 years and older. Various causes including genetic susceptibility, environmental risk factors, and exposures have been suggested in the literature. All of these cause repetitive micro-injury to the lung tissue and vasculature, which triggers a cascade of inflammatory response and fibrosis. Symptoms are nonspecific and most patients present several years after the initial radiographic changes occur. Diagnosis requires a high index of clinical suspicion supported by distinct radiographic and/or histopathologic findings. Median survival is estimated at between 2 and 3 years after diagnosis. Other than lung transplantation, no treatment has shown survival benefit. Two most recently approved medications for IPF, pirfenidone and nintedanib, can slow disease progression. Most patients have several comorbid conditions that can affect the course of their disease, including gastroesophageal reflux disease, obstructive sleep apnea, cardiomyopathy, and pulmonary hypertension. Observational studies suggested possible benefits in transplant-free survival and patients' outcomes with these medications. In addition to the new treatment options and optimal management of the comorbidities in patients with IPF, pulmonary rehabilitation remains a critical part of management and has been shown to improve quality of life and functional level. Considering the complexity of the diagnosis and management, the American Thoracic Society and European Respiratory Society published a joint statement on diagnosis and treatment of IPF.

This article provides an overview of the epidemiology, pathophysiology, and guideline-recommended approaches for the diagnosis and management of IPF.

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**I**diopathic pulmonary fibrosis (IPF), previously known as cryptogenic fibrosing alveolitis, is a chronic, progressive disease, characterized by fibrosis and worsening lung function, that primarily occurs in individuals 50 years and older.<sup>1</sup> It is the most common form of idiopathic interstitial pneumonia (IIP).<sup>2</sup> The IIPs encompass a heterogeneous group of nonneoplastic interstitial lung diseases (ILDs) resulting from direct injury to the lung parenchyma through an inflammatory response and fibrosis.<sup>3</sup> IIP includes conditions such as IPF, nonspecific interstitial lung disease, respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia. In this article, we will focus on the pathogenesis and management of IPF.

Patients with IPF have variable clinical courses and usually report slow but progressive onset of symptoms.<sup>4</sup> The diagnosis requires high clinical suspicion and distinct radiographic and histopathologic patterns.<sup>5,6</sup>

The American Thoracic Society (ATS) and European Respiratory Society (ERS) published a statement in 2000 on management of IPF,<sup>7</sup> which has been updated several times since.<sup>1,8,9</sup>

IPF has very high morbidity and mortality rates, with almost half of patients dying 2 to 3 years after diagnosis.<sup>10</sup> Most patients experience prolonged hospitalizations during the last year of life and unfavorable outcomes, contributing to significant healthcare resource usage. Population-based studies showed that patients with IPF have a 126% increased risk of emergency department visits and a 134% higher risk of hospitalization compared with age-, gender-, race-, and region-matched controls.<sup>11,12</sup>

## Epidemiology of IPF

IPF is the most common type of IIP. The incidence and prevalence in epidemiologic studies after 2000 are estimated at between 0.5-27.9 and 0.22-8.8 per 100,000, respectively.<sup>13</sup> Patients are typically diagnosed after age 50 years, and the incidence of the disease increases with age. It is also more prevalent in men and cigarette smokers.<sup>7</sup>

Historically, it has been difficult to accurately assess the epidemiology of IPF due, in part, to the fact that there was no unified definition of the disease until early 2000.<sup>7</sup> That definition is based on diagnoses

of patients with a radiographic and histopathologic pattern of usual interstitial pneumonia (UIP) and no other identifiable cause for their ILD.<sup>14</sup> In addition, differing methodologies and heterogeneous study designs that are used to determine the incidence and prevalence across populations make accurate epidemiologic estimates challenging.

A retrospective study of a Medicare population between 2001 and 2011 found that while the incidence of IPF in this population remained steady at a rate of 93.7 cases per 100,000 per year, the prevalence increased sharply, from 202.2 in 2001 to 495.5 in 2011. One reason, the authors suggested, could be increased survival time and earlier diagnosis. The annual increase was higher in older individuals, males, and Hispanic individuals.<sup>15</sup>

Conversely, an analysis of claims from US adults aged 18 to 64 years showed that the incidence of IPF decreased from 2004 to 2010, with the reduction occurring primarily in younger patients. The authors suggest that this may be due to more accurate diagnosis of IPF, especially in younger adults aged 18 to 44 years.<sup>16</sup> Although early onset of IPF is possible in rare cases, the majority of patients in this age group with a diagnosis of IPF would more likely have other conditions such as autoimmune diseases and chronic hypersensitivity pneumonitis, which could mimic the radiographic and histologic pattern of IPF. This issue has been addressed by the expert societies, and now, according to new ATS/ERS guidelines, the exclusion of other causes of ILD, such as autoimmune conditions and chronic hypersensitivity pneumonitis, is required as a part of diagnostic work-up.<sup>1,8,9</sup>

**Risk factors**

Several risk factors have been linked to the development of IPF, including genetic susceptibility, environmental and occupational exposures, tobacco smoking, comorbidities (particularly gastroesophageal reflux disease [GERD]), and possible association of viral infections.<sup>2,17</sup>

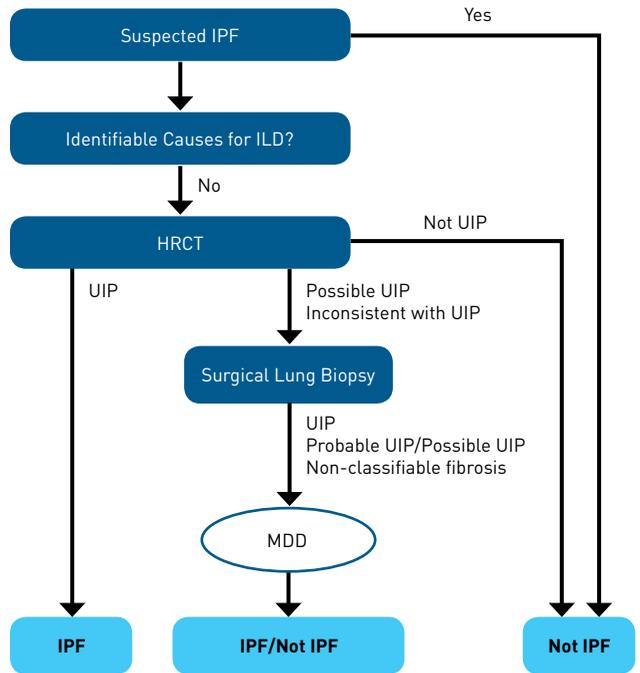
Substances linked to IPF include tobacco smoke, asbestos, silicone, mold, animal/vegetal dust, textile dust, wood smoke, and aluminum. The variation in exposure to inhaled substances may explain some of the geographic disparity observed in epidemiologic studies.<sup>2</sup> Another underlying cause may be the burden of bacteria in the lung microbiome.<sup>18</sup>

While the genome-wide association studies have identified the common genetic variants accounting for almost one-third of risk factors of development of IPF, they are limited by a lack of definite causal relationship.<sup>2</sup>

**Pathogenesis**

The understanding of the complex pathogenesis of IPF has evolved significantly over the past 2 decades. It is now generally agreed that the pathogenesis of IPF is related to epithelial injury from endogenous or exogenous events, which results in widespread fibrosis, which replaces the normal lung parenchyma. Clinically, these changes can result in decreased oxygenation, respiratory failure, and eventually death.<sup>19</sup>

**FIGURE 1.** Diagnostic Algorithm for Idiopathic Pulmonary Fibrosis<sup>8</sup>



HRCT indicates high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion among ILD experts; UIP, usual interstitial pneumonia. Reprinted with permission of the American Thoracic Society. Copyright 2017 American Thoracic Society. Raghu G, Collard HR, Egan JJ, 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. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

**Diagnosis**

**Clinical presentation**

Patients with IPF typically present in their sixth or seventh decade of life with gradual onset of nonspecific symptoms such as cough, dyspnea on exertion, fatigue, lack of energy, and gradual decline in their ability to execute daily activities. The physical examination findings are nonspecific, as well. Common findings on examination include bibasilar mid- to end-inspiratory crackles, end-inspiratory “squeaks” due to traction bronchiectasis, and, in advanced disease, clubbing of the fingernails.<sup>19</sup>

**Differential diagnosis**

The diagnostic work-up for IPF requires high clinical suspicion and a thorough history and physical examination. As illustrated in **Figure 1**<sup>8</sup>, excluding other causes is now the first diagnostic criterion (along with specific radiographic and/or histopathologic findings).<sup>8</sup> Clinicians are highly encouraged to obtain a careful history and inquire about comorbidities, medication use, environmental

**TABLE 1.** High-Resolution CT and Lung Biopsy for Diagnosis of IPF<sup>1,8</sup>

HRCT pattern	Surgical lung biopsy pattern when performed	Idiopathic pulmonary fibrosis (IPF)?
Usual interstitial pneumonia (UIP)	UIP Probable UIP	Yes
	Nonclassifiable fibrosis Not UIP	No
Possible UIP	UIP Probable UIP	Yes
	Possible UIP Nonclassifiable fibrosis	Probable
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP	No
	Possible UIP	
	Nonclassifiable fibrosis Not UIP	

CT indicates computerized tomography; HRCT, high-resolution CT. Reprinted with permission of the American Thoracic Society. Copyright 2017 American Thoracic Society. Raghu G, Collard HR, Egan JJ, 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. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

exposure, and family history.<sup>8</sup> Patients with advanced chronic hypersensitivity pneumonitis can present with honeycombing changes at the later stages of the disease, which could be misdiagnosed as IPF.<sup>8,19</sup>

Clinicians should also inquire about symptoms and signs of autoimmune conditions such as systemic sclerosis (Raynaud's phenomenon, skin rash, telangiectasia, skin tightening, severe GERD refractory to treatment, digital pitting, and sclerodactyly), rheumatoid arthritis (morning stiffness; polyarthralgia, particularly in hand and wrist; synovitis; subcutaneous nodules), myositis, and Sjogren's syndrome, which may manifest early on with lung involvement.<sup>8,20</sup> In these cases, serologic studies can be helpful in diagnosing the underlying cause. This type of ILD is often termed connective tissue disease ILD and is usually coded as post-inflammatory pulmonary fibrosis.

### Pulmonary function test

A complete pulmonary function test—including spirometry, lung volumes, and diffusing capacity of the lungs for carbon monoxide (DLCO) test—should be obtained in all patients with suspected IPF. Restrictive pattern (reduction in lung volumes), reduction in DLCO, and/or obstructive pattern are common findings. In cases when IPF co-exists with emphysema (ie, combined pulmonary fibrosis and emphysema), an obstructive pattern could be seen.<sup>21-23</sup>

### Radiographic and histopathologic findings

All patients with a high clinical suspicion of IPF should undergo high-resolution computed tomography (HRCT). Imaging may reveal reticular opacities, associated with traction bronchiectasis and honeycombing, with limited ground-glass opacities (Table 1<sup>1,8</sup>).<sup>1,8</sup>

Despite higher than 90% positive predictive value of UIP pattern on HRCT, it could also be seen in other conditions as well.<sup>24</sup> Nonetheless, given the accuracy of HRCT in recognizing a histopathologic UIP pattern, the 2011 guidelines from the ATS, ERS, Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) no longer require a surgical lung biopsy (SLB) for a definitive diagnosis in most patients. Instead, they note that the diagnosis may be based on the presence of a UIP pattern on HRCT alone in conjunction with the other diagnostic components.<sup>8,25</sup> Several observational studies demonstrated that certain HRCT findings correlate with progression of the disease and outcomes.<sup>26</sup> In our institutional cohort, we have shown that the detailed findings and extent of the fibrotic changes directly correlate with disease progression, change in spirometry indices, and overall survival.<sup>27</sup>

Many patients do not require SLB for definite diagnosis of IPF. Some experts suggest that older patients with unexplained ILD are likely to have IPF.<sup>26</sup> Clinicians should base their decision on the potential benefits for the definite diagnosis relative to the potential high risks associated with SLB. While there is some recent evidence regarding the ability of bronchoscopic lung cryobiopsy to improve diagnostic accuracy, more evidence is required.<sup>28</sup>

### Multidisciplinary discussion

Given the complexity of diagnosis, it is highly recommended to hold a multidisciplinary discussion for more accurate diagnosis. Recent guidelines call for a multidisciplinary approach involving pulmonologists, rheumatologists, radiologists, and pathologists, which has been shown to improve diagnostic accuracy (Figure 1<sup>8</sup>).<sup>1</sup>

### Prognosis and outcomes

#### Natural history of IPF

Despite current advances, IPF remains a fatal disease, albeit one with a heterogeneous course ranging from stable to rapidly deteriorating respiratory failure and death.

The risk of mortality in patients with IPF can be predicted based on several baseline and longitudinal factors, including the level of dyspnea, diffusion capacity for DLCO, desaturation during 6-minute walk test (6MWT), extent of honeycombing on HRCT, and pulmonary hypertension at baseline, as well as longitudinal changes in the levels of dyspnea, forced vital capacity (FVC), DLCO, and fibrosis on HRCT.<sup>7</sup>

While several clinical models have been suggested to predict the course of the disease, the gender, age, and physiology (GAP) index is most commonly used. The GAP index is calculated based on gender,

age, and the pulmonary physiology (percent predicted FVC and DLCO) (Table 2<sup>29</sup>).<sup>29</sup> The predictive value of the GAP index is hampered by limited clinical parameters. More accurate prognostic tools are needed.

One of the most feared complications of IPF is an acute exacerbation. It is defined as acute decline in lung function and worsening of respiratory symptoms, with no evidence of infection and exclusion of alternative causes. It occurs in 5% to 10% of patients annually, with mortality rates as high as 85% and significant risk of recurrence.<sup>30</sup> In addition to acute exacerbation of IPF, other causes of acute worsening of respiratory symptoms in patients with IPF, such as pneumonia, pulmonary embolism, or heart failure, have similar clinical presentation with comparable outcomes.<sup>31</sup> Supportive care is the mainstay of therapy.<sup>7</sup> Recently a classification of worsening of symptoms has been proposed but studies are ongoing to confirm the clinical implications and efficacy.<sup>32</sup>

**Life expectancy and survival**

The median survival of IPF is 2 to 3 years because diagnosis with a 5-year survival rate ranges between 20% and 40%.<sup>7,33</sup> A recent analysis of Medicare data found that the median survival time from all-cause mortality was 3.8 years, with survival time decreasing sharply based on age at diagnosis. Patients between age 66 and 69 years had a median survival of 8 years, compared with 4.5 years in those diagnosed between age 75 and 79 years, and 2.5 years in those diagnosed at 80 years or older.<sup>13</sup>

**Comorbidities in IPF**

The majority of patients with IPF have multiple comorbid conditions, which, rather than fibrotic disease itself, may contribute to the high morbidity and mortality they experience.<sup>34,35</sup> Comorbidities result in more frequent exacerbations and rapid decline in function and survival. Conversely, there is some evidence that obesity may convey a protective effect on mortality.<sup>36</sup> Studies suggest that identifying and treating comorbidities may improve overall outcomes, including quality of life and survival.<sup>37</sup>

Table 3<sup>37</sup> summarizes some of the common comorbidities among patients with IPF: pulmonary hypertension, GERD, chronic obstructive pulmonary disease, lung cancer, pulmonary embolism, obstructive sleep apnea, ischemic heart disease, and diabetes.<sup>37</sup>

In a retrospective study of 352 patients with IPF, 79.3% of the cohort had at least 1 comorbid condition and 57.2% had 2 or more. The multivariate analysis result indicated that each additional comorbid condition increased mortality risk by nearly 10%.<sup>38</sup> The authors suggested that the number of comorbidities relates to overall patient well-being.

The majority of patients with IPF have comorbid GERD, yet up to half may not exhibit any symptoms.<sup>8</sup> There is some evidence that GERD may be a causative factor of IPF, with animal studies documenting worsening pulmonary parenchymal damage with

**TABLE 2.** The GAP Index and Staging System<sup>29</sup>

	Predictor	Points	
G	Gender		
	Female	0	
	Male	1	
A	Age, y		
	≤60	0	
	61-65	1	
	>65	2	
P	Physiology		
	FVC, % predicted		
	>75	0	
	50-75	1	
	<50	2	
	DLCO, % predicted		
	>55	0	
	36-55	1	
	≤35	2	
	Cannot perform	3	
Total Possible Points		8	
Stage	I	II	III
Points	0-3	4-5	6-8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

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exposure to decreasing pH, and damage to the lung periphery from gastric acid.<sup>39</sup> Studies also suggest that treating GERD in IPF patients can improve survival.<sup>40,41</sup>

Guidelines for the management of IPF address the treatment of pulmonary hypertension and GERD. The updated ATS/ERS guideline on IPF treatment published in 2015 made a weak recommendation against treatment of pulmonary hypertension and weak recommendation in favor of GERD treatment.<sup>1</sup> These are suggested due to conflicting data in this field.

**Treatment**

The pharmacologic treatment of IPF has evolved substantially over the last 2 decades. Historically, many pulmonologists used various immunosuppressive and anti-inflammatory agents, until the results from a randomized clinical trial on the combination of prednisone, azathioprine, and N-acetylcysteine (PANTHER-IPF)

**TABLE 3.** Rates of Comorbidities in Patients with IPF<sup>37</sup>

Arrhythmias or atrial fibrillation	6%-19%
Arterial hypertension	14%-71%
Cardiac failure	9%-26%
COPD	6%-67%
Diabetes	10%-42%
GERD	5%-94%
Hypercholesterolemia/hyperlipidemia	6%-53%
Ischemic heart disease	6%-68%
Lung cancer	3%-48%
Obstructive sleep apnea	6%-91%
Pulmonary hypertension	3%-86%

COPD indicates chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IPF, idiopathic pulmonary fibrosis.

showed increased harm from this approach.<sup>42</sup> In 2014, the FDA approved 2 treatments for IPF: pirfenidone, an antifibrotic and anti-inflammatory agent, and nintedanib, a kinase inhibitor.<sup>43</sup>

The 2015 guidelines strongly recommend against the use of imatinib, a selective tyrosine kinase inhibitor, based on the results from a single randomized controlled trial that failed to show a mortality benefit or any reduction in time to disease progression.<sup>1,44</sup> Similarly, ambrisentan, an ET<sub>A</sub>-endothelin receptor antagonist, also earned a strong recommendation against its use based on the ARTEMIS-IPF study. That study was stopped early because of an increased risk of disease progression and respiratory hospitalizations.<sup>45</sup> The dual endothelin receptor antagonists, bosentan and macitentan, have weak recommendations against their use due to the findings of the BUILD-3 and MUSIC studies, which failed to demonstrate beneficial outcomes.<sup>46,47</sup> The 2015 update recommends against the use of warfarin in patients with IPF, unless otherwise indicated for conditions such as atrial fibrillation; however, the panel notes that other anticoagulants including the new oral agents might be beneficial.

Pharmacologic treatment of IPF is thoroughly discussed in subsequent articles of this supplement.

### Nonpharmacologic treatment

Nonpharmacologic treatment modalities of IPF include supplemental oxygen therapy, pulmonary rehabilitation, mechanical ventilation, and palliative care services.

Supplemental oxygen is typically recommended when a patient's desaturation is below 88% during a 6MWT or its equivalent.<sup>8</sup> Physicians should monitor patient oxygenation with pulse oximetry at rest and exertion at baseline and at 3- to 6-month intervals. Nocturnal oxygen may also be indicated in patients with IPF with concurrent obstructive sleep apnea. There is no evidence of survival benefit from supplemental oxygen therapy, but some studies suggest better patient comfort and improved function.<sup>48,49</sup>

Pulmonary rehabilitation remains a robust part of nonpharmacologic treatment of IPF. It includes aerobic conditioning, strength and flexibility training, education about the condition, nutritional counseling, and psychosocial support.<sup>7</sup> Clinical trials have demonstrated its beneficial impact on patients' functional status and quality of life.<sup>50,51</sup> Its long-term impact remains unclear and requires further studies, but its implementation is a crucial part of management.

Data on the role of palliative care in management of IPF are lacking and deserve more attention. Palliative services can be beneficial, particularly in advanced stages of IPF. Symptoms such as dyspnea and cough pose high symptom burden on patients and affect quality of life.

### Multidisciplinary management of IPF: unmet needs of patients

Over the last 2 decades, ATS/ERS guidelines have provided individual recommendations for the diagnosis and treatment of patients with IPF. Although the strong association of comorbid conditions and poor outcome among patients with IPF is well known, no randomized clinical trial has examined the impact of management of comorbid conditions on their survival.

Observational studies have demonstrated the ability of a bundled, multidisciplinary approach to improve transplant-free survival among patients with IPF.<sup>52</sup> This included biannual specialized interstitial lung disease visits with pulmonary function tests, annual referral to pulmonary rehabilitation, annual timed walk test and echocardiogram, therapy for GERD, screening for sleep-related disorders, and assessment for potential referral for lung transplantation.

Better adherence to this approach was associated with significantly improved survival of patients.<sup>52</sup> Although these results are not generalizable to the entire population of patients with IPF, given that the study was conducted at a tertiary referral academic medical center with a sicker cohort of patients, this approach could assist providers in better assessing patients' overall prognosis.

### Lung transplantation

Lung transplantation can improve survival among patients with IPF and should be considered in patients with moderate to severe IPF.<sup>8</sup> In May 2005, the United Network for Organ Sharing implemented the Lung Allocation Score to predict the survival benefit and determine the priority of a candidate. Since then, the actual number and the rate of patients with IPF on the lung transplantation wait list has increased.<sup>53</sup> An important criterion for receiving a lung transplant is adherence to medications, thus the pharmacist should work with patients closely to promote proper medication use.

The ideal time to refer a patient for transplantation evaluation and the choice of single or bilateral lung transplantation remain

controversial, with further studies required.<sup>7,54-57</sup> However, the consensus is in favor of earlier referral considering the unpredictable course of disease.

**Conclusion**

IPF is the most common type of idiopathic interstitial pneumonia, usually diagnosed in the sixth or seventh decade of life. The accurate and timely diagnosis of IPF remains a diagnostic challenge in clinical practice and requires a high level of clinical suspicion as well as consideration of other possible causes. Clinicians are highly encouraged to obtain a thorough history and physical examination. Serological studies, particularly in younger and female patients, are encouraged to evaluate for possible underlying autoimmune disease. Exclusion of alternative diagnosis remains the first step in diagnosis. High-resolution computed tomography of the chest with both inspiratory and expiratory images remains the pivotal component of the diagnostic work-up. A surgical lung biopsy would be necessary in a highly selected patient population, but should be obtained with careful assessment of risks and benefits.

The diagnostic assessment should involve a multidisciplinary approach among the pulmonologist, chest radiologist, and pathologist.

IPF has very high morbidity and mortality rates. Most patients rapidly progress during the last year of life and experience prolonged hospitalization.

Several aspects of IPF pathophysiology and management are not clearly understood and are the subject of ongoing research. However, advances in recent years have kept hopes high for more optimal management of and better therapies for this fatal condition. ■

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