

## Review

# Comparative Analysis of Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis: Epidemiology, Pathophysiology, Clinical Features, Diagnosis and Treatment

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**ABSTRACT:** Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial disease of unknown origin, characterized by radiological and histological features consistent with usual interstitial pneumonia (UIP). It is marked by a progressive worsening of dyspnea and a decline in lung function. Both IPF and PPF are comparable because they have poor prognoses with a median survival time from diagnosis of around 2–4 years without antifibrotic therapy. This review shows the main specific characteristics and differences of epidemiology, pathophysiology, clinical and radiological features, treatment, and prognosis of IPF and PPF.

**Keywords:** Idiopathic pulmonary fibrosis; Progressive pulmonary fibrosis; Fibrosis interstitial pneumonia; Interstitial lung disease



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## 1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial disease of unknown cause that occurs in older adults than 60 years with dyspnea, dry cough, fatigue, and progressive low quality of life. However, some patients may stay asymptomatic for a long time. The incidence and prevalence of IPF are rising globally, a trend attributed to several potential factors. The disease is particularly more prevalent among older individuals, and advancements in treatment have contributed to increased survival rates for those with IPF, further driving up prevalence statistics [1]. Exposure to cigarette smoke is one of the risk factors that may contribute to pathogenesis, and the disease is associated with radiological and histologic features of usual interstitial pneumonia (UIP). The estimated survival rate is poor. However, antifibrotic drugs have changed the course of the prognosis and quality of life of patients with IPF [2].

Progressive pulmonary fibrosis (PPF) is a severe condition that may be present in different interstitial lung diseases (ILDs) with known or unknown etiology. It is characterized by radiologic evidence of progression on tomography, including the development or worsening of traction bronchiectasias, ground glass opacities with traction bronchiectasis, fine reticulation, honeycombing, and lobar volume loss, associated with worsening respiratory symptoms (dyspnea, cough, and quality of life) and a decline in pulmonary function, characterized by an absolute decrease in forced vital capacity (FVC) of >5% predicted or an absolute reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) of  $\geq 10\%$  predicted within one year or follow up [3].

IPF and PPF are comparable entities because they progress to worse respiratory symptoms, decreased lung function, worse pulmonary tomography findings, and poor quality of life. This review aims to compare them.

## 2. Definition

### IPF

Idiopathic pulmonary fibrosis is a chronic fibrosing interstitial pneumonia of unknown origin, most commonly seen in elderly individuals. The development of the disease involves a complex interplay of genetic and immunological factors. Its course is highly heterogeneous and unpredictable, exhibiting 3 patterns of progression: slow, rapid and relatively stable, often interrupted by acute exacerbations. The estimated median survival time after diagnosis is approximately 3 to 5 years, particularly in the absence of antifibrotic therapy [4]. The main risk factors, aging, and exposure to cigarette smoke, may contribute to the pathogenesis of IPF [5].

### PPF

Progressive pulmonary fibrosis is a severe condition in patients with ILDs (excluding IPF) characterized by radiologic evidence of progression, including: 1. increased extent or severity of traction bronchiectasis or bronchiolectasis, 2. new ground glass opacity with traction bronchiectasis, 3. new fine reticulation, 4. increased extent or coarseness of reticulations, 5. new or increased honeycombing, 6. increased lobar volume loss. In addition, worsening of respiratory symptoms (dyspnea, cough, quality of life) and pulmonary function, including absolute decline in FVC > 5% predicted or absolute decline in DLCO  $\geq$  10% predicted within one year of follow-up [6].

## 3. Epidemiology

### IPF

The annual incidence of IPF in the USA is estimated to range from 6.8 to 8.8 cases per 100,000 population. Both incidence and prevalence increase with age. IPF is more common among males and has been on the rise in recent years [7]. The median survival for untreated patients is approximately 2 to 3 years post-diagnosis and 15 to 20% of patients experience acute exacerbations, which are typically severe and can be fatal [8]. Additionally, IPF is more frequently reported in males, particularly those who are middle-aged, typically between 40 and 70 years old. Around two-thirds of IPF patients are over 60 years of age at the time of diagnosis [9].

### PPF

Approximately one-third of patients with fibrosing interstitial lung disease (ILDs) other than IPF may develop PPF [10]. The overall incidence of idiopathic non-specific interstitial pneumonia (iNSIP), regardless of the progressive-fibrosing phenotype, is lower than that of IPF [11]. Some types of fibrosing ILDs are more likely to progress than others. For instance, PPF may be present in 53% of patients with unclassifiable interstitial lung disease (uILD), 40% of those with systemic sclerosis-associated ILD (SSc-ILD), 32% of patients with rheumatoid arthritis-associated ILD (AR-ILD), and 21% of patients with fibrotic hypersensitivity pneumonitis (HP) [12,13]. However, the burden of PPF and the prevalence of comorbidities are not well understood, as the diagnosis of ILDs and the recognition of PPF are often delayed, typically depending on evidence of progression obtained through regular monitoring [14].

## 4. Pathophysiology

### IPF

IPF is characterized by the excessive production and disorganized deposition of extracellular matrix (ECM) components, which, by progressively replacing the normal lung parenchyma, lead to irreversible architectural distortion and loss of organ function. IPF is of unknown cause, has several risk factors (cigarette smoking, subclinical infection, environmental pollutants, occupational exposures), and pathogenic mechanisms have been implicated in its development. Also, IPF is believed to occur in genetically predisposed individuals following recurrent alveolar epithelial cell injury, active cytokines (tumor necrosis factor TNF  $\alpha$ , interleukin IL 1, and chemokine CC motif ligand 2), and differentiation to myofibroblasts (the main collagen-producing cells). TGF- $\beta$  is secreted in an inactive form, with  $\alpha$ v $\beta$ 6 integrin playing a crucial role in its activation, and it is a potential therapeutic target in IPF [15]. The lung of patients with IPF displays several aging lung characteristics, such as cellular senescence, telomere shortening, mitochondrial and lysosomal autophagy dysfunction, and epigenetic changes [16]. The distinguishing histologic of UIP are fibroblast foci characterized by clusters of actively proliferating fibroblasts and myofibroblasts that lie in the subepithelial areas of the damaged lung [17].

## PPF

Some ILDs are considered fibro-proliferative disorders characterized by alveolar epithelial injury and fibroblastic proliferation. In contrast, other ILDs are primarily inflammatory disorders in which the pathogenic processes shift to a fibroproliferative pathway. Regardless of the underlying condition, PPF occurs through similar dysregulated cell repair mechanisms that become myofibroblasts, which secrete increased amounts of extracellular matrix. The combined with reduced matrix degradation, leads to increased tissue stiffness and loss of alveolar function. Macrophages and lymphocytes are recruited to the injury site, releasing pro-fibrotic mediators that further stimulate fibroblast activation. This creates a feed-forward loop, where the increased lung tissue stiffness further activates fibroblasts, driving a self-sustaining process of fibrosis [18,19].

## 5. Clinical Features

### IPF

IPF is clinically suspected in patients over the age of sixty. Common symptoms include dyspnea, a dry cough (which significantly affects the patient's health-related quality of life), fatigue, a gradual decline in the ability to perform daily activities and digital clubbing, which occurs in 25% to 50% of patients. These symptoms may persist for months or even years. Clinical assessment frequently reveals bibasilar mid-to-end inspiratory crackles on chest auscultation, nail clubbing and hypoxemia or desaturation [20].

Patients with idiopathic interstitial lung abnormalities (ILAs) may initially remain asymptomatic but could eventually progress to a diagnosis of IPF. Many patients with IPF have a history of smoking and/or exposure to environmental or occupational hazards. Several factors, such as aging and male gender, may increase the likelihood of developing IPF. Conversely, exposure to antigens known to cause hypersensitivity pneumonitis and the presence of autoimmune features may decrease this likelihood [13].

### PPF

PPF is characterized by worse progressive dyspnea, cough, and quality of life producing limitations in the typical activities of the patient's life. Fever and hemoptysis are no symptoms in this condition. When it is present, it should be differentiated from acute deterioration caused by drug-induced lung toxicity, infections or vasculitis [21].

## 6. Diagnosis

### Pulmonary function:

#### IPF

Abnormal pulmonary function studies include evidence of restriction. Although a decline in the FVC > 10% predicted is a predictor of mortality, the smaller declines (5–10%) have also been associated with a worse prognosis [22,23].

#### PPF

The official ATS/ERS/JRS/ALAT clinical practice guidelines define disease progression based on the following criteria: 1. An absolute decline in FVC of greater than 5% within one year of follow-up, and/or 2. An absolute decline in DLCO (corrected for hemoglobin) of greater than 10% within one year of follow-up. The guideline includes a decline in FVC of greater than 5% over one year as a criterion for progressive pulmonary fibrosis (PPF), because it was extrapolated from the IPF literature.

The INBUILD and RELIEF trials have demonstrated that smaller reductions in FVC, ranging from 5% to 10%, were associated with symptomatic or radiological deterioration and a significant predictor of mortality.

The absolute decline in DLCO (>10%) has not been a reliable endpoint in clinical trials for patients with pulmonary fibrosis due to techniques across pulmonary function laboratories, and its lack of specificity for tracking the progression of pulmonary fibrosis. However, the official ATS/ERS/JRS/ALAT clinical practice includes DLCO as a criterion for diagnosing PPF, to exclude alternative causes for a worsening DLCO before attributing any decline to progressive fibrosis. In such cases, additional evaluation, including high-resolution computed tomography (HRCT), is required [24] (Table 1).

### Radiological features:

#### IPF

The Official ATS/ ERS/JRS/ALAT clinical practice guidelines (2018) advocate using four diagnostic categories incorporating the HRCT features. These categories include a: 1. The UIP pattern, characterized by honeycombing with

subpleural and basal predominance, is a hallmark feature of UIP. This may occur with or without peripheral traction bronchiectasis, although asymmetric involvement is present in up to 25% of cases. 2. Probable UIP pattern is characterized by subpleural basal reticular abnormalities, along with peripheral traction bronchiectasis or bronchiectasis. Ground-glass opacities are not a predominant feature. 3. The indeterminate pattern shows fibrosis that does not meet the criteria for either UIP or probable UIP, and does not clearly suggest an alternative diagnosis. This may include cases with minimal subpleural ground-glass opacification or reticulation, without clear HRCT evidence of fibrosis. 4. Alternative diagnoses include mosaic attenuation (as seen in hypersensitivity pneumonitis), fibrotic retraction of the hila (indicative of sarcoidosis), bronchiectasis, and others [25] (Table 1).

**Table 1.** Differences between idiopathic pulmonary fibrosis and progressive pulmonary fibrosis.

	Interstitial Pulmonary Fibrosis	Progressive Pulmonary Fibrosis
Definition	Chronic fibrosing interstitial diseases of unknown cause associated with radiological and histologic features of UIP [4]	Condition in several patients with ILD of known or unknown etiology characterized by worsening respiratory symptoms, decline in lung function, and radiological signs of disease progression [6]
Clinical feature	Dry cough, dyspnea, digital clubbing in 25–50%, bibasal mid-to-end inspiratory crackles [20]	Worse progressive dyspnea, cough, and quality of life producing limitations in the typical activities of the patient's life [21]
Radiological evidence	<p>1. UIP Pattern: Honeycombing with or without traction bronchiectasis/bronchiolectasis Presence of irregular thickening of interlobular septa Usually superimposed with a reticular pattern, mild GGO May have pulmonary ossification</p> <p>2. Probable UIP Pattern: Reticular pattern with traction bronchiectasis/bronchiolectasis May have mild GGO Absence of subpleural sparing</p> <p>3. Indeterminate for UIP: CT features of lung fibrosis that do not suggest any specific etiology. Necessity of lung biopsy [25]</p>	<p>Pulmonary interstitial pneumonia non-IPF with one or more of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Increased extent or severity of traction bronchiectasis and bronchiectasis</li> <li>2. New ground-glass opacity with traction bronchiectasis</li> <li>3. New fine reticulation</li> <li>4. Increased extent or increased coarseness of reticular abnormality</li> <li>5. New or increased honeycombing</li> <li>6. Increased lobar volume loss [25]</li> </ol>
Physiological criteria	Abnormal pulmonary function studies include evidence of restriction. Although a decline in the FVC > 10% predicted is a predictor of mortality, the smaller declines (5–10%) have also been associated with a worse prognosis [22]	<ol style="list-style-type: none"> <li>1. Absolute decline in FVC of <math>\geq 5\%</math> within 1 year of follow-up.</li> <li>2. Absolute decline in DLCO (corrected for Hb) of <math>\geq 10\%</math> within 1 year of follow-up [23]</li> </ol>
Disease progression	IPF is progressive fibrosing interstitial pneumonia but the antifibrotics may slow down their progression until 50% [26]	Approximately 18–32% of non-IPF ILDs within 61–80 months, despite conventional treatment (glucocorticosteroids/immunosuppressants) [14]
Treatment	<p>Antifibrotics:</p> <ol style="list-style-type: none"> <li>1. Nintedanib (intracellular tyrosine kinase inhibitor that blocks pathways involved in fibrogenesis). Quality of evidence of treatment is moderate</li> <li>2. Pirfenidone Quality of evidence of treatment is moderate [27]</li> </ol>	<p>Glucocorticosteroids or immunosuppressants: (e.g., cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab)</p> <p>Antifibrotics: (patients with a UIP pattern in lung HRCT or histopathological examinations and presenting worsening respiratory symptoms, FVC decline <math>\geq 10\%</math> within 12 months)</p> <ol style="list-style-type: none"> <li>1. Nintedanib Quality of evidence of treatment is moderate [28]</li> </ol>
Prognosis	Median survival is around 2–4 years from diagnosis without antifibrotics drugs [4]	Disease progression can occur at any time. It will depend on tomography patterns and associated diseases. The immunosuppressants and antifibrotics may slow down the fibrosis progression [26]

UIP: usual interstitial pneumonia, GGO: ground glass opacity, CDT: connective tissue disease, ILD: illness lung disease, IPF: idiopathic pulmonary disease, FVC: forced vital capacity, DLCO: diffusing capacity of the lungs for carbon monoxide. UIP: unusual interstitial pneumonia, HRCT high-resolution computed tomography.

## PPF

Changes in the HRCT patterns may be significant and indicate disease progression. Reticular opacities and/or traction bronchiectasis, along with the development of honeycombing, may all represent manifestations of PPF. Comparing serial HRCT images (when comparing images side by side, evaluating identical anatomical slices) may be enough to determine the extent of fibrosis progression [28].

UIP and/or traction bronchiectasis in the HRCT features at initial diagnosis in non-IPF ILDs has consistently predicted a higher likelihood of progression [29].

Between 18% and 32% of patients with non-IPF ILDs may develop progressive pulmonary fibrosis (PPF) within five years of symptom onset. The presence of a UIP pattern is a key risk factor for PPF. Therefore, accurate identification of the ILD subtype at the time of diagnosis is crucial for effective risk stratification [18].

The optimal interval for follow-up HRCT in patients with pulmonary fibrosis to determine disease progression is unknown. Still, some guidelines suggest that between 12 and 24 months from baseline could be helpful to detect progression and influence prognosis promptly. Therefore, annual HRCT should be considered to screen for complications.

Pathological findings:

## IPF

The UIP pattern is characterized by bilateral reticulation and honeycombing, primarily affecting the peripheral regions and lower lobes. This tomographic feature has a high positive predictive value for a histologic UIP pattern, making lung biopsy unnecessary. However, the lung biopsy will be considered when the clinic and imaging are not enough for the diagnosis. Transbronchial lung cryobiopsy has been considered the primary alternative to thoracoscopic biopsy. Histologically, the heterogeneous lesions are made up of fibrosis in the interstitium with foci of cell proliferation and deposit collagen fibers, which distorts the lung architecture, the microscopic tendency towards predominantly subpleural or para septal involvement, which is more serious than in the central areas of the secondary lobule. The honeycombing reflects a situation of large, pseudocystic air spaces and corresponds to the final stage of architectural alteration seen in interstitial lung diseases [30].

## PPF

Fibrosing NSIP (nonspecific interstitial pneumonia) is characterized by diffuse, temporally uniform fibrosis with minimal associated chronic inflammation, making it the most common pattern observed in all ILDs. Other notable features include plugs of loose connective tissue, known as Masson bodies, found in the distal airway lumens and alveolar spaces, which are indicative of organized pneumonia (OP). Additionally, vasculitis and capillaritis could be frequently observed in lung biopsies of patients with autoimmune diseases [31].

## 7. Treatment

### IPF

Pirfenidone (5-methyl-1-phenylpyridin-2[1H]-one) is an orally available synthetic compound with anti-fibrotic, anti-inflammatory, and antioxidant properties. It exerts these effects by downregulating key pro-fibrotic growth factors, including TGF- $\beta$ , inhibiting the production and release of inflammatory cytokines, and reducing lipid peroxidation and oxidative stress. Analyses and meta-analyses of clinical trials have shown that pirfenidone slows disease progression and functional decline in patients diagnosed with IPF. Additionally, it is associated with a reduced risk of mortality [27]. Common adverse effects include gastrointestinal intolerance and skin reactions, such as rash and photosensitivity which are typically mild to moderate in severity and can be reversed with dose reduction or temporary discontinuation [32]. The CAPACITY trial and the ASCEND trial showed pirfenidone lowers the likelihood of respiratory-related hospitalization over 1 year of treatment in patients with IPF [33].

Nintedanib is an intracellular inhibitor that targets vascular endothelial growth factor receptors 1–3, platelet-derived growth factor receptors, and fibroblast growth factor receptors 1–3. It interferes with processes involved in the pathogenesis of IPF, such as the migration and proliferation of fibroblasts, as well as the differentiation of fibroblasts into myofibroblasts. The IMPULSIS trial demonstrated a significant reduction in the annual rate of FVC decline (109.9 mL) in IPF patients, although the mortality rate remained unchanged [34]. Nintedanib treatment was associated with a significantly lower risk of disease progression in patients with IPF and appears to offer a survival benefit [35] (Table 1).

## PPF

Immunomodulatory agents, including corticosteroids, azathioprine, mycophenolate mofetil (MMF), methotrexate, cyclophosphamide, and rituximab, are the cornerstone of therapy for ILDs. These agents have proven largely successful in managing these illnesses and can be safely administered with the implementation of specific protocols, precautions, and monitoring [36] (Table 1).

Experience with antifibrotic drugs in IPF, such as a standard progressive fibrotic disease, has led to their use being considered in patients with PPF criteria. A trial involving patients with unclassifiable interstitial lung disease (uILD) assigned 253 individuals with fibrotic pulmonary disease to receive either pirfenidone or a placebo, followed by a 24-week monitoring period. This study demonstrated that pirfenidone reduced the likelihood of a decline in percentage-predicted FVC by 1.6 times for a 0.5% decrease and by 1.9 times for a 0.10% decrease. Additionally, those who received pirfenidone had a 3.7-fold lower risk of a DLCO decline of 0.15%. However, there was no statistically significant difference in the mean percentage change predicted DLCO. The same study did not demonstrate a statistically significant difference in progression-free survival [37].

Pirfenidone was administered to patients with PPF (non-IPF) in the RELIEF trial. After 48 weeks, a significant treatment effect was observed in the pirfenidone group. The primary endpoint indicated that the decline in FVC % predicted was significantly lower in the pirfenidone group compared to the placebo group. However, due to the premature termination of the study and the associated limitations, including the small patient sample size and missing data, these results should be interpreted with caution [38]. Despite these results, the guidelines consider that the evidence is low quality about using pirfenidone in PPF, which could be a promising therapy. Pirfenidone is currently being studied in patients with SSc-ILD, RA-ILD (TRAIL-1), sarcoidosis with pulmonary fibrosis, HP with fibrosis, and pneumosilicosis.

The randomized trial INBUILD assigned 663 patients with PPF to nintedanib or placebo for 52 weeks, showed FVC declined significantly less in the nintedanib arm (107 mL) and decreased the risk of this progression 2.4 times. Also, other interesting data was an annual decline in FVC between the nintedanib and placebo arms was 128 mL/year among patients with a radiological UIP pattern. In contrast, it was 73.5 mL/year among patients with a radiological non-UIP pattern. Therefore, nintedanib decreased the risk of progression of ILD 2.3 times among patients who had a radiological UIP pattern, but there was no significant difference among patients who had a radiological non-UIP pattern [39].

Nintedanib was approved by the FDA in 2020 for the treatment of progressive fibrosing ILD and SSc-ILD. The ATS/ERS/JRS/ALAT guidelines recommend nintedanib for patients with progressive pulmonary fibrosis who, despite standard treatment, exhibit new radiological features or a decline in lung function. This drug effectively slows disease progression and may reduce all-cause mortality in patients with progressive fibrosing interstitial lung diseases (PF-ILDs) [40,41].

## 8. Prognosis

### IPF

The prognosis is generally poor, with a median survival time of 2 to 4 years following diagnosis without treatment. However, the natural history of IPF is highly variable, and the disease course in individual patients is difficult to predict. Some patients experience rapid deterioration, while others progress more slowly. In most cases, the cause of death is respiratory failure due to IPF itself. Significant advances have been made in the diagnosis and treatment of IPF. For instance, the IMPULSIS trial demonstrated that nintedanib reduced the annual rate of FVC decline (125 mL) at week 52 compared to placebo, indicating it slows disease progression [26].

### PPF

Disease progression can occur at any time, even after periods of temporary stabilization, as the long-term trajectory of interstitial lung disease and associated radiological or functional changes remains poorly understood [42]. Most patients with RA-ILD and UIP have a prognosis slightly better than that of IPF, though acute exacerbations can significantly affect survival [43]. The retrospective PROGRESS study, which followed 164 patients with interstitial diseases other than IPF for 8 years, found that 66% of cases showed greater than a 10% loss of FVC within 2 years of diagnosis [44]. The prognosis for unclassifiable ILD (Uild) is somewhat better than for IPF, but the mortality rate remains high, with one study estimating a 31% mortality rate at 5 years [45].

Factors such as the 6-min walk test (6MWT), acute exacerbations, pulmonary hypertension and the need for oxygen supplementation can contribute to a poorer prognosis.

## 9. Conclusions

This review highlights the key characteristics and differences between idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF), particularly in relation to their radiologic features, which are associated with more severe clinical manifestations and compromised pulmonary function. Both, IPF and ILDs that exhibit PPF characteristics show comparable trajectories in terms of disease progression, quality of life, and prognosis, as indicated by the usual interstitial pneumonia (UIP) tomographic pattern and the decline in lung function.

The estimated median survival for patients diagnosed with IPF is approximately 3 to 5 years. While the prognosis for ILDs may be somewhat more favorable than that of IPF, the mortality rate remains significant, with 31% of patients succumbing within five years if they do not receive antifibrotic therapy. In this context, antifibrotic medications such as nintedanib and pirfenidone have emerged as first-line treatments for IPF. Several clinical trials have demonstrated their effectiveness in patients meeting PPF criteria, especially when immunosuppressive therapies fall short.

There is growing interest in the combination of these two drugs as they operate through different antifibrotic mechanisms. However, large randomized controlled trials are still needed to determine whether combination therapy offers greater efficacy compared to a single antifibrotic drug. Future studies should focus on the use of pirfenidone in PPF non-IPF and the combination of nintedanib and pirfenidone in IPF, aiming to establish trends toward a reduced decline in forced vital capacity (FVC) and enhanced safety for these patients.

Additionally, new antifibrotic agents, such as Treprostinil and Nerandomilast, are currently in phase III trials and have shown promise in slowing the decline of FVC in IPF patients. This ongoing research is crucial for improving treatment outcomes and patient quality of life in the face of these challenging lung diseases.

## Statement on the Use of Generative AI Technologies and AI-Assisted Tools in the Writing Process

During the preparation of the manuscript Comparative Analysis of Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis: Epidemiology, Pathophysiology, Clinical Features, Diagnosis and Treatment, the authors used artificial intelligence (ChatGPT) for the purposes of translation and sentence correction tailored to the manuscript. After using this tool, the authors thoroughly reviewed, edited, and verified the accuracy, consistency, and academic rigor of the content. The authors take full responsibility for the final content of the published article, including the validity of the data, the conclusions, and all other academic elements.

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## Author Contributions

C.M.D., J.S.T. and E.C. contributed to the conception and design of the study. C.M.D. drafted the manuscript. J.S.T. and E.C. critically reviewed and revised the manuscript for intellectual content. All authors approved the final version of the manuscript.

## Ethics Statement

Not applicable.

## Informed Consent Statement

Not applicable.

## Data Availability Statement

Not applicable.

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## Declaration of Competing Interest

J.S.T. reports receiving grants and consulting fees from Boehringer, Aflofarm and Roche. C.M.D. and E.C. declare no competing interests.

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