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# Molecular Biomarkers in Idiopathic Pulmonary Fibrosis

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## Abstract

The most lethal form of interstitial pneumonia of unknown cause, idiopathic pulmonary fibrosis (IPF), is associated with a specific radiological and histopathological pattern (the so-called "usual interstitial pneumonia" pattern) and has a median survival estimated to be between 3 and 5 years after diagnosis. However, evidence suggests that IPF has different clinical phenotypes, each of which has a different disease course over time. Individual patients' natural histories of IPF are currently unpredictable, though some genetic factors and circulating biomarkers have been linked to different prognoses. IPF may be asymptomatic in its early stages, resulting in a delayed diagnosis. Pirfenidone and nintedanib have been shown to change the course of the disease by slowing the decline in lung function.

**Keywords:** Adiopathic pulmonary fibrosis • Biomarker • Diagnosis • Prediction

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, chronic lung disease. The epidemiology of this disease is not consistent due to differences in data collection methods and classification terms between studies. However, in Europe and North America, an annual incidence of 2.8 to 19 cases per 100,000 people has been reported. IPF primarily affects men over the age of 50 (median age at diagnosis is around. The disease progresses differently depending on the clinical phenotype. However, the median time from diagnosis to death is 2-4 years. IPF may be asymptomatic in its early stages, resulting in a delayed diagnosis. The most common symptoms when present are progressive dyspnoea and cough. The identification of IPF is the basis for the diagnosis.

## Description

### Development of molecular biomarkers for IPF

In theory, molecular biomarkers could be used in IPF in a variety of ways. These include identifying patients at risk for developing IPF (predisposition biomarkers), diagnosing IPF (diagnostic or screening biomarkers), determining a patient's baseline prognosis, staging disease severity and monitoring for progression (prognostic biomarkers) and identifying target engagement with a specific mechanistic response or predicting response or toxicity to therapy, either by identifying a specific subgroup most likely to respond to a therapy or predicting response or toxicity to therapy. There are currently no molecular biomarkers in widespread clinical use for IPF for any of these applications. Molecular Biomarkers in Idiopathic Pulmonary Fibrosis: Current Status and Future Prospects [1].

There are two fundamentally different approaches to discovering biomarkers, both of which have value. A candidate marker is chosen a priori based on preexisting rationale/evidence in the hypothesis-based approach. This has been the approach taken in the majority of biomarker studies in IPF to date. This approach has the benefit of a strong biological rationale and preliminary data, but it is inefficient in the discovery process. The unbiased or hypothesis-free approach employs systems biology methods (for example, genomic, transcriptomic, proteomic and integratomic) to screen a large number of candidate markers for their association with the disease or outcome of interest, greatly increasing the efficiency and scope of the discovery process but also increasing the risk of false discovery [2].

### IPF candidate molecular biomarkers

The pathogenic paradigm for IPF has shifted over the last 15 years from uncontrolled inflammation to alveolar epithelial cell dysfunction, immune dysregulation and fibroproliferation/fibrogenesis/matrix remodelling. Alveolar epithelial stress and dysfunction, according to this model, result in the activation of profibrotic signalling pathways, fibroblast proliferation and exuberant extracellular matrix deposition [3]. Tissue destruction and architectural distortion result in organ dysfunction (e.g., restricted ventilation, hypoxemia), disability (shortness of breath and exercise limitation) and death from respiratory failure. In the following sections, we will discuss and contextualise candidate biomarkers using these proposed core mechanistic pathways.

### Dysfunction of alveolar epithelial cells

**Surfactant proteins:** Type II alveolar epithelial cells produce and secrete surfactant proteins (AECs). They aid in surfactant function and transport, as well as innate host defence. Surfactant protein quantitative or qualitative abnormalities are thought to increase alveolar epithelial endoplasmic reticulum (ER) stress and activate the unfolded protein response [4].

**Kl6/muc1:** KL6/MUC1 is a large membrane-bound glycoprotein in the mucin family that is expressed on the extracellular surface of type II AECs and bronchiolar epithelial cells in the lung, as well as glandular epithelial cells in other tissues such as the pancreas and breast. It was initially studied as a potential tumour marker for adenocarcinomas, but it has since been extensively studied as a diagnostic and prognostic biomarker in ILDs. In a variety of ILDs, including IPF, KL6 expression is increased in affected lung and regenerating type II AECs [5].

## Conclusion

Over the last decade, significant advances in understanding the pathobiology of IPF have occurred, leading to the identification of numerous potential molecular biomarkers, but the field of molecular biomarkers for IPF is still in its infancy. At the moment, only two prognostic biomarkers (MUC5B and MMP7) appear promising enough to be considered for translation into clinical practise. There is currently insufficient evidence to support the use of biomarkers in other clinical roles. To advance the field, mechanistically

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informative molecular biomarkers that are practical, accurate, validated and clinically useful are required. Characterization of potential molecular biomarkers for IPF should continue to benefit from the wealth of data generated by systems biology research, which offers an unbiased approach to identifying and validating candidate biomarkers and mechanistic pathways.

## Acknowledgement

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## Conflict of Interest

There are no conflicts of interest by author.

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