Cost-effectiveness of earlier diagnosis of fibrotic interstitial lung diseases (fibrotic ILDs) and earlier treatment of its progressive form, progressive pulmonary fibrosis (PPF)
Short title: Cost-effectiveness of Earlier Diagnosis and Treatment of Interstitial Lung Diseases (ILDs)

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ABSTRACT

Introduction: Early treatment for progressive pulmonary fibrosis (PPF) improves outcomes. However, diagnosis of fibrotic-interstitial lung diseases (fibrotic ILDs), and detection of potentially emergent PPF is delayed on average by 9-12 months. New ILD diagnostic and PPF monitoring strategies are being investigated that aim to allow early treatment to improve patient outcomes.

Objective: The study investigated health economic outcomes of early diagnosis of ILD and detection of PPF in eight European countries (Belgium, Denmark, Finland, Greece, Norway, the Netherlands, Portugal, and Sweden).

Methods: A time-to-event cost-effectiveness model of reducing delays in ILD diagnosis and detection of PPF was developed. Model inputs were obtained from ILD expert clinicians, literature, and statistical progression equations based on the INBUILD trial. Discounted health economic outcomes were calculated for eight European countries.

Results: The study highlights substantial benefits from reducing the time to diagnose fibrotic interstitial lung disease (ILD) and identify progressive pulmonary fibrosis (PPF) across various ILD subtypes. Clinical advantages arise from any reduction in diagnostic delays, primarily by delaying the onset of PPF and facilitating earlier treatment of PPF with nintedanib. The model indicates that earlier diagnosis results in Quality-Adjusted Life Year (QALY) gains across all countries, with improvements ranging from 0.061 to 0.084 in the base case. Furthermore, all tested scenarios confirm the cost-effectiveness of early diagnosis of fibrotic ILD and detection of PPF in all studied countries.

Conclusion: Early diagnosis of ILD and detection of PPF yields cost-effective clinical benefits, supporting adoption of approaches to speed up ILD diagnosis and PPF detection.

SUMMARY BULLET POINTS

• Early diagnosis of fibrotic interstitial lung diseases (ILDs) and detection of progressive pulmonary fibrosis (PPF) is critical, as current diagnostic delays average 9-12 months despite early treatment improving outcomes.

• The study evaluated health economic outcomes of early diagnosis across eight European countries using a time-to-event cost-effectiveness model with inputs from ILD experts, literature, and INBUILD trial data.

• Results demonstrated that reducing diagnostic delays provides clinical benefits by delaying PPF onset and enabling earlier nintedanib treatment, resulting in Quality-Adjusted Life Year gains of 0.061-0.084 across all countries.

• All tested scenarios confirmed that early diagnosis of fibrotic ILD and detection of PPF is cost-effective in all eight European countries studied.

• The findings support the adoption of approaches to accelerate ILD diagnosis and PPF detection to improve patient outcomes.

INTRODUCTION

Chronic interstitial lung diseases (ILDs) encompass a wide and heterogenous range of lung disorders characterized by different levels of inflammation and/or fibrosis, with several different underlying causes potentially related to inhalation exposures, drugs, autoimmune diseases, familial forms with genetic drive and others considered idiopathic in nature.[1] Some fibrotic ILDs can assume progressive behavior, and this is classified as progressive pulmonary fibrosis (PPF), characterized by worsening respiratory symptoms, acute exacerbations resulting in high risk of in-hospital mortality, permanent lung function loss, resistance to immunomodulatory therapies, and early mortality.[2-4] In some cases, this progressive behavior is treatment-refractory. The risk of developing PPF varies by the underlying ILD cause; for example, sarcoidosis has a 10% lifetime risk, while hypersensitivity pneumonitis has about five times higher progression risk.[5]

ILD poses a considerable humanistic burden on patients and caregivers.[6] The overall prevalence of non-IPF fibrosing-ILDs ranged between 51.8 and 117.4 cases per 100,000 persons in six European countries (Belgium, Denmark, Finland, Greece, Norway, and Portugal) between 2014 to 2018.[5] In Europe, the number of patients with PPF experiencing at least one acute exacerbation was more than three times higher than the number of patients with ILD.[7] The estimated time from symptom onset to death in patients with PPF is 61 to 80 months.[8]

In addition to its public health burden, PPF poses an economic burden on the healthcare system, patients, and society[6]. In Europe, the average annual cost of treating PPF in 2019 was €34,530 per patient, which was 1.8 times higher than that of ILD.[7] The estimated annual aggregated income loss in the European Economic Area (EEA), accounting for losses due to annual sick days, early retirements, and permanent disability, was €1.433 billion among PPF patients. The productivity loss due to job losses was €194 million in this population.[9]

The management of ILD aims to slow disease progression, maintain lung function (as measured by the forced vital capacity [FVC]), manage symptoms, and provide palliative care. Corticosteroids and immunosuppressants are widely used to treat non-IPF fibrotic ILDs[2] The 2017 European Alliance of Associations for Rheumatology (EULAR) guidelines[10] support the use of immunosuppressant drugs for the treatment of systemic sclerosis ILD (SSc-ILD). The only molecule with an approved indication (received in July 2020 from the European Medicines Agency [EMA]) and recommended in international guidelines for the treatment of PPF is nintedanib.[11-13] In the INBUILD trial, nintedanib was shown to lower the rates of lung function deterioration and acute exacerbation in PPF patients.[14]

The diagnosis of ILD requires a multidisciplinary approach, usually involving pulmonologists, radiologists, pathologists, and rheumatologists.[2,8,15] Diagnosis of ILD,[2] and detection of PPF are challenging due to the heterogeneity and unpredictability of ILDs, often leading to delayed diagnoses.[8] Physical exams, lung function tests, and high-resolution computed tomography are the mainstays used for the detection and diagnosis of ILD and, among fibrotic ILDs to monitor for the emergence of PPF.[2] Outside SSc-ILD, no definitive diagnostic/monitoring algorithm has been identified for non-IPF fibrotic ILDs.

ILD diagnosis is often delayed due to the initial emergence of symptoms being mistaken for aging, or for more common lung diseases, not only in primary care but also among secondary care management. Failure to diagnose and provide appropriate treatment for ILD can lead to more rapid disease progression to PPF, while failure to detect and manage PPF is associated with worse health outcomes.[14,16] These challenges has been well described in idiopathic pulmonary fibrosis (IPF),[17] the most

well-known and progressive form within the PPF spectrum, that can be broadly translatable to PPF. The authors expect that existing delays in diagnosis of ILD and detection of PPF could be substantially reduced through new enabling technologies such as artificial intelligence enhanced diagnostic scans[18] and improved physician and patient education. It is expected that improvements in time to diagnosis of ILD and/or detection of PPF may be multifactorial, as there is room for improvement in multiple areas. These new developments in care would be expected to accelerate diagnosis of ILD and/or detection of PPF, leading to beneficial clinical and health economic impacts.[19-21]

This study explores the health economic benefits (e.g. quality-adjusted life years [QALYs] and incremental cost-effectiveness ratio [ICER]) of a future diagnostic and monitoring strategy which enables earlier diagnosis of fibrotic ILDs and earlier detection of their progression to PPF in eight European countries: Belgium, Denmark, Finland, Greece, Norway, the Netherlands, Portugal, and Sweden. To comprehensively account for possible future developments, the study explores the clinical and health economic impact of a wide range of possible improvements in time to diagnosis.

METHODS

Model Structure and Overview

A hybrid individual state-transition and time-to-event model was developed in Microsoft Excel® (Figure 1).[22,23] The model simulated patients with fibrotic ILD from before diagnosis over a lifetime horizon. The model tracked disease progression based on patients' lung function (i.e., declining FVC over time), as well as occurrence of key clinical events (e.g., diagnosis of non-IPF fibrotic ILD, detection of PPF in patients where PPF developed, occurrence of acute exacerbations, initiation and discontinuation of treatment, and death). Individual patient characteristics (e.g., age, sex, and baseline FVC) and their impact on clinical event risks were considered in the model.

The model explored cost and QALY differences between current clinical practice, and various alternative scenarios in which diagnosis of fibrotic ILD and detection of PPF takes place earlier in the disease course than they currently do. In both scenarios, fibrotic ILD either persisted over the patient lifetime or progressed to PPF. However, the time to fibrotic ILD diagnosis, time to development of PPF, and time to detection of PPF varied between the current and alternative scenarios due to differences in the fibrotic ILD diagnosis and PPF detection strategies.

The target population encompassed patients with undiagnosed ILD. Patients entered the simulation in the undiagnosed ILD state with a probability of progressing to PPF. Those who did not progress remained in the ILD state until death. Baseline patient characteristics were used to estimate the time-to-event of ILD diagnosis, PPF development, or death. The progression and management of ILD and PPF were represented as a combination of evolving conditions (e.g., age, FVC, costs, and utilities) and discrete events (e.g., acute exacerbation or death). As per ILD expert key opinion leader (KOL) assessment, earlier diagnosis of ILD was not modeled as preventing development of PPF, but only as delaying progression to PPF.

In patients developing PPF (both undetected PPF and detected PPF), FVC percent predicted (FVC%pred) was used in the model as a measure of the overall disease progression and was calculated every three months using a linear mixed-effects regression equation estimated from INBUILD trial data. The FVC%pred was stratified into the following categories or "health states" for use in other equations: FVC<40, 40≤FVC<50, 50≤FVC<60, 60≤FVC<70, 70≤FVC<80, 80≤FVC<90, and FVC≥90. Patients' FVC%pred at the time of PPF detection was calculated by extrapolating backwards in time to the point of PPF detection.

The model was evaluated from a payer perspective for Belgium, Finland, Greece, and Portugal, and from a societal perspective for other countries with a lifetime horizon and followed ISPOR guidelines for cost-effectiveness modeling.[24] Deterministic and probabilistic sensitivity analyses were performed to test the robustness of the model. Scenarios were conducted for all eight countries to evaluate the impact of different levels of improvement in time to diagnosis of ILD and detection of PPF, as well as to assess the clinical benefits and cost-effectiveness of earlier diagnosis and treatment across different ILD subtypes. Additionally, payer perspective scenarios were compared with the broader societal perspective base cases in Denmark, Norway, the Netherlands, and Sweden. A societal perspective was also considered as a scenario for Finland in contrast to its payer perspective base case.

Model Inputs

The model synthesized data from multiple public sources (see Supplementary Material). The key independent variables included time to diagnosis of fibrotic ILD after the emergence of the first symptoms, and time to detection of PPF behavior after it first develops. The time-to-event inputs (i.e., time from initial symptoms / beginning of the model to a fibrotic ILD diagnosis, time from initial symptoms to undetected PPF behavior, and time from undetected PPF to PPF clinical identification) in the current scenario were a weighted average of the time-to-fibrotic ILD diagnosis and PPF detection inputs informed by Wijsenbeek et al.[8] and relative frequency of PPF development informed by Hilberg et al.[5] The inputs applied in the new scenario, reflecting improvements in time to ILD diagnosis and PPF detection, were based on KOL feedback derived from structured interviews with European ILD experts (Table 1).

In the base-case analysis, the cost and clinical outcomes of an earlier diagnosis of fibrotic ILD and detection of PPF patients were assessed across eight countries. This analysis evaluates the health economic impacts of reducing the time to fibrotic ILD diagnosis by 6 months (from an initial delay of 10.6 months) and improving the time to PPF detection by 7.9 months (from an initial delay of 10.9 months).

Additionally, the base case considers a timeline of 24.9 months from the onset of ILD symptoms to the development of PPF for the 30.2% of patients who progress to PPF. The remaining 69.8% of patients do not develop PPF in the base case. For those who do develop PPF, the base case projects a 4.8-month delay in the progression to PPF as a consequence of the 6-month improvement in fibrotic ILD diagnosis time.

Table 1. **Time-to-Event Parameters for the Base Case**

Abbreviations: ILD = interstitial lung disease; SD = standard deviation; SE = standard error; PPF = progressive pulmonary fibrosis

Parameter	Current Scenario			New Scenario	
	Mean	SD	SE	Mean Adjustment (absolute change)	SD
Time since initial symptoms to diagnosis of fibrotic ILD	10.6 Month(s)	2.1 Month(s)	2.13	-6.0 Month(s)	1.20
Time since initial symptoms to undetected PPF	24.9 Month(s)	5.0 Month(s)	4.98	4.8 Month(s)	0.96
Time since undetected PPF to PPF identification	10.9 Month(s)	2.2 Month(s)	2.18	-7.9 Month(s)	1.58

Sources: current scenario inputs were informed by Wijsenbeek et al. 2019[8] and Hilberg et al. 2022[5], while new scenario inputs were informed by key opinion leaders' feedback

Analyses

The incremental impact of an earlier diagnosis of fibrotic ILD and earlier detection of PPF on cost and clinical outcomes was explored. The base case analysis evaluated the cost and clinical outcomes over a lifetime time horizon of 2,652 simulated individual patients derived from four replications each of 663 patient profiles taken from the INBUILD trial. The cost and health outcomes discount rates varied across countries (Table S24).

Scenario analyses explored outcomes based on varying improvements in delays of fibrotic ILD diagnosis and PPF detection times across all ILDs and individual subtypes in eight countries. These analyses include one scenario in which 100% of fibrotic ILD patients develop PPF (Figure 5), compared to 30.2% in the base case, to explore the clinical benefits and cost-effectiveness of early fibrotic ILD diagnosis among patients who will develop PPF. The delays in diagnosis and detection in the reference and alternative scenarios matched those in the base-case analysis.

To test uncertainty in the model parameters and identify model drivers, deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were conducted. DSA varied each parameter by ±20% from the base-case value. PSA simultaneously varied critical model parameters (e.g., disease progression, overall survival, treatment discontinuation, time-to-event equations, acute exacerbation, utilities, unit costs, time to ILD diagnosis, time to PPF development and detection) using probability distributions to reflect uncertainty. For the PSA in each country, 2,652,000 patient profiles were simulated over 1,000 model analyses.

RESULTS

Base-Case Analysis

To facilitate cross-country comparison, ICERs and incremental costs are reported in Euros (see Figure 2) based on one-year average conversion rates from the European Central Bank website.[26] ICERs ranged from €14,831 to €41,012, while incremental QALYs ranged from 0.06 to 0.09. Across all countries, additional pharmacotherapy costs drove most of the increased net incremental costs, with a median 96.25% of net incremental costs being attributed to increased pharmacotherapy costs. Nintedanib costs constituted the majority of the increased pharmacotherapy costs – i.e., in the Netherlands, 89.4% of the increased pharmacotherapy costs were due to increased nintedanib use.

Scenario Analysis

Different times to ILD diagnosis and PPF detection

Scenarios varied the reduction in time to fibrotic ILD diagnosis and PPF detection associated with future diagnostic and monitoring strategies, ranging from 0.5 months to 10 months improvement in each. As shown in Figure 3, the ICER (i.e., incremental cost per QALY) decreased with the greater reduction in time to fibrotic ILD diagnosis and PPF detection with future improved diagnostic and monitoring strategies. In each country (see Figure 3), the ICER appeared to stabilize after a few months of improvement, indicating that even modest improvements to diagnosis of fibrotic ILD and detection of PPF are likely to be similarly cost-effective as major improvements.

Different ILD subtypes across countries

The model was used to evaluate the impact of an improvement in time to diagnosis of fibrotic ILD and detection of PPF across multiple subtypes of ILD, namely unclassifiable idiopathic interstitial pneumonia (U-IIP), rheumatoid arthritis ILD (RA-ILD), idiopathic fibrotic nonspecific interstitial

pneumonia (iNSIP), fibrotic hypersensitivity pneumonitis (HP), other ILDs, and fibrotic sarcoidosis. While the base case used all patients from the INBUILD trial, these ILD subtypes were modeled using only patient profiles from the INBUILD trial that matched the corresponding subtype. Parameters for % of patients developing PPF were sourced from Hilberg et al 2022[5], and time for undetected PPF to develop, and time for ILD and PPF to be detected were populated from Wijsenbeek et al 2019[8]. The results of this analysis showed that ILD sub-types with higher incidence of PPF had higher QALYs gained and higher cost (Figure 4).

Proportion of ILD patients developing PPF

This scenario shows moderately reduced ICERs and considerably greater clinical benefits (Figure 5) compared to the base case.

Sensitivity Analyses

DSA identified the most impactful parameters, with slight variations in their relative importance across countries. These included the cost and proportion of patients receiving nintedanib, the ILD screening cost, the intercept values in the time to treatment discontinuation and overall survival risk equations, and the intercept coefficient of the utility equation. The ranking of the most impactful parameters is reported in a tornado diagram for each country in Supplementary Material (Figures S2-S9).

PSA scatter plots show that 100% of the simulations fall in the northeast quadrant, indicating the alternative strategy is more effective and more costly than current clinical practice. The cost-effectiveness acceptability curves suggest that the future diagnosis and monitoring strategy is expected to be a cost-effective option at willingness-to-pay (WTP) threshold above €21,423 in Belgium, €33,474 in Denmark, €36,187 in Finland, €15,212 in Greece, €41,412 in Norway, €32,421 in Netherlands, €32,169 in Portugal, and €33,954 in Sweden (see Figures S2-S9). Each of these values is at or below thresholds that have been reported in the economic modeling literature for these country.[25-32] This also indicates that early diagnosis of fibrotic ILD and early detection of PPF is likely to be broadly cost effective across country settings

DISCUSSION

To the best of the authors' knowledge, this study is the first to evaluate the cost-effectiveness of a scenario involving earlier diagnosis and monitoring of ILD and PPF in eight European countries. The base-case analysis revealed that earlier diagnosis and monitoring was associated with clinical gains in QALYs and would likely be cost-effective in all eight countries of the study. The QALYs gained results were similar across the countries for the base case, ranging from 0.06-0.09 QALYs gained, and varied due to different discount rates across countries. Incremental costs had more variability, ranging from €909 in Greece to €2,976 in Norway. The lowest base case ICER was €14,831/QALY gained (Greece), followed by Belgium (€20,591/QALY gained), while Norway had the highest ICER (€41,012/QALY gained).

These values are generally expected to fall at or below national WTP thresholds.[25-32] This indicates that early diagnosis of fibrotic ILD and early detection of PPF is likely to be broadly cost-effective across different country settings.

While the clinical benefit of early diagnosis and treatment of fibrotic ILD was reduced in less progressive ILD subtypes such as sarcoidosis, the additional cost was also lower. As a result, the ICER for earlier diagnosis of fibrotic sarcoidosis, though somewhat higher, remained comparable to the CER for earlier diagnosis of more progression-prone disease subtypes. This suggests that the greater clinical benefits of treating less progressive ILD subtypes may be offset by higher expenditures. However, despite higher costs incurred in early diagnosis and treatment for the more progression-prone fibrotic ILD subtypes, the early diagnosis and treatment remain cost-effective due to the greater clinical benefits.

Several limitations of this study should be considered when interpreting the results. First, the improvement in ILD diagnosis and PPF detection times in the base-case analysis was based on KOL opinion, serving as a "what-if" analysis. Scenario analyses mitigated this limitation by exploring the full range of possible improvements in ILD diagnosis times, showing that almost any improvement would likely be cost-effective. Second, the study data were derived from patients with PPF in the INBUILD trial, conservatively assuming the natural history of undetected PPF is the same as detected PPF, which may not reflect true clinical outcomes. The INBUILD trial was used to determine FVC progression in PPF only (data driven for detected PPF and backwards linear extrapolation for undetected PPF) and enrolled a selected population which could differ from the general population with PPF. The potential effects of immunosuppressants in PPF patients not treated with nintedanib was not modeled due to insufficient data. These limitations were further mitigated by sensitivity analysis testing variation in the proportion progressing to PPF, and the speed of progression in the probabilistic sensitivity analysis. FVC was assumed to be stable in the ILD state, but this assumption is expected to have minimal impact as it applies equivalently in both groups and only over the duration for which PPF has not yet developed. Third, the model's clinical benefits of early diagnosis, particularly PPF development delays, relied on ILD medical expert feedback and may not represent the actual benefits of early diagnosis. Fourth, the frequencies of healthcare resource use components in current and new scenarios were based on ILD medical expert feedback, potentially underestimating uncertainty in cost estimates, especially for unreimbursed or less-implemented technologies. Finally, it should be noted that the analysis did not consider sensitivity or specificity of any diagnostic tests, as the main focus of the study was to quantify the impact of improved time to diagnosis instead of to compare different diagnostic tests. These limitations could potentially be addressed by future research that incorporated additional data from real world evidence studies, or considered the accuracy of different screening and diagnostic tests.

Despite limitations, this study has several strengths. First, it includes a cross-country comparison, providing a comprehensive analysis of the cost-effectiveness of earlier ILD diagnosis and PPF detection across multiple European countries and allowing a broader understanding of the potential benefits and cost implications across different healthcare systems. Second, this study involves consultation with ILD medical experts to ensure that the findings align with clinical practice, enhancing the credibility and relevance of the study conclusions. Third, treatment costs may be overestimated because, in some countries, nintedanib is reimbursed via a managed entry agreement; hence, the total incremental costs may be overestimated, suggesting that the cost-effectiveness of an earlier diagnosis and monitoring of PPF patients may be even more favorable in practice. Fourth, scenario and sensitivity analyses were conducted to assess the robustness of the results and identify the key drivers of the cost-effectiveness outcomes. It should be noted that no parameter variation explored in the scenarios or sensitivity analysis affected the conclusion that earlier diagnosis of ILD and earlier detection of PPF is expected to be cost effective; these findings were consistent across the scenarios and sensitivity analysis examined.

Altogether, the results indicate that an earlier diagnosis of fibrotic ILD and a timelier detection of PPF will lead to substantial clinical benefits as a result of earlier treatment initiation. Furthermore, the anticipated earlier management of fibrotic ILD and the iterative identification of PPF is expected to deliver these clinical advantages in a cost-effective manner.

CONCLUSION

Improving the time to a fibrotic ILD diagnosis and PPF detection, thereby optimizing the time to treatment, will produce cost-effective clinical benefits for ILD patients. Consequently, this improvement

is a worthwhile and important goal for the clinical community and payers making resource-allocation decisions.

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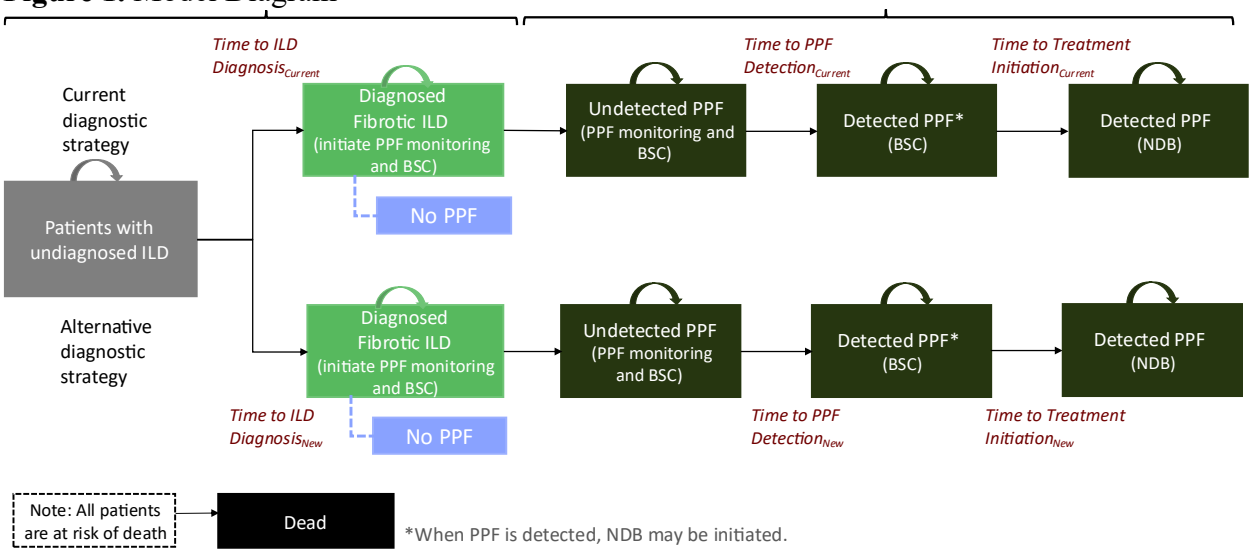
Figure 1. Model Diagram



Abbreviations: BSC = best supportive care; FVC = forced vital capacity; ILD = interstitial lung disease; NDB = nintedanib; PPF = progressive pulmonary fibrosis

Figure 2. Incremental Cost Effectiveness Ratio, Quality-adjusted Life Years, and Costs by Country in the Base-case

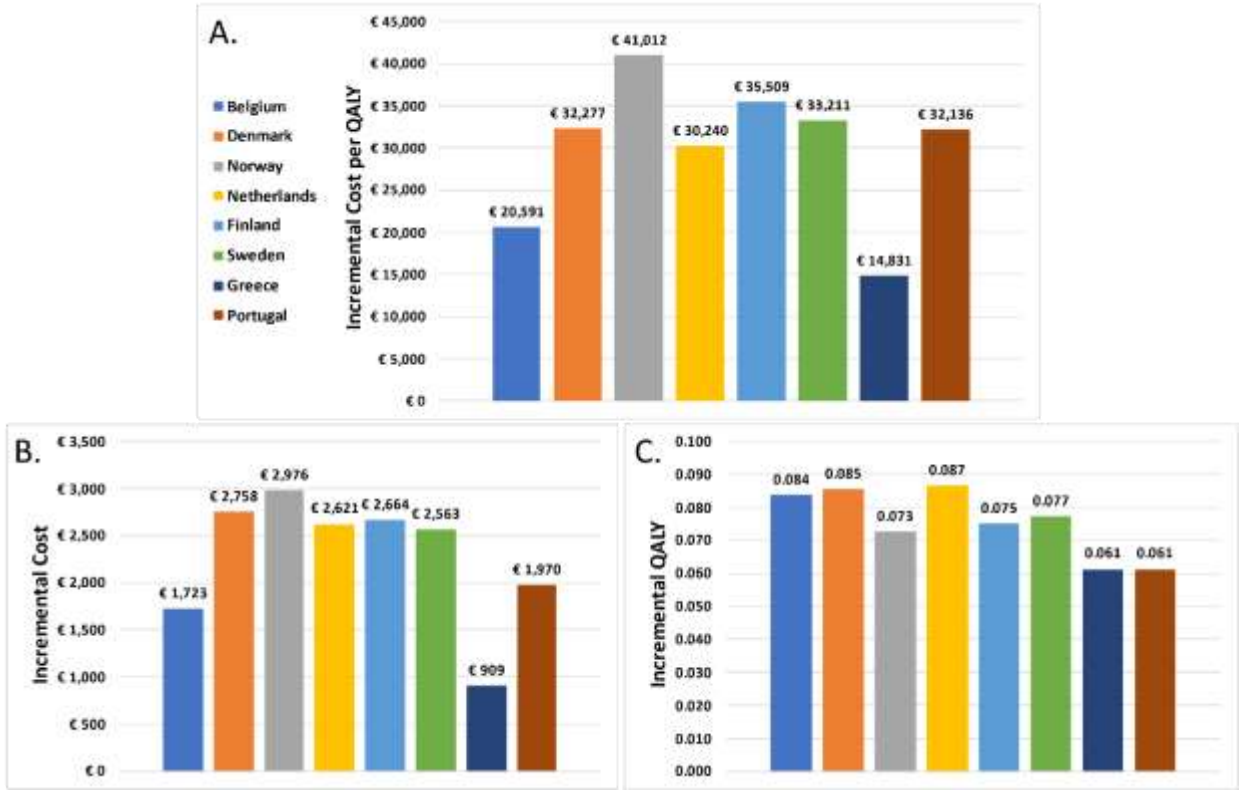


Figure 2. Base Case Results. The results calculated were **(A)** Incremental Cost-Effectiveness Ratios (ICER) **(B)** Incremental costs **(C)** Incremental quality adjusted life years (QALYs), across the 8 countries studied.

Figure 3. Incremental Cost-Effectiveness Ratio by Reduction in Times to Fibrotic ILD Diagnosis

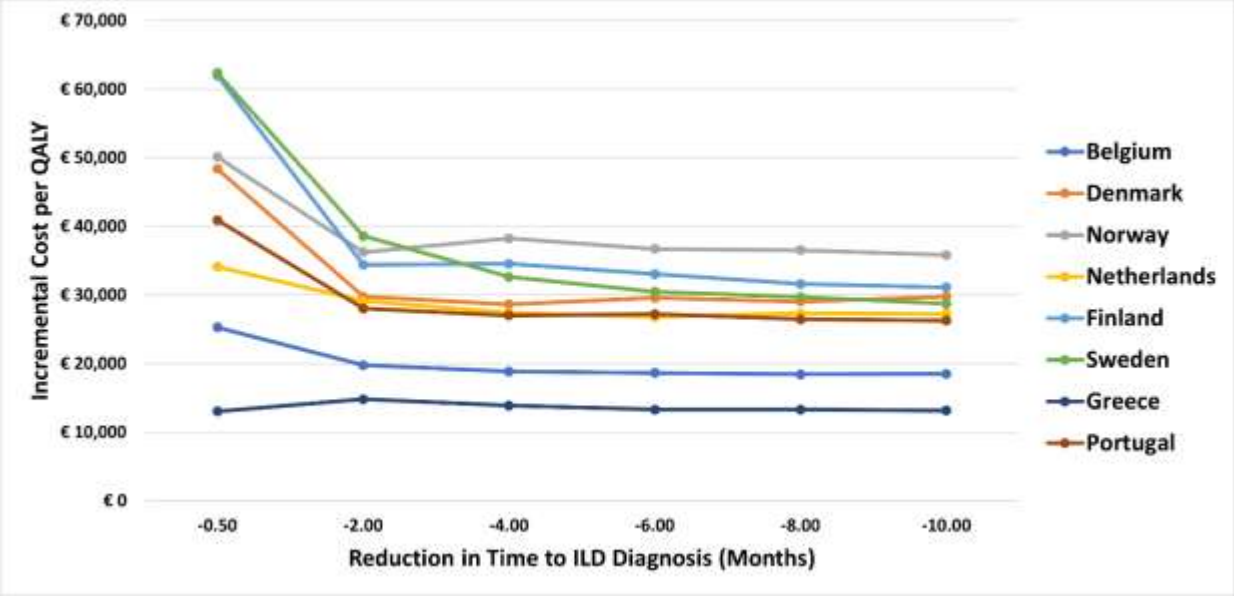


Figure 3. When an **improvement of 0.5 months in time to ILD diagnosis**, along with same improvement in time to PPF detection was assessed, the Incremental Cost-Effectiveness Ratios (ICER) were as follows: €25,275 for Belgium, €48,368 for Denmark, €50,099 for Norway, €34,126 for Netherlands, €61,984 for Finland, €62,352 for Sweden, €13,036 for Greece, €40,899 for Portugal. When an **improvement of 2 months in time to fibrotic ILD diagnosis**, along with same improvement in time to PPF detection was assessed, the Incremental Cost-Effectiveness Ratios (ICER) were as follows €19,760 for Belgium, €29,762 for Denmark, €36,253 for Norway, €29,107 for Netherlands, €34,406 for Finland, €38,598 for Sweden, €14,803 for Greece, €28,025 for Portugal. When an **improvement of 4 months in time to fibrotic ILD diagnosis**, along with same improvement in time to PPF detection was assessed, the Incremental Cost-Effectiveness Ratios (ICER) were as follows: €18,835 for Belgium, €28,632 for Denmark, €38,227 for Norway, €27,376 for Netherlands, €34,555 for Finland, €32,620 for Sweden, €13,883 for Greece, €27,012 for Portugal. When an **improvement of 6 months in time to fibrotic ILD diagnosis**, along with same improvement in time to PPF detection was assessed, the Incremental Cost-Effectiveness Ratios (ICER) were as follows: €18,637 for Belgium, €29,572 for Denmark, €36,701 for Norway, €26,803 for Netherlands, €33,058 for Finland, €30,482 for Sweden, €13,294 for Greece, €27,225 for Portugal. When an **improvement of 8 months in time to fibrotic ILD diagnosis**, along with an improvement of 7.9 months in time to PPF detection was assessed, the Incremental Cost-Effectiveness Ratios (ICER) were as follows: €18,426 for Belgium, €29,025 for Denmark, €36,530 for Norway, €27,328 for Netherlands, €31,600 for Finland, €29,706 for Sweden, €13,281 for Greece, €26,476 for Portugal. When an **improvement of 10 months in time to fibrotic ILD diagnosis,** along with same improvement in time to PPF detection was assessed, the Incremental Cost-Effectiveness Ratios (ICER) were as follows: €18,483 for Belgium, €29,761 for Denmark, €35,819 for Norway, €27,250 for Netherlands, €31,105 for Finland, €28,729 for Sweden, €13,160 for Greece, €26,261 for Portugal.

Figure 4. Clinical and Cost Impacts of Earlier Diagnosis of Fibrotic ILD and Detection of PPF by ILD subtypes Across Countries

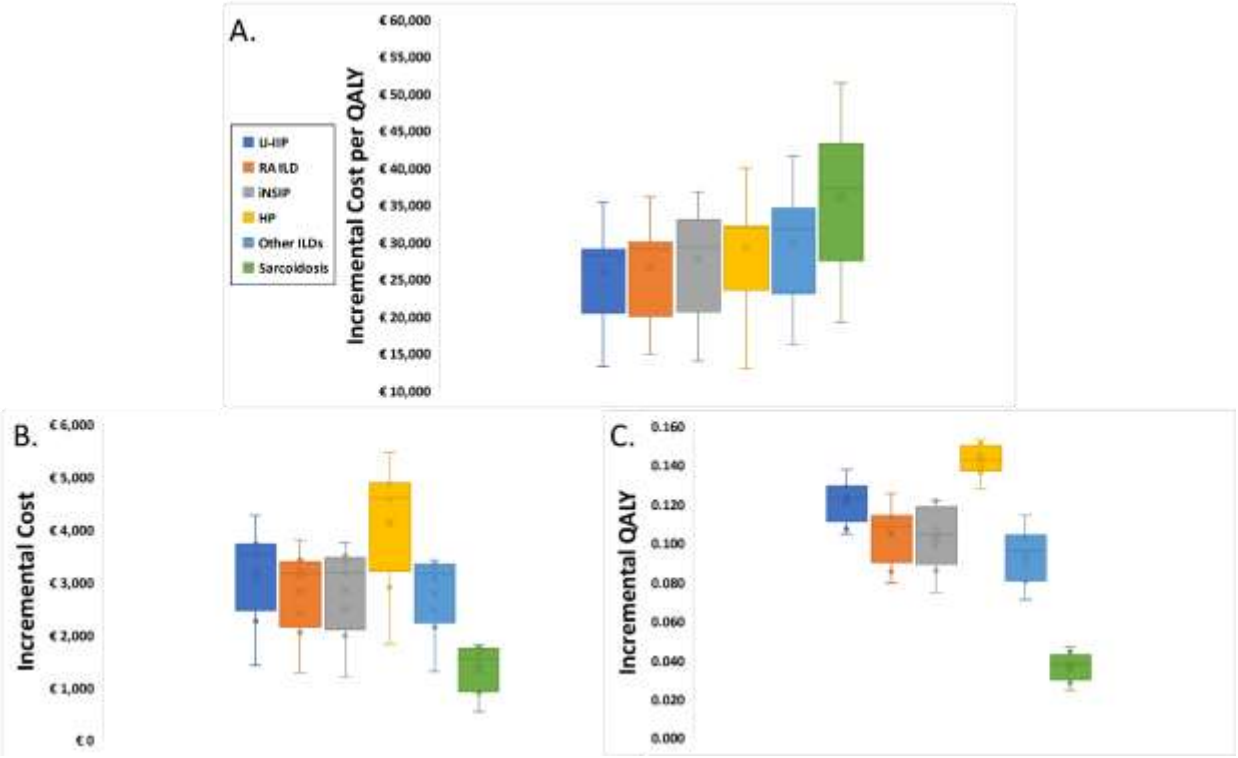


Figure 4. The incremental cost-effectiveness ratio, costs, and clinical benefits (QALYs) associated with 6 months earlier diagnosis of ILD and 7.9 months earlier detection of PPF, for six subtypes of ILD unclassifiable idiopathic interstitial pneumonia (U-IIP), rheumatoid arthritis ILD (RA-ILD), idiopathic fibrotic nonspecific interstitial pneumonia (iNSIP), fibrotic hypersensitivity pneumonitis(HP), other ILDs, and fibrotic sarcoidosis, across 8 countries (see **Table S25** for key clinical input parameters). **A.** The range of ICER outcomes across countries are displayed in the box plots. The ICER result for early diagnosis of each ILD subtype within each country is displayed as a point within each ILD subtype box. **B.** The range of incremental cost outcomes across countries are displayed in the box plots. The incremental cost results for early diagnosis of each ILD subtype within each country is displayed as a point within each ILD subtype box. **C.** The range of QALY outcomes across countries are displayed in the box plots. The incremental QALY result for early diagnosis of each ILD subtype within each country is displayed as a point within each ILD subtype box. See **Table S26** for detailed quantitative results reported in this figure.

Figure 5: Incremental Cost Effectiveness Ratio, Quality-adjusted Life Years, and Costs by Country for Fibrotic ILD Patients who Develop PPF

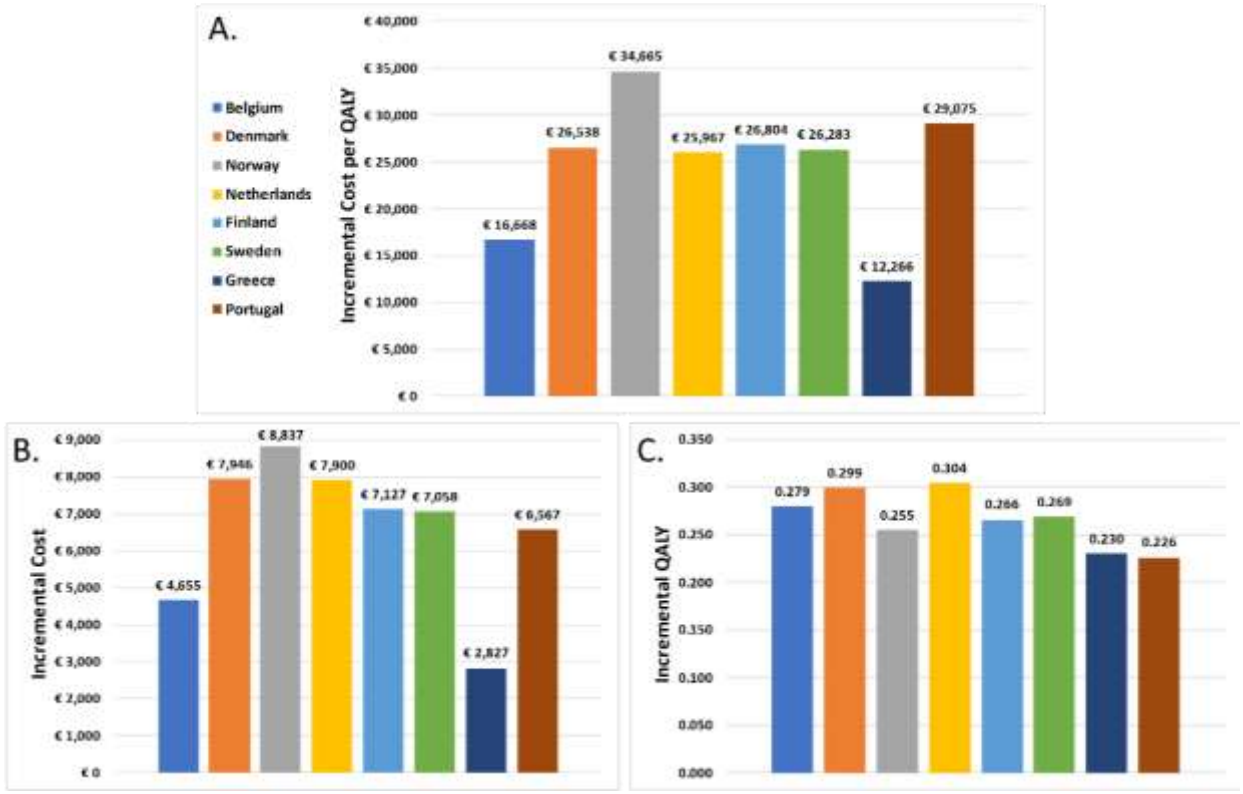


Figure 5. Scenario for ILD patients who develop PPF. The results calculated were **(A)** Incremental Cost-Effectiveness Ratios (ICER) **(B)** Incremental costs **(C)** Incremental quality adjusted life years (QALYs), across the 8 countries studied.