Using patient-level simulation to estimate long-term survival in idiopathic pulmonary fibrosis

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Background

- Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and debilitating disease that causes irreversible loss of lung function, significantly impacting patients' quality of life and life expectancy[1-3]
- When assessing the efficacy of new potential treatments for IPF in clinical trials, primary outcomes are centered on reducing or halting the progressive decline of lung function[4,5]
  - Lung function is commonly measured in terms of forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO)
- Clinical trials for new IPF treatments are generally not designed (by virtue of statistical power or follow-up duration) to establish the potential impact of treatments on overall survival[6]
  - Hence, survival extrapolation beyond the trial period is needed to evaluate both long-term effectiveness and cost-effectiveness of treatments for IPF
- A review of health technology assessments of IPF treatments found that prior state transition models were limited because overall survival was extrapolated independently of lung function[7]
- Although published mortality prediction models for IPF have linked age, sex, lung function, and recent respiratory hospitalizations to survival,[8-10] the feasibility of using these mortality prediction models in long-term disease and cost-effectiveness models has not been established

Objective

- This study assessed the feasibility of modeling long-term survival in IPF using a patient-level simulation based on IPF-specific mortality risk prediction models

Methods

Modeling disease trajectories

- We developed a patient-level simulation model to predict the natural history disease trajectories without antifibrotic treatment for patients with IPF
- The model predicts patient-level disease trajectories for key clinical parameters needed to predict mortality risk, including percent predicted forced vital capacity (ppFVC), percent predicted diffusing capacity of the lungs for carbon monoxide (ppDLCO), 6-minute walk distance (6MWD), and history of recent respiratory hospitalization
- A targeted literature review was conducted to identify 3 categories of inputs needed to model long-term patient-level disease trajectories[11]: baseline characteristics, natural disease progression, and correlation between progression in clinical parameters (**Table 1**)
- Trajectories for each clinical parameter were estimated for each patient at 6-month steps over a lifetime time horizon
- The model was run for a simulated cohort of 1000 patients, using random numbers to draw from appropriate distributions defined by the mean and standard deviation (SD) for each input parameter. Continuous variables were sampled from normal distributions, applying correlations as appropriate, and proportions were sampled from binomial distributions
- This approach to simulating individual patient trajectories was designed to realistically capture the natural heterogeneity observed in clinical practice

Table 1. Input categories used to model long-term patient-level disease trajectory

Baseline characteristics	Parameter values	References
Age, mean (SD), years	66.0 (7.6)	10
Gender, proportion		
Female	0.285	10
Male	0.715	
Proportion of patients with history of acute exacerbation	0.208	12
Baseline ppFVC		
ppFVC range for inclusion[a]		
Minimum ppFVC value	40	
Maximum ppFVC value	120	
History of acute exacerbation, mean (SD)	72.0 (15.7)	12
No history of acute exacerbation, mean (SD)	77.6 (17.0)	12
Baseline ppDLCO		
ppDLCO, mean (SD)	47.5 (9.2)	10
Correlation coefficient (baseline ppDLCO and ppFVC)	0.38	4
Parameters for those unable to perform the DLCO test[b]		8, 13, 14
ppDLCO cutoff value (inclusive)	10.0	
Proportion unable to perform DLCO test at cutoff	0.500	
Baseline 6MWD		
6MWD, mean (SD), meters	379.0 (107.0)	10
Correlation coefficient (baseline 6MWD and baseline ppFVC)	0.12	4
Natural disease progression and correlation between variables	**Parameter values**	**References**
Change in ppFVC		
ppFVC change, per 6 months, mean (SD)[c]	−3.38 (6.76)	15
Probability of acute exacerbation resulting in hospitalization[d]		
ppFVC decline over 6 months		
< 5%	0.005	16
≥ 5% and < 10%	0.020	
≥ 10%	0.058	
Change in ppDLCO		
ppDLCO change, per 6 months, mean (SD)[e]	−1.67 (6.66)	15
Correlation coefficient (change in ppDLCO and change in ppFVC)	0.29	4
Change in 6MWD		
6MWD change, per 6 months, mean (SD),[f] meters	−18.5 (74.0)	15
Correlation coefficient (change in 6MWD and change in ppFVC)	0.22	4

[a]Values based on assumptions. [b]Assumption based on references 8, 13, and 14. [c]Change in ppFVC is relative for the GAP and longitudinal GAP models, and absolute for the du Bois et al model,[10] with mean based on reference 15 and SD based on assumption. [d]Derived from reference 16. [e]Change in ppDLCO is relative for GAP and longitudinal GAP models and absolute for the du Bois et al model,[10] with mean based on reference 15 and SD based on assumption. [f]Mean is derived from reference 15 and SD based on assumption.

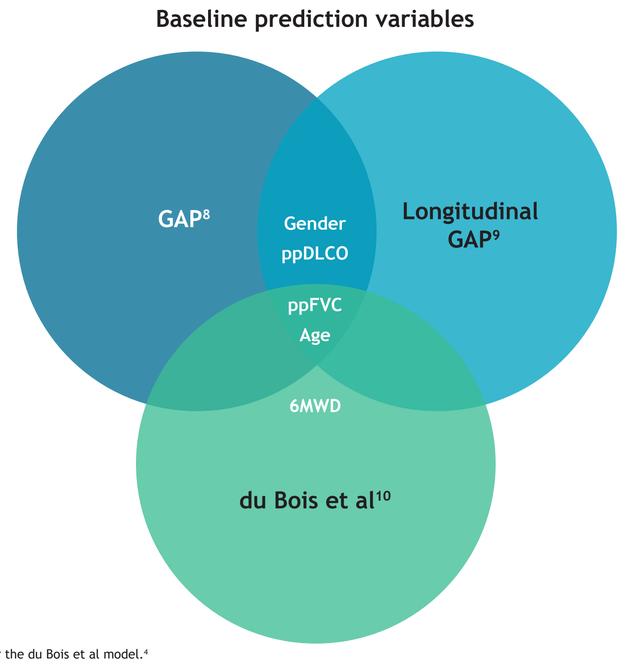
GAP, gender-age-physiology.

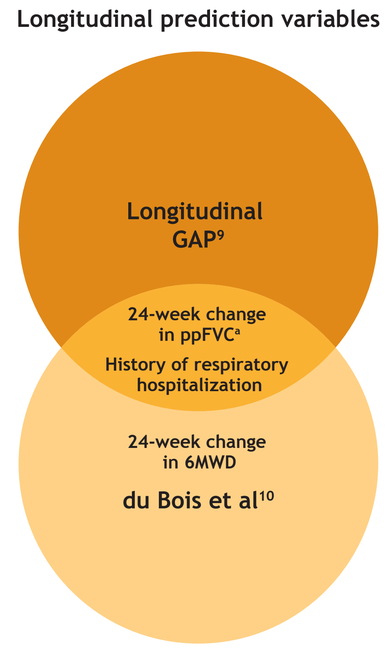
Estimating mortality

- Mortality was estimated from patients' disease trajectories using 3 different clinically relevant mortality risk prediction models: GAP,[8] longitudinal GAP,[9] and du Bois et al[10]
- The different clinical variables used when predicting mortality risk with each model are described in **Figure 1**
- At each 6-month interval, patient-level mortality probabilities were estimated from the patient- and time-specific clinical parameters relevant for each mortality risk prediction model. Annual mortality probabilities were adjusted to reflect the model's 6-month step and used to determine the probability of a patient dying within a given 6-month step

Figure 1. Characteristics of IPF mortality prediction models

Model	Description	Mortality prediction timepoints
GAP[8] (calculator and index versions)	Validated; uses commonly measured clinical baseline variables	1-year, 2-year, and 3-year risks
Longitudinal GAP[9] (point index and categorical versions)	Includes GAP model baseline variables plus 2 longitudinal variables	1-year and 2-year risks
du Bois et al[10]	Includes baseline and longitudinal variables	1-year risks





[a]24-week change in ppFVC is relative for the longitudinal GAP model[9] and is absolute for the du Bois et al model.[4]

External validation of survival estimates

- To assess the clinical plausibility of our patient-level simulation based long-term survival estimation, we compared our results with estimates of long-term survival observed in clinical and observational studies and estimates based on standard survival extrapolations models done independently of lung function
- Khor et al[15] provided a systematic review of IPF prognosis, including mortality, based on both clinical trials and observational studies. Limitations of the study include reporting survival in time intervals instead of specific timepoints and including older (before 2000) studies
- Lancaster et al[17] presented long-term survival extrapolations for nintedanib and placebo (representing best supportive care [BSC]) based on pooled analysis of 6 clinical trials

Results

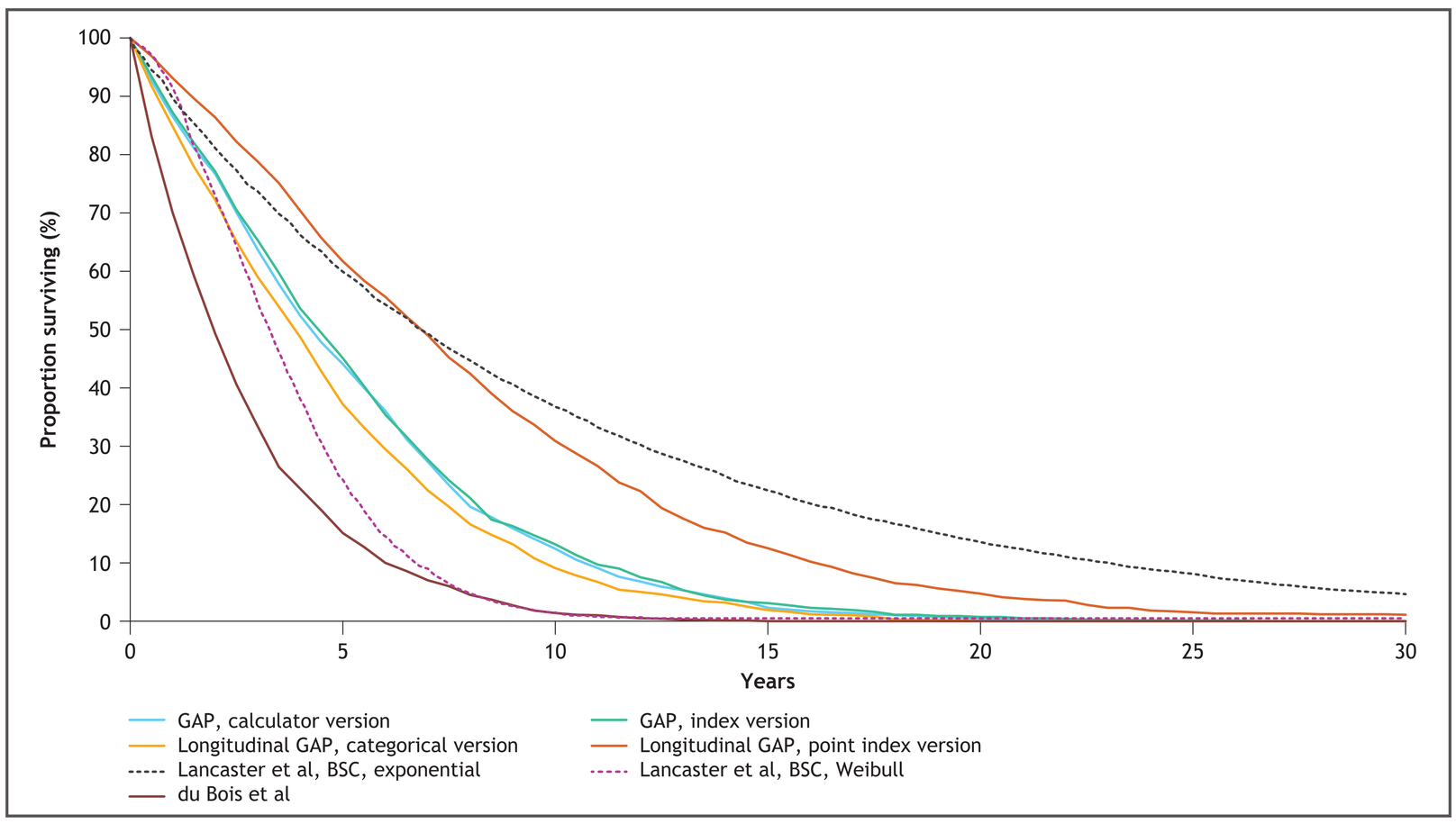
Model-predicted survival estimates

- The predicted 2-, 5-, and 10-year survival rates were 49%-86%, 14%-62%, and 1%-31%, respectively, with the highest survival estimates produced by the longitudinal GAP point index model and the lowest by the du Bois et al model (**Figure 2**)
- In addition to variations in survival estimations across models, our results also showed that the implementation approach of the longitudinal GAP model (point index vs categorical hazard ratios) resulted in considerable differences in long-term survival estimates, whereas the different implementation approach of the GAP model (calculator vs point index) had little impact

External validation of predicted survival estimates

- All models, apart from du Bois et al[10], pass through the Khor et al[15] pooled 2- to 5-year survival estimate (0.62; 95% confidence interval, 0.58-0.66) during this time period
- Despite du Bois et al[10] being below the 2-5-year estimate, it is still within the range of estimates from the studies informing the Khor et al[15] analysis
- The patient-level simulation survival estimates generally lie between the BSC exponential and Weibull extrapolations presented by Lancaster et al,[17] with 2 exceptions. The du Bois et al model[10] produced lower survival estimates, particularly in the first 5 years, and the point index version of the longitudinal GAP model produced higher survival estimates, also primarily in the first 5 years

Figure 2. Long-term survival predictions



Discussion

- A key strength of our patient-level simulation approach is the ability to explicitly model survival based on clinical inputs and IPF disease trajectories. Our results suggest that this approach predicts clinically plausible survival estimates when compared with survival estimates from published observational studies and clinical trial extrapolations
- Further research is needed to assess and understand the variation in survival estimates across IPF mortality risk prediction models. Differences in predictions across models are especially sensitive to baseline characteristics and disease progression in those parameters included in some models (eg, 6MWD)
- A challenge to the patient-level simulation approach is the need for data informing disease progression and the correlation among parameters that inform the risk prediction models, especially for a rare disease like IPF. We were able to inform most parameters from a targeted literature review,[11] but further validation is needed on estimates of correlations between disease trajectories, ppFVC change (often unclear if estimates relate to absolute or relative decline), and whether estimates of disease progression are constant over time
- A further limitation is that the IPF mortality risk prediction models were developed as clinical support tools to inform short-term mortality risk predictions. Further work is needed to assess the applicability of these models for repeated and long-term mortality risk predictions in cost-effectiveness modeling applications

Conclusions

- Patient-level simulation informed by disease progression trajectories and mortality risk prediction models is a viable approach for predicting long-term survival in IPF
- Further investigation and validation of long-term disease progression and mortality risk predictions are needed to increase the confidence in this modeling approach for use in health technology assessments

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Conflicts of interest

- KMJ and PC report employment with Bristol Myers Squibb. BE was an employee of Bristol Myers Squibb at the time the study was conducted
- WLH and OMD report employment with RTI Health Solutions, which received research funding from Bristol Myers Squibb for this study

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