Administrative Information

1. **Submission Title**:
   Development of a multi-biomarker PROLIFIC Risk Score based on **four serum proteins** by the Prognostic Lung Fibrosis Consortium (PROLIFIC)

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Drug Development Need Statement

The development of a well-qualified assay that provides prognostic information about patients with Idiopathic Pulmonary Fibrosis (IPF) is a key step that may facilitate drug development. For clinicians and patients, a clinically available panel of well-qualified prognostic biomarkers provides objective information about the expected course of disease, an information which can be incorporated into clinical trial design. Patients projected to have rapid Forced Vital Capacity (FVC) decline and/or poor survival based on specific biomarker(s) values may be more inclined to initiate novel therapies or novel combination therapies and be more adherent to treatment protocol. These patients may also more readily choose to participate in Randomized Clinical Trials (RCTs) or be advised by their physicians to do so. Conversely, patients expected to progress more slowly may be more comfortable in dose adjusting antifibrotics to maximize tolerability and quality of life.

Current evidence-based guidelines for treatment of IPF recommend the use of pirfenidone and nintedanib, two compounds with anti-fibrotic mechanisms of action, however both are associated with tolerability issues (Amati 2023). Lung transplant is the only cure for patients with IPF, however it represents a therapeutic option for only a minority of patients (George 2019). These characteristics of IPF indicate the ongoing critical importance of continuing drug discovery efforts and among others, establishing reliable prognostic indicators, predictors of response, or as surrogate endpoint tools to better understand the progressive nature of the disease and design more effective treatment modalities.

Biomarker Information and Interpretation

Biomarker name

PROLIFIC Risk Score (PRS)

Biomarker interpretation and utility

IPF is a chronic, progressive age-related interstitial lung disease with an average life expectancy of 3–5 years after diagnosis (Lederer 2018, Raghu 2018). In the United States alone, approximately 50,000 new cases of IPF are diagnosed each year (Lung.com). With the population aging worldwide, the impact of IPF to patients and healthcare resources is expected to steadily increase in the future.

The biological mechanisms of fibrosis in IPF remain poorly understood, but most likely involve recurrent subclinical injuries and chronic inflammation, genetic predispositions and poor lung re-epithelialization and repair (Spagnolo 2017).

High level of cytokines and growth factors release within the lung epithelium promote the recruitment, proliferation, and differentiation of fibroblasts into myofibroblasts, leading to excessive collagen deposition, progressive scarring, and irreversible fibrotic loss of function (Ballaye 2015, Wolters 2014).

Multiple peer-reviewed publications have consistently reported a reoccurring set of blood-based protein biomarkers linked to IPF disease progression. Despite the strength of the evidence, no harmonized and validated panel has been available to the scientific community for this context of use. To address this unmet need, the Prognostic Lung Fibrosis Consortium (PROLIFIC) was formed to develop well-qualified assays suitable for use within the context of clinical trials.

Twelve protein biomarkers were selected based on *a priori* evidence in the literature for their prognostic and mechanistic value in IPF, including markers of epithelial damage, fibrosis, inflammation and thrombosis (Table 1) for evaluation. The 12 assays were optimized into 3 multiplex panels and 2 singleplex panels on the Luminex immunoassay platform (Rules Based Medicine, a Q2 Solutions Company, Austin, TX). Preliminary analytical validation of 11 of the 12 biomarkers using commercially acquired serum plasma specimens were performed under formal protocols with design controls and pre-defined acceptance criteria (see Appendix 1) to determine suitability for the proposed intended use.

The assays were used to measure biomarker levels in serum collected from IPF patients at the time of enrollment (baseline) into the Pulmonary Fibrosis Foundation Patient Registry (Derivation Set, N=657). Statistical analyses were performed using a random coefficients longitudinal sub-model for the decline in % predicted Forced Vital Capacity (FVC) and a Cox proportional hazards sub-model for transplant free survival at one year, adjusting for sex, age, BMI, smoking pack-years, anti-fibrotic medication, and % predicted FVC and DLCO at baseline. The results were further subjected to computational analysis to determine if a prognostic algorithm could be derived that was more predictive of outcomes than individual biomarkers. Furthermore, as part of the analyses there was a desire to minimize the number of markers in the algorithm to only those whose addition contributed substantially to the prognostic value. What resulted was a 4-marker algorithm, the PROLIFIC Risk Score (PRS) that is prognostic for patient outcomes combining all three outcomes: death, transplant and ≥10% relative decline in FVC within 1 year. Furthermore, the score was divided into high and low risk of progression using a cut-off value, enabling potential patient selection/stratification into clinical trials. The model and cut-off were then validated using an independent data set, the ISABELA study data set (Validation Set, N=229), which

confirmed the original findings from the Derivation Set (e.g. n = 657). During the conduct of the validation of the independent data set, the entire 12-panel marker was analyzed. Moving forward, the remaining 8 markers will be available as part of this panel for exploratory informational purposes.

Table 1. Biomarkers selected for PROLIFIC Risk test development.

Category	Biomarker	Prior Evidence of Prognostic or Pharmacodynamic Value (Ref)
Epithelial Damage	Cytokeratin 19 fragment (CYFRA 21-1)	Baseline CYFRA 21-1 was able to distinguish individuals at risk of 12-month disease progression (C-statistic 0.70 (95% CI 0.61 – 0.79), p < 0.0001) (Molyneaux 2022)
	Surfactant Protein-D (SP-D)	Significant improvement in the 1-year mortality prediction model when serum SP-A and SP-D (area under the receiving operator curve [AROC], 0.89) were added to the clinical predictors alone (AROC, 0.79; p = 0.03) (Kinder 2009)
	sialyl Lewis A (CA-19-9)	Baseline of ≥22 U/mL was associated with a 3x increased risk of mortality (Maher 2017)
	Mucin-16 (CA-125)	Baseline of ≥12 U/mL was associated with a 3x increased risk of mortality (Maher 2017)
	Mucin-1 (KL-6)	Serum baseline level >1000 U/mL is associated with worse prognosis (Yokoyama 2006) and >1300 U/mL with increased risk of acute exacerbation (Ohshimo 2014). KL-6 ≥ 1000 U/mL associated with disease progression (HR=2.761-2.845, p=0.040-0.045) (Chung 2022)
Fibrosis	Matrix Metalloproteinase 7 (MMP-7)	Higher levels (>3.5 ng/mL) lower transplant free survival (HR=2.3, p=0.016) (Richards 2012). Higher baseline (≥3.8 ng/mL) had higher risk of worsening (HR=2.2, p=0.001) (Bauer 2017)
	Tenascin C (TNC)	Change from baseline Tenascin correlated with change from baseline FVC (van der Velden 2016)
	Periostin (POSTN)	Prognostic for FVC in the test cohort (Effect size=-3.6, p<0.001) and replication cohort (Effect size=-2.5, p=0·186) (Neighbors 2018)
Inflammation	pulmonary and activation-regulated chemokine - PARC (CCL18)	Prognostic for FVC in the test cohort (Effect size=-3.1, p=0·032) and replication cohort (Effect size=3.6, p=0·004) (Neighbors 2018)
	B lymphocyte chemoattractant - BLC (CXCL13)	6-mo survival in the highest quartile of plasma CXCL13 was 65% versus 93% in the others (HR= 5.5, P = 0.0008) (Vuga 2014). >62.1 pg/mL shorter survival (DePianto 2015)
	Soluble intercellular adhesion molecule 1 (ICAM-1)	High level (>202.5 ng/ml) associated with lower transplant-free survival (Richards 2012)
Thrombosis	Plasminogen Activator Inhibitor 1 (PAI-1)	Stable IPF =45 ng/mL vs AEx =70 ng/mL (p=0.0004), predicts survival (p=0.14) (Collard 2010)

Context of Use Statement

The PROLIFIC Risk Score (the 4-marker panel of SP-D, CXCL13, TNC, and MMP-7) is a prognostic biomarker in patients with Idiopathic Pulmonary Fibrosis (IPF) to be used as a stratification factor or as eligibility criteria in clinical trials to identify patients who are more likely to have clinical events or disease progression (an enrichment tool). as the PROLIFIC Risk Score is a composite risk score with specific cut-offs identifying low- and high-risk IPF populations for disease progression.

Analytical Considerations

Assay Development and Validation

All 12 immunoassays, either in single-plex or multiplex format, utilized the Luminex® xMAP® platform and consisted of antigen-specific antibodies optimized in a capture-sandwich format. The assays were developed under design control to ensure they meet the intended use, user needs and pre-specified acceptance criteria and were validated prior to clinical sample testing.

Detailed assay development and validation description as well as results, and statistical analyses for all single markers is presented in **Attachment 1**.

All incubations took place at room temperature. Three-levels of quality controls were prepared using either human serum with the appropriate amount of endogenous analyte or by spiking analyte into human serum. Healthy human serum and EDTA plasma were collected from consented donors at RBM, whereas serum and EDTA plasma from IPF patients were procured from external biorepositories via Discovery Life Sciences (Huntsville, AL, USA). All samples were stored at -80°C until assayed. Three levels of controls (low, mid, and high), each plated in duplicate, were tested alongside samples in each run to determine acceptability of the assay. All reagents, materials, and equipment needed to perform the validation studies, except for sample collection materials, were used exclusively at the RBM single reference laboratory site. All equipment was maintained at RBM per Equipment Control SOPs.

Clinical Considerations

The PROLIFIC consortium set out to identify low- and high-risk IPF populations based on 10% **relative** decline in % predicted forced vital capacity (FVC), death, or lung transplant in one year. To do that, we used several sets of independent data:

1. The scientific literature was used for biomarker identification.
2. PFF Patient Registry IPF serum samples were used as a derivation set (N=657)
3. The ISABELA Study Dataset used as validation set (N=229)

Here, we briefly describe the derivation and validation data sets as well as methodologies/approaches used in the IPF Prognostic Risk Score derivation process.

PFF Patient Registry Samples (Derivation Set)

The mission of the Pulmonary Fibrosis Foundation (PFF) is to accelerate the development of new treatments and ultimately a cure for pulmonary fibrosis (PF). Until this goal is achieved, the PFF is committed to advancing improved care of patients with PF and providing unequaled support and education resources for patients,

caregivers, family members, and health care providers. Since 2016, the PFF Patient Registry has enrolled and followed the care of thousands of patients at participating PFF Care Centers. Information in the PFF Patient Registry includes: patient demographics such as age and gender, details on how the diagnosis was made, test results, medications, medical events, a blood sample with consent near the time of enrollment, high resolution CT (HRCT) scans, and patient-reported outcomes. The PFF Patient Registry collected data on 2,003 patients at 42 clinical sites in the US. The Registry enrollment included 61% of the 2,003 ILD participants to have IPF. The aim of the Registry was to create a cohort of well-characterized patients with interstitial lung disease (ILD) for participation in retrospective and prospective research. Patients who meet inclusion and exclusion criteria and are being treated at a Registry site (Wang 2020).

The University of Michigan Statistical Analysis of Biomedical and Educational Research (SABER) unit served as the Registry Data Coordinating Center and managed data entered into a web based, CFR 21 Part 11 compliant electronic data capture (EDC) system by the Registry sites.

ISABELA Study Dataset (Validation Set)

ISABELA 1 and ISABELA 2 (NCT03711162 and NCT03733444) are two phase 3 randomized, double-blind, placebo-controlled studies identically designed to evaluate the efficacy and safety of ziritaxestat (GLPG1690, an autotaxin inhibitor) in patients with idiopathic pulmonary fibrosis. Collectively, these trials enrolled 1,306 participants across 27 countries worldwide. A complete description of the design and rationale for these studies including detailed enrollment criteria has been published by Maher et al. (2019). ISABELA 1 and 2 were halted in March 2021 following recommendation from the Independent Data Monitoring Committee. Data these trials generated are owned and managed by Gilead Sciences, Inc., and were collected independently from the PFF registry sample.

Here we report on a sub-cohort of 229 individuals from the ISABELA 1 (n = 73) and ISABELA 2 (n = 156) placebo arms only for whom biologic samples were processed using the same assay platform as in the PFF cohort. We chose this cohort as it closely resembles the cohort in the PFF registry. The overall demographic and baseline characteristics of both populations (PFF registry and ISABELA) also resemble previously published IPF studies for example the PROFILE study (Jenkins et al, 2015). All individuals used for analysis provided written, informed consent to future use of their data for research related to the understanding of idiopathic pulmonary fibrosis. We use these data to validate select biomarker analyses (described below) and primary results generated using the larger PFF registry sample.

A summary of demographic and baseline characteristics and clinical outcomes for the analysis population of 657 IPF patients (Table 2) shows the majority of patients were male (74.4%), White (93.9%), had a smoking history (65.0%), and were on antifibrotic treatment (66.5%). Baseline FVC was a mean of 2.65 L (68% predicted FVC). Within the first year, there were 62 deaths, 37 lung transplants, 20 subjects had ≥10% absolute decline in % predicted FVC, and 95 subjects had ≥10% relative decline in % predicted FVC (Table 2). Data for the ISABELA cohort is also presented in Table 2. There were some differences between the ethnicities be the two populations. There were also differences in outcomes with fewer deaths and no lung transplants in the ISABELA cohorts.

Table 2. IPF patient baseline characteristics and outcomes for derivation dataset (PFF Patient Registry) and validation dataset (ISABELA studies). Data are mean (SD) or n (%). FVC=forced vital capacity, DLCO=diffusion capacity of the lung for carbon monoxide, GAP=Gender Age Pulmonary Function score.

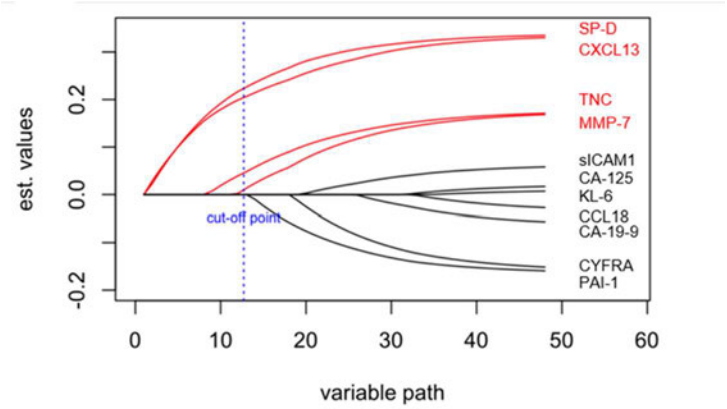
Demographics	**PFF Patient Registry n (% of total N=657)**	**ISABELA studies N (% of total N=229)**
Sex		
Female	168 (25.6%)	36 (15.7%)
Male	489 (74.4%)	193 (84.3%)
Race or ethnicity		
White	617 (93.9%)	168 (73.4%)
Black	10 (1.5%)	1 (0.4%)
Asian	14 (2.1%)	53 (23.1%)
NA	16 (2.4%)	7 (3.1%)
Ethnicity		
Hispanic or Latino	23 (3.5%)	18 (7.9%)
Not Hispanic or Latino	617 (93.9%)	202 (88.2%)
NA	17 (2.6%)	9 (3.9%)
Smoking History		
No	230 (35.0%)	58 (25.3%)
Yes	427 (65.0%)	171 (75.7%)
Antifibrotic treatment	437 (66.5%)	51 (22.3%)
Baseline Clinical Data	**Mean (SD)**	
Age, years	70.69 (8.08)	70.08 (6.79)
BMI	29.19 (5.18)	27.42 (4.29)
Smoking Pack-Years	17.35 (22.11)	N/A
Pulmonary Function		
FVC, liters	2.65 (0.78)	2.93 (0.78)
FVC, % predicted	0.68 (0.17)	0.78 (0.17)
DLCO, mL/min/mm Hg	11.71 (4.58)	12.58 (4.08)
DLCO, % predicted	39.93 (14.17)	44.84 (13.86)
GAP score	5.67 (1.09)	4.05 (1.27)
Clinical Outcomes at 1 year	**n (%), Mean (SD)**	
Death	62 (9.4%)	6 (2.6%)
Time to death, years	0.52 (0.27)	0.89 (0.11)
Lung Transplant	37 (5.6%)	0 (0%)
Time to lung transplant, years	0.46 (0.25)	--
≥10% absolute decline in % pred FVC	20 (3.0%)	31 (13.5%)
≥10% relative decline in % pred FVC	95 (14.5%)	50 (21.8%)

Multi Marker Statistical Analysis Performed in the PFF Patient Registry

Statistical analyses were performed to define a composite binary outcome of reaching an estimated 10% decline in % predicted forced vital capacity (FVC), death, or lung transplant in one year. Penalized logistic regression was used to select prognostic biomarkers using the Least Absolute Shrinkage and Selection Operator (LASSO) method. The resulting model with selected biomarkers was used to fit a logistic model, which was used to derive a risk score which was evaluated by Area Under the Receiver Operator Characteristic (AUROC) curve for its predictive performance. All the statistical analyses were adjusted for sex, age, BMI, anti-fibrotic medication, smoking pack-year, % predicted FVC, and % predicted DLCO. The outcomes from this derivation set were applied

to the ISABELA validation set. The LASSO method reduces overfitting by enforcing penalties to the features. Four biomarkers (MMP-7, TNC, SP-D, and CXCL13) were associated with the binary outcome of death, lung transplant, or ≥ 10% relative decline of % predicted FVC, which had a higher event rate due to FVC decline (14.5%), and therefore had the highest overall event rate (total 29.5%) (Figure 1).

Figure 1. LASSO logistic regression and solution paths of biomarker coefficients for disease progression. Binary outcome of death, lung transplant, or ≥ 10% relative decline of % predicted FVC.



Using the biomarkers selected by LASSO logistic regression, next the coefficients for the features in each model were calculated while adjusting for sex, age, BMI, anti-fibrotic medication, smoking packs per year, % predicted FVC and % predicted DLCO at baseline. The coefficients for each biomarker were then combined to form the multi-marker PROLIFIC Risk Score. For the composite binary outcome model of death, lung transplant, or ≥ 10% relative decline of % predicted FVC, the multi-marker PROLIFIC risk score is calculated as follows, with ln(C)=natural log of the absolute concentration of the serum protein in units of ng/mL, except for CXCL13 which is in units of pg/mL :

Prolific Risk Score = [redacted]

The sensitivity and specificity of these multi-marker risk scores were plotted and the AUROC was calculated. The outcome for the multi-marker risk score for the composite of death, lung transplant, or ≥ 10% relative decline of % predicted FVC is shown in figure 2A with AUC= 0.796. Using this model, the quartiles of the individual risk scores show clear separation for the composite event rate, with similar patterns among males and females, with or without antifibrotic mediation (Figure 3).

Figure 2. Summary of AUROCs for multi-marker risk scores in PFF Patient Registry dataset (A) and ISABELA validation dataset (B). A. Performance of multi-marker risk score for death, lung transplant, or ≥ 10% relative decline of % predicted FVC (total event rate = 29.5%. Selected biomarkers are SP-D, CXCL13, TNC, and MMP-7. B. Performance of multi-marker risk score (SP-D, CXCL13, TNC, and MMP-7) for death, lung transplant, or ≥ 10% relative decline of % predicted FVC in the ISABELA study validation dataset (total event rate = 24.5%).

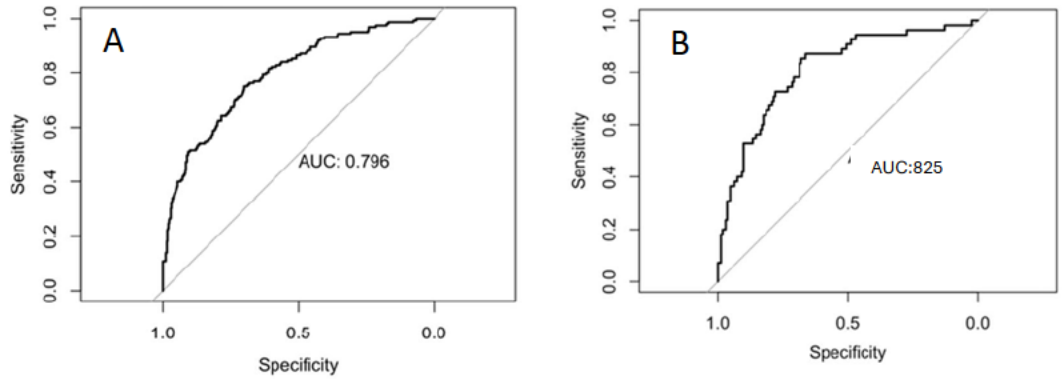
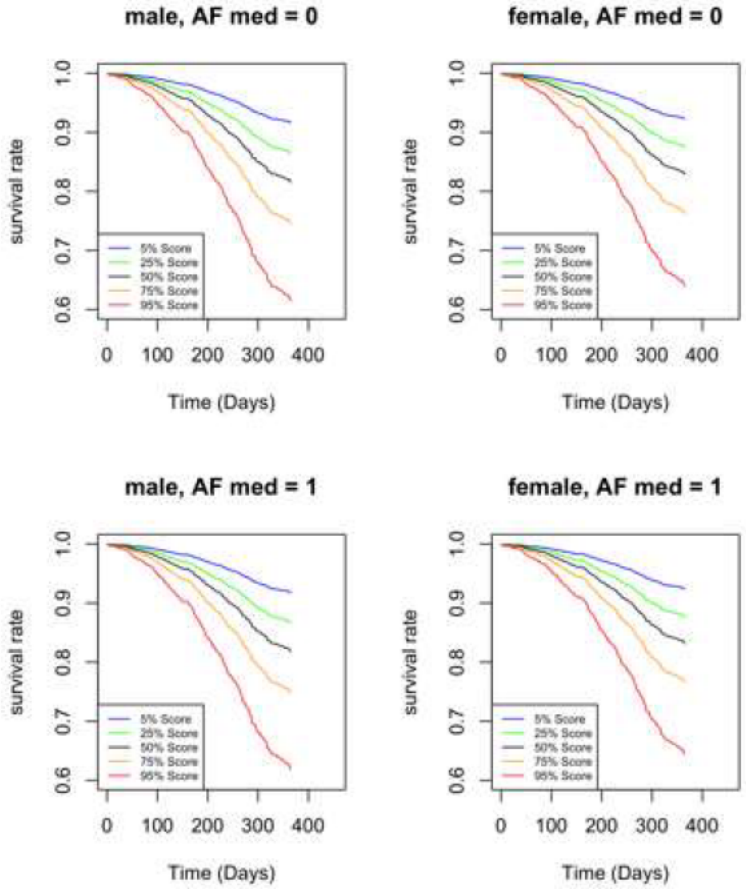


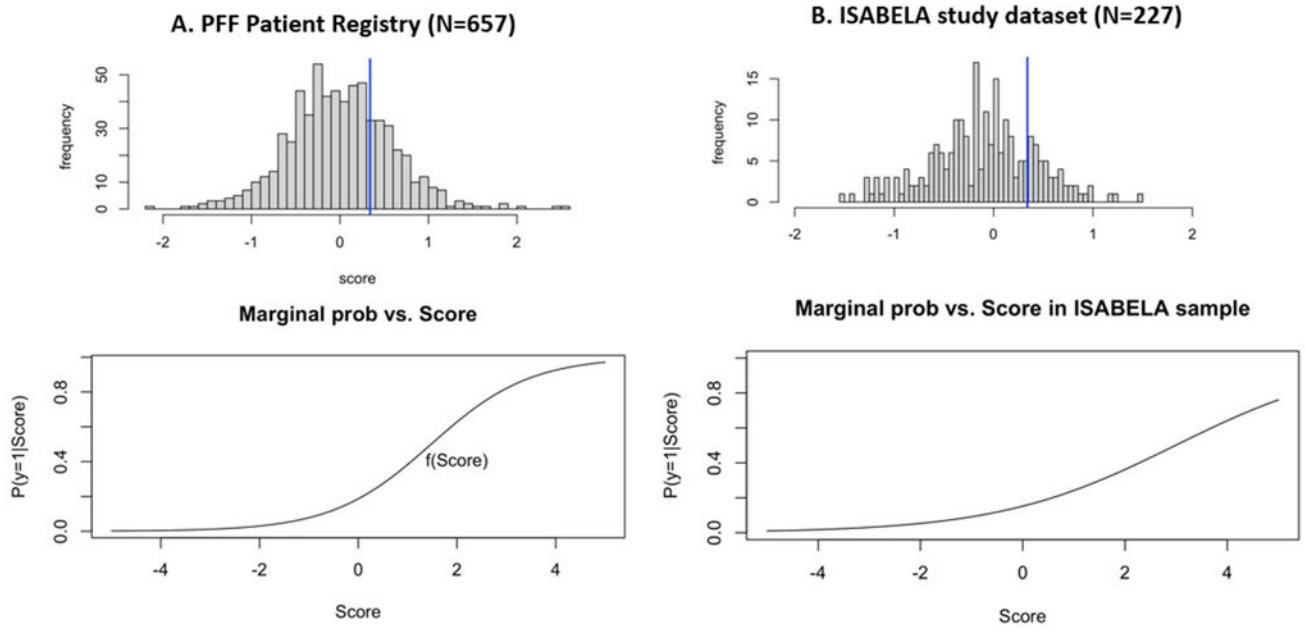
Figure 3. Probability of disease progression for multi-marker risk score for death, lung transplant, or ≥ 10% relative decline of % predicted FVC.



Calculating ROC Cut Points of High/Low Risk Populations (Derivation Set)

The optimal cut-off value for this model was calculated based on the Youden J statistic at [redacted] which demonstrated good performance (sensitivity = 0.752, specificity = 0.699) and categorizes 26.6% of the IPF population from the PFF Patient Registry dataset as high risk in this derivation cohort (Figure 4A). Applying this same cut-off value of [redacted] to the ISABELA study dataset yielded a similar model performance with calculated AUC of 0.825 (Figure 2B) (sensitivity=0.764, specificity = 0.715) and categorized 21.6% of this IPF population as high risk in this validation cohort (Figure 4B).

Figure 4: Distribution of prognostic risk scores (death, lung transplant, or ≥ 10% relative decline of % predicted FVC) within PFF Patient Registry dataset (A) and ISABEL study dataset (B). Prognostic Risk Score = [redacted]. The vertical blue line indicates the optimal cut-off value of [redacted].



Medical Utility

The development of a well-qualified assay that can measure prognostic biomarkers is a key step that may, in the future, inform clinical practice and facilitate drug development. For clinicians and patients, a clinically available panel of well-qualified prognostic biomarkers, provides objective information about the expected course of disease. Knowing the likely disease trajectory should empower patients and strengthen shared decision making. Patients projected to have rapid FVC decline and/or poor survival based on the PROLIFIC Risk Score may be more inclined to initiate antifibrotics and be more adherent with therapy. They also may undergo transplantation evaluation sooner and/or be more proactive in clinical trial participation. Conversely, patients expected to progress slowly may be more comfortable in dose adjusting antifibrotics to maximize tolerability and quality of life. Furthermore, the frequency of testing and travel to clinic sites may be adjusted based on an expected course.

Clinical Trial Applications

There is a need in clinical trials, particularly in early phases of drug testing, to assess the potential for clinical benefit. The efficiency at which current IPF trials can identify therapeutic effects on FVC decline are limited by high variability in disease progression rate across patients. In this setting, the availability of analytically robust and well validated prognostic biomarkers assays is crucial. The PROLIFIC Risk Score, given its prognostic utility for rapid decline, may allow for more balanced randomization of treatment groups, as well as the enrollment of smaller, better statistically powered early proof of concept trials. Toward this goal, the PROLIFIC Risk Score can now be integrated into clinical trials for IPF for patient stratification by disease progression rate at enrollment. Changes in PROLIFIC Risk Score may also allow for earlier detection of therapeutic response, while providing insight into mechanism of action of novel therapies.

Decision Algorithm in Selection onto Clinical Trials

To determine the individual's PROLIFIC Risk Score, the patient's serum is first tested for the markers, SP-D, CXCL13, TNC, and MMP-7, and then a composite score is generated by inserting each of the biomarker results into the PRS formula. If the resultant value is ≥[redacted], the patient is considered high risk of IPF progression and if the resultant value is <[redacted], the patient is considered low risk of progression.

Once a prognostic risk category is assigned, then risk categories can be used independently or in conjunction with other risk categories to enrich early and late clinical trials with patients, based upon risk category in studies evaluating novel drugs. For example, high risk patients could be enrolled in Randomized Clinical Trials (RCTs) evaluating novel anti-fibrotic drugs versus Standard of Care (SOC) (i.e. an enrichment strategy for the primary clinical outcome). Similarly, patients could be stratified onto the trials to see if there is a benefit to either group with respect to therapy potentially in conjunction with other therapies.

Benefits and Risks of Applying Clinical Decision Tool

To date, evaluation of novel drugs, focuses on the average treatment effect in the overall IPF population requiring phase 3 (registrational) clinical trials involves relatively large sample sizes to demonstrate superiority to SOC. This is due in part to the lack of robust prognostic biomarkers to define the rate of events resulting in the inclusion of very heterogenous populations at risk. Use of the PROLIFIC Risk Score as a prognostic marker should significantly address this issue to improve RCT efficiency (enrichment strategy).

The risk to the patient of misclassification is related to assigning them to a low-risk category when in fact the individual is at high risk. However, this patient would still be receiving currently approved standard therapies for IPF prescribed, as a result of general medical practice aligned with medical guidelines for IPF. Conversely, in patients misclassified as high-risk when in fact they are at low risk may lead to inclusion in trials where novel drugs may be of limited or no benefit to the patient vs SOC. However, the current absence of a standard prognostic marker of disease progression in RCTs results in exposure of all patients to the potential treatment risks or benefits agnostic risk of disease progression. To mitigate misclassification, ongoing studies should enhance the accuracy of the PROLIFIC Risk Score prognostic biomarker.

Previous Qualification Interactions and Other Approvals (if applicable)

N/A

Attachments

Attachment 1

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