Poster

A clinical-molecular signature of progression of idiopathic pulmonary fibrosis (IPF)

American Thoracic Society (ATS) International Conference

May 13-18, 2022

SC-US-74354

A clinical-molecular signature of progression of idiopathic pulmonary fibrosis (IPF)

Justin M Oldham,[1] Megan L Neely,[2,3] Hillary Mulder,[2] John A Belperio,[4] Nina M Patel,[5] Christian Hesslinger,[6] Jamie L Todd[2,3] on behalf of the IPF-PRO Registry investigators

[1]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of California at Davis, Sacramento, CA, USA; [2]Duke Clinical Research Institute, Durham, NC, USA; [3]Duke University Medical Center, Durham, NC, USA; [4]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [5]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [6]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany.

INTRODUCTION

- IPF is a progressive fibrosing interstitial lung disease with an unpredictable clinical course.
- Several plasma proteins have been linked to increased mortality in patients with IPF, but few predict decline in forced vital capacity (FVC).[1] Change in FVC is used to assess progression of IPF and biomarkers that predict near-term decline in FVC are needed.

AIM

- To develop a clinical-molecular signature that identifies patients with IPF at risk of near-term decline in FVC.

METHODS

- The cohort was drawn from the IPF-PRO Registry, a multicenter US registry that enrolled patients with IPF that was diagnosed or confirmed at the enrolling center in the prior 6 months.[2]
- Concentrations of 58 plasma proteins at baseline (enrollment) were determined using an ELISA-based multiplex platform.
- **Disease progression was defined as death, lung transplant, or relative decline in FVC (mL) ≥5% in the 12 months after enrollment.**
- Using progression as the dependent variable, elastic net logistic regression was used to derive a **predictive model of progression using the 58 protein covariates and 10 clinical covariates assessed at enrollment** (age, sex, race, FVC % predicted, DLco % predicted, oxygen use at rest, oxygen use with activity, smoking history, ILD in a first-degree relative, taking anti-fibrotic therapy). An IPF progression score was generated using model coefficient estimates. The score was dichotomized into a **low-risk versus high-risk clinical-molecular signature (CMS)** based on sensitivity and specificity metrics. Change in FVC from baseline to 12 months was compared between these groups using an ANCOVA model.

CONCLUSIONS

- A CMS composed of circulating proteins and clinical factors can identify patients with IPF at high risk of near-term decline in FVC.
- Such a signature could be used to enrich clinical trial cohorts with patients who are more likely to experience FVC decline during follow-up.
- Optimization of this clinical-molecular signature, followed by external validation, is needed.

RESULTS

Baseline characteristics (n=278)

Age, years	71 (66, 75)
Male	209 (75%)
White, non-Hispanic	260 (94%)
Past or current smoker	190 (68%)
FVC % predicted	69.9 (60.9, 80.3)
DLco % predicted	40.6 (32.1, 49.5)
Supplemental oxygen use*	
None	177 (64%)
At rest	56 (20%)
With activity but not at rest	44 (16%)
Anti-fibrotic drug use	131 (47%)

Values are median (Q1, Q3) or n (%). *Data not available for 1 patient.

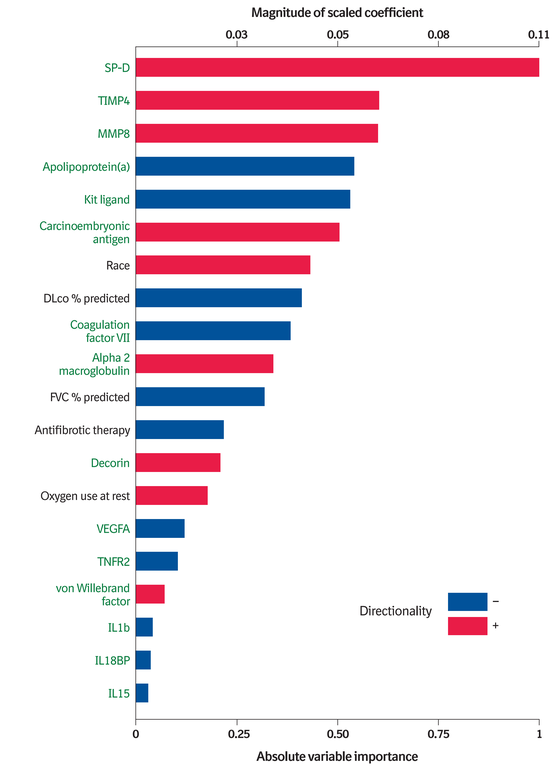
Clinical-molecular signature (CMS)

- Of 271 patients with no missing data for the proteins or clinical covariates evaluated, 147 (54%) were classified as progressive.
- Fifteen protein biomarkers and five clinical covariates were selected by the predictive model of progression.
- 167 patients (62%) had a low-risk CMS and 104 (38%) had a high-risk CMS with a sensitivity of 0.56 and a specificity of 0.83.

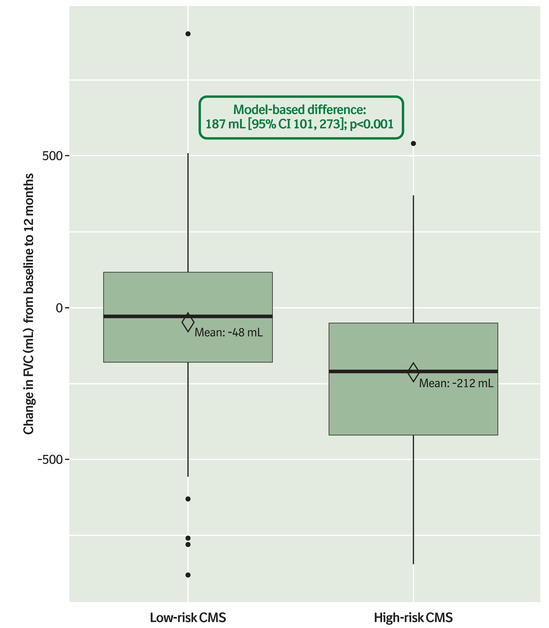
Performance of CMS for predicting progression

Area under the curve	0.74
Sensitivity	0.56 (95% CI 0.48, 0.65)
Specificity	0.83 (95% CI 0.75, 0.89)
Positive predictive value	0.80 (95% CI 0.71, 0.87)
Negative predictive value	0.62 (95% CI 0.54, 0.69)

Variable importance of protein biomarkers (green) and clinical covariates (black) as predictors of progression of IPF



Change in FVC (mL) from baseline to 12 months in patients with low-risk and high-risk CMS



The diamond represents the mean, the horizontal line the median, and the box the interquartile range.
The whiskers extend to the most extreme point that is less than or equal to 1.5 x the interquartile range.
The dots represent data points falling outside the range covered by the whiskers.

REFERENCES
1. Bowman WS et al. Front Med (Lausanne) 2021;8:680997.
2. O'Brien EC et al. BMJ Open Respir Res 2016;3:e000108.

ACKNOWLEDGEMENTS AND DISCLOSURES
The IPF-PRO/ILD-PRO Registry is funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) and coordinated by the Duke Clinical Research Institute. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment for the development of this poster. Elizabeth Ng and Wendy Morris of FleishmanHillard, London, UK, provided editorial and formatting assistance, which was contracted and funded by BIPI. BI was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations. Justin Oldham has received fees from BI, Lupin, AmMax Bio and United Therapeutics. Jamie Todd has received grants from the National Institutes of Health, AstraZeneca, BI, CareDx; has served on advisory boards for Natera and Altavant Sciences and is an employee of DCRI, which receives funding support from BIPI to coordinate the IPF-PRO/ILD-PRO Registry.

Scan QR code or visit URL for a webpage featuring all BI-supported publications at ATS 2022.
https://www.usscicomms.com/respiratory/ATS2022

Scan QR code or visit URL for a device-friendly version of this poster including an MP4 with a voiceover from the lead author.
https://www.usscicomms.com/respiratory/ATS2022/Oldham/

IPF-PRO Registry enrolling centers: Albany Medical Center, Albany, NY; Baylor College of Medicine, Houston, TX; Baylor University Medical Center at Dallas, Dallas, TX; Cleveland Clinic, Cleveland, OH; Columbia University Medical Center/New York Presbyterian Hospital, New York, NY; Duke University Medical Center, Durham, NC; Froedtert & The Medical College of Wisconsin Community Physicians, Milwaukee, WI; Houston Methodist Lung Center, Houston, TX; Lahey Clinic, Burlington, MA; Loyola University Health System, Maywood, IL; Lynchburg Pulmonary Associates, Lynchburg, VA; Medical University of South Carolina, Charleston, SC; National Jewish Health, Denver, CO; NYU Medical Center, New York, NY; Piedmont Healthcare, Austell, GA; Pulmonary Associates of Stamford, Stamford, CT; PulmonIx LLC, Greensboro, NC; Renovatio Clinical, The Woodlands, TX; Salem Chest and Southeastern Clinical Research Center, Winston Salem, NC; South Miami Hospital, South Miami, FL; St. Joseph's Hospital, Phoenix, AZ; Stanford University, Stanford, CA; Temple University, Philadelphia, PA; The Oregon Clinic, Portland, OR; Tulane University, New Orleans, LA; UNC Chapel Hill, Chapel Hill, NC; University of Alabama at Birmingham, Birmingham, AL; University of California, Davis, Sacramento, CA; University of California Los Angeles, Los Angeles, CA; University of Chicago, Chicago, IL; University of Cincinnati Medical Center, Cincinnati, OH; University of Louisville, Louisville, KY; University of Miami, Miami, FL; University of Michigan, Ann Arbor, MI; University of Minnesota, Minneapolis, MN; University of Pennsylvania, Philadelphia, PA; University of Pittsburgh, Pittsburgh, PA; University of Virginia, Charlottesville, VA; UT Southwestern Medical Center, Dallas, TX; Vanderbilt University Medical Center, Nashville, TN; Vermont Lung Center, Colchester, VT; Wake Forest University, Winston Salem, NC; Washington University, St. Louis, MO; Weill Cornell Medical College, New York, NY; Wilmington Health and PMG Research, Wilmington, NC; Yale School of Medicine, New Haven, CT.

Poster presented at the American Thoracic Society International Conference, 2022.

SC-US-74354