pulmonary fibrosis, it will facilitate the use of serum CYFRA 21–1 as a biomarker in the real-world clinical practice. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Hajime Fujimoto, M.D.
Corina N. D'Alessandro-Gabazza, D.M.D.
Taro Yasuma, M.D.
Tetsu Kobayashi, M.D.
Esteban C. Gabazza, M.D., Ph.D.*
Mie University
Tsu, Mie, Japan

ORCID ID: 0000-0001-5748-1499 (E.C.G.).

*Corresponding author (e-mail: gabazza@doc.medic.mie-u.ac.jp).

References

1. Molyneaux PL, Fahy WA, Byrne AJ, Braybrooke R, Saunders P, Toshner R, *et al.* CYFRA 21-1 predicts progression in IPF: a prospective longitudinal analysis of the PROFILE cohort. Am J Respir Crit Care Med [online ahead of print] 01 April 2022; DOI: 10.1164/rccm.202107-1769OC.
2. Kim YC, Park KO, Choi IS, Kim HJ, Lim SC, Bom HS. A comparison of serum CYFRA 21-1 and SCC Ag in the diagnosis of squamous cell lung carcinoma. *Korean J Intern Med (Korean Assoc Intern Med)* 1996;11:50–57.
3. Wieskopf B, Demangeat C, Purohit A, Stenger R, Gries P, Kreisman H, *et al.* Cyfra 21-1 as a biologic marker of non-small cell lung cancer. Evaluation of sensitivity, specificity, and prognostic role. *Chest* 1995;108:163–169.
4. Cho HY, Kyung MS. CYFRA 21-1 and placental growth factor as screening markers for endometriosis. *Med Sci Monit* 2019;25:1087–1092.
5. Kuessel L, Zeisler H, Ristl R, Binder J, Pateisky P, Schmid M, *et al.* The usefulness of CYFRA 21-1 to diagnose and predict preeclampsia: a nested case-control study. *BMC Pregnancy Childbirth* 2016;16:339.
6. Zhao T, Jin Y, Mao G, Wei Y, Wu G, Ye X, *et al.* CYFRA 21-1 is an early predictor of chemotherapeutic effectiveness in advanced nonsmall cell lung cancer: an observational study. *Medicine (Baltimore)* 2016;95:e5748.

Reply to Fujimoto *et al.*

From the Authors:

We are grateful to Fujimoto and colleagues for their interest in our work (1). As they note, there remains an unmet need in clinical practice for biomarkers to aid in the diagnosis, prognostic assessment, and treatment of patients with idiopathic pulmonary fibrosis (IPF) and other forms of interstitial lung disease. We believe that CYFRA 21–1 has the potential to fulfill some of these roles (1, 2).

In interpreting our work, it is important to note that the assay used for measuring CYFRA 21–1 was a commercially available research ELISA and not a Good Laboratory Practice (GLP) standard bioanalytical assay. For this reason, we observed batch-by-batch variation in readings; this can be appreciated when comparing the median values obtained in our discovery and validation cohorts. Although within-batch comparison of CYFRA 21–1 values is valid, between-batch comparisons cannot easily be made. Thus, there is limited utility in providing absolute thresholds of CYFRA 21–1 for distinguishing either IPF from healthy controls or stable from progressive disease.

However, as suggested by Fujimoto and colleagues, receiver operator curve analysis gives some indication of the potential biomarker value of CYFRA 21–1. The c-statistic for distinguishing cases of IPF from healthy control subjects was 0.81 (95% confidence interval [CI], 0.74–0.88; $P < 0.0001$) in our discovery cohort and 0.77 (95% CI, 0.71–0.84; $P < 0.0001$) in our validation cohort. The capacity for CYFRA 21–1 to distinguish progressive from stable cases of IPF was 0.70 (95% CI, 0.61–0.79; $P < 0.0001$) in the discovery cohort and 0.65 (95% CI, 0.59–0.71; $P < 0.0001$) in the validation cohort.

Several important steps are required before recently reported biomarkers of IPF progression (1, 3, 4) and treatment response can be effectively used in the clinic (5). One of these is assay development and validation; to this end, we are pleased to note that CYFRA 21–1 is now available as a high-sensitivity, high-throughput, clinic-ready assay (Roche Diagnostics). Another important step is the replication of our findings in separate IPF populations and the rigorous defining of clinically useable thresholds. To this end, we hope that ongoing biomarker discovery studies will build on our findings and allow the integration of molecular data into routine practice to improve the care of patients with IPF. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Philip L. Molyneaux, M.D., Ph.D.
Imperial College London
London, United Kingdom
and
Guy's and St. Thomas' National Health Service Foundation Trust
London, United Kingdom

Toby M. Maher, M.D., Ph.D.*
Imperial College London
London, United Kingdom
Guy's and St. Thomas' National Health Service Foundation Trust
London, United Kingdom
and
University of Southern California
Los Angeles, California

On behalf of all the authors

ORCID ID: 0000-0001-7192-9149 (T.M.M.).

*Corresponding author (e-mail: toby.maher@med.usc.edu).

References

1. Molyneaux PL, Fahy WA, Byrne AJ, Braybrooke R, Saunders P, Toshner R, *et al.* CYFRA 21-1 predicts progression in IPF: a prospective longitudinal analysis of the PROFILE cohort. *Am J*

Originally Published in Press as DOI: 10.1164/rccm.202205-0835LE on May 18, 2022

Respir Crit Care Med [online ahead of print] 01 Apr 2022; DOI: 10.1164/rccm.202107-1769OC.
2. Stock CJW, Hoyles RK, Daccord C, Kokosi M, Visca D, De Lauretis A, *et al.* Serum markers of pulmonary epithelial damage in systemic sclerosis-associated interstitial lung disease and disease progression. *Respirology* 2021;26:461–468.
3. Jenkins RG, Simpson JK, Saini G, Bentley JH, Russell AM, Braybrooke R, *et al.* Longitudinal change in collagen degradation biomarkers in idiopathic pulmonary fibrosis: an analysis from the prospective, multicentre PROFILE study. *Lancet Respir Med* 2015; 3:462–472.
4. Organ LA, Duggan AR, Oballa E, Taggart SC, Simpson JK, Kang'ombe AR, *et al.* Biomarkers of collagen synthesis predict progression in the PROFILE idiopathic pulmonary fibrosis cohort. *Respir Res* 2019;20:148.
5. Chau CH, Rixe O, McLeod H, Figg WD. Validation of analytic methods for biomarkers used in drug development. *Clin Cancer Res* 2008;14: 5967–5976.

Remote 6-Minute-Walk Testing in Patients with Pulmonary Hypertension: Further Validation Needed?

To the Editor:

The 6-minute-walk test (6MWT) provides insight on functional status, disease severity, and therapeutic efficacy in people with chronic lung disease. The need for digital-technology enabled healthcare provisions that mitigate in-clinic patient visits accelerated during the coronavirus disease (COVID-19) pandemic. Accordingly, the report of LaPatra and colleagues (1) in the April 1 issue of the *Journal* on the feasibility, safety, and accuracy of performing "remote" 6MWTs in nonclinical settings for pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) is timely and promising. Using and incorporating locations chosen by study participants, audiovisual guidance from study personnel, and companion "support" for each participant, the authors found "no systematic difference" in average 6MWT distance (6MWD) between in-clinic versus remote settings, with excellent concordance between the in-clinic and remote walks. Other than in one patient (lightheadedness, tinnitus), no adverse events were reported during the remote walks. The authors did, however, find that 6MWD was shorter (∼20 m) in masked versus unmasked participants during remote walks. While acknowledging that their findings require replication, the authors conclude that remote 6MWTs may be feasible and valid in stable patients with PH. We applaud the authors for their work; however, two aspects of their conclusions warrant further consideration.

Observing that facemasks were associated with decreased 6MWD (remote setting), the authors suggest that repeat, unmasked studies may be warranted when masking is associated with a reduction in in-clinic 6MWD. Recently, however, we found that facemask wearing had no effect on arterial oxygen saturation, perceptual responses to exercise, or 6MWD in 45 group 1 PAH patients in-clinic (2), which is consistent with reports in healthy individuals (3) and those with lung disease (4). Although not clear why, it is possible that the impact of facemask wearing on 6MWD may be different in-clinic versus remote settings. Based on the available evidence, we would not at this time endorse repeat 6MWT without versus with face-masking in the clinic setting.

Second, LaPatra *et al.* suggest that 6MWD is not different in-clinic vs. remote settings but that wearing a facemask negatively impacts 6MWD. However, closer inspection of the data reveals that 6MWD differed by ⩾50 m in ∼10 patients (40% of cohort) and by ⩾100 m in ∼5 patients (20% of cohort) in-clinic versus remote settings. By comparison, the difference in 6MWD with versus without a facemask was ⩾50 m and ⩾100 m in only ∼5 (23% of cohort) and ∼2 (9% of cohort) patients, respectively. Comparison of the Deming regression fit to the perfect concordance line for 6MWD in-clinic versus remote settings suggests that patients with a shorter 6MWD distance "perform better" in-clinic whereas patients with a longer 6MWD "perform better" in remote settings. This does not appear to be as true for 6MWD with versus without a facemask, with better clustering of datapoints around the perfect concordance line (*see* Figure 2 in original report) (1). Two questions arise: *1*) do patients with lower exercise capacity (presumably sicker patients) perform better during in-clinic versus remote walk tests; and *2*) despite no difference in group mean 6MWD in-clinic versus remote settings, could substantial intra-individual heterogeneity exist in the concordance between in-clinic and remote 6MWTs? Speculatively, it is possible that sicker patients with more impairment "perform better" in clinical settings secondary to direct supervision from healthcare professionals, making remote-based 6MWTs less appropriate in such individuals. Also, given that 6MWD differed by ⩾50 m in-clinic compared with remote settings in ∼40% of patients, we suggest that the applicability of remote-based 6MWT as an accurate and valid marker of functional status, disease severity, and therapy efficacy requires further validation. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Scott A. Helgeson, M.D.
Charles D. Burger, M.D.
John E. Moss, M.D.
Tonya K. Zeiger, R.R.T.
Bryan J. Taylor, Ph.D.*
Mayo Clinic
Jacksonville, Florida

ORCID IDs: 0000-0001-7590-2293 (S.A.H.); 0000-0001-5229-941X (B.J.T.).

*Corresponding author (e-mail: taylor.bryan@mayo.edu).

Originally Published in Press as DOI: 10.1164/rccm.202204-0762LE on May 24, 2022

References

1. LaPatra T, Baird GL, Goodman R, Pinder D, Gaffney M, Klinger JR, *et al.* Remote 6-minute-walk testing in patients with pulmonary hypertension: a pilot study. *Am J Respir Crit Care Med* 2022;205:851–854.