critical to provide recommendations of boosters until more studies evaluating these populations were available. Because our study did not include patients with severe asthma who were not on biologics, the reduced responses we observed may have been owing to disease or treatments and not necessarily from the biologics alone.

In all, there may have been no differences in vaccine responses among the four diseased cohorts in Liao and colleagues owing to the limitations of patient populations, timing of the vaccine titers, and the types of the vaccines administered. Thus, understanding the kinetics of protective immunity over time in these diseased cohorts is critical. Nonetheless, Liao and colleagues performed a valuable study, and together with the findings in the study by Runnstrom and colleagues, we emphasize the importance of repeat boosters for patients with severe asthma whether they are on biologics, have pulmonary disease, or have other chronic illnesses. That said, it is essential that we continue to study these vulnerable patients with the emergence of new SARS-CoV-2 variants after the primary vaccine series and repeat boosters to appreciate the initial responses and durability of protective immunity. ■

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The Need for a CYFRA 21-1 Cutoff Value to Predict Clinical Progression of IPF in Clinical Practice

To the Editor:

We read with much interest the article by Molyneaux and colleagues on the concentrations of CYFRA 21–1 in patients with idiopathic pulmonary fibrosis published online in your prestigious journal (1). The authors found that the serum concentration of CYFRA 21–1 is significantly higher in patients with idiopathic pulmonary fibrosis than in a healthy population and that it can predict disease progression and overall mortality in idiopathic pulmonary fibrosis patients, suggesting the potential usefulness of serum CYFRA 21–1 as a diagnostic and prognostic biomarker (1). Unfortunately, a specific cutoff value of CYFRA 21–1 was not defined in the study to use as a reference in clinical practice. Although the mean CYFRA 21–1 values were statistically different between healthy subjects and patients with idiopathic pulmonary fibrosis, most data from healthy subjects appear to overlap those from patients with idiopathic pulmonary fibrosis, making it difficult to determine a cutoff value for distinguishing both groups (1). The receiver operating characteristic curve analysis has been used in previous studies to define the most appropriate cutoff value of serum CYFRA 21–1 to differentiate benign from malignant disease, advanced from early cancer clinical stage, and squamous cell from small cell carcinoma (2, 3). Cutoffs of serum CYFRA 21–1 calculated from receiver operating characteristic curves were also useful for diagnosing preeclampsia and endometriosis and predicting response to therapy and prognosis in patients with cancer (3–6). These previous observations suggest that receiver operating characteristic curve analysis of serum CYFRA 21–1 concentration in subjects from the PROFILE (Prospective Observation of Fibrosis in the Lung Clinical Endpoints) study could also provide a cutoff value to diagnose the disease and predict clinical outcomes in idiopathic pulmonary fibrosis. We believe that if the authors can provide the cutoff value of serum CYFRA 21–1 for diagnosing and predicting clinical progression in idiopathic

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

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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. ■

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