months after cessation of treatment (4). In a randomized controlled trial of 64 children with obstructive sleep apnea, a 6-week treatment with intranasal budesonide significantly improved the severity of mild obstructive sleep apnea and underlying adenoidal hypertrophy compared with placebo; this effect persisted for at least 8 weeks after cessation of therapy (5). A metaanalysis of five randomized trials including a total of 349 patients concluded that that nasal steroids can significantly improve nasal obstruction symptoms and reduce adenoid size in children with moderate to severe adenoidal hypertrophy (6). This is the likely mechanism of the improvement of sleep-disordered breathing in children who receive intranasal steroids. I agree with Kheirandish-Gozal and Gozal, who concluded, "These findings justify the use of topical steroids as the initial therapeutic option in otherwise healthy children with mild obstructive sleep apnea" (5).

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References

1. De Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med* 2012;185:12–23.
2. Mansfield LE, Diaz G, Posey CR, Flores-Neder J. Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide. *Ann Allergy Asthma Immunol* 2004;92:240–244.
3. Brouillette RT, Manoukian JJ, Ducharme FM, Oudjhane K, Earle LG, Ladan S, Morielli A. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J Pediatr* 2001;138:838–844.
4. Alexopoulos EI, Kaditis AG, Kalampouka E, Kostadima E, Angelopoulos NV, Mikraki V, Skenteris N, Gourgoulianis K. Nasal corticosteroids for children with snoring. *Pediatr Pulmonol* 2004;38:161–167.
5. Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics* 2008; 122:e149–e155.
6. Zhang L, Mendoza-Sassi RA, César JA, Chadha NK. Intranasal corticosteroids for nasal airway obstruction in children with moderate to severe adenoidal hypertrophy. *Cochrane Database Syst Rev* 2008;(3) CD006286.

Plasma Proteins for Risk Prediction in Idiopathic Pulmonary Fibrosis

To the Editor:

In response to issues raised by Drs. Ley and Collard in their editorial (1) regarding outcome prediction in idiopathic pulmonary fibrosis (IPF), we clarify here certain aspects of our work (2).

The editorial authors repeatedly mention that we identified "serum" biomarkers (1). Plasma is the unclotted cell-free fraction of the blood; serum is obtained after blood is allowed to clot. In our study (2), we identified biomarkers in plasma. Because plasma and serum contain different protein repertoires, we would strongly advocate not using them interchangeably in biomarker discovery or validation.

The editorial authors assert, "biomarker predictors were inconsistently identified in a separate validation cohort," but fail to discuss the remarkable consistency of our results. Four of the five biomarkers predicted transplant-free survival in both cohorts. More importantly, mortality prediction by our personalized clinical and molecular mortality index (PCMI) was highly consistent between derivation and replication sets, with C-statistics for early

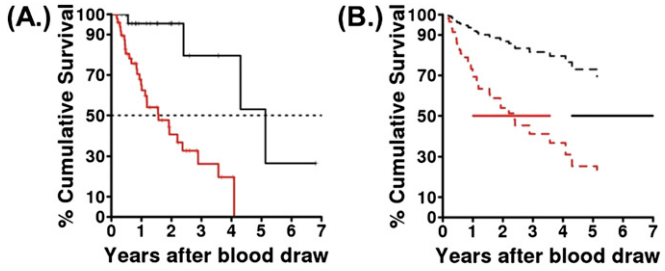

Figure 1. Outcome prediction based on personalized clinical and molecular mortality index (PCMI). *Panel A* was originally published as Figure 4A in Reference 2. (*A*) PCMI predicts mortality in idiopathic pulmonary fibrosis. *Solid lines* show published mortality curves. *Red line* shows PCMI $\geq$ 330; *black line* shows PCMI $<$ 330. Median survival after blood draw was 5.2 and 1.6 years, respectively. (*B*) Survival curves for mortality with lung transplant as a competing risk. *Broken lines* are survival curves; *solid lines* are confidence intervals on the medians from data in Figure 4A; *red line* shows PCMI $\geq$ 330; *black line* shows PCMI $<$ 330 (hazard ratio = 4.37, $P = 0.0018$). Estimated medians are comfortably within confidence intervals from published analysis.

mortality exceeding 80% (3). Determining this consistency was possible in this study only because we had two cohorts, unlike all previous peripheral blood biomarker studies in IPF, or as a matter of fact, many recently published clinical risk prediction studies (see examples in References 3–5).

As the editorial authors point out, increased availability of lung transplantation requires that it be addressed in IPF outcome studies. Several data analytic methods can be applied, including the Fine-Gray model cited by the authors, cause-specific incidence models, and multistate models incorporating disease progression, lung transplantation, and mortality (6). In the case of our study, treating lung transplant as a competing risk did not substantially alter the results (Figure 1), highlighting the robustness of PCMI.

We agree with the editorial authors that additional studies on molecular biomarkers are needed, but we disagree on what types of studies. Based on the impressive reproducible performance of PCMI in predicting patient outcome at presentation in two cohorts larger than most previously published molecular biomarker studies in IPF, we believe that the question of whether blood proteins contain prognosis-relevant information is largely resolved. Biomarker studies should now be designed to determine the utility of molecular markers in patient management (i.e., transplant prioritization) and to determine whether changes in biomarkers during the course of disease indicate shifts in the patient's risk profile.

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References

1. Ley B, Collard HR. Risk prediction in idiopathic pulmonary fibrosis [editorial]. *Am J Respir Crit Care Med* 2012;185:6–7.
2. Richards TJ, Kaminski N, Baribaud F, Flavin S, Brodmerkel C, Horowitz D, Li K, Choi J, Vuga LJ, Lindell KO, *et al.* Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012;185:67–76.
3. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, *et al.* Ascertainment of

individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;184:459–466.
4. Collard HR, Calfee CS, Wolters PJ, Song JW, Hong SB, Brady S, Ishizaka A, Jones KD, King TE Jr, Matthay MA, *et al*. Plasma biomarker profiles in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2010;299:L3–L7.
5. Kinder BW, Brown KK, McCormack FX, Ix JH, Kervitsky A, Schwarz MI, King TE Jr. Serum surfactant protein-a is a strong predictor of early mortality in idiopathic pulmonary fibrosis. *Chest* 2009;135:1557–1563.
6. Beyersmann J. Competing risks and multistate models with R. New York: Springer; 2011.

Monitoring the Temporal Changes of Respiratory Resistance: A Novel Test for the Management of Asthma

To the Editor:

Modern management of asthma requires a comprehensive diagnostic approach and assessment of exacerbations. The former is based on medical history, physical examination, and demonstration of airway instability by bronchial challenges or peak expiratory flow (PEF) monitoring (1). Though measuring the PEF is useful to assess the natural variability of bronchial tone, it is effort dependent, needs cooperation by the patient, may alter airway caliber, and requires a long period of observation (2, 3). In addition, its sensitivity is less than that of bronchial challenges (4) and similar to symptoms (5). Symptoms and use of rescue drugs and PEF monitoring are used for risk prediction, though they weakly correlate with each other and clinical outcomes (6–9), and are usually applied retrospectively, thus precluding prediction of adverse events in real life (10).

Here we provide evidence that home monitoring of inspiratory resistance (Rinsp) by a newly developed noninvasive technology based on forced oscillation technique (FOT) with great sensitivity to assess lung function (11–13) may be a reliable tool to diagnose asthma and predict acute deterioration of airway function.

Ten nonsmokers with mild asthma and 10 healthy control subjects (Table 1) had FOT measured at home for 2 minutes twice a day for 6 consecutive months with a portable FOT device (11). Baseline lung function was normal in the healthy subjects but consistent with mild airflow obstruction in the subjects with asthma, as suggested by an FEV_1/slow vital capacity below lower limits of normality and FEV_1 as %predicted near normal. The lack of significant differences in Rinsp between groups was presumably the result of the mild peripheral airflow obstruction in asthma, high variability of the measurement, and limited number of subjects in the study. An intuitive user interface provided visual and acoustic feedbacks to the subjects. Artifacts due to glottis closure and anomalous breaths were automatically discarded by the device's software. The data were encrypted and transmitted through the Internet to a central server for storage and further analysis. For each measurement, the mean and standard deviation of Rinsp were used to build time series of its coefficients of variation (CV_{RINSP}) at 2, 4, 8, 16, and 32 consecutive days. Risk predictors for acute deterioration of airway function were estimated from the conditional probability that an increase of Rinsp greater than or equal to twice the predicted respiratory resistance (14) occurred within the next 4, 7, 15, or 30 days given the CV_{RINSP} values observed in the previous 8 days. The trial was approved by the Ethical Committee of the S. Luigi Hospital (Orbassano, Torino, Italy).

TABLE 1. MAIN ANTHROPOMETRIC AND BASELINE LUNG FUNCTION DATA

Variables	Subjects with Asthma	*P* Value	Control Subjects
Sex, M/F	7/3	0.08	3/7
Age, yr	35 ± 15	0.07	47 ± 11
BMI, $kg \cdot m^{-2}$	25 ± 4	0.37	23 ± 2
FEV_1, L	3.00 ± 0.38	0.80	3.08 ± 0.69
FEV_1, %pred	87 ± 11	0.01	108 ± 14
FEV_1/SVC, %pred	85 ± 9	0.05	93 ± 6
TLC, %pred	102 ± 11	0.23	109 ± 11
RV, %pred	109 ± 34	0.86	103 ± 20
Rinsp, $cmH_2O \cdot s \cdot L^{-1}$	3.51 ± 1.11	0.14	2.88 ± 0.45

Definition of abbreviations: BMI = body mass index; Rinsp = inspiratory resistance at 5 Hz; RV = residual volume; SVC = slow vital capacity; TLC = total lung capacity.
Data are mean ± SD.

At all time scales (2, 4, 8, 16, and 32 d), CV_{RINSP} was significantly larger in subjects with asthma than in healthy subjects ($P < 0.001$) (Figure 1, *left panel*). A time window of only 4 days provided 90% sensitivity and specificity for morning or evening CV_{RINSP} with respect to the diagnosis of the disease.

The occurrence of an acute deterioration of airway function within 1 week was predicted by computing CV_{RINSP} over a period of only 8 days with a probability of 100% when CV_{RINSP} was greater than 0.44 (Figure 1, *right panel*), but not by the average Rinsp.

There are several reasons for CV_{RINSP} to be highly accurate for both diagnosis and prediction of acute deterioration of airway function in asthma. First, Rinsp is the most sensitive functional parameter of airway caliber (11–15) and is unaffected by lung volume history (3). Second, our technology allows accurate measurements of lung function over mid-tidal inspiration, thus avoiding the artifacts of expiratory flow limitation or glottis closure on resistance. Third, unlike the recommended analysis of PEF (1), the variability of Rinsp in the present study was estimated from the CV. The advantages of this approach stem from the concept that fluctuations in biological signals often follow power-law distributions, thus carrying more useful information than mean values (10, 16–20). For clinical practice, it is remarkable that a time window of only 4 days (Figure 1, *left panel*) was highly sensitive and specific to distinguish subjects with asthma from normal subjects. Nevertheless, future studies should address the role of average Rinsp in addition to CV_{RINSP} for diagnostic and prognostic purposes.

Even though the number of subjects enrolled was low, the results are encouraging and might open new horizons in the field. Spirometry, or indeed any other lung function tests, cannot capture the fundamental characteristic of the disease: namely, the changes in lung function over time. Home monitoring of lung function by FOT does so in only a few days and can be easily and noninvasively performed by the patient. In addition, the analysis of the fluctuations of Rinsp can be used to form powerful risk predictors of acute deterioration of airway function and, possibly, asthma exacerbations. Even though this study was limited

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