Forced Expiratory Volume in 1 Second Variability Helps Identify Patients with Cystic Fibrosis at Risk of Greater Loss of Lung Function

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Objective To evaluate several alternative measures of forced expiratory volume in 1 second percent predicted (FEV_1 %pred) variability as potential predictors of future FEV_1 %pred decline in patients with cystic fibrosis.

Study design We included 13 827 patients age ≥6 years from the Epidemiologic Study of Cystic Fibrosis 1994-2002 with ≥4 FEV_1 %pred measurements spanning ≥366 days in both a 2-year baseline period and a 2-year follow-up period. We predicted change from best baseline FEV_1 %pred to best follow-up FEV_1 %pred and change from baseline to best in the second follow-up year by using multivariable regression stratified by 4 lung-disease stages. We assessed 5 measures of variability (some as deviations from the best and some as deviations from the trend line) both alone and after controlling for demographic and clinical factors and for the slope and level of FEV_1 %pred.

Results All 5 measures of FEV_1 %pred variability were predictive, but the strongest predictor was median deviation from the best FEV_1 %pred in the baseline period. The contribution to explanatory power (R^2) was substantial and exceeded the total contribution of all other factors excluding the FEV_1 %pred rate of decline. Adding the other variability measures provided minimal additional value.

Conclusions Median deviation from the best FEV_1 %pred is a simple metric that markedly improves prediction of FEV_1 %pred decline even after the inclusion of demographic and clinical characteristics and the FEV_1 %pred rate of decline. The routine calculation of this variability measure could allow clinicians to better identify patients at risk and therefore in need of increased intervention. *(J Pediatr 2016;169:116-121)*.

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Cystic fibrosis (CF) is characterized by the progressive, irreversible loss of lung function caused by chronic pulmonary infection with resultant inflammatory destruction of the airways and parenchyma.[1] We previously have evaluated risk factors for lung function decline in children and adolescents[2] and in adults.[3] In children and adolescents, high lung function, *Pseudomonas* infection, pancreatic enzyme use, pulmonary exacerbations, and persistent crackles were among the important predictors of accelerated decline in the forced expiratory volume in 1 second (FEV_1).[2] Overall risk factors were similar in adults aged 18-24 years,[3] but in adults aged 25 years and older, only pancreatic enzyme use predicted accelerated decline.

The loss of lung function, however, generally is not a simple monotonic decline. Indeed, Sanders et al[4] reported that lung function loss tends to occur during and/or after pulmonary exacerbations, with as many as 25% of patients with CF not returning to at least 90% of their pre-exacerbation FEV_1 baseline within 3 months after treatment. In addition, there is substantial variability about the trend line of progressive decline in FEV_1 values.[5] We have found previously that for adolescents increased variability around the FEV_1 trend line as measured by the SD independently predicted the subsequent loss in lung function by early adulthood.[6]

We hypothesized that variability in FEV_1 over time could be an important additional predictor of subsequent lung function decline in patients with CF. Although much of the variability in FEV_1 may be the result of clinician-treated pulmonary exacerbations, we elected to study variability rather than exacerbations because variability reflects all acute lung function decline events (whether or not they are identified as pulmonary exacerbations by clinicians). Furthermore, we expected the association would be most striking in individuals with high lung function, in part because they have further to decline and in part because they may be less likely to be treated aggressively.[7] If a formal measure

%pred	Percent predicted
CF	Cystic fibrosis
FEV_1	Forced expiratory volume in 1 second

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The Epidemiologic Study of Cystic Fibrosis was supported by Genentech, Inc (San Francisco, CA). W.M., D.VanD., J.W., and M.K. received honoraria from Genentech for serving as members of the Scientific Advisory Group for the Epidemiologic Study of Cystic Fibrosis and have served as consultants to Genentech. D.P. and A.F. are employees of ICON Clinical Research, which was paid by Genentech for providing analytical services for this study. J.W. was previously an employee of Genentech.

http://dx.doi.org/10.1016/j.jpeds.2015.08.042

of variability adds materially to our predictive ability, this new variable could be combined with clinical findings to improve the identification of patients at risk for more rapid lung function decline. Our objective in this analysis was to evaluate several different measures of FEV_1 variability as potential predictors of lung function decline, including evaluating the predictive ability of variability in FEV_1 alone and after controlling for demographic and clinical factors and for the slope and level of FEV_1.

Methods

The Epidemiologic Study of Cystic Fibrosis was a multicenter, prospective, epidemiologic observational study of US patients with CF from 1994 to 2005 that included more than 30 000 patients.[8] Encounter-based data were collected on demographics, signs and symptoms of lung disease, nutritional measures, respiratory microbiology, spirometry, and clinical care. Informed consent was obtained on the basis of decisions by local human subjects review boards. Patients were included in this analysis if they were age ≥6 years between 1994 and 2002. Four-year analysis intervals were used, each consisting of a 2-calendar-year baseline period and a 2-calendar-year follow-up period. We required ≥4 FEV_1 measurements spanning ≥366 days in both of these periods. FEV_1 percent predicted (%pred) values were calculated by the use of equations from the Global Lungs Initiative.[9] The best FEV_1 %pred values were identified during the baseline period, the overall 2-year follow-up period, and the second year of the follow-up period. We obtained information on signs and symptoms and nutritional status from the encounter closest to the date of the best FEV_1 %pred in the baseline period and microbiology information from any positive culture during the baseline period.

FEV_1 variability was characterized by the use of 5 different measures applied to all FEV_1 %pred values recorded during the baseline period. We used all values recognizing that patients with more advanced lung disease would tend to have more measurements, but we wanted to evaluate the predictive strength of those extreme deviations. The simplest measures were the maximum and median deviations from the best observed FEV_1 %pred in the baseline period (**Figure 1**, A). These measures were chosen because clinicians tend to refer back to the best recently observed FEV_1 and the simplicity of their calculation. Three additional measures evaluated variability around the trend line fitted to the baseline FEV_1 %pred values: the maximum absolute deviation from the trend line, the median absolute deviation from the trend line, and the SD of FEV_1 %pred values about the trend line (**Figure 1**, A). These measures take account of the overall trend in lung function. The SD has been used previously,[6] and the other 2 measures are potential simplifications. The 2 outcomes evaluated were the change from the best FEV_1 %pred in the baseline period to the best in 2-year follow-up period and the best in the second year of the follow-up period (**Figure 1**, B).

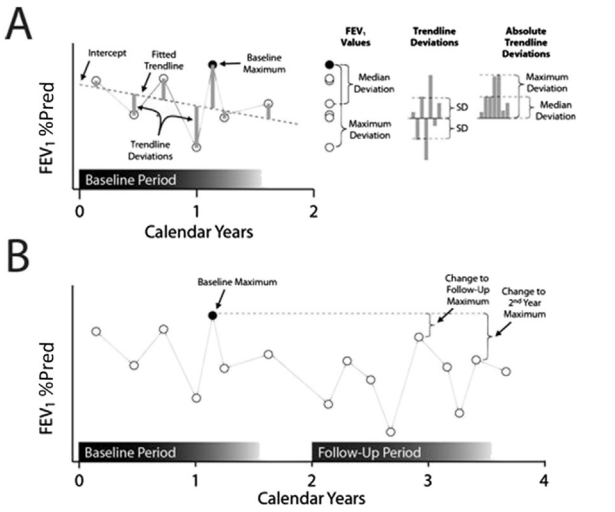

Figure 1. **A,** Schematic representation of measures of variation from the best (maximum FEV_1 %pred during baseline) and from the fitted trend line: median and mean deviations of FEV_1 values from the best and deviations from the trend line, including the maximum absolute deviation, the median absolute deviation, and the SD. **B,** Schematic representation of outcome measures: calculated change in lung function from best FEV_1 %pred in baseline to the best in the overall follow-up period, and the best in the second year of follow-up.

Patients could contribute more than one 4-year analysis interval as long as the baseline periods did not overlap. The analysis intervals were stratified into 4 lung-disease stages based on the patient's best FEV_1 %pred during the baseline period (≥100, 70 to <100, 40 to <70, and <40). Multivariable regression was then used to relate the measures of baseline FEV_1 variability to the FEV_1 outcomes after we controlled for the slope and intercept of the FEV_1 baseline trend line and age, sex, race (non-Hispanic white vs other), genotype (homozygous F508del, heterozygous F508del, other, unknown), daily cough, daily sputum, clubbing, crackles, wheeze, *Pseudomonas aeruginosa* positive in the baseline period, *Staphylococcus aureus* positive in baseline period, weight for age percentile, and height for age percentile. These variables have been reported previously to be related to rate of decline in lung function.[2,3,6] Additional details on the definition of these variables are available in Morgan et al.[8]

All analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, North Carolina). *P* values less than .05 were considered statistically significant. No adjustment was made for multiple comparisons.

Results

Of the 27 340 patients who were age 6 years and older, 21 050 had sufficient FEV_1 measurements during a potential 2-year baseline time period; 14 134 of these patients also had adjacent follow-up periods to form at least one 4-year analysis