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## Variability of FEV and Criterion for Acute Pulmonary Exacerbation

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# Variability of FEV<sub>1</sub> and criterion for acute pulmonary exacerbation

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## A commentary on

### Probability of treatment following acute decline in lung function in children with cystic fibrosis is related to baseline pulmonary function

by Morgan WJ, Wagener JS, Yegin A, Pasta DJ, Millar SJ, Konstan MW. *J Pediatr* (2013) 163(4):1152–7. doi:10.1016/j.jpeds.2013.05.013

Morgan et al. (1) concluded that cystic fibrosis (CF) in children and adolescents with a high baseline forced expiratory volume (FEV<sub>1</sub>) were less likely to have a therapeutic intervention or slower rate of FEV<sub>1</sub> decline after a single acute decline in FEV<sub>1</sub> of 10%. This conclusion is not well supported due to the arbitrary criteria used for defining a pulmonary exacerbation, as explained below.

First, only a single low FEV<sub>1</sub> value defined an exacerbation. However, FEV<sub>1</sub> measurements are notoriously variable from test-to-test; Taylor-Robinson et al. (2) showed that the baseline fluctuations have a wide range of about 60%. FEV<sub>1</sub> tests are sensitive to time of day, health status, mood, tiredness, lack of sleep, medical instruction, nutritional status, acute comorbidities, and other factors Cystic Fibrosis Foundation (3). Given that a single FEV<sub>1</sub> assessment was used, rather than the average of repeated measurements on different days, evidence that the assessment values were technically accurate.

Second, an exacerbation was defined as a single 10% decline in FEV<sub>1</sub> in the above study without any explanation as to why 10% was chosen nor why a range of declines were not evaluated to determine

the sensitivity and specificity of different criteria (by testing several criterion values such as 5, 15, 20, and 25%). A threshold of 10% is nearly within the noise level of the FEV<sub>1</sub> measurements (2, 4). This leaves open the possibility that the findings in the study would not hold if a slightly greater (or smaller) value was used, such as 8 or 12%.

Furthermore, regarding the use of the cutoff of 10%, there is no agreement on the optimal cutoff for separating pulmonary exacerbations from the large natural technical variations in FEV<sub>1</sub> from test-to-test, a variation that has been found to be higher in CF without evidence of concomitant changes in the severity of the condition (4, 5). National treatment guidelines (5) for acute pulmonary exacerbations in CF was based on the work of Fuchs et al. (6), a clinical trial of DNAase that only incidentally mentioned 10% as a criterion if 4 of 12 other signs or symptoms were present in a population of adults and children. In a more comprehensive study on children under six years of age, Rabin et al. (7) and Regelman et al. (8) defined exacerbations operationally by whether or not pulmonologists decided to intensify treatment using antibiotics. These authors found the average FEV<sub>1</sub> decline to be 20% in children under 6 years of age, these investigators proposed a refinement of the criterion to 15% or higher, rather than 10% suggested by Fuchs et al. (6), under the condition that a 15% decline would only be considered an exacerbation if two other clinical signs were concurrent, such as increased cough frequency, new crackles, or hemoptysis. Evidence on the best cutoff value is consequently nearly absent and remains to be determined. The most logical path

follow would be to first test the full range of pulmonary decline criterion, perhaps from 0 to 30%, to determine the optimal criterion, and then to conduct a focused study on this value. The findings from such a range analysis could be of great value in helping further refine the criterion for an exacerbation based on FEV<sub>1</sub> decline, rather than assuming a single value at this early stage.

The study has many prominent strength including well-defined hypotheses, very large sample size, analysis by age group, excellent statistical analysis, clearly presented findings, excellent flow of logic, and others. However, due to the shortcomings described above, we suggest further study of the above critical questions before the findings are implemented in practice.

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