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Understanding the Relationship Between Sweat Chloride and Lung Function in Cystic Fibrosis

To the Editor:

In a recent issue of *CHEST* (January 2013), Durmowicz et al¹ highlight the finding that despite improvement in both cystic fibrosis (CF) transmembrane conductance regulator (CFTR) and pulmonary function in clinical trials of ivacaftor (recently approved by the US Food and Drug Administration for individuals with CF and the G551D mutation), there does not appear to be a direct correlation between changes in sweat chloride (a measure of CFTR function) and changes in FEV₁ (an established efficacy measure). They also were unable to identify a minimum threshold for change in sweat chloride that was associated with FEV₁ improvement.

Despite the findings, lack of a linear correlation between the changes in these outcome measures should not diminish the potential utility of sweat chloride for predicting clinical outcomes. Although the data presented failed to show a population level threshold for change in sweat chloride, the absolute sweat chloride concentrations after treatment in the two ivacaftor trials were not assessed. While adult sweat chloride values are highly variable across CF and healthy control subjects,² concentrations < 60 mM are typical among individuals without CF, and intermediate values are associated with a more benign clinical course. In reanalysis of the ivacaftor trial data, Seliger et al³ show that nearly every participant has a resulting sweat chloride \leq 80 mM after 2 weeks of treatment, which does not provide the spectrum of response required to readily establish a linear correlation with another outcome. Thus, correlation between changes in sweat chloride and change in FEV₁ may not fully capture the predictive ability of sweat chloride.

There is no doubt that FEV₁ variability across and within individuals poses a challenge for clinical research in CF. That variability comes from years of infection, inflammation, and structural damage to the lung and can confound treatment effects. Before a meaningful quantitative relationship between CFTR activity and lung function or other clinical outcomes can be established, more work must be done to better understand the complex collection and interaction of physiologic and clinical measures in CF, particularly across diverse patient populations. The evaluation of younger patient populations with mild disease (and for whom lung function cannot be reliably measured nor acute changes expected) poses a particular challenge and highlights the need for robust pharmacodynamic parameters predictive of clinical response. Further discussions between regulatory agencies, trial sponsors, and community advocates will be necessary for monitoring the evolution of biomarkers in the regulatory approval process to ensure availability of beneficial and safe therapies.

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REFERENCES

1. Durmowicz AG, Witzmann KA, Rosebraugh CJ, Chowdhury BA. Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience. *Chest*. 2013; 143(1):14-18.
2. Farrell PM, Rosenstein BJ, White TB, et al; Cystic Fibrosis Foundation. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153(2):S4-S14.
3. Seliger VI, Rodman D, Van Goor F, Schmelz A, Mueller P. The predictive potential of the sweat chloride test in cystic fibrosis patients with the G551D mutation [published online ahead of print April 26, 2013]. *J Cyst Fibros*. doi: 10.1016/j.jcf.2013.03.004.

Response

To the Editor:

We thank Dr Heltshe and colleagues for their letter in response to our article to *CHEST* in which we noted the lack of correlation