function when the decrease in ppFEV$_1$ is related largely to airway destruction or fibrosis. Ongoing real-world studies (8) using morphometric analysis of computed tomography scans before and after the initiation of ETI may help in further understanding the anatomical determinants of lung function improvement after the initiation of CFTR modulators. ■

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Reply to Martin *et al.*

From the Authors:

We thank Martin and colleagues for their interest in our publication reporting early effects of elexacaftor–tezacaftor–ivacaftor (ETI) in people with cystic fibrosis (PwCF) (1), and we wish to respond to three key topics addressed in their letter to the editor. First, the authors propose that the relative contributions to percentage predicted FEV$_1$ from reduction in mucus obstruction in the airways versus less reversible airway damage (e.g., fibrosis or small-airway obliteration) may be a key factor in the modest correlation we identified between improved lung function and improved CFTR (cystic fibrosis transmembrane conductance regulator) activity measured by sweat chloride concentration. We agree with this premise, which is consistent with our explanatory framework of heterogeneity of response to ETI in our large study cohort with varied baseline disease status and medication use before initiating ETI. We concur that it is likely that early gains in FEV$_1$ after starting highly effective CFTR modulator drug therapy occur primarily through improved mucociliary clearance and reduced airway obstruction, as seen with ivacaftor (2). Whether additional improvement in lung function can develop with continued use of modulator therapy, perhaps related to reduced airway inflammation or structural disease, is unclear but of great interest (3).

Second, the authors raise the question of whether CFTR correction greater than that achieved by ETI will result in additional airway clearance improvement. This query is also important, and significantly greater change in FEV$_1$ with newer agents, if seen, would suggest that further enhancement of airway clearance is possible. Our study (PROMISE [A Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function]; NCT 04038047) includes a substudy focused on mucociliary clearance and mucus properties in sputum samples, which may offer additional outcomes to consider in future work

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comparing ETI with novel CFTR modulator regimens. We agree that uncertainty remains regarding the threshold of CFTR correction needed to normalize mucus properties and mucociliary clearance.

Third, the authors identify value in lung imaging in studies of CFTR-directed therapies. We concur and are excited to see both computed tomography and magnetic resonance imaging outcomes included in observational studies of PwCF being treated with highly effective modulator drug therapy (RECOVER [Real World Clinical Outcomes With Novel Modulator Therapy Combinations in People With CF; NCT 04602468] and HyPOINT [Hyperpolarized Imaging for New Treatments; NCT 04259970]). Indeed, commonly implemented outcome measures (e.g., spirometry, self-reported symptoms, risk of acute pulmonary exacerbation) may be more challenging to use in some studies, as PwCF experience overall better pulmonary health. Continued advances in these and other functional imaging techniques of the lung may play a larger role in measuring or understanding the impact of certain interventions (e.g., modulator drug therapy). We would add only that in comparative trials with new drug agents capable of greater CFTR correction, lack of evidence of greater mucociliary clearance as reflected by lung function or imaging outcomes does not preclude important health benefits for other organ systems such as the gastrointestinal tract; these other benefits may be particularly relevant for systemic therapies or those started earlier in life, when CFTR correction may prove most beneficial. ■

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