Despite these limitations, the data presented here are promising; they put new bricks in the understanding of immunological disorders following brain injury, in the understanding of potential relationship between these disorders and neurological prognosis of brain-injured patients, and in the pathophysiology of HSV reactivation in ICU patients. Moreover, since recent interventional studies targeting HSV or CMV in ICU patients were negative (8–12), the question of a more personalized treatment has been raised; the challenge being to determine which categories of patients may potentially benefit from an antiviral treatment. The present study clearly opens a new door by identifying a potential population that might be targeted for a prophylactic antiviral treatment. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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How Should the Effects of CFTR Modulator Therapy on Cystic Fibrosis Lung Disease Be Monitored?

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene leading to structural and/or functional abnormalities of CFTR, an ion channel that regulates transepithelial chloride conductance. CF lung disease is characterized by dehydration of secretions, mucus plugging of airways, inflammation, and infections leading to progressive loss in pulmonary function and, ultimately, respiratory failure (1). The CFTR modulator combination therapy elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) significantly increases CFTR function in patients with one or two CFTR F508del alleles (2) and results in remarkable clinical benefits, including improvements in nutritional status, and in relevant respiratory outcomes (3–6). In CF clinical practice, lung function is traditionally measured by spirometry and expressed as FEV_1, and percent predicted FEV_1 ($ppFEV_1$) improves with effective therapy. However, previous studies have shown that the sensitivity of FEV_1 to detect early CF lung disease is inferior to the lung clearance index (LCI), a measurement of ventilation

Originally Published in Press as DOI: 10.1164/rccm.202204-0730ED on May 17, 2022

inhomogeneity calculated from multiple-breath washout (MBW). LCI is an established outcome for the assessment of early and mild lung disease and is therefore used in pediatric clinical trials, including the phase 3 ELX/TEZ/IVA trials in school- and preschool-aged children with CF (5, 7, 8). In patients with more advanced CF lung disease, LCI has so far not been commonly used, other than in observational trials such as Prospective Longitudinal Study of CFTR-dependent Disease Profiling in Cystic Fibrosis (9). Limited data are also available for monitoring structural changes in early CF lung disease and how they relate to functional measurements, although a previous study had shown good correlations between LCI and magnetic resonance imaging (MRI) scores in infants, toddlers, and older children with CF (10). However, data on comparison of responses in LCI and MRI scores to effective CFTR modulator therapy are currently lacking.

In this issue of the *Journal*, Graeber and colleagues (pp. 311–320) present their findings on the effects of ELX/TEZ/IVA on LCI and MRI scores in adolescent and adult patients with CF after 8–16 weeks of therapy (11). A total of 91 patients heterozygous for CFTR F508del and a minimal function mutation (F508del/MF) or homozygous for F508del (F508del/F508del) were included in this prospective observational postapproval multicenter trial. Similar to the recent Prospective Study to Evaluate Biological and Clinical Effects of Significantly Corrected CFTR Function study report (12), the authors observed significant improvements in sweat chloride concentration, body mass index, and pulmonary function in both groups treated with ELX/TEZ/IVA; $ppFEV_1$ increased by 14.5% in F508del/MF and by 12.5% in F508del/F508del patients.

LCI before initiation of ELX/TEZ/IVA was increased above the upper limit of normal (ULN) in 36 out of 40 (90%) of the F508del/MF patients and improved with therapy by 23.4% on average. On follow-up, 15 (37.5%) patients had normal LCI below the ULN. In the F508del/F508del patients, LCI improved by 15.3% on average. LCI was above the ULN in 31 out of 39 (79.5%) patients before and below the ULN in 17 (43.6%) after initiation of ELX/TEZ/IVA. In those F508del/F508del patients pretreated with dual CFTR modulators LUM/IVA or TEZ/IVA, LCI also improved after switching to ELX/TEZ/IVA. Similarly, MRI global scores improved by 25.6% and morphology score by 26.7% in F508del/MF patients and by 29.3% and 35.5% in F508del/F508del patients, respectively. The MRI subscores for mucus plugging and for wall thickening/bronchiectasis were the dominant morphological abnormalities detected by MRI and most affected by ELX/TEZ/IVA therapy. Changes in MRI perfusion score did not reach statistical significance with the numbers of patients studied.

Why is this study important and what can we learn from it? Mucus hypersecretion and plugging of peripheral airways is a hallmark of early CF lung disease (1, 13). Effective therapy, such as ELX/TEZ/IVA or future CFTR modulator drugs, should therefore be started as early in life as possible; however, it is not clear to date how efficacy of these treatments could be best monitored or compared. MBW with LCI is easy to perform, as it is measured during tidal breathing. The increase in LCI in CF lung disease and decrease (improvement) with therapy is likely a reflection of improved mucus obstruction, although the technique does not allow for a regional assessment of the lung. Chest imaging by computed tomography or MRI scans, in contrast, involve radiation for the former and may require sedation and/or intubation and mechanical ventilation in younger children. However, chest imaging by computed tomography or MRI allows for detailed regional analysis using morphofunctional scores rated in each lung lobe. The MRI global score used in the work by Graeber et al. comprises subscores for bronchial wall abnormalities (wall thickening and/or bronchiectasis), mucus plugging, abscesses and/or sacculations, consolidations, and special findings such as pleural effusion (14). In this regard, it is interesting that changes in LCI with ELX/TEZ/IVA therapy correlated significantly with changes in $ppFEV_1$ ($r = -0.599$; $P < 0.001$) but not with changes in MRI global score or morphology and perfusion subscores, although there was high concordance of improvement in LCI and MRI global score (75.9%) as well as morphology (79.3%) and perfusion subscores (58.6%). The lack of correlation suggests that LCI and MRI scores measure different aspects of disease manifestation and that the information obtained from these methods is therefore complementary. In fact, although increased LCI and changes in LCI in response to CFTR modulator therapy may be directly related to CFTR function, hydration of airways, and mobilization of secretions, and thus represent reversible airway mucus plugging, the MRI bronchial wall abnormalities subscore includes both potentially reversible (wall thickening) and nonreversible (bronchiectasis) features. However, the lack of correlation in this study may also be explained by the fact that paired LCI/MRI data were only available in approximately half of the study participants. Another limitation is that although sufficient numbers of patients with CF with each genotype (F508del/MF and F508del/F508del) were included, the follow-up on ELX/TEZ/IVA therapy was relatively short (8–16 wk). Longer observation intervals may be needed to allow visualization of changes in lung morphology not directly related to airway mucus clearance and to assess whether later changes in morphology could be related to factors such as improvement in airway inflammation with therapy.

In summary, this well-designed study provides promising results and new insights into the potential roles of MBW/LCI and of lung MRI for monitoring functional and structural changes in established CF lung disease in response to effective modulator therapy. Future studies to evaluate the sensitivity of LCI and lung imaging techniques in response to CFTR modulator therapy should also be conducted in younger children with CF and milder disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Omics and Lung Function: A Need for Integration

DNA methylation (DNAm) plays a role in a wide range of biological processes, including regulation of gene expression, reproduction, and development, and in chronic diseases and aging (1). The development of methodologies allowing the rapid and low-cost assessment of DNAm has enabled epigenome-wide association studies (EWASs) in large population studies that have increased our understanding of both the effect of environmental exposures on the methylome and the role of methylation in many diseases (2).

Maternal tobacco smoke exposure has shown highly specific changes in the offspring's epigenome at birth (3) that persist for decades (4). DNAm is a biomarker of tobacco smoke exposure (5) and is predictive of future asthma (6) and chronic obstructive pulmonary disease (COPD) (7). DNAm differences at birth have been shown to predict lung function growth trajectories (8) and to be associated with lung function and lung function decline in adulthood (9).

In this issue of the *Journal*, Lee and colleagues (pp. 321–336) describe the largest multiethnic EWAS of cross-sectional lung function to date in more than 17,500 individuals (Figure 1) (10). The differential methylation of 1,297 CpGs was associated with FEV_1, FVC, or FEV_1/FVC (after adjusting for technical experimental factors, estimated cellular composition, genetic ancestry, and smoking). Of these, 1,240 were newly described and 73 related to COPD. When comparing across ancestries, 294 lung function associated CpGs were unique to European or African ancestry, and 395 CpGs were unique to never- or ever-smokers. A key finding was that associated methylation marks were enriched for transcription factors, point toward accessible chromatin, and a druggable epigenome.

A major strength of this multiethnic study is the interrogation for functional and biologic relevance through gene expression, causal modeling, and colocalization efforts. Although limited by lack of longitudinal lung function modeling and limited assessment of lung tissue, this careful and comprehensive analysis provides a template for further investigations.

Given that DNAm is influenced by cell type, genetic variation, and environmental exposures, the large number of CpG sites associated with lung function is to be expected. This is reinforced by the rise in respiratory diseases in the past decades. Our genetic sequence has not changed, but the impact of the environment is magnified through the plasticity of our epigenomes. Variable methylation associated with reduced lung function may result from differences in past environmental exposures (either indirectly as biomarkers of exposure or on the casual pathway); the effect of genetic sequence variants that themselves are associated with low lung function; or as a consequence of disease processes such as inflammation (11). Given these potential relationships among methylation, lung function (LF), and disease, interpretation of the

Supported by NIH grants R01 AI121226 (J.W.H.) and R01 HG011393 (D.L.D.).

Originally Published in Press as DOI: 10.1164/rccm.202205-0928ED on May 24, 2022