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Defining the Clinical Utility of the Lung Clearance Index Are We There Yet?

The last decade has witnessed dramatic improvements in cystic fibrosis (CF) therapeutics with the introduction of a novel class of drugs known collectively as “CFTR modulators” (1). Most recently, a combination of modulators has made it possible to eventually offer “highly effective modulator therapy” (HEMT) to an estimated 90% of the U.S. population with CF (2, 3). Also, the data accumulated from multiple clinical trials has provided clear evidence for what constitutes as a disease-modifying effect in the natural history of CF. It is clearly recognized that in order for patients with CF, in particular young children, to continue to benefit from innovative therapies such as HEMT, there is a need to target therapies before irreversible lung damage has occurred. However, the ability to avert lung disease progression in CF is contingent on early detection and timely intervention. This will require the availability of tools that are both sensitive and feasible in the routine clinical setting. It is now well established that lung disease begins very early in life in children with CF (4, 5), with impaired mucociliary clearance being a hallmark and at the root of all the respiratory complications that patients experience (6, 7). Therefore, great attention has historically been paid to the accurate detection and monitoring of airway obstruction as a reflection of CF airway disease at all stages of disease progression. CF clinicians are highly familiarized with the use of spirometry, and in particular the FEV₁, as a useful tool for the detection of airway obstruction and to support clinical decision-making. However, an already large body of evidence has demonstrated that significant lung disease can be present in the face of a normal FEV₁ (8, 9). This fact, in addition to the robust and persistent changes seen in FEV₁ in response to HEMT, have identified a need to bring to the clinic assessment tools that will be more sensitive to the presence of airway disease. Perhaps of greatest importance is also the ability of such a tool to detect detrimental changes as well as support therapeutic

intervention and assist in monitoring the response to such an intervention to evaluate its effects.

As a result, an array of functional and image-testing modalities have been and continue to be actively investigated on CF for their ability to provide an accurate assessment of airway disease (10–14). Thanks to technological advances, parameters obtained from the multiple-breath washout technique have emerged as providing an alternative, sensitive assessment of airway function. Among the parameters that can be estimated from the multiple-breath washout the number of FRC volume turnovers required to clear a tracer from the lungs or Lung Clearance Index (LCI) has demonstrated great sensitivity to early airway disease (15). The LCI provides a metric for the degree of heterogeneity in gas distribution present throughout the tracheobronchial tree, a key aspect of CF pathophysiology. Intensive clinical research conducted over the past few years has already demonstrated the value of the LCI in the research setting, helping to establish it as an important endpoint for clinical trials (16–18). However, there are still important gaps in the information required to understand its potential role in the clinical setting. In this issue of the *Journal*, Perrem and colleagues (pp. 977–986) provide evidence from a two-center prospective study on the value of the LCI as an outcome measure when applied to the routine clinical setting in the care of children with CF (19). The focus of the study was on respiratory events experienced over a 2-year period, and although clinical decisions were not formalized by the study protocol or guided by the measurements performed in the children that participated in the study, there are several valuable insights gained from the study results. Some important considerations need to be taken into account to interpret their results in their full context. First, as it has progressively become an expectation for children with CF, this cohort had, for the most part, fairly normal pulmonary function by spirometry and morbidity features typically associated with CF such as weight loss, *Pseudomonas* infection, hemoptysis, and radiographic changes that were of rare occurrence. Second, the investigators had to develop a categorization scheme to qualify the respiratory events experienced by these children, as many would not have fulfilled the classic definitions of CF pulmonary exacerbation but still had changes in their treatment regimens, primarily through courses of antibiotics.

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This basically defines this cohort as the emerging new face of CF, in which it is more challenging to apply evidence on the basis of the available guidelines for care. If anything, this makes their cohort well suited for assessing the role of the LCI to support the care decisions for children with mild evidence for active lung disease. Their study demonstrated that the LCI detected a detrimental change in association with respiratory events and without complete return to baseline values after intervention. In addition, a detrimental change in LCI (defined as a 10% increase from baseline) performed better than FEV₁ at identifying a respiratory event, but not all events were associated with either measurement worsening by this criteria. However, as has been observed with FEV₁ for this setting, the mean magnitude for change in LCI with respiratory events was not as large as what could be desired by it being larger than the variability of the test, which, in this case, was 15% (20).

For any given parameter applied to decision making, the magnitude of change that could be considered clinically significant should be larger than the difference seen between repeated measurements without intervention or change in clinical status. Besides the significance of a change, the clinical utility is certainly what is desired in practice, as it provides a better assessment of the value of a given test or intervention by identifying a meaningful benefit to the individual patient. Unfortunately, there is no clear-cut definition of what will constitute as “clinically useful” for the management of CF lung disease, as this is likely to be multidimensional and could include aspects such as biologic, economic, personal, and societal domains. The “minimal clinically important difference” has been frequently used to identify a significant change in a patient’s condition and understand the effects of an intervention that captures the net efficacy. Multiple ongoing studies are aimed at providing a clearer understanding as to the role that the application of the LCI may play in the clinical setting, but its minimal clinically important difference seems elusive. A recent example of a randomized interventional trial did not demonstrate benefits when decisions to intervene were based in the detection of an absolute change in LCI of 1 unit (21). So, are we there yet? As Perrem and colleagues conclude, their study may be interpreted as suggesting that LCI and FEV₁ are complementary measures that capture different dimensions of CF lung disease with not too much overlap, so their use together provides a more robust assessment than using either measure alone. Taking into account that we are entering a new era in which the combination of the universal application of newborn screening and the expanding availability of HEMT are generating a cohort of children with “new CF,” we need additional studies to develop innovative management protocols based on the application of the most sensitive tools available. ■

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8 The Role of Individual and Neighborhood Factors on Racial Disparity in Respiratory Outcomes Won't You Be My Neighbor?

Racial disparity is not new. Although usually considered within the context of the criminal justice system (1), it has also recently been brought to the fore in relation to the coronavirus disease (COVID-19) pandemic (2). Although often associated with discrimination, it is not the same thing; by definition, disparity highlights a *difference* in experience, with racial disparity being defined as that usually associated with biology, linked with physical characteristics such as skin color or hair texture, and certainly racial discrimination and segregation have biological effects (3). Additionally, there is an evidence base around health disparities and “weathering” as a risk factor (4). So, although the discussion around racial disparity and health care is not new (5), it is important to understand how far we have come, so that we can learn what we can do better. Implicit in that is appreciating what we can and cannot change.

In this issue of the *Journal*, Ejike and colleagues (pp. 987–997) investigate to what extent both individual and neighborhood socioeconomic status (SES) factors contribute to racial disparities in chronic obstructive pulmonary disease (COPD) outcomes (6). They included more than 2,500 current and former smokers, with and without COPD, recruited to SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) (7) and assessed whether racial differences in symptoms, functional and imaging outcomes, or exacerbation risk could be explained by individual and/or neighborhood SES factors. They separately and sequentially adjusted for individual-level SES (income and education) and neighborhood SES (poverty rate, educational attainment, unemployment rate, median household income, Area Deprivation Index, and food access) in the models. Individual-level information was obtained at baseline enrollment into the SPIROMICS cohort. Neighborhood-level data were obtained from the 2010 U.S. Census Bureau American Community Survey and SPIROMICS AIR, with food access information from U.S. Department of Agriculture food stores at census-tract level. Each model provided a measure of association between race and the outcome of interest, and then the difference in strength of the measures was evaluated using the difference method (8). Following this, mediation proportion

(proportional reduction in exposure-outcome from before and after adjustment with mediators by both neighborhood and individual level) was tested.

It is important to note that very few people in the original data set were mixed or other race, and in fact only 529 Black people were included. People of mixed race, those of “other” race, and those not reporting race or having missing data around race were all excluded from the analyses, and yet they may have been the most important to include to understand in this setting. Although the paper may have been easier to follow if only those with COPD had been included, it is worth noting that Black individuals were less likely to have a COPD diagnosis before enrollment, perhaps due in part to access to health care or insurance access, and in these analyses, people needed to have a 20 pack-year smoking history to have a diagnosis of COPD.

The authors found that Black individuals were younger and less educated, had lower income, were more likely to be current smokers, lived in areas with worse poverty, had lower household income and higher unemployment, and were more likely to have limited food access than white individuals. With respect to outcomes, Black individuals had worse symptoms and quality of life, were at higher risk of exacerbation, and had more air trapping on computed tomographic imaging than white individuals.

The authors reported that individual-level SES contributed up to 35% of the racial disparities seen, with the largest explanatory effect for 6-minute-walking distance (6MWD) and quality of life (St. George’s Respiratory Questionnaire). When considering neighborhood SES, associations between race and outcomes were generally attenuated, and neighborhood SES explained more of the variance compared with individual SES alone for 6MWD and rate of hospitalization. In the models including both individual and neighborhood SES, the associations between race and dyspnea, quality of life, and 6MWD were no longer statistically significant. Overall, combined individual and neighborhood SES accounted for up to 69% of the race outcome association with COPD health-related outcomes, with individual-level and neighborhood-level SES explaining 12–35% and 26–54% of the racial disparities in respiratory outcomes, respectively. Additional neighborhood factors were considered in sensitivity analyses, including urban/rural status and region. The influence of SES on healthcare coverage was also briefly discussed.

The relationship between race and individual and neighborhood SES with respect to COPD outcomes is complex. Although there have been some studies investigating racial

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