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On a New Approach to Assess Bronchodilator Responsiveness

To the Editor:

The American Thoracic Society (ATS) and European Respiratory Society (ERS) joint guidelines for spirometry define a "positive" bronchodilator (BD) response (BDR) as a 0.2 L *and* a 12% increase in either forced expiratory volume in 1 second (FEV_1) or in forced vital capacity (FVC) (1). This categorization does not always have clinical significance or therapeutic implications and often fails to separate asthma from chronic obstructive pulmonary disease (COPD). Furthermore, those with reduced lung function may fail the $\Delta \geq 0.2$ L criterion, whereas those with larger volumes at baseline may fail the 12% rule (2–4). The percentage change after BD administration is a continuous variable, and one threshold does not optimally differentiate responders from nonresponders (5–7). Recently, Hansen and colleagues (8) recommended a nonbinary BDR classification based *only on* FEV_1, using absolute *or* percentage changes from baseline. The authors differentiated between negative, minimal, mild, moderate, and marked responses by using the following thresholds: ≤ 0 L/$\leq 0\%$, ≤ 0.09 L/$\leq 9\%$, ≤ 0.16 L/$\leq 16\%$, ≤ 0.26 L/$\leq 26\%$, and >0.26 L/$>26\%$, respectively (Figure 1A). The study correlated BDR categories with respiratory exacerbations, radiological airway measurements, dyspnea, exercise performance, and quality of life scores (8). The article, however, does not make clear the partition method used. If the absolute and percentage change criteria are to be met simultaneously (logical operator "*and*"), many tests remain uncharacterized, falling into discordant brackets. If the correct operator is "*or*," the article does not specify which classification schema was used for discordant categories. For example, if a test shows mild BDR because $\Delta FEV_1 \in (0.09–0.16$ L) and moderate responsiveness because percentage change in $FEV_1 \in (16–26\%)$, then how does one classify it (Figure 1)? One option is to consider the lowest impairment (Figure 1B, "up-sweep"), when the actual formula starts categorizing from the lowest severity category. For example, the formula classifies a change of 8% in FEV_1 as minimal BDR and would not reconsider the higher degree of impairment (e.g., of 0.15 L as mild BDR) while moving up to the next stratum. Another option is grading the severity by the highest impairment (Figure 1C, "down-sweep") (i.e., formula starts categorizing BDR from the highest degree of impairment). For example, a change >0.26 L categorizes a test as marked BDR and does not consider a lower impairment (e.g., a 15% increase) later on while moving down the categories, as the patient has already been labeled.

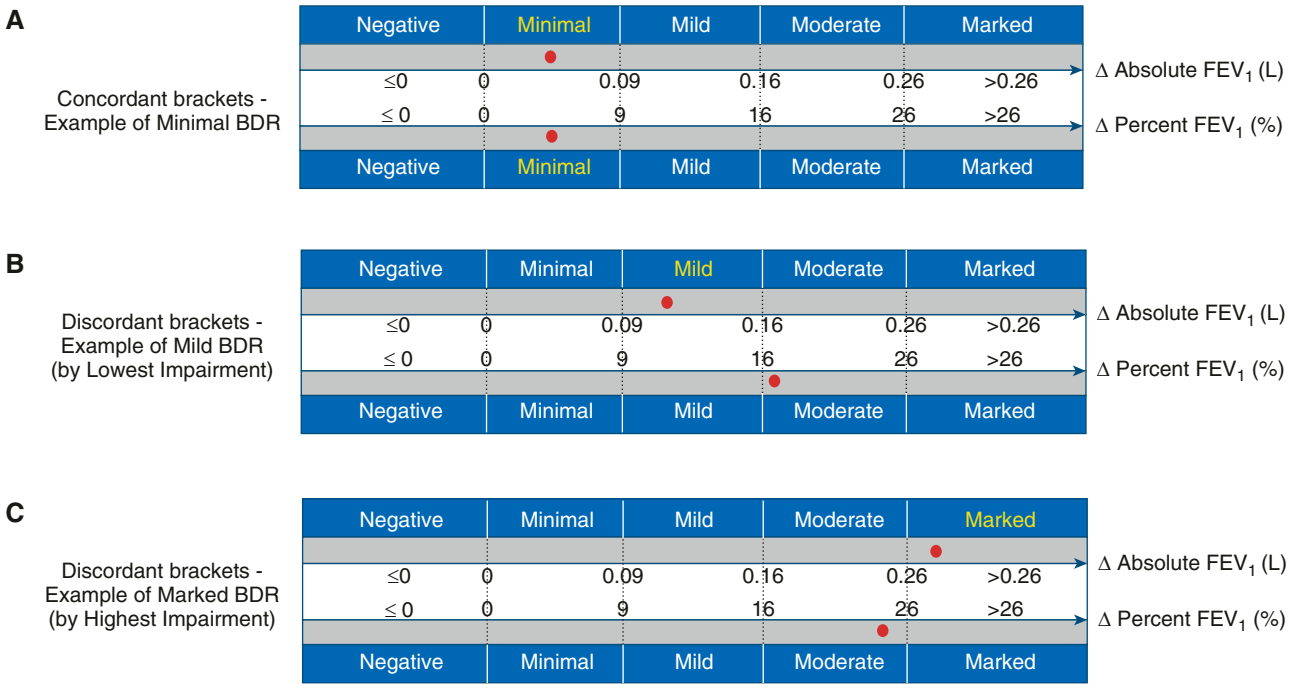

Figure 1. New bronchodilator response (BDR) categories. (*A*) Concordant brackets. In one example, red circles identify minimal BDR per Δ forced expiratory volume in 1 second (FEV_1) between 0 L and 0.09 L and per Δ percentage change in FEV_1 (from baseline) between 0% and 9%. (*B*) Discordant brackets adjudicated by the lowest impairment. The example shows mild BDR per ΔFEV_1 between 0.09 L and 0.16 L ("up-sweep"). (*C*) Discordant brackets adjudicated by the highest impairment. The example shows marked BDR, as ΔFEV_1 is above 0.26 L ("down-sweep"). Red dots are examples of values in the specific intervals/categories shown.

We perform here several analyses on a large battery of tests with the intent to clarify the optimal BDR characterization equation (8).

Methods

Pre- and post-BD spirometry was performed at two institutions (Cleveland Clinic [$n = 20{,}687$ between 1993 and 2004] and Atlanta Veteran Affairs Healthcare System [$n = 4{,}330$ between 2009 and 2015]) following ATS/ERS standards (9–11) after 360 mcg of inhaled albuterol administration and using a Jaeger MasterLab system. Administration of β-adrenergic BD in the form of short-acting (albuterol) and long-acting (salmeterol and formoterol) agents was discouraged within 6 and 24 hours, respectively; for antimuscarinic agents, short-acting (ipratropium) and long-acting (tiotropium) agents were recommended to be held before the test for a minimum of 8 and 24 hours, respectively. No patients were on ultra–long-acting β-adrenergic (e.g., indacaterol, olodaterol, and vilanterol) or antimuscarinic agents (e.g., glycopyrrolate, umeclidinium, and aclidinium) in the older Cleveland cohort; for the very few subjects who were on ultra–long-acting BD in the Atlanta laboratory (a more recent cohort with a standard formulary), they were recommended to stop them at least 36 hours in advance. Global Lung Initiative normal reference values were used (12). Analyses and graphs were performed in JMP Pro15 (SAS Institute). The study received local institutional research approvals.

Results

The study analyzed 25,017 consecutive acceptable spirometry tests that included pre- and post-BD measurements. Median (interquartile range) age was 62 (52–70) years; 35% were women, 79% were white, and 20% were Black. Approximately 24% of the tests met the ATS/ERS "positive" BDR criteria (Figure 2A). By ΔFEV_1 or $\Delta FVC \geq 0.2$ L, BDR was present in 19% and 31%, respectively. By percentage change in FEV_1 or percentage change in FVC ⩾12%, standard "positive" BDR was present in 25% and 18%, respectively.

A "negative" BDR ($\Delta FEV_1 \leq 0$ and $\%FEV_1 \leq 0\%$) was present in 7,272 (29%) tests. By ΔFEV_1 (L) as sole criterion, 27%, 18%, 14%, and 12% tests showed minimal, mild, moderate, and marked BDR, respectively. By percentage change in FEV_1 as sole criterion, 36%, 18%, 11%, and 5% had minimal, mild, moderate, and marked BDR, respectively. A conservative ΔFEV_1 (L) *and* percentage change FEV_1–based definition led to 24%, 6%, 4%, and 4% minimal, mild, moderate, and marked BDR, respectively. However, 8,556 (34%) tests remained uncharacterized, falling into discordant intervals (Figure 2B).

Using the lowest impairment schema (Figure 2C), 40%, 18%, 9%, and 4% show minimal, mild, moderate, and marked BDR, respectively. Alternatively, a classification based on highest impairment leads to 24%, 18%, 16%, and 13% minimal, mild, moderate, and marked BDR, respectively (Figure 2D). Figures 3A and 3B show mosaic plots of BDR categories by lowest versus highest impairment. Expectedly, all classifications remain identical in the "negative" category, and marked BDR by lowest impairment is also 100% concordant. Similarly, BDR classification by highest impairment has 100% concordance for minimal BDR. For the other categories, the degree of discordance remains significant, as the ultimate diagnosis is very method dependent.

Discussion

Clarification on the stratification schema proposed by Hansen and colleagues is necessary, as BDR categories were not explicitly

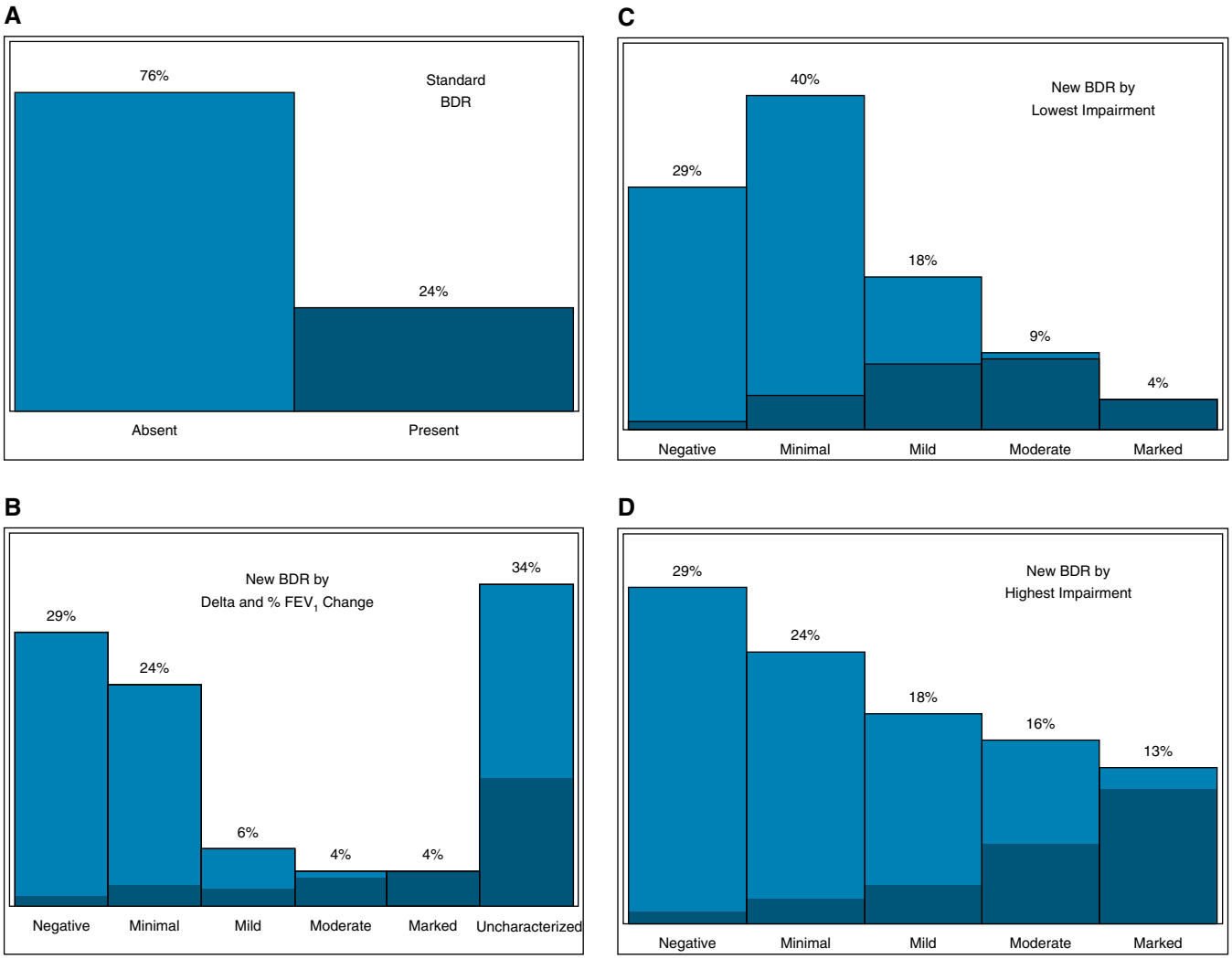

Figure 2. Histograms showing bronchodilator response (BDR) categories by various criteria. (*A*) Standard BDR, with "positive" category highlighted (dark blue portions or columns in all panels). (*B*) Conservative BDR categories by Δ forced expiratory volume in 1 second (FEV_1) (L) *and* Δ percentage change in FEV_1 (from baseline), which leaves approximately one-third of tests uncharacterized. (*C*) New BDR categories using the prespecified thresholds for either ΔFEV_1 (L) *or* Δ percentage change in FEV_1 (from baseline) and adjudication by the lowest impairment in the discordant brackets. (*D*) New BDR categories using the prespecified thresholds for either ΔFEV_1 (L) *or* Δ percentage change in FEV_1 (from baseline) and adjudication by the highest impairment in the discordant brackets.

characterized in the original article (8). In their investigation on a subgroup of COPDGene (13), authors found negative, minimal, mild, moderate, and marked BDR in ∼21%, 28%, 20%, 18%, and 13% of tests, respectively (8). This BDR distribution most closely resembles our BDR classification based on highest impairment (Figure 2D), with 29%, 24%, 18%, 16%, and 13% of tests in the same categories. As the categorization by lowest impairment leads to little moderate or marked BDR (9% and 4%, respectively; hence, unlikely to be useful), we conclude that criteria used were based on the largest functional derangements.

Interpreting BDR has been a matter of significant debate for decades (14–17). Baseline FEV_1 of individuals tested for BDR varies widely (3), and overcoming healthy population-based confidence intervals (18) for volumes and percentage changes may be too restrictive. It has been previously asserted that a 6–7% change in FEV_1 represents a meaningful threshold, corresponding with a mean ΔFEV_1 of 0.09–0.10 L (3) (i.e., close to the minimal clinically important difference) (19). Analyzing BDR on 313 tests, Hansen and colleagues (4) found that >70% failed ATS/ERS FEV_1 criteria, whereas ∼40% of failures showed $\Delta FEV_1 \geq 0.1$ L (∼6% improvement). Of those with pre-BD FEV_1 <1 L, >50% had $\Delta FEV_1 \geq 0.1$ L (∼6% increase), whereas only 11.4% were "positive" by ATS/ERS criteria (3).

In summary, a "down-sweep" approach in defining BDR based on the *highest* functional impairment in either Δ *or* percentage change FEV_1 is likely the best classification to use under the new framework. The categorization (4) requires further validation in other populations, especially in its ability to stratify daily symptomatic burden, functional impairment, and long-term outcomes. In the future, it is conceivable that some of these novel BDR categories may end up being relumped or further split into new groups that have relevance for patient quality of life, subjective

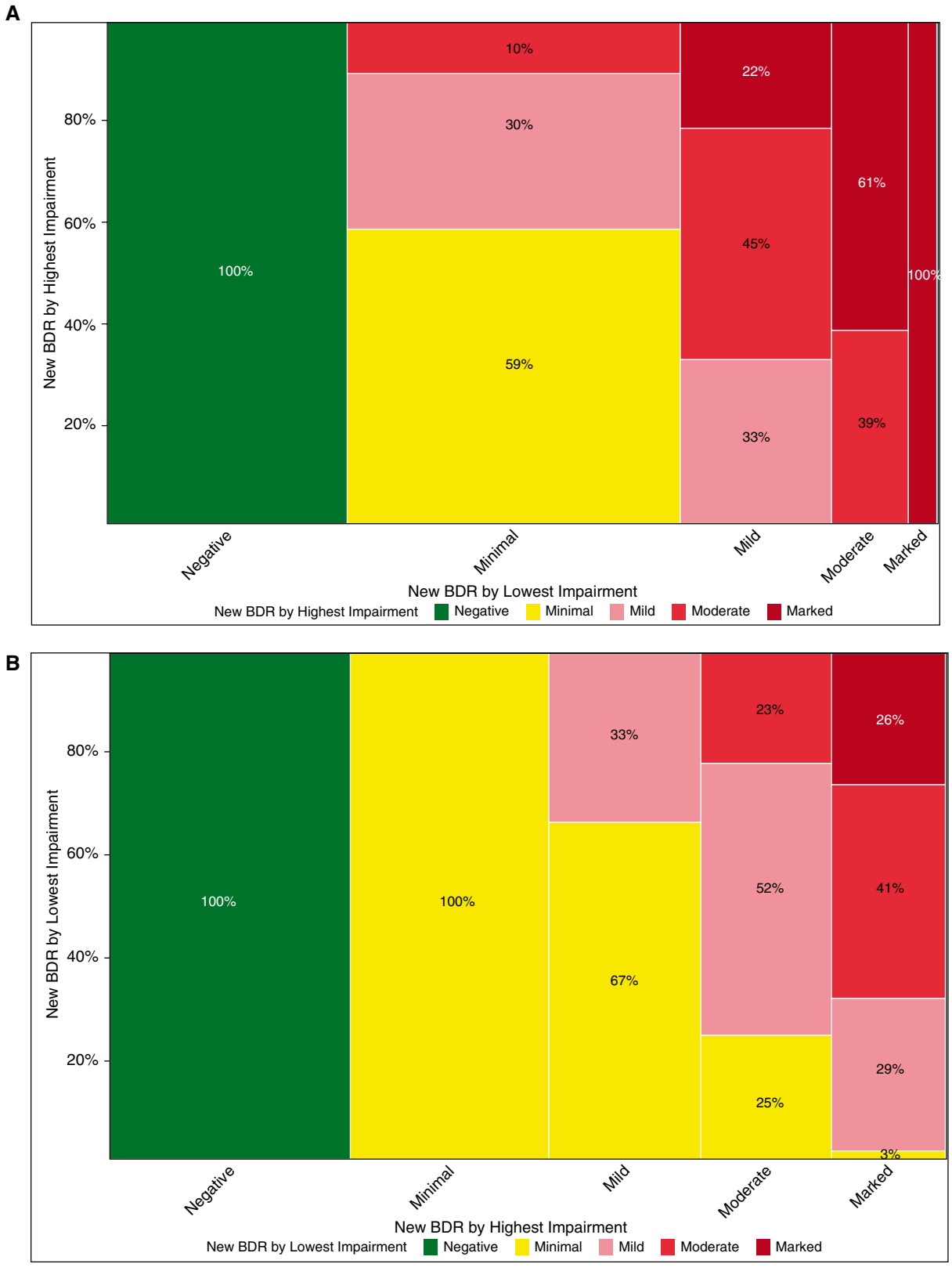

Figure 3. Mosaic plots showing contingency analyses for the nominal categories of negative, minimal, mild, moderate, and marked bronchodilator response (BDR). (*A*) New BDR by lowest impairment (*x*-axis) versus highest impairment (*y*-axis). (*B*) New BDR by highest impairment (on *x*-axis) versus lowest impairment (*y*-axis).

improvement, and other objective outcomes or for further endophenotypic stratifications of for personalized therapeutics. For example, the new BDR framework may prove to be a useful tool in defining asthma–COPD overlap and for other "fuzzy" phenotypes of obstructive lung disease and, possibly, to better define disease subgroups that would benefit more from specific BD agents.

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Vitamin D Deficiency Is Associated with Increased Nontuberculous Mycobacteria Risk in Cystic Fibrosis

To the Editor:

Individuals with cystic fibrosis (CF) are at markedly increased risk of pulmonary nontuberculous mycobacteria (NTM) infection (1–3), which is associated with accelerated lung function decline. Although structural lung disease likely contributes to elevated NTM risk in this population, identification of modifiable risk factors may help to reduce these morbid infections in CF. Vitamin D is important for host control of *Mycobacterium tuberculosis* (4, 5), but to date, few studies have explored the relationship between vitamin D deficiency (VDD) and NTM infection (6). Because of pancreatic exocrine insufficiency, individuals with CF are at high risk for VDD (7). In this analysis, we investigate our hypothesis that VDD is a risk factor for incident NTM respiratory isolation in CF.

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Author Contributions: Study conception and initial design: M.T.J. and K.A.C. Methodological input: K.J.P. and N.L. Data acquisition: W.J.R., Y.S., M.N.S., and J.A.N. Data analysis: Y.S. and K.J.P. First draft of the manuscript: W.J.R., Y.S., and K.J.P. Critical revision of the manuscript: A.S., N.L., M.T.J., and K.A.C. Approval of the final version of the manuscript: all authors.

Methods

We conducted a retrospective cohort study of adults (≥18 yr old) with CF cared for at the Johns Hopkins CF Center between January 1, 2007, and December 31, 2018 (institutional review board approval #IRB00153445). Clinical and demographic data were extracted from the CF Foundation Patient Registry (8) and chart review. Individuals with at least one serum 25-OH vitamin D value