On the Power and Risks of the Percent of Predicted

Because proper interpretation of pulmonary function tests (PFTs) depends critically on the predicted normal values, the availability of new reference values, such as those from the National Health and Nutrition Examination Survey (NHANES)[1] or the Health Survey for England,[2] poses important challenges and evaluative opportunities for investigators/authors, respiratory care clinicians, and pulmonary-function laboratory directors. Specifically, in an era in which large population-based assessments provide new reference values that may differ from pre-existing values,[1,2] adoption of new reference values may confound longitudinal interpretation of PFTs, especially if the observer pays undue attention to the percent-of-predicted value to the exclusion of considering the actual value or the normal predicted value to which the observed value is being compared. This issue has special timeliness, because the American Thoracic Society recently endorsed use of the NHANES reference values for spirometry,[3] prompting all laboratories that comply with this recommendation to switch to the new NHANES reference values.

Consider the recent example of a situation from our practice, which emphasizes the potential pitfalls of inattention to changes in the reference value used and of overreliance on the percent-of-predicted value. Mr X, a patient with known alpha-1 antitrypsin deficiency,[4] was referred to us from a center in Chicago for consideration of specific therapy with pooled-human-plasma alpha-1 antitrypsin, which is an effective (albeit expensive) treatment.[5] Available records from the referring physician included a printout of the most recent PFT results (with spirometry, volumes, and diffusing capacity of the lung for carbon monoxide [D_{LCO}]) and handwritten notes from prior PFT sessions. There appeared to be a dramatic drop in his D_{LCO} from normal (2 years ago) to 68% of predicted currently. This perceived change prompted concern about progressive loss of alveolar/capillary units, consistent with emphysema, and a recommendation to initiate alpha-1 antitrypsin augmentation therapy and to seek a second opinion at The Cleveland Clinic. Later retrieval and review of the actual printouts from the patient's earlier PFT sessions showed that the previously used D_{LCO} standards were based on those of Burrows et al[6] (in which the predicted D_{LCO} is 28 mL/min/mm Hg for this patient), but that the predicted values had more recently been changed to those of Crapo et al[7] (in which this patient's predicted D_{LCO} is 42 mL/min/mm Hg). Importantly, the change in the standard val-

ues used was unannounced on the PFT report printout and escaped the referring clinician's attention, which prompted concern about the falling D_{LCO} and the out-of-city referral. In fact, testing in our laboratory indicated that the patient's D_{LCO} had not changed over several years; rather, the impression of a dramatic drop in D_{LCO} was based on undue attention to the percent-of-predicted D_{LCO} value, which had, in fact, only appeared to decrease because they had switched to a higher reference value (ie, from the reference equations of Burrows et al[6] to those of Crapo et al[7]).

As another example of the power and risks of the percent of predicted and the potential pitfalls of switching reference equations, percent-of-predicted values are often criteria for consideration for clinical procedures and inclusion or exclusion from clinical trials. As an example, in the recent National Emphysema Treatment Trial (NETT) of lung-volume-reduction surgery (LVRS) for severe emphysema,[8–10] the high-risk group (for which LVRS is now deemed contraindicated) was defined as individuals whose forced expiratory volume in the first second (FEV_1) was $\leq 20\%$ of predicted and who had a homogeneous pattern of emphysema on chest computed tomography and/or a D_{LCO} of $\leq 20\%$ of predicted.[10] Furthermore, eligibility for inclusion in the NETT was also based on percent-of-predicted lung function, including an FEV_1 $\leq 45\%$ of predicted (and $\geq 15\%$ of predicted in those ≥ 70 years old), total lung capacity $\geq 100\%$ of predicted, and residual volume $\geq 150\%$ of predicted.[8] Imagine the difficulties that might be posed in generalizing the results of the NETT if different lung-function reference values were used. For example, in the worst hypothetical case, patients who would be ineligible because they are in the high-risk NETT group according to the reference values used in the NETT[11] could be eligible for LVRS if other reference values were used, and they therefore might be placed at risk for adverse outcomes.

To underscore the impact and risks of using different reference equations on the interpretation of an individual patient's pulmonary function, classification of lung-disease severity, and eligibility for clinical trials, Tables 1 and 2 present percent-of-predicted values for 2 "standard" patients (66-year-old white men, 173 cm tall, weight 70 kg), based on several different reference equations.[6,7,11–17] As shown in Table 1, use of 5 different reference values for FEV_1 and D_{LCO} produces discordant conclusions regarding the patient's candidacy for LVRS based on whether

Table 1. Impact of Predicted Value on Determining Risk With Lung-Volume-Reduction Surgery in a Standard Patient*

Measure	Actual Value	Percent-of-Predicted Value Based on Reference Equation of:				
		Crapo et al[7]	ECSC[12]	Miller et al[13]	Cotes[14]	Burrows et al[6]
D_{LCO} (mL/min/mm Hg)	5.8	18.6	21.9	22.1	22.8	29.7
High-Risk for LVRS?	NA	Yes†	No†	No†	No†	No†
Spirometry	Actual Value	Crapo et al[11]	Knudson et al[15]	Glindmeyer et al[16]	NHANES[1]	Morris et al[17]
FEV_1 (L)	0.65	19.3	20.4	22.4	20.5	22.5
FVC (L)	2.56	59.3	70.9	70.9	62.2	60.9
FEV_1/FVC (%)	25.4	NA	NA	NA	NA	NA
High-Risk for LVRS?	NA	Yes†	Yes†	No†	No†	No†

*"Standard patient" means a 66-year-old white man, height 173 cm, weight 70 kg.
†As discussed in the text, assessment of a patient's risk with LVRS is based on several criteria. High-risk patients are defined as those whose FEV_1 is ≤ 20% of predicted and who have either homogenous emphysema on computed tomography or D_{LCO} ≤ 20% of predicted. The predicted values from Crapo et al were used for spirometry[11] and diffusing capacity[7] by the NETT group in their designation of high-risk candidates for LVRS.[9]
ECSC = European Coal and Steel Community
D_{LCO} = diffusing capacity of the lung for carbon monoxide
LVRS = lung-volume-reduction surgery
NA = not applicable
FEV_1 = forced expiratory volume in the first second
NHANES = National Health and Nutrition Examination Survey III
FVC = forced vital capacity
NETT = National Emphysema Treatment Trial

Table 2. Impact of Predicted Value on the Spirometric Assessment of Obstruction* in a Standard Patient

	Actual Value	Percent-of-Predicted Based on Reference Equation of:				
		Crapo et al[11]	Knudson et al[15]	Glindmeyer et al[16]	NHANES[1]	Morris et al[17]
FEV_1 (L)	2.18	65	68	77	69	75
FVC (L)	3.20	74	89	89	75	76
Measured FEV_1/FVC (%)	68.1	68.1	68.1	68.1	68.1	68.1
Percent-of-Predicted FEV_1/FVC (% and LLN)	NA	78.0 (69.7)	79.7 (69.0)	78.6 (69.3)	74.4 (64.4)	69.9 (57.1)
Obstruction Present	NA	Yes, moderate	Yes, moderate	Yes, moderate	No	No

*"Spirometric assessment of obstruction" means that the measured FEV_1/FVC is less than the predicted lower limit of normal in a "standard patient" (a 66-year-old white man, height 173 cm, weight 70 kg).
NHANES = National Health and Nutrition Examination Survey III
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
NA = not applicable
LLN = lower limit of normal

the FEV_1 and D_{LCO} values exceed 20% of predicted. For four of the reference equations,[6,12–14] the percent-of-predicted D_{LCO} values exceed the 20% high-risk criterion (ie, from 21.9% to 29.7% of predicted), but not for the reference equation from Crapo et al[7]), with which the D_{LCO} is 18.6% of predicted. For the FEV_1, two of the reference equations show values below 20% of predicted,[11,15] and three show values above 20% of predicted.[1,16,17]

In Table 2, a second "standard" patient's classification regarding the presence of airflow obstruction (ie, whether the FEV_1/FVC ratio falls below the lower limit of the predicted normal) is compared using 5 different reference equations.[1,11,15–17] Conclusions regarding the presence of airflow obstruction are discordant; three of the reference

equations[11,15,16] support the presence of below-normal FEV_1/FVC, whereas the other two equations[1,17] do not.

Overall, this discussion and the analyses in Tables 1 and 2 highlight the challenges posed by changing reference values and serve as important reminders to users and to proponents of new reference values about needed evaluations and actions when new PFT reference values are adopted. Indeed, relatively little attention has been given to assessing the interpretive impact of changing reference values, both cross-sectionally and longitudinally.[18–21]

As further evidence of the lack of attention to reference equations, Ghio et al reported that 2.2% of responding directors of pulmonary training programs stated that they were unaware of which reference equation was used in

their pulmonary-function laboratory.[21] In our view, adopting new reference values (such as the new NHANES values,[1] by laboratories that comply with the American Thoracic Society recommendations[3]) creates responsibilities for all stakeholders: the investigators/authors of studies that propose new reference values, the directors of pulmonary-function laboratories, and respiratory-care clinicians who use PFT results in managing patients. For the investigators/authors and laboratory directors, we suggest the following responsibilities:

1. The laboratory and/or authors of new reference values must carefully assess the impact of adopting the new values on the interpretation of PFT results, both cross-sectionally and longitudinally. Specifically, rather than only assessing how the switch might affect the percent-of-predicted values at a single point in time, the laboratory and/or authors should assess how the percent-of-predicted values would change the longitudinal interpretation of PFTs and whether changes in the percent-of-predicted values could cause misinterpretation of test results by creating a misimpression of a new decline or improvement in pulmonary function. One approach would be to offer percent-of-predicted values for the PFTs using 2 clearly labeled and differentiated values: the old reference value and the newly adopted reference value, at least for the short-term, after implementing the new reference values. This would alert clinicians to the use of a new standard and prompt them to consider and evaluate the impact of the new predicted value on their patient's results. Surely, had this been done in the case of Mr X above, we daresay the patient's anxiety about having developed emphysema, possibly needing expensive therapy, and the expense of traveling to another city for consultation might have been averted. Having proposed this step, we are aware that, currently, technical limitations of most PFT equipment systems preclude such dual reporting. That said, we believe that the importance of taking this step leads us to encourage manufacturers to implement this change.

2. As another precaution, the laboratory should clearly indicate on the PFT report that a new reference value is being used and that the interpretation of the test results must be made in the context of this new standard. In this era of electronic communication of PFT results, providing such a notice is easy and should also be done. For the respiratory clinician who uses and depends on the PFT results in managing patients, the possibility that reference values can change must prompt close attention to the predicted values and avoidance of sole dependence on the percent-of-predicted values in reports. Also, respiratory clinicians must be aware of the introduction and adoption of new standards, such as those of NHANES[1] or the Health Survey of England,[2] and of current recommendations regarding their use.[3]

Overall, the power and risks of the percent of predicted rest upon the reliability of the reference values for the individual being tested, on the clinician's intelligent interpretation of the results, and on the laboratory's and investigator's attention to interpretive pitfalls as new reference values are adopted. The power of the percent of predicted will be preserved and the risks will be minimized to the extent that new reference values can be implemented with care by those promoting and using them.

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Chest physician Richard V Ebert
with patient performing a spirogram
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