# Lung function: what constitutes (ab) normality?

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## BACKGROUND

Defining whether pulmonary function test (PFT) results are outside the expected range has obvious diagnostic implications. Many physicians assume that any value outside ± 20% of the predicted value or $FEV_1/FVC$ < 0.7 indicates abnormality. Current guidelines strongly support the statistical "limits of normal" to classify test results as low—less than the lower limit of normal (LLN)—or high—greater than the upper limit of normal (ULN).[1] Does it really matter? If so, can we safely use across-the-board LLN/ULN criteria in clinical populations?

## OVERVIEW

Table 1A shows that the fifth percentile for $FEV_1$ and FVC are systematically higher than 80% of the predicted value in younger men and women (LLN > 0.7 for $FEV_1/FVC$), and the opposite is seen in the elderly. In contrast, the LLN for "static" lung volumes and $DL_{CO}$ are typically lower than 80%, regardless of age and sex. Table 1B shows spirometric results of a young non-smoking overweight woman who had reported recurrent episodes of dyspnea: 0.7 < $FEV_1/FVC$ < LLN suggested an obstructive ventilatory defect. Table 1C shows spirometric results of an elderly former smoker woman reporting chronic dyspnea and productive cough. Her symptoms, her chest CT scans showing emphysema and bronchial wall thickening, and an $FEV_1/FVC$ ratio < 0.7, despite the latter being above the LLN, were deemed consistent with obstruction. Both patients reported marked improvement with the use of inhaled formoterol/budesonide.

Our uncertainty on what constitutes normal $FEV_1$, FVC, and $FEV_1/FVC$ increases with aging, that is, the LLN is far from the predicted values in the elderly (Table 1A). Thus, values < 80% of predicted might be well within the expected range in the elderly yet abnormal in the young. Sticking rigidly to the 80% or 120% threshold is even more problematic for lung volumes, markedly increasing the rate of false positives (Table 1A). This does not imply that the statistical limits of normal are immune to errors. The best example is the LLN threshold for $FEV_1/FVC$: up to a third of elderly subjects at risk for COPD with LLN < $FEV_1/FVC$ < 0.7 showed a range of resting and exercise abnormalities consistent with COPD.[2] In fact, minimal variations in the cutoff value to define the threshold of normality for $FEV_1/FVC$ have

**Table 1.** Panel 1A shows a comparison of the fifth percentile (5th p) of the lower limit of normal (LLN), expressed as absolute and percent of predicted (pred) values for several lung function parameters in four White subjects with different sexes and ages. Observe the potential bias (red columns) introduced if a fixed percent of pred threshold (e.g., 80% of pred) is used. Notwithstanding, while the 5th-p criterion can appropriately identify the state of disease in a young woman despite an $FEV_1/FVC$ > 0.7 (Panel 1B), it failed to diagnose obstruction in a symptomatic elderly woman presenting with a value lower than the fixed threshold of 0.7 (Panel 1C). See the text for further elaboration. yo: years old; and FRC: functional residual capacity.

| A | Young Male 20 yo/175 cm | | | Young Female 20 yo/165 cm | | | Elderly Male 70 yo/175 cm | | | Elderly Female 70 yo/165 cm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5th p | Pred | % Pred | 5th p | Pred | % Pred | 5th p | Pred | % Pred | 5th p | Pred | % Pred |
| FVC | 4.27 | 5.27 | 81.0 | 3.14 | 3.92 | 80.1 | 3.03 | 4.09 | 74.0 | 2.15 | 2.54 | 73.1 |
| $FEV_1$ | 3.64 | 4.49 | 81.0 | 2.76 | 3.44 | 80.2 | 2.24 | 3.10 | 72.2 | 1.66 | 2.28 | 72.8 |
| $FEV_1/FVC$ | 0.74 | 0.85 | 87.0 | 0.76 | 0.88 | 86.3 | 0.62 | 0.76 | 81.2 | 0.64 | 0.78 | 82.0 |
| TLC | 5.13 | 6.47 | 79.3 | 4.05 | 5.03 | 80.5 | 5.45 | 6.89 | 79.1 | 4.08 | 5.15 | 79.2 |
| FRC | 2.14 | 3.12 | 68.6 | 1.79 | 2.54 | 70.4 | 2.56 | 3.68 | 69.6 | 2.05 | 2.89 | 70.9 |
| RV | 0.57 | 1.37 | 41.6 | 0.48 | 1.09 | 44.0 | 1.45 | 2.43 | 59.6 | 1.21 | 2.01 | 60.2 |
| $DL_{CO}$ | 25.1 | 31.7 | 79.1 | 17.7 | 22.4 | 79.0 | 18.4 | 25.1 | 73.3 | 14.6 | 19.4 | 75.2 |

| B ♀, 17 yo 149 cm | Measured | % Pred | LLN | Z-Score |
|---|---|---|---|---|
| FVC, L | 2.13 | 69.8 | 2.45 | -2.545 |
| $FEV_1$, L | 1.63 | 59.4 | 2.21 | -3.364 |
| $FEV_1//FVC$ | 0.76 | 84.7 | 0.79 | -1.916 |

| C ♀, 85 yo 167 cm | Measured | % Pred | LLN | Z-Score |
|---|---|---|---|---|
| FVC, L | 1.66 | 64.8 | 1.76 | -1.849 |
| $FEV_1$, L | 1.11 | 57.8 | 1.31 | -2.184 |
| $FEV_1//FVC$ | 0.67 | 87.6 | 0.61 | -1.046 |

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a marked impact on the proportion of all cases in the entire population that can be attributed to the exposure (smoking). This is particularly true in the elderly since, as mentioned, variability is larger; thus, a sizeable fraction of patients with COPD will show "preserved" $FEV_1/FVC$, that is, greater than the fifth percentile (Table 1C).[3] In many circumstances, values within the "grey zone" (e.g., between 80% of predicted and LLN; 120% of predicted and ULN; or LLN < $FEV_1/FVC$ < 0.7) should be individually interpreted in the light of the pre-test likelihood of abnormality.[4]

## CLINICAL MESSAGE

Using fixed thresholds (such as 80% or 120% of the predicted value) to classify PFT results as abnormal can lead to substantial mistakes, usually resulting in "under-calling" of disease in the young and "over-calling" of disease in the elderly. The statistical LLN, however, is far from being a panacea: interpretation of PFTs will always be an N = 1 study, requiring careful clinical correlation to judge the normalcy of values close to the proposed threshold.[5]

## REFERENCES


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