ERS/ATS Technical Standard on Interpretive Strategies for Routine Lung Function Tests

Executive Summary

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Keywords; pulmonary function; interpretation; spirometry; reference equations

Word count: 3335

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Introduction

Pulmonary function tests (PFTs) / Respiratory function tests reflect the physiological properties of the lungs (e.g., airflow mechanics, volumes, gas transfer). These tests have been used for decades to help diagnose lung disease, explain dyspnea, and monitor disease progression and treatment response. In addition, PFTs haven been employed in population studies of the association between exposures and lung health. In 2005 the ATS/ERS Task Force on the Standardization of PFTs published a series of technical documents (1-4) and those for spirometry (5) and diffusing capacity (T_LCO or D_LCO) (6) have recently been updated, and an update on lung volumes is forthcoming. This document is an update for the interpretation strategies of routine PFTs (3).

Appropriate interpretation of PFTs requires measurements that meet technical specification for test performance and quality (4-6). Lower quality tests must be interpreted with greater uncertainty as they may not reflect functional abnormalities. PFT interpretation also relies on clear reporting of results and the ATS standards for reporting PFTs are recommended (7).

Interpreting technically acceptable PFT results has three aspects:

> 1) Classification of observed values as within/outside the normal range with respect to a population of healthy individuals. This involves consideration of the measurement error of the test, the inherent biological variability of measurements between individuals, and between repeated measurements in the same individual;
>
> 2) Integrating knowledge of the physiologic determinants of test results into a functional classification of the identified impairments (e.g., obstructive, restrictive);
>
> 3) Integrating any identified patterns with other clinical data to describe a differential diagnosis that can guide therapy and estimate prognosis for an individual.

These are three distinct and complementary aspects of interpretation. This document addresses only the first two aspects. The final integration of pulmonary function results into a diagnosis or management plan is beyond the scope of this technical standard on physiological interpretation.

In this executive summary we highlight the key recommendations and supporting evidence from the Technical Standard document for PFT interpretation. A full exposition of these recommendations, rationale, and future work is presented in the complete statement.

Methods

Task force members were selected by the ATS Proficiency Standards for Pulmonary Function Laboratories Committee, as well as ERS leadership. Conflicts of interest, including academic conflicts, were declared and vetted throughout the duration of the Task Force. Six of the 16 Task Force members are current or past members of the GLI Network Executive. A comprehensive literature search was conducted and available literature was used to inform the committee's discussions and recommendations. The reported standards were reached by consensus amongst the expert committee and apply to all settings globally (clinical interpretation, research studies,

tertiary, community and primary care). Consensus was reached after all Task Force members agreed on the final version.

Comparison of Measured Values to a Healthy Population

Global Lung Function Initiative (GLI) reference equations for spirometry (8), diffusing capacity (9) and lung volumes (10) should be used to define the expected range of values in healthy individuals.

The range of values expected in a healthy population is expressed using reference equations derived from data collected from healthy individuals. Typically, height, age and sex are used to estimate expected lung function in health and account for the wide biological variability observed within and between populations. Differences in height and body proportions between populations (e.g. leg length versus trunk length) have been observed (11) and may account for some of the observed differences in lung function between populations. The reasons for observed differences in lung function between people around the world are multifactorial and not fully understood. The narrow definition of health may contribute to the observed differences, as 'healthy' individuals may include people exposed to risk factors for poor lung health during their lifetime. There are ongoing efforts to better understand the geographical, environmental, genetic and social determinants of health that play a role in explaining these observed differences. It is important that individuals have their lung function assessed against the appropriate reference population for that individual. The historical approach of fixed adjustment factors for race is not appropriate, introduces inaccuracies and is unequivocally discouraged. An individual's medical history, symptoms, and social circumstances must be considered when applying PFT results to inform clinical decision making.

Global Lung Function Initiative Equations

The Global Lung Function Initiative (GLI) reference equations are available for spirometry (8), D_LCO (9) and lung volumes (10), and facilitate standardized reporting and interpretation of pulmonary function measurements. These three GLI equations are internally consistent, providing a single suite of PFT equations. GLI D_LCO equations and GLI static lung volumes are currently based on measurements predominantly from individuals of European ancestry due to insufficient data from other populations.

Guidelines regarding the use of reference equations relating specific population groupings are currently under development, so these recommendations are based on the current evidence designed to increase the precision of determining whether the results are outside of the expected range for an individual. There is no single reference equation equally applicable to all populations. There is a trade-off between applying references equations that are specific to population groupings versus a single standard for all. Different approaches may be warranted in different contexts. Therefore, at this time we recommend employing the appropriate GLI spirometry equations based on self-reported ancestral origins if known, should be used as a way to standardize lung function measurements for sex, age and height. If ancestral origins are unknown or uncertain, the GLI "other" equations which represent "a muti-ethnic population"

should be used. PFT reports and research publications must include the specific reference equation that is used.

Limits of Normal

The 5th and 95th percentile limits (-1.645 and +1.645 z-scores) of the healthy population can be used to identify individuals with unusually low or high results, respectively.

A reference range represents the distribution of values that are expected in a healthy population and the lower limit of normal (LLN) represents a cut-off to define results that are outside the range of values typically observed in health. This approach is used for many clinical outcomes in medicine(12-14). The 5th percentile represents a trade-off between incorrectly classifying a low value in a healthy individual and missing a clinically significant reduction in lung function (i.e., increased sensitivity for less specificity). For tests that may be outside the normal range in either direction (e.g., lung volumes or D_LCO), the potential for false positives increases to 10% but the probability in a given individual for which these tests are requested based on concerns for lung disease is lower because there is a higher likelihood (pretest probability) that lung function will be outside the normal range (15). The LLN does not necessarily indicate a pathophysiological abnormality, nor is it a clinically meaningful threshold to diagnose disease. It provides an indication of whether the observed result can be expected in otherwise healthy individuals of similar age, sex and height. A result within the expected range for a subject does not exclude the presence of a disease process impairing function. For example, a drop from the 95th percentile to the 10th percentile is a very significant change but still leaves lung function within normal limits.

The widely used cut-offs of 80% predicted for FEV_1 (% predicted = Observed*100/Predicted) and the 0.70 cut-off for FEV_1/FVC are not recommended. Percent of predicted does not take into account the observed age-related changes in measurement variability (Summary Figure 1). These 'rules of thumb' only approximate the LLN in the mid-range of age, where screening or case-finding for obstructive disease is most likely to be conducted. The simplicity of these cut-offs has resulted in their use across the age spectrum leading to systematic misinterpretation of results, particularly for women, children and older adults (16, 17).

Bronchodilator Responsiveness Testing

Changes in FEV_1 and FVC following bronchodilator responsiveness testing should be expressed as the percent change relative to the individual's predicted value. A change >10% of the predicted value indicates a positive response (Box 1).

Bronchodilator responsiveness (BDR) testing assesses the change in respiratory function in response to bronchodilator administration. The BDR result reflects the integrated physiological response of airway epithelium, nerves, mediators, and airway smooth muscle, along with structural and geometric factors that affect airflow in the conducting airways (3, 18-20).

Expressing the Results of a Bronchodilator Responsiveness Test

The 2005 PFT interpretation standard recommended using a combination of absolute and relative change from baseline as evidence of BDR, namely >200 ml AND >12 % increase in FEV_1 and/or FVC (3). The major limitation to this approach is that the absolute and relatives change in FEV_1 and FVC are inversely proportional to baseline lung function, and are associated with height, age and sex in both health and disease (18, 19, 21-23). These factors influence the accuracy of identifying an abnormal BDR (22) and the previous approach to define BDR is no longer recommended.

Box 1: Determination of a bronchodilator response

$$\text{Bronchodilator Response} = \frac{(\text{Post-bronchodilator value (l)} - \text{Pre-bronchodilator value (l)}) * 100}{\text{Predicted value (l)\#}}$$

A change of >10% is considered a significant BDR response.

#Predicted value should be determined using the appropriate GLI spirometry equation.

For example: A 50-year-old male; 170 cm in height has a pre-bronchodilator FEV_1 of 2.0 liters and a post-bronchodilator FEV_1 of 2.4 liters. The predicted FEV_1 is 3.32 liter (GLI 2012 'other' equation).

$$\text{Bronchodilator Response} = \frac{(2.4-2.0)* 100}{3.32} = 12.1\%$$

Therefore, their BDR is reported as an increase of 12.1% of their predicted FEV_1 and classified as a significant response.

We recommend reporting the change in FEV_1 or FVC as the increase relative to the predicted value (see Box 1) which minimizes sex and height difference in assessing BDR (18, 19, 22). Based on the current evidence we recommend a BDR be classified as a change of >10% relative to the individual's predicted value for FEV_1 or FVC (see Box 1 for example calculation). The recommended BDR threshold balances the available data and consistency across age groups. As there were limited data in children and young adults to inform recommendations; further evidence is needed to validate this approach in children.

Natural changes in Lung Function over time

There are limited data to support a single recommendation for interpreting PFT reproducibility. Two distinct approaches should be used to express natural changes in lung function: conditional change scores for children and FEV1Q for adults.

The interpretation of a series of lung function measurements and identifying meaningful changes in lung function over time are often used to guide clinical decisions. Ideally an individual's pre-disease measure of lung function, or baseline should be used as a reference. Comparison with the

rate decline observed in a group of healthy individuals can help to determine if rate of decline is greater than what can be expected in health. The 2005 PFT interpretation statement recommended a meaningful change as one greater than the biological variability (and measurement error) of a test. Previous literature also suggested an absolute change in FEV_1 (e.g., 100 ml) or the relative change from a previous assessment (e.g., a 10% change in FEV_1 from baseline in healthy individuals) to indicate clinically meaningful changes. However, changes over time have been demonstrated to be dependent on age, sex, baseline lung function and disease severity, limiting the generalisability of these approaches (24, 25).

Considerations in children

Lung function measurements in children are more variable than in adults. This is due to both the physiology of the chest wall muscles as well as cognitive development which may influence test quality and biological variability. We identified one recently published study that demonstrates conditional change scores can be used to identify changes in lung function greater than what can be expected in healthy children and young people (25) which adjusts for longitudinal changes in FEV_1 z-score and conditions on the initial FEV_1 value (see Box 2). This concept has yet to be validated, extended to adults, or applied to other lung function indices but may be a reasonable tool to facilitate interpretation

Box 2: Calculation of a conditional change score

The change score is defined as $\frac{zFEV_{1t2}-(r* zFEV1_{1t1})}{\sqrt{1}-r^2}$ where $zFEV_1$ at t_1 and t_2 are the observed z-scores at the initial and second time point, and r is defined as 0.642 – 0.04*time(years) + 0.020*age (years) at t_1. Changes within +/- 1.96 change scores are considered within the normal limits.

For example, a 14-year-old male (170 cm) with a lung function drop from -0.78 z-scores (90.6% predicted) to -1.60 z-scores (80.6% predicted) within 3 months (r=0.907) has a corresponding change score of -2.12 which is outside the limits of normal. The same drop over a period of 4 years (r = 0.769) corresponds to a change score -1.56, which is within the limits of normal variability.

Considerations in adults

In occupational medicine, where repeated measurements are made annually (or further apart) a 15% threshold has been proposed as a change outside the biological variability of the test and considered clinically relevant (26). FEV_1Q is the FEV_1 divided by the sex-specific 1st percentile values of the absolute FEV_1 values found in adults with abnormal lung function, 0.4 liter for women and 0.5 liter for men (27). Under normal circumstances one unit of FEV1Q is lost approximately every 18 years and about every 10 years in smokers (28) and the elderly (26, 29) (see Box 3). Over a short interval, or even annually the FEV_1Q should remain stable. Changes in

the FEV_1Q may indicate a precipitous change in lung function This approach is recommended as an alternative approach to interpretation of serial measures in adults but is not appropriate for children and adolescents.

Box 3: Calculation of FEV_1Q in adults

FEV_1Q is the observed FEV_1 in liters divided by the sex-specific first percentile of the FEV_1 distribution found in adult subjects with lung disease; these percentiles are 0.5 liters for males and 0.4 liters for females. The index approximates to the number of turnovers remaining of a lower survivable limit of FEV_1.

For example, a 70-year-old woman with an FEV_1 of 0.9 liters would have an FEV_1Q of 0.9l/0.4 liter or 2.25. Values closer to 1 indicate a greater risk of death.

Severity of Lung Function Impairment

A three-level system to assess the severity of lung function impairment using z-score values should be used; z-score > -1.645 are normal, z-scores between -1.65 and -2.5 are mild, z-scores between -2.5 and -4 are moderate and z-scores < -4 are severe.

The magnitude of lung function deviation from what is expected of healthy individuals, having accounted for age-dependent variability, can be used to determine the association with objective outcomes such as quality of life or mortality (30-34). As lung function impairment is a continuum, setting multiple fixed boundaries to define grades is in some sense artificial and may imply tiered differences that are unfounded. Furthermore, the severity of lung function impairment is not necessarily equivalent to disease severity which encompasses quality of life, functional impairment, imaging, etc.

The 2005 PFT interpretation statement recommended severity grading for airflow obstruction using percent of predicted FEV_1 with 5 levels using cut values of 70%, 60% 50% and 35% (3). The use of percent of predicted does not give uniform gradation across age (17, 35) (Summary Figure 2). We do not recommend the use of percent predicted to assess severity or make definitive treatment decisions. To account for an individual's sex, height, age, and ethnic background the previous severity scale for airflow obstruction were adapted for z-scores with cut values of -2, -2.5, -3 and -4 (36).

Classification of Physiologic Impairments by Pulmonary Function Tests

The interpretation of PFTs should focus on values of airflow, lung volume and gas transfer measurements to recognize patterns of altered physiology. PFTs alone should not be used to diagnose a specific pathologic condition.

PFT interpretations should be clear, concise and informative to help understand whether the observed result is normal, and, if not, what type of physiological impairment is likely involved. In addition, repeated assessment of PFTs is important to detect clinically meaningful deviations

from an individual's previous results. In this document we will review the interpretation of measurements made by spirometry, lung volumes, and D_LCO as they relate to underlying pathophysiology.

Routine PFTs address three functional properties of the lungs:

1) Airflow (measurements of inspiratory and expiratory airflow)
2) Lung volumes and capacities (gas volumes at both maximal inspiration and at maximal expiration – total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC)
3) Alveolar-capillary gas transfer (usually measured by single breath uptake of carbon monoxide (CO) over time), referred to as the diffusing capacity of the lung for CO (D_LCO) or the transfer factor of the lungs for CO (T_LCO)

Abnormalities in these three functional properties are conventionally classified into obstructive ventilatory, restrictive ventilatory, and gas transfer limitations or impairments (Summary Table 1).

Ventilatory Impairments Defined by Spirometry

Airflow impairment and Airflow Obstruction

Recognizing the normal physiologic events involved in expiratory "airflow limitation" we use the term "airflow obstruction" to refer to pathological reduction in airflow from the lungs that leads to a reduced FEV_1/FVC ratio.

An obstructive ventilatory impairment is defined by FEV_1/FVC (or VC) below the LLN defined as the 5^{th} percentile of a normal population (Summary Summary Table 2). This spirometric definition is consistent with the 1991 ATS (37), and 2005 ATS/ERS (3) recommendations, but differs from the definition suggested by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the ATS/ERS guidelines on COPD which use a fixed FEV_1/FVC value of 0.7 to define an obstructive ventilatory impairment (38, 39). This latter definition is not recommended.

Dysanapsis and Other Patterns of Abnormality Impairments in FEV_1, FVC and FEV_1/FVC

For healthy individuals, the meaning of a low FEV_1/FVC ratio accompanied by an FEV_1 within the normal range is unclear. This pattern may be due to "dysanaptic" or unequal growth of the airways and lung parenchyma (40). While this pattern has been thought to be a normal physiologic variant (37), new data suggest that it may be associated with the propensity for obstructive lung disease (41, 42).

The "Non-Specific" Pattern: A Low FEV_1 and FVC, with Normal FEV_1/FVC

The pattern of reduced FVC and/or FEV_1, normal FEV_1/FVC, and normal TLC, has been termed the "non-specific" pattern. We now know that this pattern can reflect a number of different

ventilatory impairments including reduced effort, a restrictive ventilatory impairment, or be an early consequence of small airway disease with air trapping and/or emphysema (43, 44). In current and former patients who smoke when TLC is not available, (typically in population based studies) the non-specific pattern has been labelled "preserved ratio-impaired spirometry" or "PRISm" which, in follow-up has been shown to be associated with both more typical restrictive or obstructive patterns (45-47). As with any pattern involving a low FVC, TLC should be measured to confirm restriction, as clinically indicated

Central and Upper Airway Obstruction

Central airway obstruction and upper airway obstruction affects the airways outside lung parenchyma. These may occur in the intrathoracic airways (intrathoracic trachea and main bronchi) or extrathoracic airways (pharynx, larynx, and extrathoracic portion of the trachea). In their early stages these markedly reduce peak expiratory flow (PEF) with little or no decrease in FEV_1 and/or FVC.

Ventilatory Impairments Defined by Lung Volume Measurements

Restrictive Impairments

A reduction in lung volumes defines a restrictive ventilatory impairment and is classically characterized by a reduction in TLC below the LLN (5^{th} percentile)

Summary Table 4). Typically the FVC and FEV_1 are also reduced and a normal FEV_1/FVC ratio indicates that only restriction is present.

Obstructive Impairments

Obstructive ventilatory impairments are generally assessed with spirometric measurements of expiratory airflow. As noted above, however, there are specific lung volume patterns associated with airflow obstruction that generally reflect hyperinflation/air trapping (Table 4).

Mixed Ventilatory Impairments

A mixed ventilatory impairment is characterized by the coexistence of obstruction and restriction and is present when both FEV_1/FVC and TLC are below the LLN (5th percentile). Since FVC may be equally reduced in either obstruction or restriction, the presence of a restrictive component in an obstructed individual cannot be inferred from simple measurements of FEV_1 and FVC.

Gas Transfer Impairments Defined by D_LCO

Gas transfer is commonly assessed by measuring the uptake of carbon monoxide (as a surrogate for oxygen) by the lungs. The normal range for D_LCO and VA should be based on the 5^{th} centile and 95^{th} percentile (9, 48). In the setting of a normal V_A, K_{CO} also has 5^{th} and 95^{th} percentile values. However, because K_{CO} will rise in a non-linear fashion as lung volumes fall (smaller lung gas volumes mean more rapid CO concentration changes due to an increasingly higher surface area to volume ratio), this "normal" range for K_{CO} progressively loses meaning as lung volumes decrease.

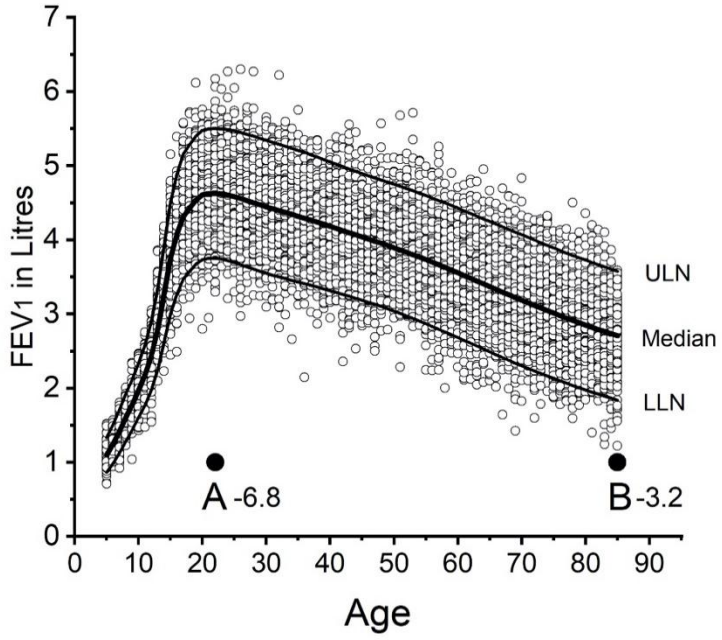
The Future of Pulmonary Function Test Interpretation

In the era of precision medicine and novel prediction tools, more sophisticated diagnostic models should be developed to identify more accurately the early determinants of reduced lung function. The development of artificial intelligence (AI)/machine learning (ML) approaches to PFT interpretation is encouraged. AIML-based software has the potential to provide more accurate and standardized interpretations and serve as a powerful decision support tool to improve clinical practice (49, 50). AIML may also help to develop personalized, unbiased prediction of normal lung function.

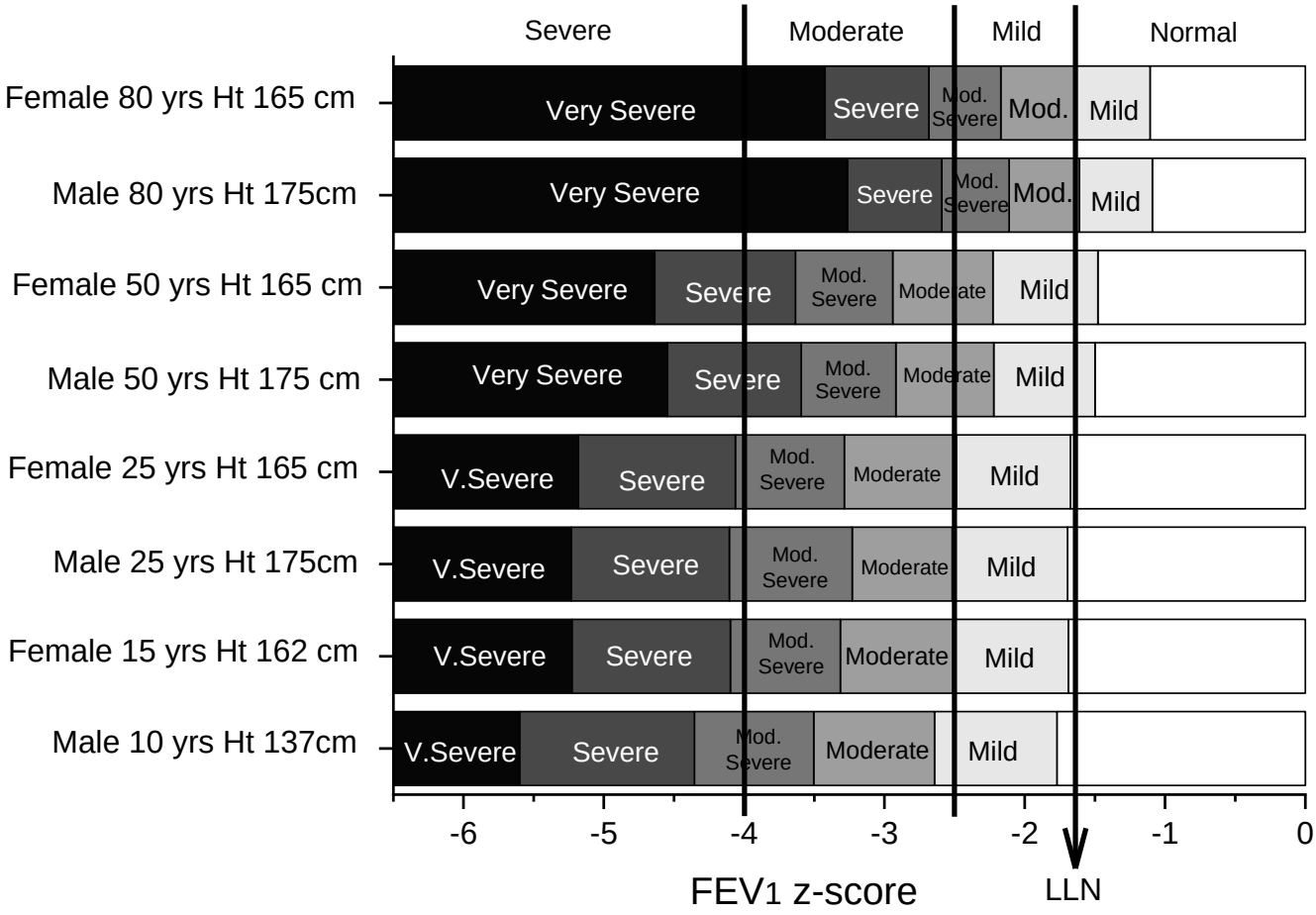
Conclusion

Interpreting PFTs must take into account a level of uncertainty relating to (i) how representative the obtained result was of the individual's lung function at the time of testing, (ii) how the pre-test probability of disease may influence what is the appropriate threshold for that individual, and (iii) how valid the reference population against which the test is being judged is for the individual.

In the future it may also be reasonable to set clinical decision-making thresholds for a test based on clinical risk and observed clinical outcomes.. A more comprehensive approach than simply relying on whether results are within or outside the normal range is necessary for the appropriate interpretation of lung function when pre-screening for employment, for tracking the effects of exposure, for disability assessment, and for risk assessment for therapies potentially toxic to the lungs. Interpreting PFT results must always consider the inherent biological variability of the test and the uncertainty of the test result.



Summary Figure 1. Plot of population FEV_1 data for males of median height for age between ages 5 to 85 years with the upper limit of normal (ULN 95th percentile), lower limit of normal (LLN 5th percentile) and median predicted shown as solid lines derived from GLI spirometry equations (8). The LLN for a man aged 22 is at 81.1 % predicted but is 67.9 % predicted for a man of the same median height aged 85. Participants A and B both have an FEV_1 of 1.0 L giving a z-score of -6.8 for individual A and -3.2 for individual B.



Summary Figure 2 A plot of the old ATS/ERS 2005 recommended thresholds for degree of lung function reduction of airflow obstruction using 70%, 60%, 50% and 35% of predicted FEV1 for eight individuals with the FEV_1 cut points expressed as z-score values on the abscissa scale. The lower limit of normal (LLN) at the 5^{th} percentile (-1.645) is shown as a vertical arrow.

Summary Table 1 Functional Classification of Common Impairments Assessed by Conventional PFTs and their Pathophysiological Determinants

Obstructive ventilatory impairments*	Narrowing of the airways in the lung by physical obstruction or by dynamic airway collapsing. More proximal airway properties determine airflow resistance at large lung volumes and drive the FEV_1/FVC measurement; more distal airway properties determine airflow resistance at small lung volumes and drive flow measurements later in a maximal exhalation. Because airway obstruction impairs lung emptying, it is often accompanied by air trapping and hyperinflation that may reduce the FVC but is more directly assessed by the RV measurement.
Restrictive ventilatory impairments*	Reduction in the size of the lungs. This may reflect lung parenchymal abnormalities or an inability to fully inhale due to extrapulmonary factors (e.g., weakness, chest wall abnormalities, obesity). Lung restriction reduces FEV_1, FVC, (but not the FEV_1/FVC ratio) and TLC.
Gas transfer impairments	Reduction in transport of gas (carbon monoxide transfer as a surrogate for oxygen) between the alveolar spaces and alveolar capillary blood. This may be due to a reduction in alveolar surface area, abnormal alveolar-capillary membrane properties, or reduced pulmonary capillary blood (hemoglobin) volume.

* Many authorities also use the term "ventilatory impairments" to group obstructive and restrictive impairments.

Summary Table 2 Classification of Ventilatory Impairments Defined by Spirometry. Reduced or elevated results are defined by the lower and upper limits of normal respectively.

	FEV_1	**FVC**	**FEV_1/FVC**	**Comments**
Obstructive impairments	Normal/↓	Normal	↓	
Restrictive impairments	↓	↓	Normal/↑	TLC reduced to confirm
Non-specific pattern (51)	↓	↓	Normal	TLC normal; additional testing may be helpful (e.g. bronchodilator response, Raw). When TLC is not available, this pattern has been described in population-based studies as preserved ratio-impaired spirometry (PRISm), in current and former smokers (45)
Muscle weakness	↓	↓	Normal	Lack of sharp Peak Expiratory Flow
Suboptimal effort	↓	↓	Normal	Lack of sharp Peak Expiratory Flow
Mixed disorder	↓	↓	↓	Need lung volumes to confirm
Dysanapsis(42)	Normal	Normal /↑	↓	May be normal variant

Summary Table 3 Classification of Ventilatory Impairments Defined by Lung Volumes

	TLC	FRC	RV	FRC/TLC	RV/TLC	Comments
Large lungs	↑	↑	↑	Normal	Normal	Normal variant above ULN
Obstruction	Normal /↑	Normal /↑	↑	Normal /↑	↑	Hyperinflation if FRC/TLC or RV/TLC elevated; gas trapping if only RV/TLC elevated (e.g., COPD)
Simple Restriction	↓	↓	↓	Normal	Normal	e.g., ILD
Complex Restriction	↓	↓	Normal /↑	Normal	↑	When the FEV_1/FVC is normal complex refers to the process contributing to restrictive process that disproportionally reduces FVC relative to TLC. (e.g., small airway disease with gas trapping and obesity).
Mixed Disorder	↓	Normal /↓	Normal /↑	Normal /↑	Normal /↑	Typically, FEV_1/FVC is reduced (e.g., combined ILD and COPD)
Muscle weakness	↓	Normal/↓	↑	↑	↑	When effort appears sufficient
Suboptimal effort	↓	Normal	↑	↑	↑	Especially when effort appears insufficient
Obesity	Normal /↓	↓	Normal /↑	Normal /↓	Normal /↑	ERV low; reduced TLC at very high BMI (>40)

Summary Table 4 Summary of Types of Spirometrically defined and Lung Volume Defined Ventilatory Impairments.

Ventilatory Impairments	Patterns
Obstruction	• $FEV_1/FVC < 5^{th}$ percentile. • Decrease in flow at low lung volume may reflect small airway disease in individuals. • Concomitant decrease in FEV_1 and FVC most commonly due to poor effort but may reflect airflow obstruction. Recommend lung volumes. • Measurement of absolute lung volumes may assist in diagnosis and assessment of hyperinflation. • Measurement of airflow resistance may assist in diagnosis.
Restriction	• $TLC < 5^{th}$ percentile • Reduced FVC does not prove restrictive impairment but may be suggestive of restriction when FEV_1/FVC is normal or increased. • Low TLC from single breath test not reliable, especially with low FEV_1/FVC. • A normal FVC usually excludes restriction
Mixed	• FEV_1/FVC and TLC both $< 5^{th}$ percentile.

Summary Table 5. Summary of differences between the 2005 and 2021 Interpretation Standards.

2005 ATS/ERS Statement	2021 ATS/ERS Technical Standard
General comments: • Using PFT interpretation to aid in clinical diagnosis and decision making	General comments: • More emphasis on using PFTs to classify physiology, not make a clinical diagnosis • Emphasis on uncertainty of interpretation, especially near LLN
Reference Equations • Use of race/ethnic specific equations preferred over using adjustment factors • Spirometry: In USA: NHANES 3 recommended In Europe: no specific equations recommended • Lung Volumes and DLCO: In USA and Europe: no specific equations recommended	Reference Equations: • Recommendation to use GLI reference equations for spirometry, lung volumes and D_LCO • More emphasis on incomplete understanding of role of race/ethnicity on lung function • Clarify that biological sex, not gender be used to interpret lung function
Defining Normal Range • General use of LLN = 5^{th} percentile • Use of fixed ratio $FEV_1/FVC < 0.7$ not recommended • Use of 80% predicted to define normal not recommended	Defining Normal Range • General use of LLN = 5^{th} percentile and ULN = 95^{th} percentile • Use of fixed ratio $FEV_1/FVC < 0.7$ not recommended • Use of 80% predicted to define normal not recommended
Bronchodilator Response • >12% and 200 ml in FEV_1 or FVC from baseline • 4 doses of 100 mcg salbutamol; wait 15 minutes	Bronchodilator Response • >10% of predicted value in FEV_1 or FVC • Choice of protocol for administering bronchodilator not specified
Interpretation of Change Over Time • Variable changes over time depending on normal vs. COPD and time period (within a day, week to week, year to year)	Interpretation of Change Over Time • Conditional change score in children • FEV1Q in adults
Severity of Lung Function Impairment • Using FEV_1 (includes obstruction or restriction): ○ Mild = FEV_1 > 70% predicted ○ Mod = 60-69% predicted ○ Mod-Severe = 50-59% predicted ○ Severe = 35-49% predicted ○ Very severe = < 35% predicted • D_LCO:	Severity of Lung Function Impairment • For all measures use z-score: ○ Mild = -1.65 to -2.5 ○ Mod = -2.51 to -4.0 ○ Severe = > -4

○ Mild = >60% predicted and < LLN ○ Mod = 40-60% predicted ○ Severe = < 40% predicted	
<u>Classification of Physiological Impairments</u> • Airflow obstruction: $FEV_1/FVC < 5^{th}$ percentile, using largest VC; lung volumes to detect hyperinflation or air trapping; elevated airway resistance; central/upper airway obstruction • Restriction: ○ TLC < 5^{th} percentile and normal FEV_1/VC ○ Mixed = FEV_1/VC and TLC < 5^{th} percentile • Gas Transfer Impairment: ○ D_LCO, KCO < 5^{th} percentile ○ Importance of adjustments for Hb, COHb	<u>Classification of Physiological Impairments</u> • Airflow obstruction: $FEV_1/FVC < 5^{th}$ percentile, using FVC; lung volumes to detect hyperinflation or air trapping; dysanapsis; non-specific pattern and PRISm; central/upper airway obstruction • Restriction: ○ TLC < 5^{th} percentile ○ Simple vs. complex restriction ○ Hyperinflation ○ Mixed • Gas Transfer Impairment ○ $D_LCO < 5^{th}$ percentile ○ Using VA, KCO to classify low D_LCO

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