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Task force report

# ERS/ATS technical standard on interpretive strategies for routine lung function tests

Sanja Stanojevic, David A. Kaminsky, Martin Miller, Bruce Thompson, Andrea Aliverti, Igor Barjaktarevic, Brendan G. Cooper, Bruce Culver, Eric Derom, Graham L. Hall, Teal S. Hallstrand, Joerg D. Leuppi, Neil MacIntyre, Meredith McCormack, Margaret Rosenfeld, Erik R. Swenson

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

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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 have been employed in population studies of the association between exposures and lung health. The American Thoracic Society/European Respiratory Society Task Force on the Standardization of PFTs published a series of technical documents in 2005 (1-4). The technical standards 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 to the interpretation strategies of routine PFTs (3).

Interpretation of technically acceptable PFT results has three key 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, as well as the inherent biological variability of measurements both between individuals and between repeated measurements in the same individual; 2) The integration of knowledge of physiologic determinants of test results into a functional classification of the identified impairments; 3) Integration of the identified patterns with other clinical data to inform differential diagnosis and guide therapy. These are three distinct, yet 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 guidance on physiological interpretation.

Appropriate interpretation of PFTs requires measurements that meet technical specification for test performance and appropriate levels of quality (6-8). Poorer quality tests must be interpreted with greater uncertainty as the measurement may not reflect functional impairments. Interpretation also relies on clear reporting of results; therefore, current ATS standards for reporting of PFTs are recommended (9). Technical aspects of PFT measurement, equipment and biological controls are summarized in the ERS/ATS standards for each PFT (6-8).

This document considers the 2005 recommendations and incorporates evidence from subsequent literature to establish new standard for PFT interpretation. The key distinction between the previous recommendations and the current ones is the emphasis on the uncertainty of measurement and interpretation.

## 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 by the ATS throughout the duration of the Task Force. Six of the 16 Task Force members are current or past members of the Global Lung Function Initiative Network Executive. A comprehensive literature search was conducted by a professional librarian using the following databases: Ovid MEDLINE®, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE® 1946-Present, Embase Classic, Embase 1947 to 2019 March 29, Wiley Cochrane. The search terms are listed in Figure 1. All identified publications were screened by two members of the Task Force at the title/abstract level.

Publications identified as relevant for this Task Force were read in full by at least one member of the Task Force. The literature search was systematic but not a formal systematic review of the evidence. 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 (10), diffusing capacity (11) and lung volumes (12) should be used to define the expected range of values in healthy individuals.***

Summaries of data collected in otherwise healthy individuals provide meaningful benchmarks against which to compare an individual's PFT results. The range of values expected in a healthy population is expressed using population-based reference equations that, ideally, are derived from large and representative samples of healthy individuals (i.e., never smokers, without a history of respiratory disease). There are hundreds of published reference equations for different populations and for each PFT. Comparison of published reference equations and individual results derived from different reference equations demonstrate large differences that may be attributed to real population differences in lung function or simply sampling variability with equations derived from small samples. The lack of standards for how to derive and use PFT reference equations has led to considerable confusion in the interpretation of PFT results.

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. Height *per se* is not a direct determinant of lung size but is a reasonable proxy for chest size. Differences in height and body proportions (e.g. leg length, trunk length) have been observed between populations (13). The determinants of the observed differences in height and chest size are multifaceted and must be considered during PFT interpretation. Age has two important contributions to the expected range of lung function in health. In childhood, somatic growth (i.e., height) is strongly linked to chronological age, except during periods of rapid growth and development, such as puberty, when there is asynchrony between height and thoracic volume and thus disproportionate growth between lung parenchyma and airway caliber (14, 15). In older adults the rigidity of the chest wall, chest wall muscles, and the elasticity of the lung, change with the normal aging process (16, 17). Sex is an important predictor of lung size, even after accounting for differences in height (18-21). Thus, while gender identity should be respected, use of biological sex will yield a more accurate prediction of lung function. The effect of gender-affirming hormonal therapy on lung function is poorly understood, so the appropriate reference equation for transgender individuals is currently not known. Timing of gender reassignment, especially during adolescence, may impact lung growth and development and thus needs to be considered when interpreting results during adulthood (22, 23). Considerations for individuals in whom standing height cannot be measured are summarized in the technical standards for each PFT (6-8).

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. The difference by population groupings that were observed in the GLI data may represent genetic differences or health disparities and thus reflect social and environmental determinants of health. The specific contribution that genetic ancestry plays in the regional differences that were observed in GLI data remains uncertain. Furthermore, assigning ethnicity is challenging. 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 and is unequivocally discouraged (24, 25). As there are observed population differences in body proportions (13, 26, 27) and lung function (28, 29), in some contexts it may be relevant to interpret results for an individual relative to that of a similar ancestral grouping, whereas in others it may be more appropriate to compare to the whole population. Caution over which equation is applied is necessary to ensure the same reference equations are applied across serial encounters. 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 (10), $D_LCO$ (11) and lung volumes (12) and facilitate standardized reporting and interpretation of pulmonary function measurements. These three GLI equations (spirometry, $D_LCO$, lung volumes) are internally consistent, providing a single suite of PFT equations which will avoid discordant results between PFTs and potential misclassification of physiological phenotypes. The GLI equations include the largest samples of healthy individuals and represent a single standard to compare observed measurements applicable across all ages. The GLI equations also explicitly describe the between-subject variability across age, such that the limits of normal are age-specific. Despite the name, the GLI do not include individual data from all populations around the world, and do not explicitly consider the factors that may contribute to the observed differences in lung function between populations. Spirometry equations are available for four specific population groupings and as well as a composite "other" equation which represents a multi-ethnic population (Table 1). The GLI "other" equation was mathematically derived from the four population-specific equations, including the white group, and represents an average across these populations. GLI reference ranges for $FEV_1/FVC$ ratio appear relatively independent of population differences and will result in more consistent interpretation between populations. GLI $D_LCO$ equations and GLI static lung volumes are currently based on measurements predominantly from individuals of European ancestry due to insufficient reference data from other populations.

Further studies 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 reference equations that are specific to population grouping

versus a single standard for all. Different approaches may be warranted in different contexts. Therefore, at this time 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 should be used. PFT reports and research publications must include the specific reference equation that is used.

## Differences from the Previous Recommendations:

The 2005 ATS/ERS Interpretation strategy (3) recommended the use of the National Health and Nutrition Examination III Survey (NHANES III) spirometry reference equations for individuals in North America. The NHANES III spirometry data are included within the GLI equations and, overall, the predicted values are similar, with a few notable differences. The NHANES III derived separate equations for Mexican Americans and Caucasians, whereas the GLI equations do not make this distinction, as re-analysis of the NHANES III data reveals minimal differences between expected lung function in these populations (30). The GLI equations span a wider age range (3-95 years) than NHANES III (8-80 years). There have been notable differences observed in predicted values between the two equations for adults older than 65 years (31-33). The 2005 ATS/ERS Interpretation document did not make specific recommendations for reference equations in Europe and elsewhere, although the European Community for Steel and Coal (ECSC) equations have been used widely. There are demonstrable differences between the predicted values from ECSC and GLI, where the predicted GLI values are consistently higher than ECSC.(34-36)

## Special Considerations for $D_LCO$

The overall recommendation to use the GLI reference equations also applies to $D_LCO$ (11). Interpretation of $D_LCO$ values requires adjustment for equipment dead space and barometric pressure (altitude), which should be done by the equipment software before calculating predicted values (11). Changes in hemoglobin, carboxyhemoglobin and carbon monoxide back pressure must also be considered when interpreting results. This is particularly important in situations where patients are being serially monitored for possible drug toxicity, and where hemoglobin is subject to large shifts (e.g., chemotherapy for cancer) (7). The clinician must incorporate information about hemoglobin concentrations on an individual basis while interpreting results. It is recommended that the reference value be adjusted for measured hemoglobin concentration.

## Special Considerations for Lung Volumes

The overall recommendations for reference equations also apply to the interpretation of lung volumes. GLI (12) and other reference equations for lung volumes adjust for height but not weight. However, lung volumes can be affected by obesity, with significant reductions in Functional Residual Capacity (FRC) and Expiratory Reserve Volume (ERV) at BMI > 30 $kg/m^2$ (37, 38), with similar findings in children and adolescents when obesity is defined as > $97^{th}$ percentile (39). In extreme obesity, both obstructive and restrictive ventilatory impairment patterns are seen (40). Nonetheless, measured lung volumes for the majority of obese individuals still fall within the normal range, and total lung capacity (TLC) is usually not reduced until BMI > 40 $kg/m^2$ (37). The typical patterns of obstruction and restriction may be altered in obesity, thus, in the context of obesity results observed outside the normal range need to be interpreted with greater uncertainty

(41). Measurements of lung volumes are also impacted during pregnancy and results need to be interpreted cautiously both during pregnancy and in the post-partum period (42).

## Practical Considerations

PFT reports must include the reference equations applied for each index (9). Caution should be applied to interpretation of results where different reference equations or combinations of reference equations are used for each test (or indices) as there may be differences in the healthy populations used to derive the equations. A change in reference equations must be clearly documented and communicated, as an individual's results may appear to change based solely on the change in reference equation (34, 43-45). If reference equations are changed, interpretation of trends should include re-calculation of prior predicted values as well as comparison of raw values to avoid misinterpretation. If standing height, biological sex or ancestral background are not known, the report must clearly state what is assumed.

Validation of reference equations in individual PFT laboratories with a small sample of healthy individuals (e.g., 100) is not recommended. Differences due to sampling variability alone can be as large as 0.4 z-scores (6-9% predicted) even when the same equipment and protocols are used, and the sample size is at least 1,000 (46).

## Limits of Normal

***The 5$^{th}$ and 95$^{th}$ 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.***

Ideally limits of normal ought to be based on an individual's pre-disease measure, or baseline. Further clinical decision-making requires relevant thresholds based on prognosis or clinical risk of adverse outcomes. To date no satisfactory outcome-based thresholds for lung function have been defined; therefore, careful consideration of the medical and exposure history of an individual is necessary when interpreting lung function results when using the limits of normal. Further research to establish a comprehensive disease-specific clinical approach to interpretation (not simply relying on whether results are within or outside the normal range) is necessary. It is the consensus of the committee that the percentile limits represent a standardized and unbiased approached to identify values outside the range of expected results from a normal population.

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 (47-49). Population defined z-scores or percentile values describe the chance the observed result falls within the distribution of values in healthy individuals (Figure 2). At the 5$^{th}$ percentile (corresponding to a z score of -1.645), there is a 5% chance that the results in a healthy individual would be at or below this level, as shown in Figure 2. At the 1$^{st}$ percentile, there would be a 1% chance. Since typically for spirometry, low values are considered abnormal, it has become standard to define the LLN as the 5$^{th}$ percentile, accepting that this will result in 5% of healthy individuals having a false positive result (i.e., being incorrectly classified as having an abnormal result). The 5$^{th}$ 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 compared with using a lower percentile). 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 (50). 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 95$^{th}$ percentile to the 10$^{th}$ percentile is a very significant change but still leaves lung function within normal limits.

The LLN need not be the 5th percentile. With adequate supporting evidence, the LLN could be adjusted lower when PFTs are performed in the absence of elevated risk (e.g., screening the general population). For example, when screening a general population, a more conservative lower limit of 2.5% (-1.96 standard deviations or z-scores) or even 1% (-2.326 standard deviations or z-scores) will reduce the number of false positives. The specific LLN that is used must be clearly documented in PFT reports. Results that are close to the LLN should be interpreted with caution and considered in the context of the individual patient's medical history, physical findings, and pre-test probability of disease. This further emphasizes that the person interpreting PFTs should be informed of the patient's context and not solely rely on the numbers generated in reports.

The widely used cut-offs of 80% of predicted for $FEV_1$ (% predicted = Observed*100/Predicted) and the 0.70 cut-off for the $FEV_1$/FVC ratio are strongly discouraged (51). Percent of predicted does not take into account the observed age-related changes in measurement variability (Figure 3). 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 (Figure 4). 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 (52, 53). For example, the LLN for $FEV_1$ varies from 81% predicted at the age of 10 to 68% predicted at the age of 85 (Figure 3; Table 2).

The limits of normal derived from data collected in healthy individuals represents a cross-sectional snapshot of an otherwise healthy population, and the range of values does not represent ideal lung growth and development expected under optimal social and environmental conditions. Therefore, neither simple cut-offs nor the 5$^{th}$ percentile should be used as absolute diagnostic criteria, as there is a gradual increase in risk the further away from the range of values observed in health (Figure 2). There is considerable overlap in the range of values in health and disease resulting in a "zone of uncertainty" (Figure 5). Early life exposures and cumulative environmental exposures have negative effects on the growth and development of the lungs that pre-dispose individuals to lung disease in later life (54, 55). For some ventilatory impairments, development of airflow obstruction is characterized by a slowly progressive decline in $FEV_1$ relative to FVC, (56) and it is likely that early stages of airflow obstruction will be present before the $FEV_1$/FVC value falls below the LLN.

## Future Directions

There is an urgent need to develop more precise and individualized ways to define what normal lung function should be under ideal growth and environmental conditions. There is a need to

understand the factors that contribute to population differences and environmental influences in lung function and the impact of using ethnic specific equations on clinical decisions in populations around the world. There is also a need for data to better define the relationship between risk factors, lung function, and outcomes that would allow a shift from the interpretive dichotomy of normal/abnormal to a more realistic probability assessment as lung function declines through lower percentiles or z-scores.

## 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.***

When clinically indicated the bronchodilator responsiveness (BDR) test 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, 57-59). The choice of bronchodilator, dose, and mode of delivery is a clinical decision. The relative merits of different protocols (e.g., delivered dose) are unclear. Recommended BDR protocols are included in the 2019 ATS-ERS Spirometry standard (5). The concept of a response to bronchodilators must not be confused with "reversibility" of airflow obstruction, which is a qualitative term reflecting the normalization of $FEV_1$/FVC (and hence airflow obstruction) after bronchodilator administration (60). Here we address how to interpret acute changes in lung function after bronchodilator administration and do not consider how BDR can be used to make diagnostic or clinical decisions.

### Expressing the Results of a Bronchodilator Responsiveness Test

Interpretation of BDR can employ two approaches: 1) the upper limit of the changes expected in a healthy population; or 2) a threshold at which a clinically meaningful event occurs. The upper limit of the changes expected in a healthy population may not be clinically relevant (61). Although data are limited for clinically meaningful thresholds across a range of diseases and age groups, there is evidence related to survival to support a threshold-based approach (27, 57, 59, 62, 63). In over 4,000 patients referred for BDR in a hospital laboratory those with BDR greater than 8% of predicted $FEV_1$ had a lower subsequent mortality than those with BDR below this threshold (62). Thus, a threshold approach that is supported by both methods (i.e., the % of predicted value threshold) should be used until further data are available (27).

Established methods to assess the change in $FEV_1$ and FVC after administration of a bronchodilator include: (i) an absolute change from the initial value, (ii) a relative change related to the initial value, (iii) a change related to the individual's predicted value, or a combination of these options. The combination of an absolute and relative change (% change) in $FEV_1$ and FVC from baseline as evidence of BDR was recommended in the 2005 interpretation statement (i.e., > 200 ml AND > 12 % increase in $FEV_1$ and/or FVC) (3). The major limitation to this approach is

that the absolute and relative changes 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 (57, 59, 62-64). The use of approaches (i) and (ii) to define a BDR are no longer recommended.

We recommend reporting the change in $FEV_1$ or FVC as the increase relative to the predicted value which minimizes sex and height difference in assessing BDR (57, 59, 62). Two studies of collated epidemiological data in healthy adults reported the upper limit (95% percentile) of the range of responses in healthy individuals of the BDR to be 11.6% and 10.1% of predicted for $FEV_1$ and 10.2% and 9.6% of predicted for FVC (59, 62). Similar changes of 8.5% for $FEV_{0.75}$ in young children have been reported (65). BDR in FVC, rather than $FEV_1$, has been shown to better reflect the physiological processes of air trapping (66-70). Based on these considerations, it is recommended that BDR be classified as a change of >10% relative to the predicted value for $FEV_1$ or FVC (see Box 1 for example calculation). This approach avoids misinterpretation due to the magnitude of the baseline lung function level. Over-reliance on strict cut-offs for BDR should be avoided as these cut-offs are prone to the same limitations as for limits of normal. Importantly, this is not equivalent to a 10% change between pre- and post-bronchodilator measurements.

Changes in forced expiratory flows (e.g., PEF or $FEF_{25-75\%}$) are highly variable and significantly influenced by changes in FVC such that pre- and post-bronchodilator measurements are not comparable (3).

**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.

## Future Directions

The recommended BDR threshold balances the available data and consistency across age groups. There were limited data in children and young adults to inform recommendations; further evidence is needed to validate this approach in children. Future research is also needed to understand the impact of bronchodilator protocols (e.g., delivered dose) on results. The ability of an acute response to bronchodilators to predict future clinical status other than survival is unclear and BDR does not accurately differentiate between types of airway diseases (71-73). Further evidence is needed to support anchor-based approaches associated with outcomes other than survival. Finally,

there are limited data regarding changes in pulmonary function indices derived from lung volumes, gas transfer, and airway resistance following bronchodilator administration.

## Natural changes in Lung Function over Time

***There are limited data to support a single recommendation for interpreting PFT reproducibility. Two distinct approaches were identified to express natural changes in lung function: conditional change scores for children and $FEV_1Q$ 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. Accelerated lung function decline, irrespective of baseline lung function, is associated with poor clinical outcomes (74, 75). Interpretation of serial measurements relies on accurate limits of reproducibility of a PFT index, including the natural changes over time and the changes that would be considered outside both the normal biological variability over short and long periods of time.

### Reproducibility

Previous recommendations define a meaningful change as one greater than the biological variability (and measurement error) of a test. 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) has historically been used 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 (76, 77). Furthermore, these limits were derived from population data in healthy individuals and do not necessarily reflect clinically meaningful outcomes for a specific disease or condition (78).

Visual representation of serial measurements (e.g., trend graph) may be included as part of a PFT report. A decline in lung function observed from multiple measurements over time is more likely to reflect a real change in lung function than two measurements alone.

### 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. Interpretation of serial measurements during periods of rapid growth and development (e.g., adolescence and early adulthood) require special attention to avoid misinterpreting the normal plateau of lung growth. Examination of absolute measures should be used to verify 'decline' in this period. Generally, limits of reproducibility applied in children are extrapolated from studies in adults and do not consider the unique developmental aspects of childhood, including how somatic and lung growth are not always synchronous. 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

(77). The conditional change scores adjust 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 (170cm) 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 adults over the age of 25 years, $FEV_1$ typically declines in healthy non-smokers by 30 mL/year (79, 80); however, this does not necessarily translate into a threshold of change that can be expected within an individual between two repeated measurements. 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 (80). These limits would not necessarily apply to an individual with a chronic progressive lung disease where the follow-up interval is shorter. Individualized approaches that consider the test quality, time interval between tests, an individual's baseline lung function, as well as the clinical findings at the time of measurement are needed for accurate interpretation.

An alternative approach is the $FEV_1Q$, that is the $FEV_1$ divided by the sex-specific 1st percentile values of the absolute $FEV_1$ values found in adults with lung disease, 0.4 liter for women and 0.5 liter for men (81). $FEV_1Q$ expresses $FEV_1$ in relation to a "bottom line" required for survival, rather than how far an individual's result was from their predicted value. Under normal circumstances one unit of $FEV_1Q$ is lost approximately every 18 years and about every 10 years in smokers and the elderly (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 and can be used as an alternative approach to gauge meaningful changes over time in adults. $FEV_1Q$ 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 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.

## Further Research

There is a paucity of data describing natural variability in lung function indices within an individual over time across all ages, PFTs, and disease groups (82). Future work is urgently needed to identify a minimum clinically important difference for each lung function test and index that is anchored to disease specific outcomes. Further research addressing the short (months), annual and long (years) term changes in healthy individuals is urgently needed. Disease specific anchor-based approaches that link to clinically meaningful endpoints are strongly recommended to define appropriate thresholds for clinical interpretation.

## 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 (83-87). The association between lung function reported as z-scores with all-cause mortality in patients for $FEV_1$, FVC and $D_LCO$ is shown in Figure 6 (88). 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.

The previously recommended severity levels for airflow obstruction used percent 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 gradations across age (53, 89). To account for an individual's sex, height, age, and ethnic background the previous severity scale for airflow obstruction was adapted for z-scores with cut values of -2, -2.5, -3 and -4 (88, 90). Z-score cut levels between -1.65 and -2.5 have little difference in risk of death and were therefore merged into a mild group (Figure 6). Individuals with z-score between -2.5 and -4 exhibit a moderate risk of mortality and these categories were therefore merged into the category called 'moderate. The proposed three-scale system reduces the previous two lower categories into one for mild impairment and extends the moderate levels to improve the fit for gradation of mortality risk (88).

Importantly the severity of lung function impairment is not necessarily equivalent to disease severity which encompasses quality of life, functional impairment, imaging, etc. Disease severity will be influenced by many other possible clinical features not related to lung function impairment such as anemia, neuromuscular weakness or drug side effects, to mention just a few. There are numerous questionnaires designed and validated to assess the severity of symptoms and impairment (91-94) and are outside the scope of this work. In addition, the association between the proposed gradations and survival in children has not been evaluated.

## Rationale for z-scores

Z-scores express how far an observed lung function value is from the predicted value after accounting for sex, age, height and ancestral grouping, expressed in standard deviations. This is the method recommended for determining the limit of normality and for stating the degree of lung function impairment. Percentile values are easily derived from z-scores and explicitly indicate the probability a healthy individual would have a result below this level and where the individual's result lies in relation to the healthy population. Percentile values are useful in assessing results around the normal range but are less useful for extreme values.

T-scores are similar to z-scores but are expressed in the number of standard deviations an observation is below a maximum predicted value achieved during early adulthood for an individual of the same sex, height, and ancestral grouping (95). However, T-scores assume that population level maximum lung function can be maintained throughout adulthood. Furthermore, T-scores cannot be applied to children and young adults.

Assessing severity of impairment using z-scores is more consistent across age and sex than percent predicted (88, 90). Figure 7 shows the previously recommended categories for airflow obstruction using percent predicted (i.e.,70%, 60%, 50% & 35% defining mild, moderate, moderately severe, severe, and very severe) for 8 different people at their respective z-score values. Older age has the greatest differences in interpretation between % predicted and z score cut-points such that the 80-year-old individual is deemed to have a mild impairment using % predicted thresholds when their lung function is within the normal range using z-scores. Figure 7 shows that percent predicted creates problems in equitable grading with mild impairment, but z-scores have problems with respect to severe grading in older subjects as many older individuals will be classified as severe.

## Other approaches

In adults $FEV_1Q$ has been found to be better than z-scores, percent predicted and $FEV_1$ standardized by powers of height (e.g., $FEV_1 \cdot ht^{-2}$ and $FEV_1 \cdot ht^{-3}$) in predicting survival (81, 96, 97), COPD exacerbations (98), and adverse health outcomes (99). There is also evidence that the $FEV_1Q$ approach may be more useful to differentiate lung function impairment within the 'severe' group and in older adults (81, 96, 97), but $FEV_1Q$ has not been adequately explored in children and adolescents.

## Considerations in the Elderly

Reference equations for lung function indices represent the range of values expected in healthy individuals of the same sex, height and age. The number of healthy individuals over age 80 in reference cohorts is smaller and may represent a selected population of survivors. In older individuals, interpreting lung function as an absolute measure, such as $FEV_1Q$, may be more meaningful than using reference equations. There is evidence that extrapolating predicted values from a younger age may address some of these issues (32, 33). Nonetheless interpretation at the extremes of the age and/or height ranges has greater uncertainty and requires careful consideration.

## Future directions

Assessing the severity of lung function reduction should be linked to important clinical outcomes (survival, exacerbations, admissions, symptoms, imaging, etc.) which may be disease specific. $FEV_1Q$ and other reference-free indices should be explored in this way. $FEV_1Q$ highlights that survival better relates to how far the $FEV_1$ is above a 'survivable bottom line' rather than how far it has dropped from a predicted value. Simpler grading with fewer tiers as proposed should be investigated for a broader range of lung function indices, and for different diseases in both children and adults.

# 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 (inspiratory and expiratory); 2) Lung volumes and capacities – total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC); and 3) Alveolar-capillary gas transfer (measurement of carbon monoxide (CO) uptake over time), expressed as the transfer capacity of the lung for CO ($T_LCO$), also known as the diffusing capacity of the lung for CO ($D_LCO$). Abnormalities in these three functional properties are conventionally classified as obstructive ventilatory, restrictive ventilatory, and gas transfer limitations or impairments (Table 3).

## Ventilatory Impairments Defined by Spirometry

### Airflow limitation and Airflow Obstruction

Expiratory airflow is generally assessed by spirometry, with the most important indices being the $FEV_1$, FVC, and the $FEV_1$/FVC ratio. In normal lungs, airflow is determined by the magnitude of expiratory driving pressure (expiratory muscles and elastic recoil) and the size and visco-elastic properties of the lungs and airways. Maximal airflow is generally assessed spirometrically and may be limited by different diseases that lead to different outcomes: (a) Impaired expiratory muscle function (weakness or poor effort – neuromuscular ventilatory impairment), reduced elastic recoil or reduced chest wall expansion which reduce peak expiratory flow, $FEV_1$ and FVC, with a variable $FEV_1$/FVC ratio; (b) Physical obstruction of a central airway (i.e., outside of lung parenchyma), which can affect the trachea/major bronchi and leads to a disproportionate reduction in PEF compared to $FEV_1$ with variable $FEV_1$/FVC ratio; (c) Intra-pulmonary airflow obstruction produced by premature airway collapse, bronchoconstriction or airway inflammation/wall thickening/oedema leading to airway narrowing. These obstructed airways reduce peak expiratory flow and $FEV_1$ to a much greater extent than any reduction in FVC so the $FEV_1$/FVC is characteristically low (100-102).

***While we recognize 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 lower limit of normal (LLN), which is defined as the 5$^{th}$ percentile of a normal population (Figure 8; Table 4). This spirometric definition of airflow obstruction is consistent with the 1991 ATS (103), and 2005 ATS/ERS (3) recommendations; however, it contrasts with the definitions 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 (104, 105).

The earliest changes associated with respiratory diseases that produce airflow obstruction are thought to occur in the smaller, more distal airways (106). Since the total cross-sectional area of the small airways is very large, they offer little resistance to airflow at high lung volumes and impairment limited to these airways have little impact on maximal airflow as measured by the $FEV_1$ (107). However, as exhalation proceeds during a maximal forced exhalation maneuver, these smaller airways decrease in caliber, with a marked increase in resistance, which can reduce expiratory flow substantially at lower lung volumes. In addition, loss of elastic recoil with emphysematous changes in lung parenchyma also contribute to reduction in maximal expiratory flow (108). This results in a slowing of flow in the terminal portion of the spirogram, even when the initial part of the spirogram is barely affected (100-102). These reductions in late-or-mid-expiratory flow are best appreciated by examination of the flow-volume loop where a characteristic concave shape is thought to reflect small airway dysfunction (Figure 9b and Figure 9c), compared to the normal flow volume curve shown in Figure 9a.

A number of attempts have been made to quantify these small airway impairment, especially when the $FEV_1$ and the $FEV_1$/FVC ratio are normal ("isolated small airway dysfunction") (109). A common approach is to measure the average flow between 25% and 75% of exhaled FVC ($FEF_{25-75\%}$); however, mid-range flow measurements during a forced exhalation are highly variable, poorly reproducible, and not specific for small airway disease in individuals (110). Furthermore, mid-range flow measurements usually do not add to clinical decision making beyond information

contributed by the $FEV_1$, FVC and $FEV_1$/FVC (111). There is insufficient evidence to support the use of spirometry to identify small airway dysfunction (112). There has been recent interest in $FEV_3$/FVC (113) or $FEV_3/FEV_6$ (114) providing more sensitive indication of airflow obstruction in adults when $FEV_1$/FVC is still in the normal range. Other tests such as oscillometry, multiple breath washout, and imaging, may also provide evidence of airflow obstruction when $FEV_1$/FVC is normal (115).

## Dysanapsis and Other Patterns of Impairment 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 (116). While this pattern has been thought to be a normal physiologic variant (103), new data suggest that it may be associated with the propensity for obstructive lung disease (117, 118). Factors associated with this pattern in healthy people included male sex, younger age, and taller stature, with higher FVC above predicted and higher terminal flows as seen by $FEF_{75}$ (119). A high FVC with a low RV can be seen in this instance (normal $FEV_1$ but low $FEV_1$/FVC). Whether this pattern represents airflow obstruction will depend on the prior probability of obstructive disease and possibly on the results of additional tests, such as bronchodilator response, $D_LCO$, gas- exchange evaluation, and measurement of muscle strength or exercise testing.

## 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. This pattern was described in the 2005 ATS/ERS interpretation statement and was thought to relate to airflow occlusion/collapse, but we now know that this interpretation was too simple. Indeed, this pattern can reflect reduced effort, a restrictive ventilatory impairment, or be an early consequence of small airway disease with air trapping and/or emphysema (120, 121) . However, measurement of a low TLC is necessary to confirm restriction.

In the setting of reduced effort, the non-specific pattern reflects the failure of the individual to inhale or exhale completely, resulting in a "falsely low" $FEV_1$ and FVC. It may also occur when the flow is so reduced that the subject cannot exhale long enough to empty the lungs to RV. In this circumstance, the flow–volume curve should appear concave downward toward the end of the maneuver. In this case the volume time curve can also be informative and may help to differentiate between glottis closure, and sudden interruption of the expiration due to poor effort, and even other causes.

The non-specific pattern may be an early indicator of a restrictive process in which FVC reduction is not yet accompanied by a reduction in RV. A low TLC under these circumstances would confirm restriction. In contrast, in early obstruction, small airway collapse can reduce FVC and increase RV before the $FEV_1$/FVC ratio falls. Three-year follow-up of the non-specific pattern has demonstrated continued non-specific pattern in $2/3^{rd}$ of people, with the other $1/3^{rd}$ having been diagnosed with overt obstructive or restrictive disease. In current and former people 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 (122-124). As with any pattern involving a low FVC, TLC should be measured to confirm restriction, as clinically indicated

When the non-specific pattern is observed in an individual performing a maximal, sustained effort, it may be useful to repeat spirometry after treatment with an inhaled bronchodilator. Significant improvement in the $FEV_1$, FVC, or both would suggest the presence of some degree of bronchial responsiveness. Another approach is to compare the FVC to an untimed slow vital capacity (SVC). If the SVC is significantly larger than the FVC (> 100 ml (125)), it implies that airway collapse is occurring during the forced exhalation (126).

## Alternative Spirometric Indices and Supplementary Tests Assessing Ventilatory Impairments

The use of VC (i.e., the largest VC of the SVC and FVC) in place of FVC in the ratio (i.e., $FEV_1$/VC) was recommended in the 2005 interpretation document. Using VC in this ratio for identifying obstruction may be more sensitive but not as specific compared to $FEV_1$/FVC (127). The recording of FVC is easier to standardize because there are many ways to record VC, some using different equipment, and VC is very dependent on the preceding flow and volume histories (128). In health, FVC does not differ significantly from VC (10). The use of FVC for the $FEV_1$/FVC ratio should be used as they both should come from forced expiratory manoeuvres using the same equipment and there are robust reference equations for the $FEV_1$/FVC ratio but not for $FEV_1$/VC. Using the previously recommended $FEV_1$/VC to diagnose airflow obstruction will increase the uncertainty about the validity of the diagnosis especially in the older population.

In adults the $FEV_6$ may be substituted for FVC and appears accurate in diagnosing obstruction (129-133), but this only applies if the appropriate LLNs (134) for the $FEV_1/FEV_6$ are used (GLI equations do not include $FEV_6$). $FEV_2$ or $FEV_3$ have also been shown to be useful surrogates for the estimation of FVC in terms of providing an accurate diagnosis of obstruction (135).

Another measure of an obstructive ventilatory impairment derived from spirometry is the inspiratory capacity (IC). A reduction in IC usually reflects an elevated FRC due to air trapping. IC, when expressed relative to the TLC, correlates closely with acute exacerbations and survival in individuals with COPD, and reduction in IC during exercise is an important determinant of dyspnea and exercise intolerance (136).

Multiple other indices derived from analysis of the forced expiratory maneuver, such as measures of the slope or curvature of the flow-volume loop, have been identified (137). In the future, techniques using artificial intelligence/machine learning of the expiratory flow-volume loop may offer more accurate assessments of small airway function (138).

In people with early manifestations of lung disease, and especially in children, spirometry values can be normal even in those with confirmed disease. Other measurements of airway function may supplement spirometry in assessing ventilatory impairments. Airway resistance ($R_{aw}$) measured by body plethysmography, and its volume-related measures of specific Raw ($sR_{aw}$) or specific airway conductance ($sG_{aw}$), are not commonly used to identify airflow obstruction. They are more sensitive for detecting narrowing of extrathoracic or large central intrathoracic airways than of

more peripheral intrathoracic airways. However, measurements of respiratory system resistance by the non-invasive techniques of oscillometry, which require only tidal breathing, may be useful in individuals who are unable to perform a maximal forced expiratory maneuver, including very young children (139-142).

## Central and Upper Airway Obstruction

Central airway obstruction and upper airway obstruction occur in 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). These conditions in the early stages may not lead to a decrease in $FEV_1$ and/or FVC, but peak expiratory flow (PEF) can be severely reduced. The indices presented in Table 5 may help to distinguish intrathoracic from extrathoracic airway obstruction. Therefore, an increased ratio of $FEV_1$ (in mL) to PEF (L/min) can alert the clinician to the need for an inspiratory and expiratory flow–volume loop (143). An $FEV_1$/PEF ratio > 8 ml/L/min in adults suggests the presence of central or upper airway obstruction (144). Poor initial effort can also affect this ratio. Importantly, a progressively severe upper airway obstruction will ultimately reduce the $FEV_1$ and $FEV_1$/FVC (VC) ratio.

Examination of the expiratory flow-volume loop can be very helpful in assessing an upper airway obstruction. When a forced expiratory effort is acceptable, the *repeatable* pattern of a plateau of forced inspiratory flow in the presence of relatively normal expiratory flow suggests variable, extrathoracic upper airway obstruction (Figure 9d). Conversely, the pattern of a repeatable plateau in forced expiratory flow with relatively normal inspiratory flow suggests variable, intrathoracic central airway obstruction. The pattern of a repeatable plateau in both forced inspiratory and expiratory flows suggests fixed central or upper airway obstruction (Figure 9e). With unilateral main bronchus obstruction, a rare event, maximum inspiratory flow tends to be higher at the beginning than towards the end of the forced inspiration because of a delay in gas filling (Figure 9f). In this instance, during forced expiration, flow initially diminishes during forced expiration as the rapidly emptying regions of the lung empty, but then flow plateaus in the mid-portion of the expiratory loop as the slower emptying regions now dominate expiratory flow. Another pattern of flow oscillations (saw-tooth pattern) may be occasionally observed on either the inspiratory or expiratory phase, and likely represents a mechanical instability of the airway wall. The absence of classic spirometric patterns for central airway obstruction does not accurately predict the absence of pathology (145). As a result, clinicians need to maintain a high degree of suspicion for this problem and refer suspected cases for direct endoscopic inspection or imaging of the airways.

## Ventilatory Impairments Defined by Lung Volume Measurements

Spirometry can only suggest a restrictive pattern, and lung volume measurements are necessary to confirm this. Lung volume measurements start with determinations of FRC by gas wash-in/washout analyses or body plethysmography. Thereafter, expiration to RV and inspiration to TLC define fractional lung volumes.

Typically, measurement of TLC and fractional lung volumes discussed below add little to spirometric measurements in identifying an obstructive ventilatory impairment; however, in the setting of borderline or atypical spirometric patterns these measurements may be helpful (146-

149). An increase in RV or RV/TLC above the 95$^{th}$ percentile may indicate hyperinflation or air trapping due to the presence of airway obstruction (102). Indeed, one of the earliest manifestations of small airway disease is an increase in RV or RV/TLC due to premature airway closure and air-trapping. With progression, lung hyperinflation and air trapping are reflected by increases in FRC or FRC/TLC and often in TLC. An increased FRC/TLC indicates a reduced inspiratory capacity (IC), which is a hallmark of COPD and closely associated with reduced exercise tolerance and dyspnea (150). Note that an increased RV/TLC may also be seen with muscle weakness or suboptimal effort and in some restrictive processes when TLC is reduced proportionally more than RV (151, 152) (Table 4).

## 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) (Figure 10; Table 6). A typical example is shown in Figure 9g. The presence of a restrictive impairment may be suspected from spirometry alone when FVC is reduced, $FEV_1$/FVC is normal or increased, and the flow–volume curve shows a convex pattern (reflecting high elastic recoil). However, a reduced FVC by itself does not prove a restrictive ventilatory impairment. Indeed, it is associated with a low TLC less than half the time (153, 154). Conversely, in adults a normal FVC and $FEV_1$/FVC are highly reliable at ruling out restriction as measured by low TLC (153). Note that a high PEF with normal $FEV_1$ may be seen in early interstitial lung disease before restriction limits FVC (155).

In most restrictive disease processes, the $FEV_1$, FVC and TLC are typically reduced in roughly the same proportion; this pattern is known as "simple restriction". However, some individuals present with a reduction in FVC that is out of proportion to the reduction in TLC, indicating a disproportionately elevated RV. This pattern is termed "complex restriction", and is associated with processes that impair lung emptying, such as neuromuscular disease, chest wall restriction, or occult obstruction with gas trapping. When associated with a low $FEV_1$/FVC ratio, it is termed a "mixed" disorder indicating the presence of both significant airflow obstruction and restriction. (156).

## 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. These patterns involve reduced VC, IC, and FVC with increased FRC and RV. Obstructive diseases, because they interfere with intra-pulmonary gas mixing, may also have important effects on gas dilution or washout techniques to measure FRC, $V_A$ and TLC. In these conditions, TLC assessed by gas dilution techniques will be low since only communicating gas volume is measured. In the presence of airway disease, a low TLC from a single-breath test (such as $V_A$ from the $D_LCO$) should not be interpreted as demonstrating restriction, since such measurements systematically underestimate TLC. The same is true of measuring lung volumes by multiple breath helium dilution or nitrogen washout (157). The degree of underestimation of lung volume increases as airflow obstruction and regional maldistribution of gas worsen. In the presence of severe airflow obstruction, TLC can

be underestimated by a gas dilution method by as much as 3 liters, greatly increasing the risk of misclassification of the type of physiological phenotype (158-160). A method of adjusting the single- breath $V_A$ for the effect of airflow obstruction has been published but needs further validation (125, 161). In the case of severe airflow obstruction, lung volume may be overestimated by body plethysmography, possibly due to heterogenous time constants (resulting in underestimation of alveolar pressure by mouth pressure) and increased extrathoracic airway compliance (160).

## Mixed Ventilatory Impairments

A mixed ventilatory impairment is characterized by the coexistence of obstruction and restriction and is defined physiologically 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. A typical example is presented in Figure 9h. If $FEV_1$/FVC is low, FVC is below its LLN, and there is no measurement of TLC by body plethysmography, it is possible that the reduction in FVC is due to an increased RV but a superimposed restriction of lung volumes cannot be ruled out (162). Conversely, when $FEV_1$/FVC is low and FVC is normal, a superimposed restriction of lung volumes can almost always be ruled out (153, 154). Mixed obstruction and restriction commonly involves the combination of a pulmonary parenchymal disorder plus a non-pulmonary disorder, such as COPD plus congestive heart failure (163). In cases where expiratory airflow obstruction and restriction are concomitantly present, the sensitivity of a reduced $FEV_1$/FVC or reduced TLC to identify one of these conditions is reduced. Table 7 shows a summary of spirometric and lung volume patterns with obstructive, restrictive and mixed ventilatory impairments.

## 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. In general, overall CO uptake is determined by the alveolar-capillary membrane surface area and diffusion properties, the volume of capillary blood hemoglobin in contact with alveolar gas ($V_c$), and the reaction rate ($\theta$) between hemoglobin and CO. The importance of hemoglobin cannot be overemphasized, and all interpretations must have the reference values adjusted for hemoglobin content.

The primary measurements are $K_{CO}$ (the measured CO concentration change over time) and $V_A$ (the volume of gas containing CO measured by the dilution of an inert tracer gas in the inspired volume). Their product ($D_LCO = K_{CO} \times V_A$) is the key index that is interpreted for gas transfer, with its pathophysiological importance previously reviewed (164, 165).

Interpreting a reduced $D_LCO$ must be done with these concepts in mind. The normal range for $D_LCO$ and VA should be based on the $5^{th}$ percentile and $95^{th}$ percentile (6, 11). 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. This is why in the setting of low $V_A$, a so-called "normal" $K_{CO}$ (often expressed as $D_LCO/V_A$) cannot "correct" for low lung volumes (154). Defining an impaired $K_{CO}$ in the setting of a low $V_A$ has minimal evidence to inform interpreters

and, in practice, becomes an empirical exercise often focusing on the observed $K_{CO}$ percent predicted (166). Figure 11 depicts a reasonable interpretation algorithm using $D_LCO$ along with $K_{CO}$, and $V_A$.

It is also useful to compare $V_A$ to TLC measured by body plethysmography to determine whether test gas maldistribution may contribute to lowering the $D_LCO$ (i.e., CO uptake can only be determined for the regions in which the test gases distribute). The normal value for the ratio of $V_A$/TLC in adults is ~ 0.85-0.90 (166). Values significantly below this suggest that gas mixing impairments are likely contributing to a low measured $D_LCO$. In the absence of plethysmographic lung volume data, the presence of a steep downward slope to the inert gas tracing during exhalation suggests the possibility of gas maldistribution. There are no ideal ways to adjust for these conditions and the interpreter can only note that the problem exists (167, 168).

## The Future of Pulmonary Function Interpretation

Normal results from routine PFTs do not exclude physiological impairment, especially in mild disease and in children. Specialized PFTs when used together with routine PFTs, may provide a more comprehensive and multidimensional evaluation of lung function and may further improve interpretation. There is also rapid development of wearable devices which allow continuous monitoring of ventilatory indices during daily life (i.e., under natural physiological conditions) (169). Together with applications that capture and interpret data, and integrated enterprise and cloud data repositories, wearable devices will provide novel solutions for personalised respiratory medicine, including tele-monitoring of respiratory function.

In the era of precision medicine and novel prediction tools, more sophisticated diagnostic models should be developed to more accurately identify early determinants of reductions in lung function. Longitudinal data across the life course is essential to identify opportunities for early intervention. There is exciting research in this field that will likely provide significant improvements, especially around the uncertainty of measurements. There are ongoing efforts devoted to the development of artificial intelligence (AI) and machine learning (ML) approaches to both novel tests as well as currently standard tests. The updated interpretation standards may inform future AIML algorithms and ensure uncertainty is considered in the algorithm. Examples of uses in standard tests include AI analysis of the expiratory flow volume pattern as noted above along with measurements of inert gas washout and the CO measurements through the $D_LCO$ exhalation maneuver (170). AIML-based software may also provide more accurate and standardized interpretations and may serve as a powerful decision support tool to improve clinical practice (171, 172). AIML may help to develop personalized, unbiased prediction of normal lung function. AIML may enhance the analysis of lung function data by identifying complex, multidimensional patterns associated with disease subtypes. While such algorithms may help to reduce any bias from poor quality data (172), AIML must use only good quality data in training to avoid introducing bias into any algorithms.

The widespread use of electronic health records (EHR)(173) for data collected during the course of routine clinical practice and large clinical databases from multicentre randomised controlled trials offer unique data sources for training AIML algorithms. These algorithms may be combined with Natural Language Processing, a set of methods which apply linguistics and ML to large corpora of clinical textual passages in order to extract structured information at a large scale. Using linguistics and computer science to process and understand text written in natural language has the

potential to extract relevant information on a large scale. Sharing and using individual data requires a robust and appropriate internationally recognised ethical, legal and information governance framework which has yet to be established.

## Conclusion

When interpreting PFT results, a clinician must interpret a particular result as within or outside the normal range for an individual of that age, sex, height and ethnic background based on reference equations, and consider how measures of lung function change over time. Interpretation of 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 pre-test probability of disease may influence what is the appropriate threshold for each individual, and (iii) how valid for the individual is the reference population against which the test is being judged.

The requirements for obtaining a technically acceptable measurement have already been set out (4, 5, 7). The quality of individual effort must therefore also be considered when assessing how representative the obtained result is of the individual's lung function. A poor-quality result might be sufficient to answer a particular clinical question, such as if there is sufficient function to perform a lobectomy. However, a poor-quality result should ideally be repeated before important decisions are made from the result. Some lung function indices are inherently more reproducible over time, such as $FEV_1$, $FEV_6$ and FVC, and will lead to more certainty in decision making than less reproducible tests.

There is clearly a level of uncertainty about the best choice of reference equations that considers an individual's sex, geographic and ancestral background. The GLI equations are the most generalizable suite of equations to date. Nonetheless it remains unclear how to apply such a reference equation without introducing the possibility of bias. Clinicians must always take this increased uncertainty into consideration when making diagnoses and treatment recommendations.

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 to interpretation (not simply relying on whether results are within or outside the normal range) is imperative for appropriate interpretation of lung function when pre-screening for employment, tracking the effects of exposure, for disability assessment, and risk assessment for therapies potentially toxic to the lungs. To date no satisfactory outcome-based thresholds for lung function have been defined; therefore, careful consideration of the medical and exposure history of an individual is necessary when interpreting lung function results.

Importantly, clinicians should take time to explain PFT results to individuals and how these are used to guide decisions. A recent survey of people living with respiratory conditions found that more than half (59.4%) did not know what $FEV_1$ meant or what it represented for their condition (174). People living with respiratory conditions, as well as those referred for PFT, may want to know what their results mean for them.

Translation of these recommendations to clinical practice will require a paradigm shift whereby the idea of an absolute level of ideal lung function (i.e., the predicted value) is replaced in favor of a range of values that are observed in the majority of individuals without respiratory disease (i.e.,

z-scores or percentiles). Graphical displays on the report can be helpful in communicating results. Interpretation of results should consider the inherent biological variability of the tests and the uncertainty of the test result. We anticipate that these interpretation recommendations will be considered in future disease specific guidelines.

Table 1. Summary of GLI equations for spirometry and current evidence regarding application of these equations in different populations.

| GLI reference population | GLI data sources | Population/Ancestral origin | Considerations |
|---|---|---|---|
| White | Europe, Israel, Australia, USA, Canada, Brazil, Chile, Mexico, Uruguay, Venezuela, Algeria, Tunisia | White (European) Hispanic (European) | Suitable for use in white European populations (36, 175, 176) |
| Black | African American | Black (North America) | |
| South East Asian | Thailand, Taiwan, China (including Hong Kong) | Asian | |
| North East Asian | Japan, Korea | | North East Asian equations demonstrate poor fit when applied to contemporary populations (29) |
| Multi-ethnic | Average of the other 4 GLI groups | Multiracial; Black South Africa (177); India (178); Unknown; | Indian(178) and South African (177) data based on single prospective study in children |

Table 2. The 5th percentile values (Lower Limit of Normal) for various lung function indices expressed as percent predicted for four individuals. GLI reference equations were used for all indices (10-12). The table demonstrates that the equivalent % predicted value at the lower limit of normal varies considerably for individuals of different ages and for each pulmonary function index and highlights the potential bias introduced when using percent of predicted thresholds for defining normal limits.

| | **A:**<br>**Male**<br>**Age 10**<br>**Height 137 cm** | **B:**<br>**Female**<br>**Age 15**<br>**Height 162 cm** | **C:**<br>**Male**<br>**Age 25**<br>**Height 175 cm** | **D:**<br>**Female**<br>**Age 25**<br>**Height 165 cm** | **E:**<br>**Male**<br>**Age 80**<br>**Height 175 cm** | **F:**<br>**Female**<br>**Age 80**<br>**Height 165 cm** |
|---|---|---|---|---|---|---|
| **$FEV_1$** | 81.3 | 80.5 | 80.5 | 80.2 | 69.4 | 70.0 |
| **FVC** | 81.2 | 80.4 | 80.9 | 79.9 | 72.0 | 70.0 |
| **$FEV_1$/FVC** | 87.4 | 87.8 | 86.9 | 87.2 | 80.0 | 80.5 |
| **TLC** | 78.0 | 79.8 | 80.0 | 80.4 | 77.8 | 77.6 |
| **FRC** | 70.9 | 69.9 | 69.6 | 72.5 | 69.8 | 70.7 |
| **RV** | 40.6 | 40.9 | 49.1 | 52.5 | 55.7 | 57.7 |
| **$D_LCO$** | 75.4 | 77.5 | 79.0 | 77.8 | 72.4 | 74.5 |

Table 3. 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 lung. This may reflect lung parenchymal 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. Impaired gas transfer is generally assessed by analysis of carbon monoxide uptake during a breath-hold ($D_LCO$). Some conditions can lead to an increase in gas transfer. |

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

Table 4. 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 (121)** | ↓ | ↓ | 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 (122) |
| **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(118)** | Normal | Normal /↑ | ↓ | May be normal variant |

Table 5. Lung Function Indices Capable of Differentiating Extrathoracic from Intrathoracic Obstruction in adults (142-144, 155)

| | **Extrathoracic Obstruction** | | **Intrathoracic Obstruction** |
|---|---|---|---|
| | **Fixed** | **Variable** | |
| **PEF** | Decreased | Normal or decreased | Decreased |
| **$FIF_{50}$** | Decreased | Decreased | Normal or decreased |
| **$FIF_{50}/FEF_{50}$** | ~1 | <1 | >1 |

Table 6. 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 and RV/TLC elevated; gas trapping if only RV/TLC elevated (e.g., COPD) |
| **Simple Restriction** | ↓ | ↓ | ↓ | Normal | Normal | e.g., ILD |
| **Complex Restriction(156)** | ↓ | ↓ | 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. TLC is reduced especially with diaphragm weakness. RV is increased especially with expiratory muscle weakness. |
| **Suboptimal effort** | ↓ | Normal | ↑ | ↑ | ↑ | Especially when effort appears insufficient |
| **Obesity** | Normal /↓ | ↓ | Normal /↑ | Normal /↓ | Normal /↑ | ERV low; reduced TLC at very high BMI (>40) (37) |

Table 7. Summary of Types of Spirometrically defined and Lung Volume defined Ventilatory Impairments.

| Ventilatory Impairments | Patterns |
|---|---|
| **Obstruction** | • $FEV_1/FVC < 5^{th}$ percentile.<br>• Decrease in flow at low lung volume may reflect small airway disease in individuals (100, 101, 108).<br>• Concomitant decrease in $FEV_1$ and FVC most commonly due to poor effort but may reflect airflow obstruction or a restrictive pattern. Recommend lung volumes.<br>• Measurement of absolute lung volumes may assist in diagnosis and assessment of hyperinflation(108).<br>• Measurement of airflow resistance may assist in diagnosis(139). |
| **Restriction** | • TLC $<5^{th}$ percentile<br>• Reduced FVC does not prove restrictive impairment but may be suggestive of restriction when $FEV_1/FVC$ is normal or increased.<br>• Low TLC from single breath test not reliable, especially with low $FEV_1/FVC$ (125).<br>• A normal FVC usually excludes restriction(153) |
| **Mixed** | • $FEV_1/FVC$ and TLC both $< 5^{th}$ percentile. |

# Figure Legend

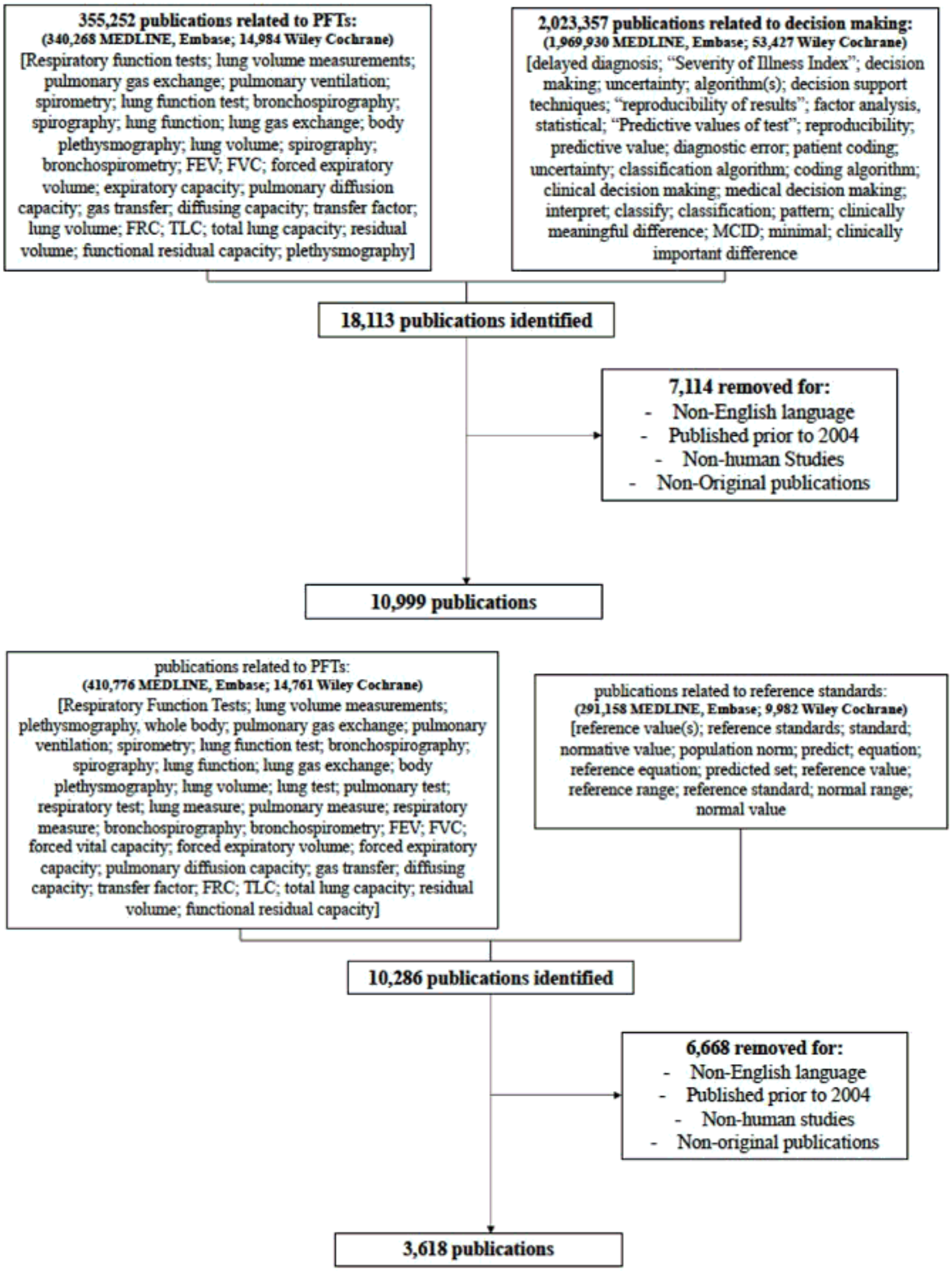

Figure 1. Summary of literature search terms and results a) reference equations for lung function and b) interpretation of pulmonary function tests.

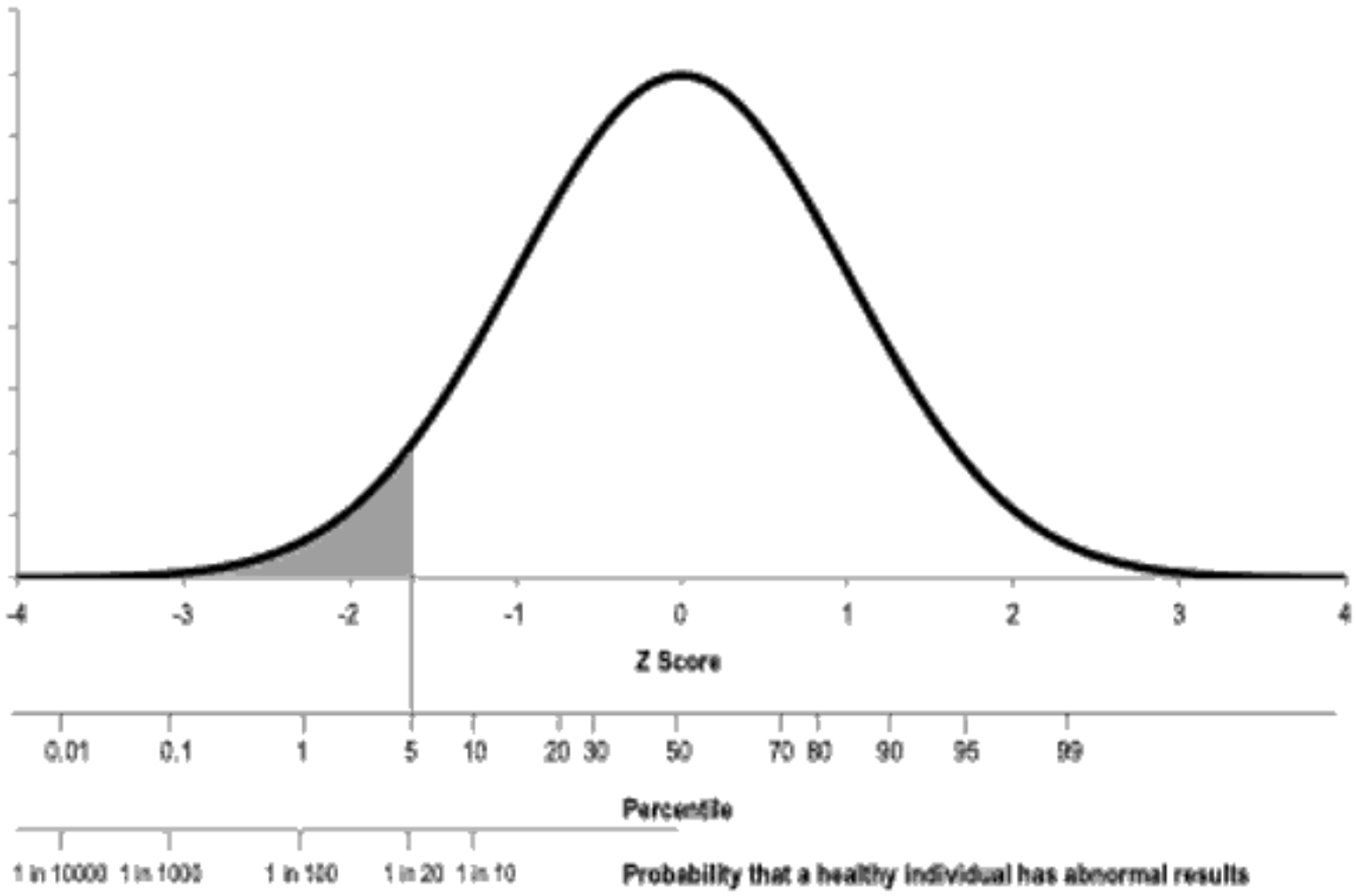


Figure 2. The normal distribution with z-scores and percentiles displayed. Percentile can be interpreted as the probability that a healthy individual has results inside the normal range (i.e., the false positive rate).

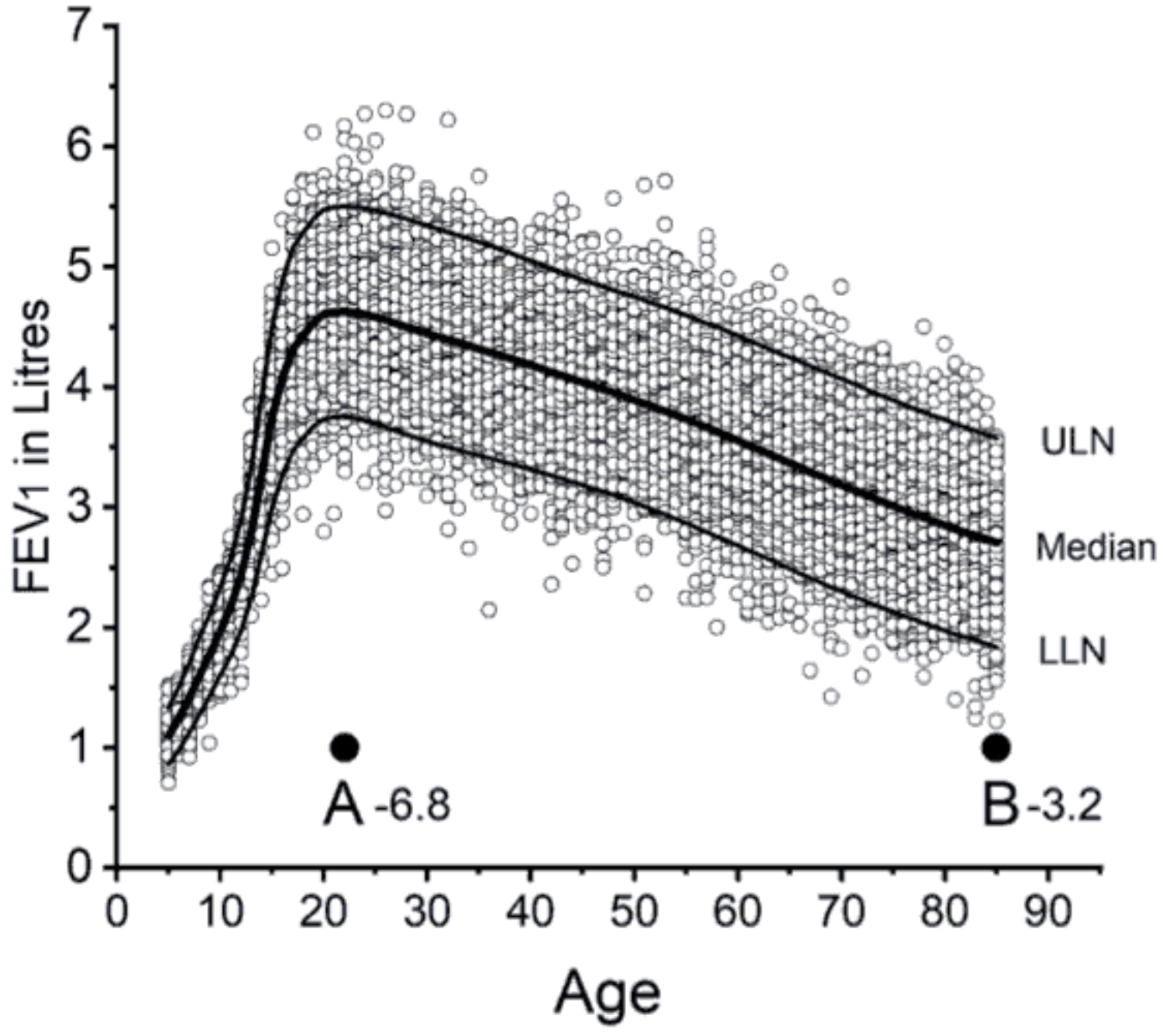


Figure 3. Plot of population $FEV_1$ data for males of median height for age between ages 5 to 85 years with the upper limit of normal (ULN 95$^{th}$ percentile), lower limit of normal (LLN 5$^{th}$ percentile) and median predicted shown as solid lines derived from GLI spirometry equations (10). The 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.

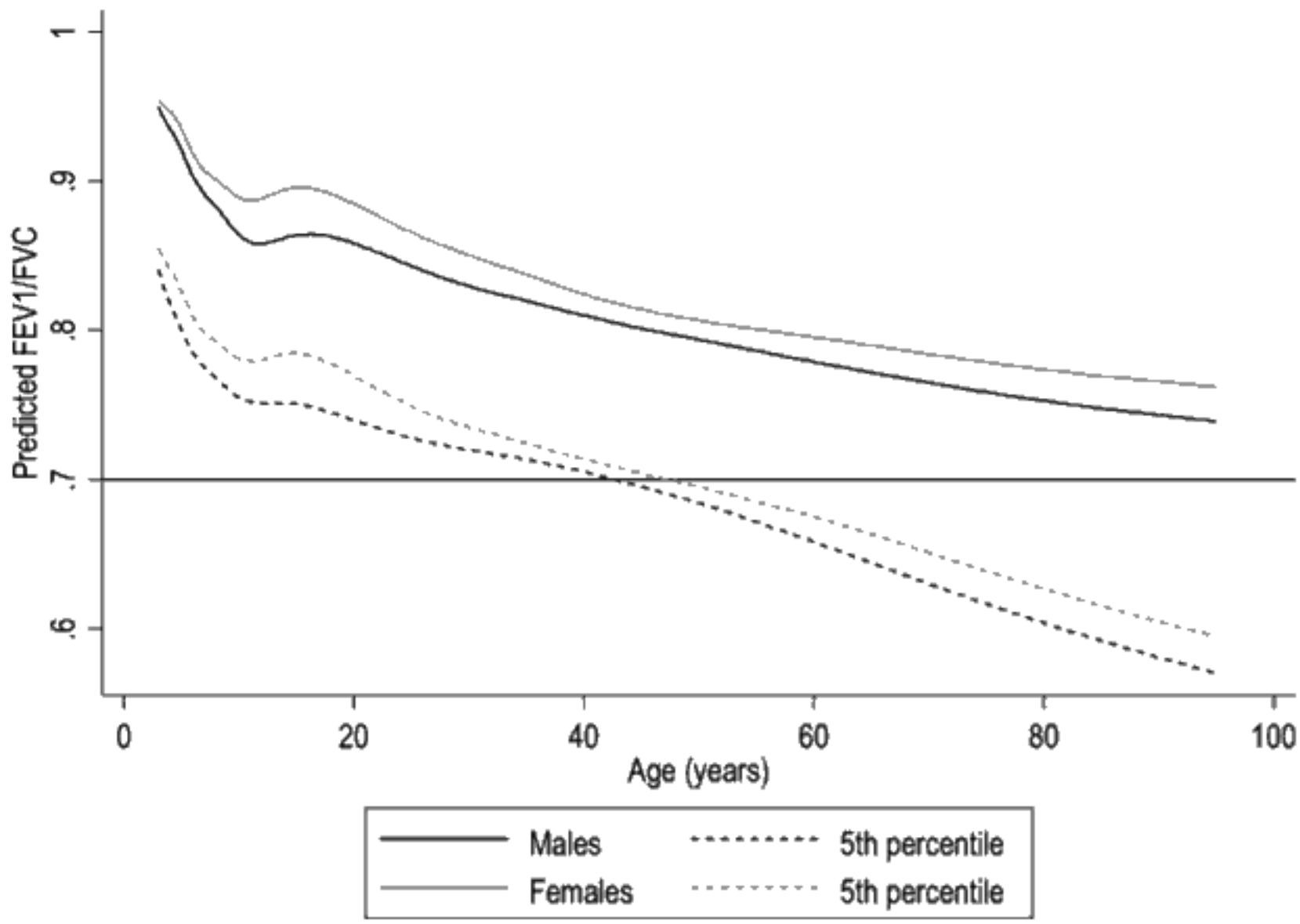


Figure 4. $FEV_1$/FVC predicted and limits of normal compared with the fixed cut-off of 0.7

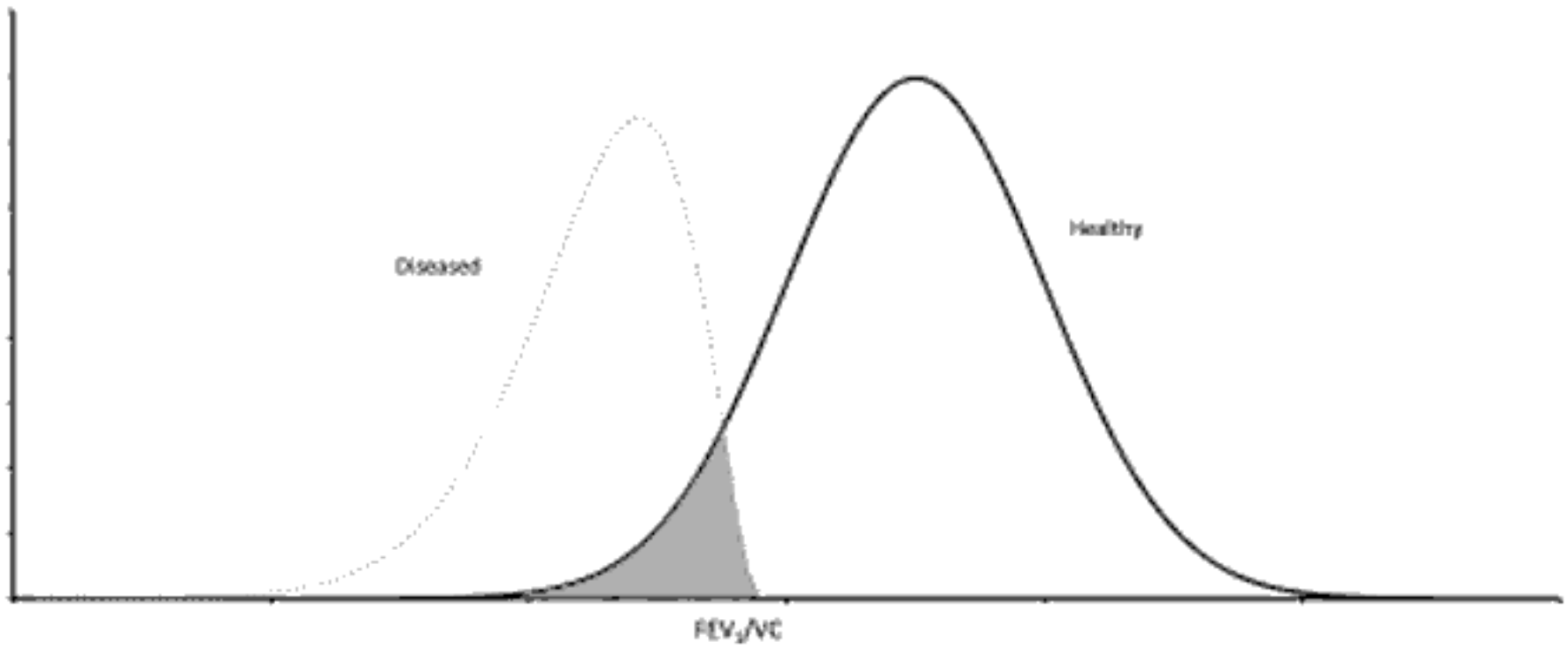


Figure 5. Theoretical distribution of health and disease. The shaded area is the zone of uncertainty.

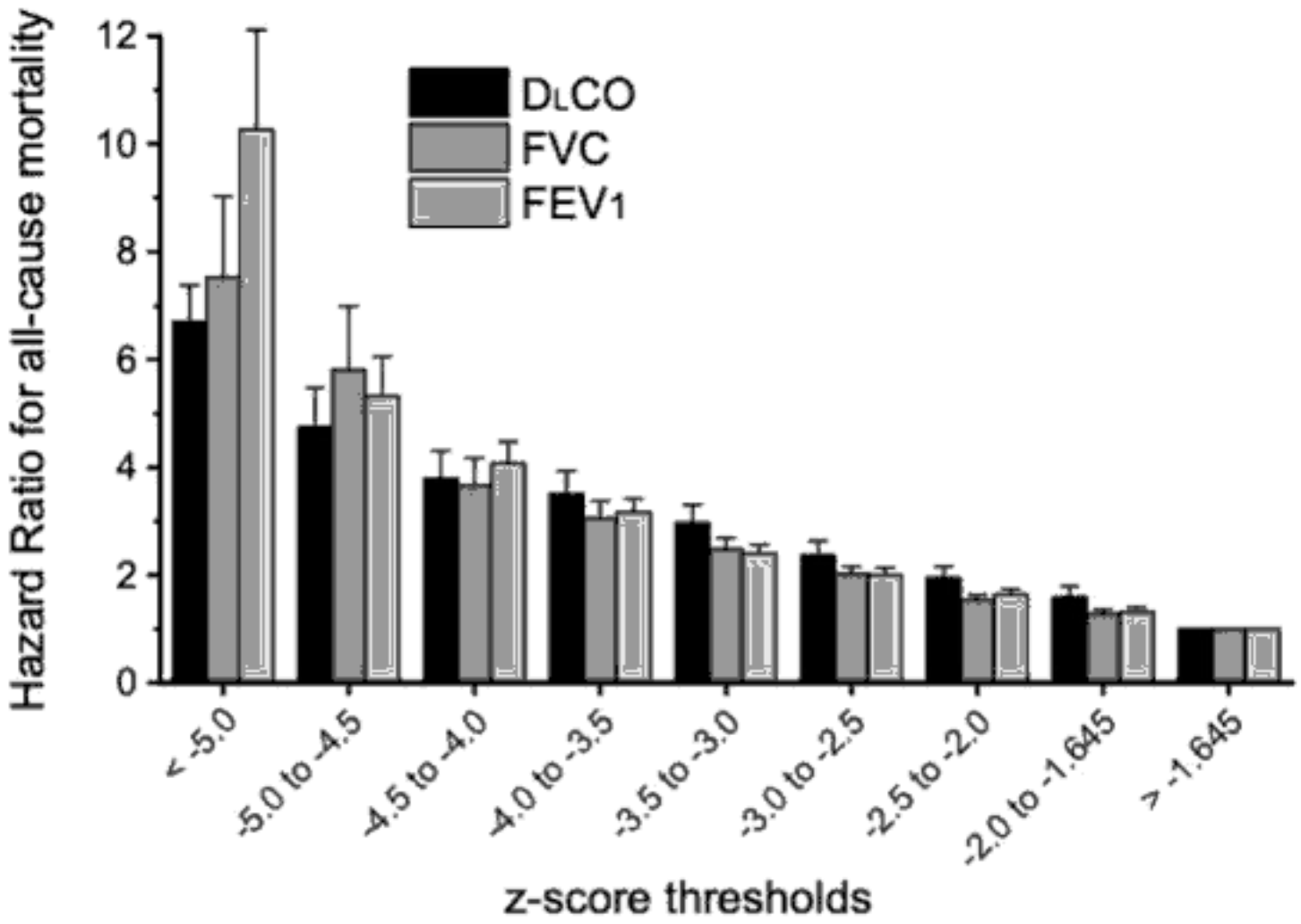


Figure 6. Plots of hazard ratios with 95% confidence limit for all-cause mortality for $D_LCO$, FVC and $FEV_1$ for bins of z-score values. For FVC and $FEV_1$ this was from 27,021 participants between the ages of 20 and 97 years (comprising 13,899 from a population survey, 1094 individuals with COPD (100) and 12,028 individuals seen in the clinic) and for $D_LCO$ this was from 13,829 clinic patients (88). HR were derived from Cox proportional hazard regression stratified for age and sex. The comparator for mortality were all participants with z-scores above the lower limit of normal (-1.645) who were assigned HR=1.

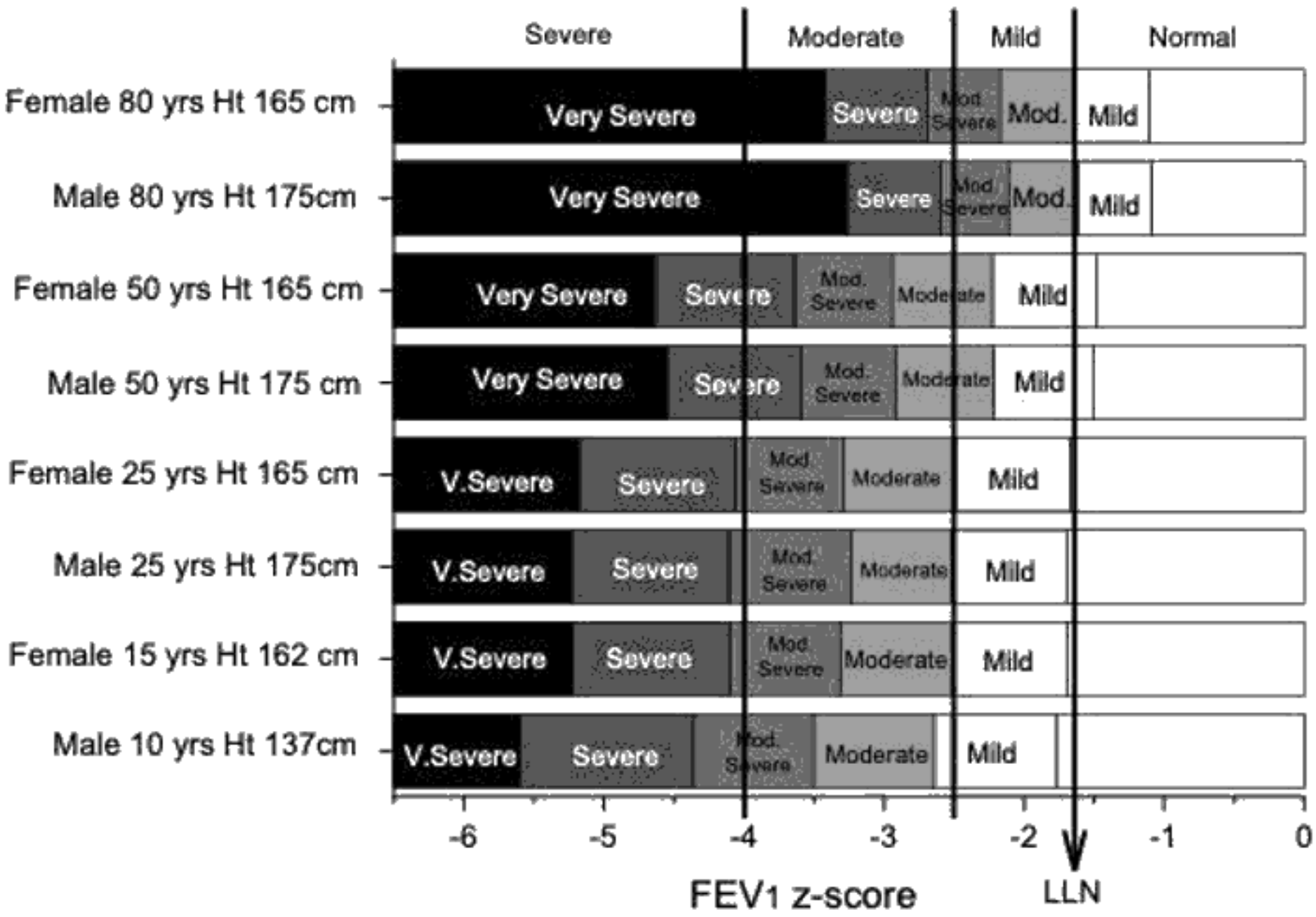


Figure 7. A plot of the old ATS/ERS 2005 recommended thresholds for degree of lung function reduction grading of airflow obstruction using 70%, 60%, 50% and 35% of predicted $FEV_1$ for eight individuals with the $FEV_1$ cut points expressed as z-score values on the abscissa scale. The lower limit of normal (LLN) at the 5$^{th}$ percentile (-1.645) is shown as a vertical arrow and the two new proposed cut levels of -4 and -2.5 z-score are shown as solid lines with the new gradings above.

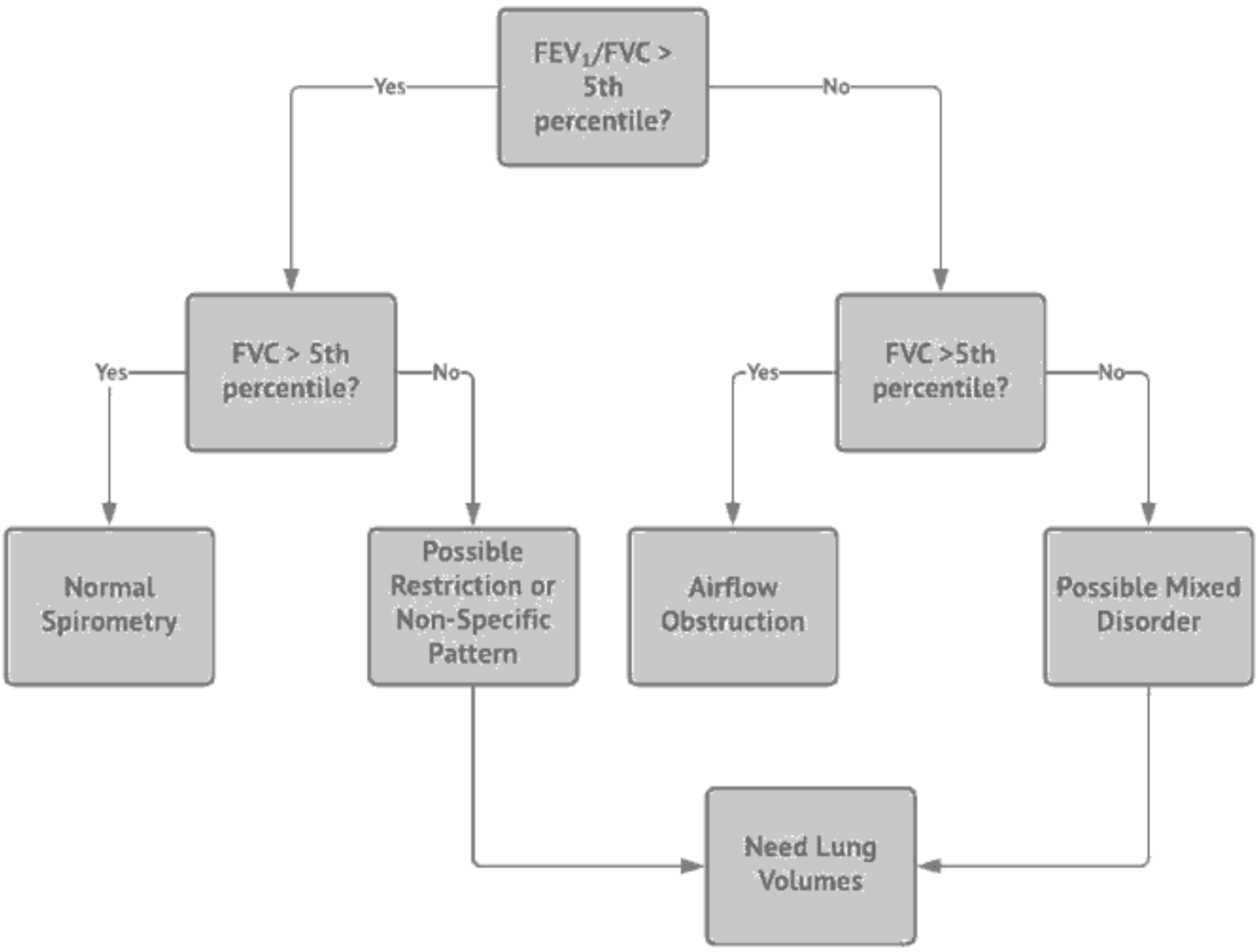


Figure 8. Approach to Interpretation of Spirometry. Beginning with the ratio of $FEV_1$/FVC, determine whether obstruction is present based on whether the ratio is low (right side of figure). If obstruction is present, then assess the FVC to determine whether there is simply obstruction or whether there may be concomitant restriction ("mixed disorder"). Measurement of TLC will define restriction, so if TLC is normal, then there is only obstruction, but if TLC is low, then there is concomitant restriction. If the $FEV_1$/FVC is normal, signifying no obstruction (left side of figure), then once again assess the FVC. If it is normal, then spirometry is normal, but if it is low then there may be possible restriction. This must be determined by measurement of TLC. If the TLC is low, then spirometry is consistent with restriction. If restriction is ruled-out by a normal TLC, then the pattern of impairment of low FVC with normal $FEV_1$/FVC has been dubbed the possible restriction or non-specific pattern, which may include diseases causing obstruction or restriction. Restriction presenting as the "non-specific" pattern is often caused by a chest wall or neuromuscular disorder.

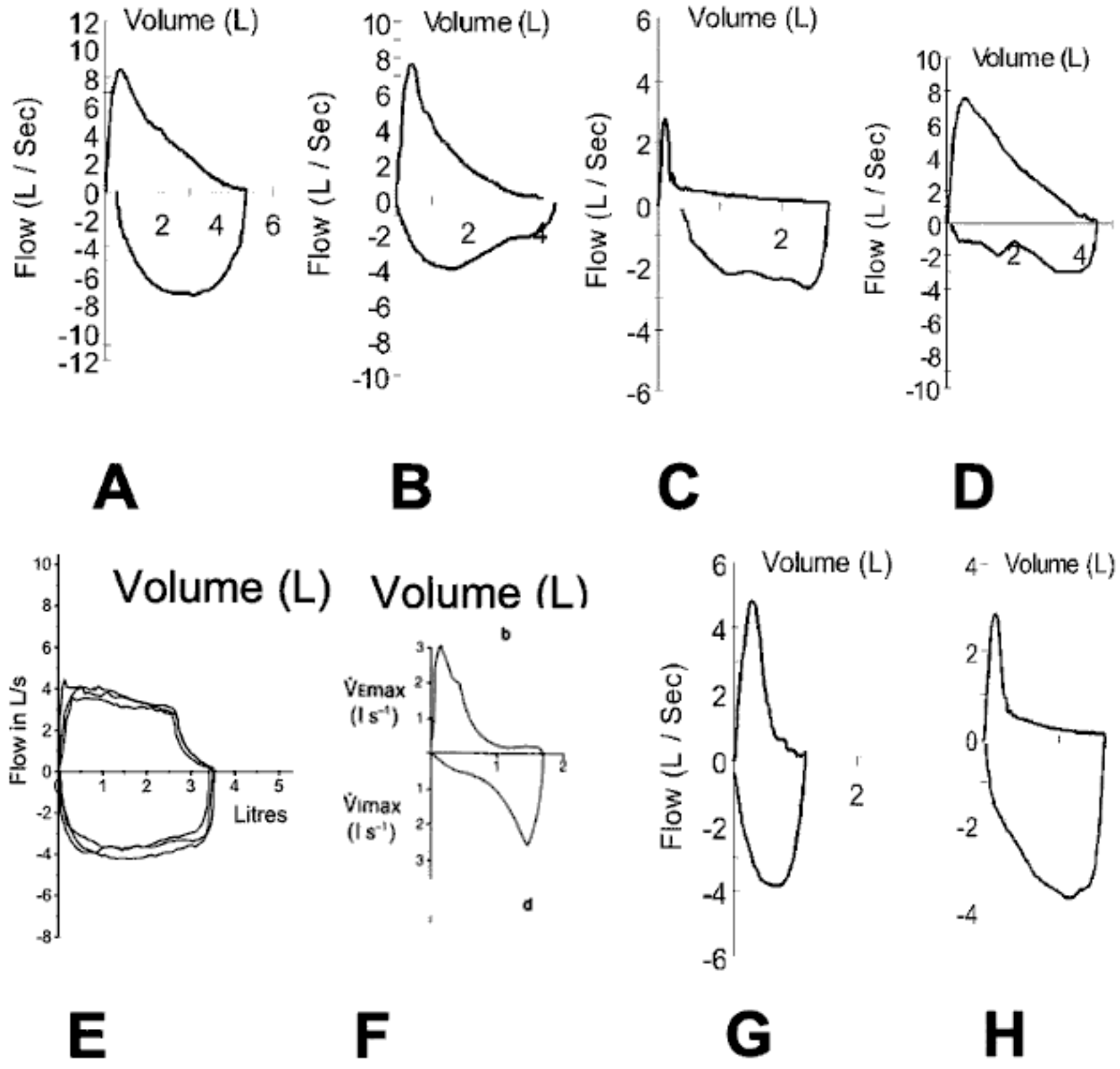


Figure 9. Examples of typical Flow-Volume Loop Configurations for a) normal; b) mild-moderate obstruction; c) severe obstruction; d) variable extrathoracic obstruction; e) fixed large/central airway obstruction; f) unilateral main stem bronchial obstruction (179); g) restriction; and h) mixed disorder.

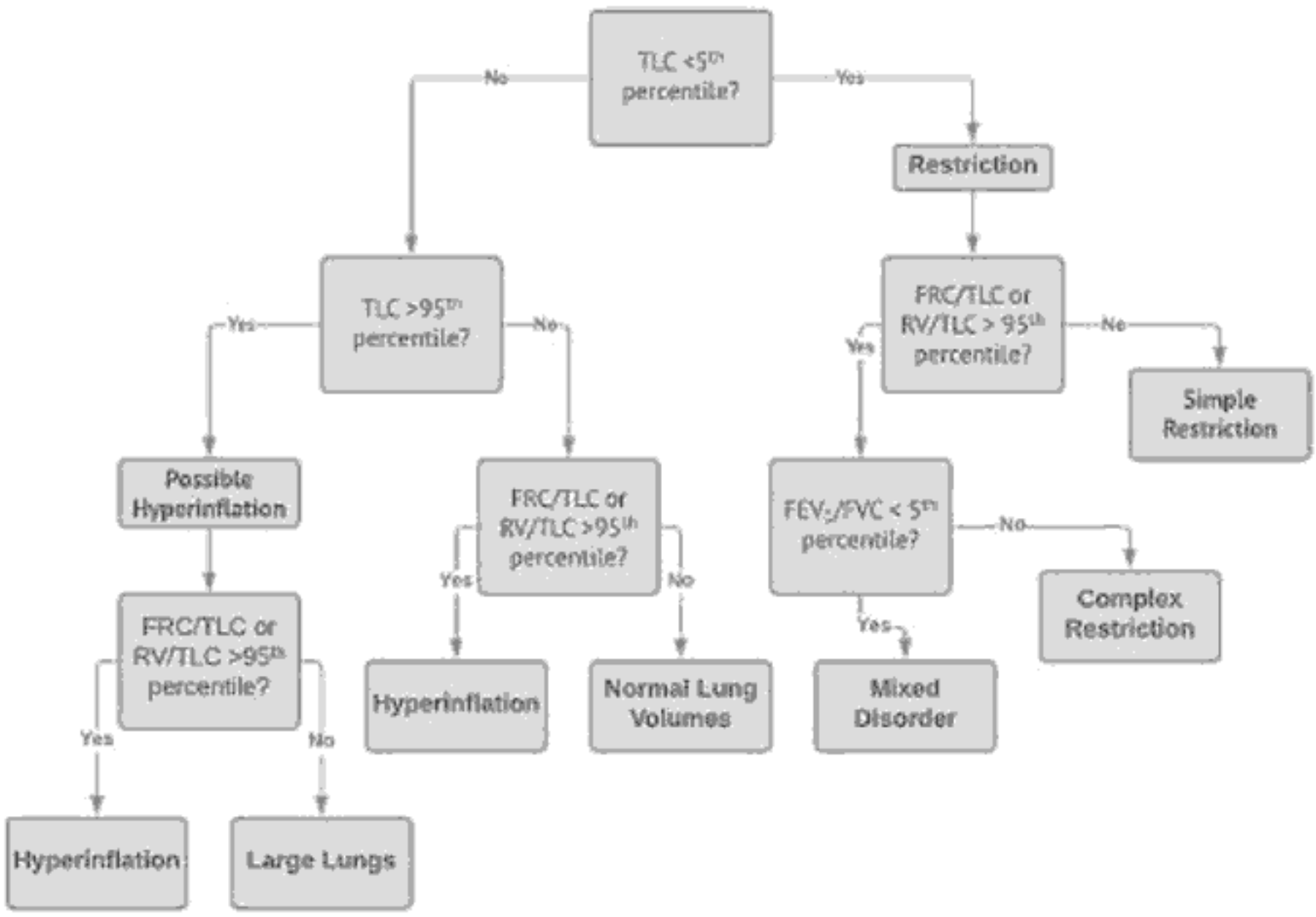


Figure 10. Approach to Interpretation of Lung Volumes. Beginning with the TLC, determine whether restriction is present based on whether the TLC is low (right side of figure). If restriction is present, then assess the relative size of FRC or RV to the TLC: if the FRC/TLC or RV/TLC are elevated, then determine if there is airflow obstruction based on the $FEV_1$/FVC ratio. If obstruction is present, then this is a mixed disorder, but if not present, then it may be a form of "complex restriction", which implicates more than one process occurring to lower the FVC out of proportion to the reduction in TLC. Obesity or neuromuscular disease are common causes of complex restriction. If the FRC/TLC and RV/TLC ratios are normal in the setting of reduced TLC, then simple restriction is present. If the TLC is normal, ruling out restriction (left side of figure), then the next step is to determine if lung volumes are overall normal, or the individual has large lungs, or they may be hyperinflated, by following the pathways indicated. Note that hyperinflation may occur with TLC, FRC and RV, or may occur with FRC or RV alone; in the former situation, the rise in TLC indicates loss of elastic recoil, so is likely due to emphysema, whereas in the latter situation, the increase in FRC or RV without increase in TLC may be seen in chronic bronchitis or asthma.

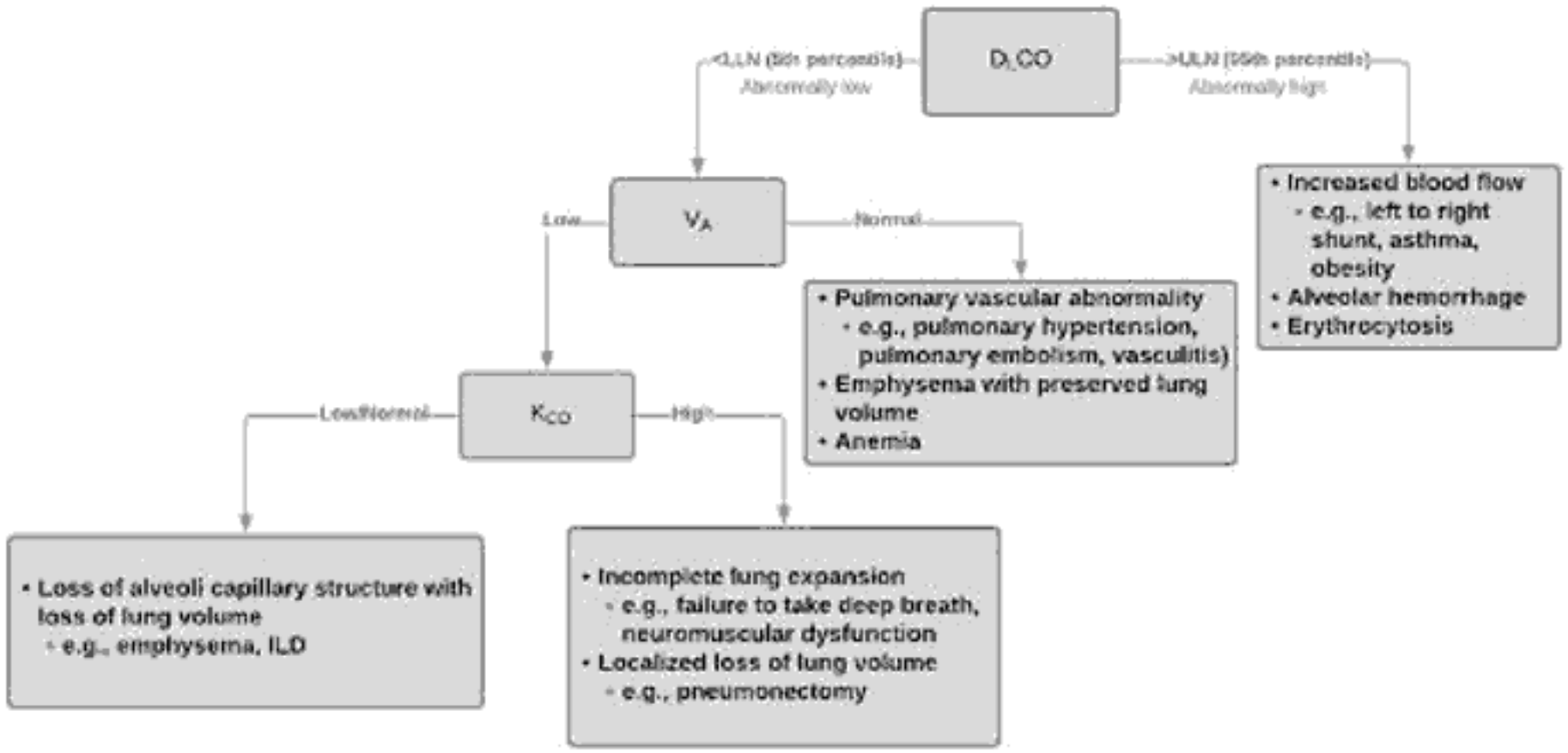


Figure 11. Approach to interpretation of $D_LCO$. First determine if the $D_LCO$ is low, or high, based on the lower and upper bounds defined by the 5th and 95th percentiles of the reference values. A high $D_LCO$ is almost always due to increased pulmonary blood volume, as in a left to right shunt, increased hemoglobin, as in erythrocytosis, or free hemoglobin in any component of the airway, as in alveolar hemorrhage.(180) To further understand the cause of a low $D_LCO$, next examine its components, $V_A$ and $K_{CO}$. If $V_A$ is normal then this is consistent with pulmonary vascular impairment, emphysema with preserved lung volume, or anemia. If $V_A$ is low and $K_{CO}$ is low or normal, then there is typically loss of alveolar capillary structure, such as in interstitial lung disease, or emphysema with loss of lung volume. If $V_A$ is low and $K_{CO}$ is high, then there is a low lung volume state, either due to localized loss of lung volume, such as from lung resection, which may raise $K_{CO}$ somewhat, or incomplete lung expansion, such as failure to fully inspire, which can increase $K_{CO}$ substantially.

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

## Executive Summary

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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 $FEV_1Q$ 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 $FEV_1Q$ 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

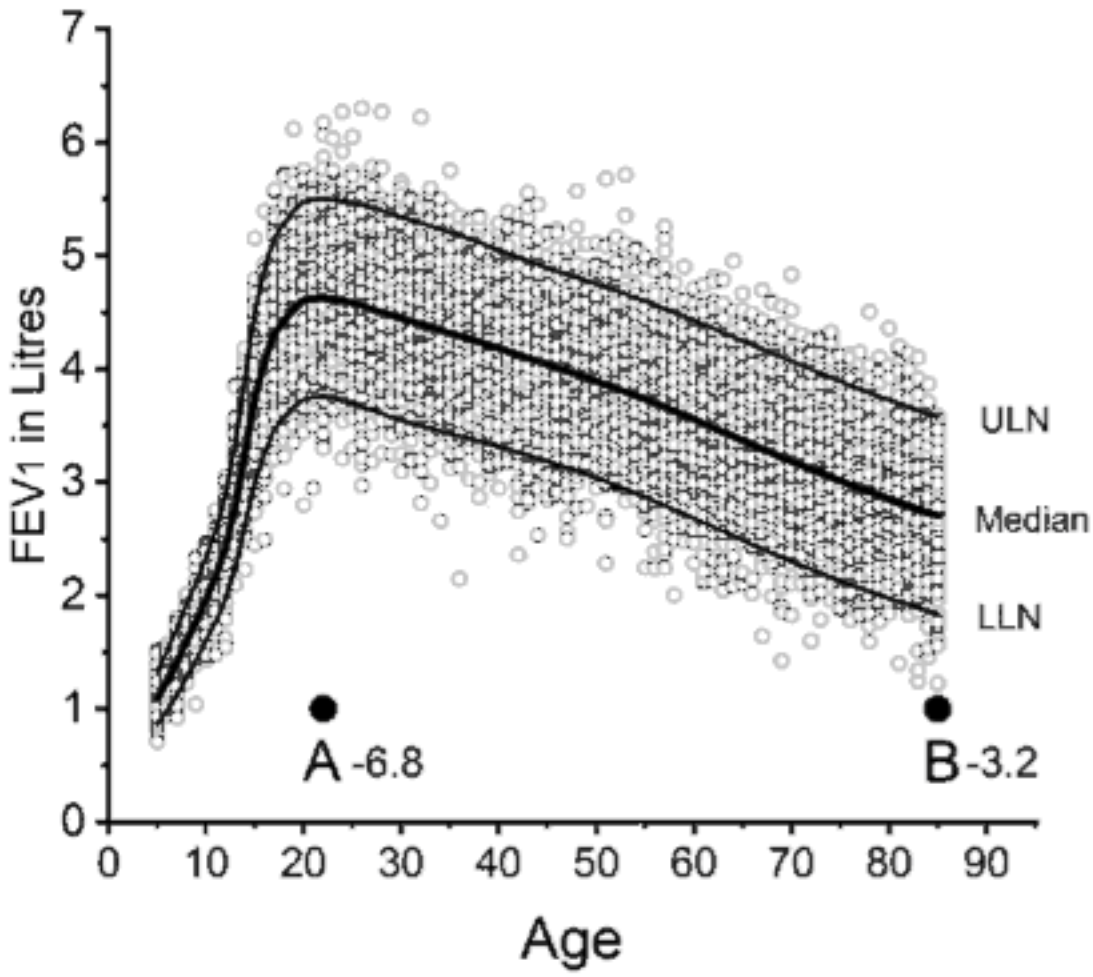
In the era of precision medicine and novel prediction tools, more sophisticated diagnostic models should be developed to identify more accurately the early determinants of reduced lung function. The development of artificial intelligence (AI)/machine learning (ML) approaches to PFT interpretation is 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

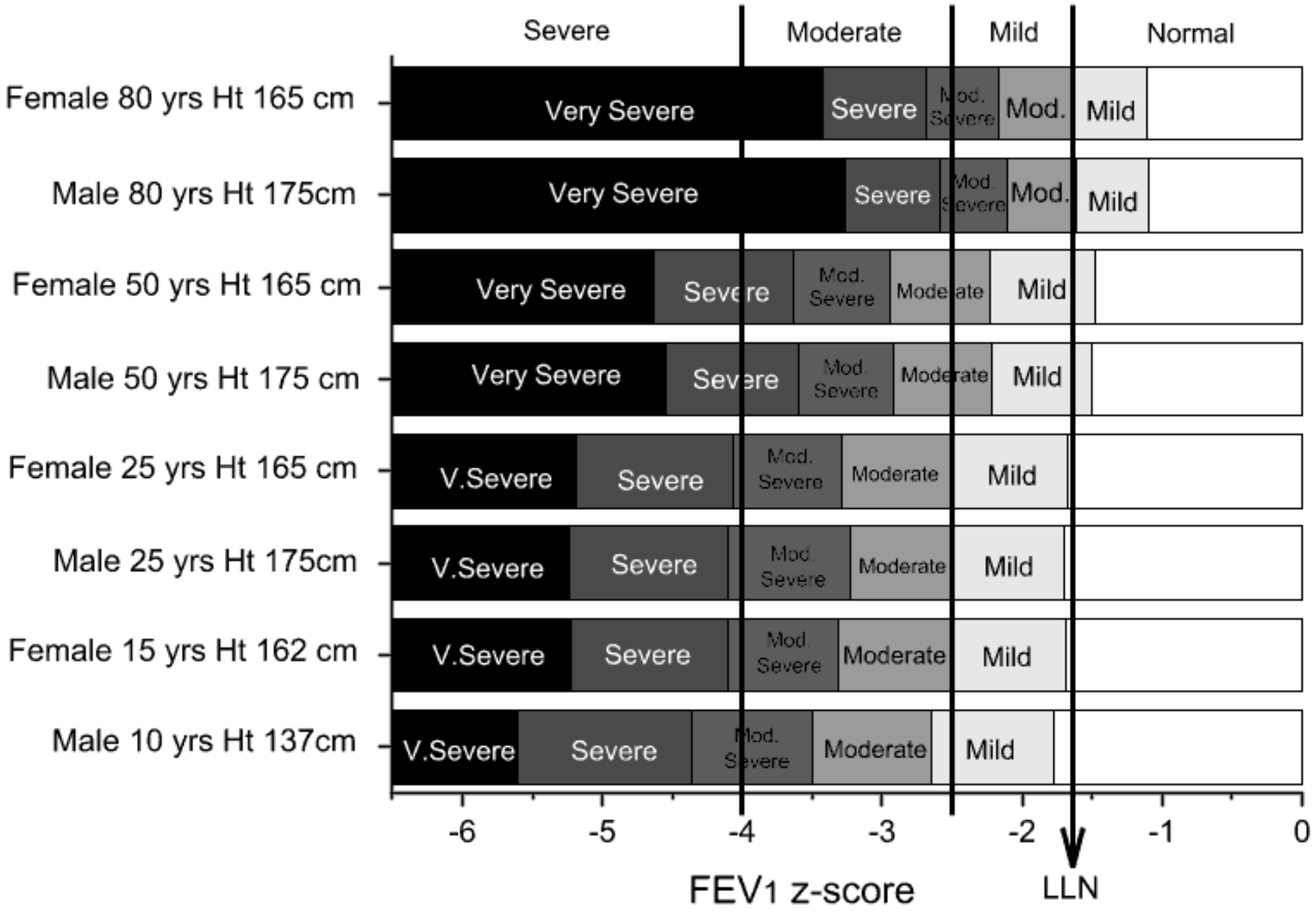
Interpreting PFTs must take into account a level of uncertainty relating to (i) how representative the obtained result was of the individual's lung function at the time of testing, (ii) how the pre-test probability of disease may influence what is the appropriate threshold for that individual, and (iii) 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 95$^{th}$ percentile), lower limit of normal (LLN 5$^{th}$ 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).<br><br>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.<br>• Decrease in flow at low lung volume may reflect small airway disease in individuals.<br>• Concomitant decrease in $FEV_1$ and FVC most commonly due to poor effort but may reflect airflow obstruction. Recommend lung volumes.<br>• Measurement of absolute lung volumes may assist in diagnosis and assessment of hyperinflation.<br>• Measurement of airflow resistance may assist in diagnosis. |
| **Restriction** | • TLC < 5th percentile<br>• Reduced FVC does not prove restrictive impairment but may be suggestive of restriction when $FEV_1/FVC$ is normal or increased.<br>• Low TLC from single breath test not reliable, especially with low $FEV_1/FVC$.<br>• A normal FVC usually excludes restriction |
| **Mixed** | • $FEV_1/FVC$ and TLC both < 5th percentile. |

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

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

| | |
|---|---|
| ○ Mild = >60% predicted and < LLN<br>○ Mod = 40-60% predicted<br>○ Severe = < 40% predicted | |
| <u>Classification of Physiological Impairments</u><br>• 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<br>• Restriction:<br>○ TLC < 5th percentile and normal $FEV_1/VC$<br>○ Mixed = $FEV_1/VC$ and TLC < 5th percentile<br>• Gas Transfer Impairment:<br>○ $D_LCO$, KCO < 5th percentile<br>○ Importance of adjustments for Hb, COHb | <u>Classification of Physiological Impairments</u><br>• 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<br>• Restriction:<br>○ TLC < 5th percentile<br>○ Simple vs. complex restriction<br>○ Hyperinflation<br>○ Mixed<br>• Gas Transfer Impairment<br>○ $D_LCO$ < 5th percentile<br>○ Using VA, KCO to classify low $D_LCO$ |

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