

# Landmark papers in respiratory medicine

## Changes in FEV<sub>1</sub> over time in COPD and the importance of spirometry reference ranges: the devil is in the detail

Spirometry plays a pivotal role in the diagnosis and management of COPD and other respiratory diseases. Since lung function varies with age, height, sex and ethnicity, accurate interpretation is dependent upon using appropriate reference ranges. In this article, we will present two landmark papers: one on changes in forced expiratory volume in 1 s (FEV<sub>1</sub>) over time in COPD [1] and the other focussing on spirometry reference ranges produced by the Global Lung Function Initiative (GLI) [2].

### Rate of FEV<sub>1</sub> decline over time in COPD

The 1977 review published by FLETCHER and PETO [3] entitled “The natural history of chronic airflow obstruction” highlighted the importance of FEV<sub>1</sub> as a sensitive measure of rapid decline in lung function in a male smoking population over a 7-year period. For many, this article helped shape their understanding of chronic obstructive airway physiology and how to interpret pulmonary function in relation to ageing and lung disease. It highlighted the importance of understanding the complex processes contributing to rapid decline in lung function, especially in the early stages of airways disease.

It was over 30 years later, in 2011, that VESTBO *et al.* [1] presented the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints). This was a large observational study of 2163 patients of varying COPD severity followed

over 3 years. This study provided new insights and revealed a more complicated nature of COPD progression (decline in FEV<sub>1</sub> from baseline) than previously thought. The aim of the study was to review the variability and determinants of the rate of decline in FEV<sub>1</sub> over time in COPD. They also explored whether patient assessments or biomarkers in subgroups of COPD could predict changes in FEV<sub>1</sub>.

### Important findings of the ECLIPSE study

Over a 3-year period, the mean $\pm$ SE rate of decline in FEV<sub>1</sub> (33 $\pm$ 2 mL $\cdot$ year<sup>-1</sup>) was not hugely greater than in healthy nonsmokers. In patients with COPD, the FEV<sub>1</sub> decline varied significantly, with between-patient standard deviation of 59 mL $\cdot$ year<sup>-1</sup>. Surprisingly, only 38% of the cohort had a significant decline of 40 mL $\cdot$ year<sup>-1</sup>, 31% had between 21 and 40 mL $\cdot$ year<sup>-1</sup>, and 8% had an increase of 20 mL $\cdot$ year<sup>-1</sup>.

The rate of decline over time was associated with several factors. Early-stage COPD patients had a faster rate of decline in FEV<sub>1</sub> than those with later-stage COPD, suggesting a concept of “burnout”. The number of cumulative pack-years had no association with FEV<sub>1</sub> rate of decline. However, current smoking was strongly associated with an additional 21 mL $\cdot$ year<sup>-1</sup> decline in FEV<sub>1</sub>. Exacerbations were weakly associated with an accelerated decline in FEV<sub>1</sub> of 2 mL $\cdot$ year<sup>-1</sup> and emphysema on computed

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 @ERSpublications

**A discussion of two landmark papers highlighting the use of spirometry as a sensitive measure of the rate of decline in FEV<sub>1</sub> in COPD, and the importance of using the Global Lung Function Initiative reference data** <http://bit.ly/2CONHqa>



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tomography was associated with an excess loss of 13 mL·year<sup>-1</sup>. A significant bronchodilator response was associated with an accelerated decline of 17 mL·year<sup>-1</sup> and patients that were on standard care over the 3-year period, and medications such as inhaled corticosteroids/long-acting  $\beta$ -agonists, had a slow decline in lung function.

The ECLIPSE study showed that the rate of decline in FEV<sub>1</sub> in COPD varied greatly and had no strict association with severity. This reflects a more heterogeneous type of disease with a variable rather than a fixed course with different natural histories. This landmark paper has helped us to begin to better understand the complex nature of COPD physiology based on evolving clinical phenotypes, cigarette smoking, exacerbation frequency, biomarkers and symptom severity and their relationships to lung function decline. The rate of decline in FEV<sub>1</sub> is highly variable, with an increased rate of decline in current smokers, those with significant bronchodilator reversibility, and patients with emphysema.

### Conclusions and implications of the ECLIPSE study

Understanding airway disease physiology from an early stage, as well as the factors that contribute to phenotypes, disease mechanisms, endotypes and treatable traits, allows us to find potential tailored approaches to halt disease progression [4]. There is emerging evidence that, in addition to clinical biomarkers and imaging, providing a combination of high-quality lung function testing for early-stage small airways disease (*e.g.* spirometry, diffusing capacity, lung clearance index by multiple-breath washout (N<sub>2</sub> washout), forced oscillation technique and lung volume measurement) will allow us to provide detailed physiological profiling of patients. Together with population-matched reference values, such testing will allow a better understanding of disease physiology and identification of treatable traits, and in the future will help us to manage patient conditions appropriately.

### The Global Lung Function Initiative

There are several hundred publications of spirometry reference ranges available; however, many are based on small sample sizes and age ranges and often do not fully account for the impact that growth and development, as well as ageing, have on lung function. Inappropriate use of reference equations can lead to misinterpretation of lung function [5]. The GLI gained official European Respiratory Society (ERS) Task Force status in April 2010, but the conceptual framework for this group started in the 1990s, fuelled by enormous input, expertise and enthusiasm from Philip Quanjer and made possible by generous contributions from collaborators from around the

world. The GLI group identified a need for a sufficiently large representative population sample of normative spirometry values across the entire age range, and had the expertise to apply appropriate statistical methodology to generate new reference equations. “Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations” was published in 2012 [2].

### Summary of the GLI-2012 spirometry reference equations

The GLI spirometry team identified and contacted authors who had published spirometry reference data and asked them to submit spirometry data from asymptomatic lifelong nonsmokers. Datasets were obtained from 73 centres across the globe. They performed rigorous *post hoc* quality control to ensure international recommendations were met and to minimise variability. After exclusions due to medical history or lack of essential background details such as ethnic group, 74187 records of healthy nonsmokers aged 2.5–95 years were combined, and reference equations were derived for four ethnic groups: 1) Caucasians, 2) African Americans or “Black”, 3) North East Asians (*e.g.* North China and Korea) and 4) South East Asians (*e.g.* South China, Thailand, Malaysia, *etc.*). For individuals not represented by these four groups, or of mixed ethnic origins, a composite equation taken as the average of the above equations was provided to facilitate interpretation until a more appropriate solution is developed.

### Advantages of the GLI spirometry equations

The GLI-2012 equations are the most robust spirometry reference equations to date. The main advantage of these equations is that there is a smooth transition across the ages (*i.e.* no changes from paediatric to adult equations) and a well-defined lower limit of normal (LLN) for all ages. The group demonstrated that the scatter around predicted values is not constant, but varies with age, such that fixed thresholds for abnormality (*e.g.* 80% predicted for FEV<sub>1</sub> or 0.70 for the FEV<sub>1</sub>/forced vital capacity (FVC) ratio) across all ages are inappropriate and can lead to significant misclassification. Using z-scores, which indicate how many standard deviations a measurement is from its predicted value, overcomes the bias due to age, height, sex and ethnicity, and is useful for defining the LLN. The American Thoracic Society (ATS) and the ERS both recommend the use of the fifth centile (*i.e.* –1.64 z-scores) to define the LLN [6].

The GLI group also found that, by combining such a large number of spirometric data and applying sophisticated statistical methods, they identified physiological patterns previously masked by insufficient power. When comparing the

FEV<sub>1</sub>/FVC ratio against age they observed a “kink” at puberty, which probably reflects the changes in chest dimensions and respiratory mechanics during puberty [7].

Similar patterns of growth and development were observed across different ethnic groups; however, there was a notable offset amongst ethnic groups. On average, FEV<sub>1</sub> and FVC were found to be reduced by ~14% in Black individuals, by 11% and 3% in those from South East and North East Asia, respectively, and by 7% in those classified as “other” or of mixed ethnicity. However, in all ethnic groups, FEV<sub>1</sub> and FVC differed proportionally from the values in Caucasians, such that FEV<sub>1</sub>/FVC remained virtually independent of ethnic group. This signifies the proportionate scaling of lung size due to differences in body build across the ethnic groups and allows uniform definition of airways obstruction based on the LLN for FEV<sub>1</sub>/FVC. Thus, interpretation of spirometry across the ages and differing ethnicities has been improved, and interpretation errors due to inappropriate reference equations should have been minimised.

### Further information about the GLI equations

The GLI reference equations have been endorsed by the ERS, ATS, Australian and New Zealand Society of

Respiratory Science (ANZSRS), Asian Pacific Society for Respirology (APSR), Thoracic Society of Australia and New Zealand (TSANZ) and American College of Chest Physicians (ACCP). Further information can be found on the GLI website ([www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools.aspx](http://www.ers-education.org/guidelines/global-lung-function-initiative/spirometry-tools.aspx)), which contains free software for interpreting results and has a list of several independent publications that validate the GLI spirometry equations. It also contains information on reference ranges for other lung function measurements.

### Summary

Spirometry is the most commonly used lung function test and is an essential tool for the diagnosis and treatment of respiratory diseases such as COPD. However, the devil is in the detail. Spirometry should be performed according to published guidelines and appropriate reference data should be used for interpretation. Knowledge of expected change over time is useful for tracking disease progression and for medical intervention. Furthermore, spirometry should be interpreted in the context of clinical symptoms and other assessments such as breathlessness scores, and it important to include additional high-quality lung function tests where required.

### Affiliations

Jane Kirkby<sup>1</sup>, Raffaella Nenna<sup>2</sup>, Aisling McGowan<sup>3</sup>

<sup>1</sup>Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK. <sup>2</sup>“Sapienza” University of Rome, Rome, Italy.

<sup>3</sup>Connolly Hospital, Blanchardstown, Ireland.

### Conflict of interest

J. Kirkby has nothing to disclose. R. Nenna has nothing to disclose. A. McGowan reports honoraria for lectures from Mundipharma, outside the submitted work.

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