Adopting universal lung function reference equations

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Adopting the GLI 2012 lung function reference equations is an essential and urgent task for laboratories worldwide http://ow.ly/nIoyk

Since the dawn of spirometry and testing lung function [1, 2], clinicians have been aware that the values obtained from testing an individual's lung function can reflect the effects of lung diseases, and that this can be helpful with regard to all aspects of disease prevention and management. It was also recognised that the values obtained were also a reflection of the subject's sex, age and height; so to maximise the clinically relevant signal from the tests these aspects first needed to be taken into account. Studies were then undertaken to record lung function in subjects free from disease and free from the effects of tobacco smoke in order to have reference ranges of lung function.

Clinicians have had to decide which of the many available prediction equations to use for their patients, realising that the different equations might lead to different judgements about the results obtained, because predicted values might vary by as much as 1 L for forced expiratory volume in 1 s (FEV_1) [3]. Guidance in this choice has been based on the reference population being appropriate for the patients and the equipment used for recording the lung function being equivalent. Other considerations include the age span of the reference population and the statistical approach used to derive the various predicted equations. Many European centres used the equations derived for the European Community for Steel and Coal (ECSC) [4]. However, it was still evident that different hospitals in a given locality might use very different prediction equations [5], meaning a patient's outcome might vary depending on which hospital they were tested at.

The Global Lung Initiative (GLI) was set up by the European Respiratory Society in 2010 with the remit to produce spirometry prediction equations that spanned all ages and could be used globally. These equations (GLI 2012) have been successfully produced [6] to the benefit of patients worldwide. Great credit should be given to the team that worked diligently to deliver these on time. Since the publication of the GLI 2012 prediction equations there have been validation studies undertaken in a wide range of ethnicities in British children [7] and in an Australasian population between 4–80 years [8], and these have shown that the GLI 2012 equations were appropriate.

In this issue of the *European Respiratory Journal*, QUANJER *et al.* [9] outline the possible effect that changing to the GLI 2012 equations might have in clinical practice. In this study, the authors compared hospital spirometry data in adults from Australia and Poland using the GLI 2012, ECSC and National Health and Nutrition Examination study (NHANES III) [10] prediction equations. The authors found that the GLI 2012 equations gave predictions similar to NHANES III values but were higher than ECSC. While there was little difference in identifying an obstructive spirometric pattern, the frequency of a restrictive pattern was higher when using GLI 2012 compared to ECSC and lower when using NHANES III.

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The GLI 2012 reference equations for spirometry have, by definition, international appeal for global standardisation for lung function. In 2005, the European Respiratory Society and the American Thoracic Society jointly published a series of lung function standardisation documents in the *European Respiratory Journal*, including spirometry [11] and its interpretation [12]. These updated the existing standards and have been widely embedded in pulmonary function laboratory practice, and have been adopted as usual practice by national respiratory societies around the world. However, they did not mandate the use of any particular reference equations, so there is now a sense of relief with the advent of the GLI 2012 equations because they embrace all ages and ethnicities in one coherent set of reference equations. This will simplify the confusion around which equations are appropriate to interpret spirometry. There is also the benefit of a seamless transition from childhood to adulthood using the same equations (GLI 2012), which removes the complication of switching to adult equations during longitudinal monitoring of patients with diseases such as cystic fibrosis [13]. There are many simultaneous factors such as height, growth and anatomical changes to consider when determining reference equations across adolescence [14]. In 2008, STANOJEVIC *et al.* [15] produced the first spirometry reference equations that provided smooth transition curves from childhood through adolescence during rapid growth and adulthood (age range 4–80 years). The GLI 2012 equations have been a further development of these and include a larger population, more ethnicities and a much older age range up to 95 years. This means we no longer need to extrapolate a prediction equation beyond the age range it was developed for, hoping that it will be appropriate for our elderly patients.

The GLI team used a sophisticated statistical approach to obtain the reference equations which included taking into account the range in variability with age. Younger and older subjects show higher variability than subjects in middle age. The GLI reference ranges use lower and upper limits of normal, and express a subject's results in terms of standardised residuals (z-scores). These state the number of population standard deviations the result is from predicted, which is the correct methodology for identifying if a result is unusual or unexpected [4, 12]. The use of well-defined lower limits of normal is more accurate [16] than the convenience of using a fixed cut-off value across all age groups. In addition, the widely used per cent predicted method is not based on any agreed scientific principle and leads to 20% misclassification of disease compared to the use of z-scores [17].

The paper by QUANJER *et al.* [9] in this issue of the *European Respiratory Journal* demonstrates that while there will be minor changes in the interpretation of spirometry, as a result of changing reference values, the impact is trivial compared to the errors being made by using incorrect methodology such as per cent of predicted and fixed ratio for FEV_1/forced vital capacity. So now the task before us is to get laboratories to change to the GLI 2012 equations. Lung function equipment manufacturers need to implement them in their equipment software as soon as possible, to allow access for all healthcare workers testing spirometry. The GLI working party have conducted a survey with the manufacturers of pulmonary function equipment, and the details about the implementation of the GLI 2012 equations into their software is included in a helpful table on their website [18]. In addition, spread sheets can be downloaded from the GLI website to help calculate results for patients, and there is a program, more suited to researchers, that calculates reference values for large datasets. However, these spread sheets are not so convenient for day-to-day use in the lung function laboratory.

Other issues for future consideration are the addition of GLI reference equations for static lung volumes and gas transfer testing in laboratories. Researchers will need to continue to check their results for any anomalies arising from use of the current and future GLI equations, such as sex, ethnic, age or height biases, so that the process can be continuously refined to the benefit of all our patients.

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