Global Lung Function Initiative

Key points

- The Global Lung Function Initiative (GLI) Network was established as a result of international collaboration, and altruism between researchers, clinicians and industry partners. The ongoing success of the GLI relies on network members continuing to work together to further improve how lung function is reported and interpreted across all age groups around the world.
- The GLI Network has produced standardised lung function reference values for spirometry and gas transfer tests.
- GLI reference equations should be adopted immediately for spirometry and gas transfer by clinicians and physiologists worldwide.
- The recently established GLI data repository will allow ongoing development and evaluation of reference values, and will offer opportunities for novel research.

Educational aims

- To highlight the advances made by the GLI Network during the past 5 years.
- To highlight the importance of using GLI reference values for routine lung function testing (*e.g.* spirometry and gas transfer tests).
- To discuss the challenges that remain for developing and improving reference values for lung function tests.

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The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together

The Global Lung Function Initiative (GLI) Network has become the largest resource for reference values for routine lung function testing ever assembled. This article addresses how the GLI Network came about, why it is important, and its current challenges and future directions. It is an extension of an article published in *Breathe* in 2013 [1], and summarises recent developments and the future of the GLI Network.

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The problem

Even when using the highest standards of quality and technical ingenuity, results from lung function tests can only be clinically valid if interpreted using robust, relevant and reliable reference values. Reference equations are widely available for a wide range of populations and even for subpopulations within countries. In fact, there are >400 published equations for spirometry alone. Consequently, default values set by the manufacturers may be adopted, irrespective of whether they are appropriate for the ethnic or age group of the subject being tested. Differences between equations arise from factors such as how healthy subjects were selected (with respect to exclusion criteria, age range, ethnicity and sex), the number of subjects included (sample size), equipment, testing protocols, quality control and, very importantly, the statistical approach used to derive the equations

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[2–5]. These differences can have a major effect on how lung function results are interpreted, with results from the same subject being abnormal using one equation while falling within the normal range in another [2, 6, 7]. Previously, the use of the Third National Health and Nutrition Examination Survey (NHANES III) equations in the USA [8] and the European Community for Steel and Coal (ECSC) equations in Europe [9] were recommended. Although very robust, the NHANES III equations only span the age range 8–80 years, and are limited to Caucasian, African American and Hispanic populations, whereas the ECSC reference equations were derived from white European adult males working in coal mines and steel works, with values for female adults approximated as 80% of that for a male of similar age and height.

One of the long-standing problems with lung function reference equations for has been the lack of a single reference source to seamlessly monitor patients from childhood into old age. Historically, due both to the difficulty in recruiting populations across the entire age range and in modelling such data to take into account the changing relationship between lung size, age and height during the life span, separate equations have been developed for children and adults. Furthermore, it is only during the last decade that reliable spirometry data have become available in preschool children (3–6 years) [10]. This, in turn, led to the "stitching" together of paediatric and adult equation, which inevitably led to discontinuities in the interpretation of results [6]. The rapid growth observed during childhood meant that many paediatric equations relied on height alone, the omission of age leading to bias both during the preschool years and during puberty [11]. A key barrier to creating an "all-age" equation was the limited statistical methodology available at the time. For many decades, reference equations were derived using simple linear regression technique to describe the relationship between lung function outcomes and age and/or height, which made it challenging to describe lung function accurately in both children and adults using the same equations. More recently, the availability of more flexible methodologies has allowed modelling of complex non-linear relationships across a wide age spectrum.

The solution

In 2008, a group of clinicians, physiologists and researchers was convened by Xaver Baur (Germany) at the European Respiratory Society (ERS) Annual Congress in Berlin, Germany, to discuss the problem and to propose solutions. The ideal solution would have been to conduct a multinational population study, since this would allow standardisation of population sampling, equipment, protocols and quality control. However, the logistic constraints of recruiting thousands of individuals, many of whom would have had to be excluded due to respiratory disease or smoking history, together with the realisation that securing funding for a multimillion-dollar project during a global financial recession was highly unlikely, meant that alternative approaches needed to be explored.

One such alternative was to collate existing data sources, as originally suggested by Philip Quanjer (the Netherlands) in 1995. Quanjer *et al*. [12] demonstrated that data from numerous studies could be successfully combined to create a single, more robust reference equation. At that time, he suggested that "There is potentially much to be gained from starting an international database to this end, to which researchers who have performed studies which comply with international standards could submit their cross-sectional and longitudinal data" [12].

The feasibility of such an approach had been explored just prior to the 2008 ERS Annual Congress meeting, in that a multinational project, led by Janet Stocks and Sanja Stanojevic (UK). The Asthma UK Growth Charts for Spirometry project had successfully pooled existing normative data to produce the first sex-specific all-age reference equations for spirometry, which spanned 4–80 years of age [13]. These were subsequently extended down to 3 years, after collating available reference data from young children 3–7 years of age [11]. A key feature of this study was that the three-dimensional nature of the relationship between height, age and lung function, and the complex growth patterns observed during puberty were modelled seamlessly to produce a single all-age equation, using a novel approach developed by Tim Cole (UK) [14]. While the all-age Asthma UK spirometry growth charts provided much needed proof of concept for this methodological approach, they were only applicable to white subjects of European descent, leaving much still to be done if improved interpretation of lung function, both worldwide and in increasingly multiethnic populations, was to be achieved.

Development of the Global Lung Function Initiative Network

The serendipitous meeting of individuals from a range of respiratory medicine disciplines from around the world in 2008, just at the time when more robust statistical methods for analysing lung function results across all ages had been developed, was the catalyst for establishing the Global Lung Function Initiative (GLI) Network. Four chairs were selected to represent a range of disciplines and regions around the world (Janet Stocks, Xaver Baur, Bruce Culver (USA) and Graham Hall (Australia)), together with an analytical team (Philip Quanjer, Sanja Stanojevic, Tim Cole and Janet Stocks). The group proposed an ERS Task Force that aimed to

pool and collate as much of the existing available spirometry data from heathy individuals around the world to derive all-age, multiethnic reference equations. ERS Task Force status for the GLI was granted in April 2010, and although the American Thoracic Society (ATS) was unable to fund any new projects that year, it was actively involved in supporting the initiative.

As the result of established collaborations with researchers worldwide since the 1990s, Philip Quanjer had already accumulated a library of anonymised normative spirometry data from >30000 healthy subjects. Gaining permission from lead investigators to use these data for the GLI gave the project a vital head start. Further requests *via* respiratory societies and collaborative networks as well as to lead investigators of published papers, resulted in >160000 sets of anonymised spirometry data from healthy individuals being submitted. The project received overwhelming support and enthusiasm across multiple respiratory disciplines.

The GLI Network was largely based on collaboration, altruism and a common goal: to improve how lung function is interpreted. The network grew quickly, with >400 members from around the world expressing interest and participating in workshops that were held at international conferences such as those of the ERS and ATS. Importantly, everyone involved in the GLI contributed time and effort on an entirely voluntary basis, an essential component given that the entire Task Force budget only facilitated travel and meetings between Task Force Chairs.

A unique aspect of the GLI Network was the inclusion of manufacturers of pulmonary function test equipment; while manufacturers did not provide any funding to the GLI Network, by attending the open meetings, manufacturers were able to express the needs of the broader respiratory community, to highlight the challenges of updating and changing reference equations from a practical perspective, and provide invaluable insight into the educational materials that would be needed to educate laboratory staff, patients and clinicians when switching to the new equations. These relationships were pivotal to the successful dissemination and rapid implementation of the reference equations across spirometry devices as soon as the equations were published in 2012.

The formation of the GLI Network, together with a rich data resource, and the availability of novel statistical methodology provided, for the first time, an opportunity to develop a standardised and unified global approach to interpreting lung function results across all ages that were applicable across many different ethnic groups. With such limited funding, the success of the GLI would never have been possible without the dedication, perseverance and ingenuity of Philip Quanjer. Retired at the time, Prof. Quanjer dedicated almost 3 years of around-the-clock efforts to collate and analyse the data, and to maintain the GLI website, until the latter function was transferred to the ERS in 2015.

Impact of the GLI spirometry reference equations

The ERS GLI Spirometry Task Force derived continuous prediction equations and their lower limits of normal (LLNs) for key spirometric indices [15]. The GLI Network shared over >160000 data points from 72 centres in 33 countries. Some data were eliminated because they could not be used (mostly missing ethnic group data and some outliers), which left 97759 records of healthy nonsmokers (55.3% females) aged 2.5–95 years. Reference equations were derived for healthy individuals aged 3–95 years for a number of ethnic groups including Caucasians (*i.e.* white subjects of European descent, n=57395), African Americans (n=3545), and North (n=4992) and South East Asians (n=8255), where North Asian refers to Korea and China north of the Huaihe River and Qinling Mountains, and South East Asian refers to Thailand, Taiwan and China (including Hong Kong) south of the Huaihe River and Qinling Mountains. In addition, since many individuals were either not represented by these four groups or were of mixed ethnic origin, a composite equation was derived as the average of available data to facilitate interpretation in such individuals until a more appropriate solution is developed with appropriate data. Spirometric values including forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) differed proportionally between ethnic groups from that in Caucasians, such that FEV_1/FVC remained virtually independent of ethnic group (figure 1).

The GLI-2012 reference equations currently provide the most reliable spirometric prediction equations for the 3–95-year age range and include appropriate age-dependent LLNs. The GLI equations have been endorsed by all major international respiratory societies and adopted as the recommended reference equation by many national respiratory societies.

Beyond spirometry

Since full interpretation of lung function often requires results from more than one lung function test, there was a unanimous decision to expand the GLI to include reference equations for the transfer factor of the lung for carbon monoxide (T_{LCO}) (also known as the diffusing capacity of the lung for carbon monoxide (D_{LCO})) and static lung volumes. In 2013, the GLI T_{LCO} Task Force, again supported by the ERS, was initiated. Over a period of 2 years, 12660 T_{LCO} measurements in healthy individuals were collected from 19 centres in 14 countries. As a result of methodological differences

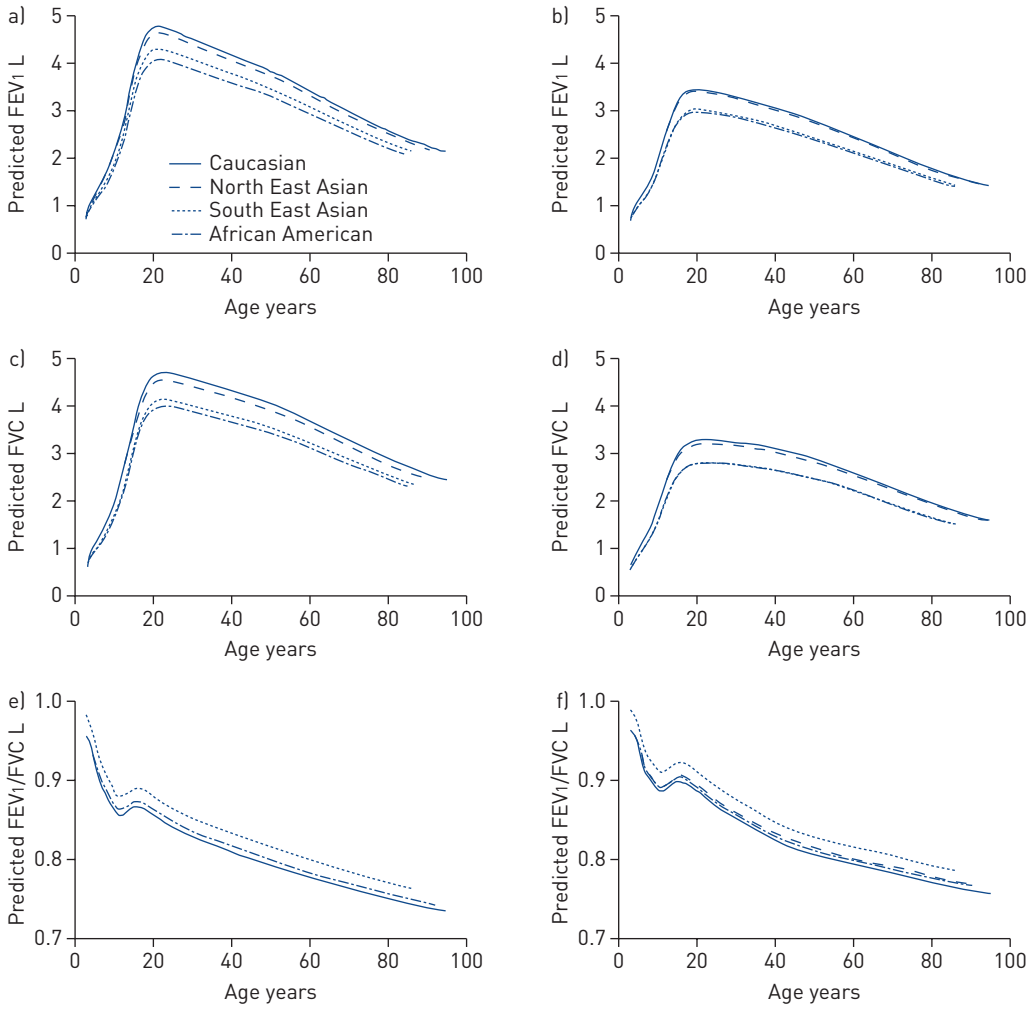

Figure 1 *Predicted values for a, b) FEV1, c, d) FVC and e, f) FEV1/FVC by sex and ethnic group. a, c, e) Males and b, d, f) females. Graphs were generated using mean height for age in Caucasians to illustrate proportional differences between ethnic groups of the same height and age; in practice, differences in height for age further affect predicted values. The rise and fall in FEV1/FVC around adolescence is due to differential changes in FEV1 and FVC. Reproduced from [15].*

in equipment settings and study populations, T_{LCO} had to be harmonised prior to collation. All data were uncorrected for haemoglobin concentration, but adjusted for partial pressure of oxygen, gas concentration and anatomic dead space volume.

Reference values for Caucasians aged 4–80 years were derived for T_{LCO}, carbon monoxide transfer coefficient and alveolar volume (figure 2) [17]. A major limitation of these new T_{LCO} equations is that they are limited to Caucasian subjects. Only 15% of the data collected were from non-Caucasians, which meant it was not possible to investigate ethnic differences in outcomes. Fortunately, FEV_1 data submitted as part of the T_{LCO} dataset, and largely based on individuals who were not part of the original GLI spirometry dataset, had good fit overall with the GLI spirometry equations. This supports the use of the GLI spirometry and T_{LCO} reference equations together, even though they are based on different populations. The GLI T_{LCO} equations have been published in the *European Respiratory Journal* [17].

In 2016, the GLI Static Lung Volumes Task Force was established, and is now well underway. Since static lung volumes can be measured with a variety of techniques (single or multiple breath, quiet or forced rebreathing, nitrogen or helium dilution, multiple indicator gases, body plethysmography), data are being collected separately for each technique and will be investigated for agreement.

Beyond predicted values

Beyond providing standardised reference equations, the GLI Network has reignited debate and discussion around how lung function is interpreted. Whereas in clinical chemistry, classification of normal and abnormal test results is based on the 95% reference interval, it has become an ingrained habit in respiratory medicine to express measured values as "per cent of predicted". This tradition probably arose from a recommendation by Bates and Christie [18]: "a useful general rule is that a

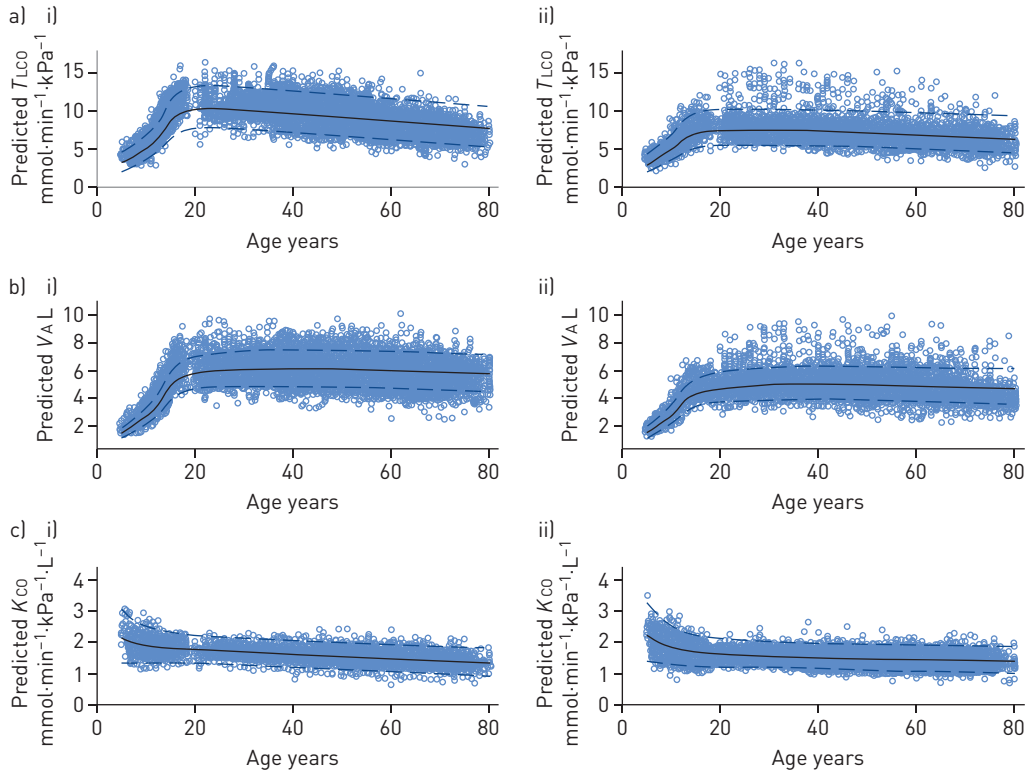

Figure 2 *a) Predicted T_{LCO} in i) 4859 males and ii) 4851 females), b) alveolar volume (V_A) (standard temperature and pressure, dry) in i) 4793 males and ii) 4837 females) and c) carbon monoxide transfer coefficient (K_{CO}) in i) 4793 males and ii) 4837 females. The solid line represents the predicted values for age (assuming an average height at each) and the dashed lines represent 95% confidence limits. Prediction equations are overlaid on observed values. The average height used in children was the 50th height-for-age centile from the US Centers for Disease Control and Prevention growth charts [16] whereas in adults, the average height observed in the study population was used (172 cm in males and 162 cm in females). Reproduced from [17].*

deviation of 20% from the predicted normal value probably is significant". This suggested that 80% of predicted was the LLN. Although this rule of thumb was uncritically adopted, it is only valid if the scatter around the predicted value has a standard deviation approximating 10% and is proportional to the mean predicted value, neither of which is the case, as shown in multiple studies [19–21]. The methodology used to derive the LLN for all GLI equations takes into account that the spread of values around the predicted values is not uniform, and that the LLN is age and outcome dependent. Using an appropriate LLN is essential in order to differentiate between health and disease accurately across the entire life span.

Geriatric considerations

Populations worldwide are rapidly ageing [22]. By 2050, the World Health Organization estimates that 400 million people will be aged ≥80 years [22]. The ageing shift is accompanied by substantial clinical challenges, including multimorbidity, polypharmacy and a highly sedentary state [23, 24]. It is therefore not surprising that respiratory symptoms, such as dyspnoea, chronic bronchitis and wheezing, are also highly prevalent in older persons and are likely to be multifactorial in origin [25, 26].

Accordingly, among older persons with respiratory symptoms, high diagnostic accuracy is a necessity when attributing the underlying mechanism to a respiratory impairment [23–27]. Because it rigorously accounts for age-related changes in lung function, the GLI approach represents a major step forward in establishing an age-appropriate and clinically meaningful definition of a respiratory impairment [13, 15, 28]. In addition, by minimising the misidentification of normal-for-age lung function as a respiratory impairment [29], the GLI approach may avoid the use of inappropriate and potentially harmful respiratory medications in older persons, as well as delays in considering other diagnoses among older persons with respiratory symptoms [23–27].

Nevertheless, there remain some limitations regarding the use of GLI reference equations in older persons. Specifically, as acknowledged in the 2012 GLI report [15], increased representation of persons aged >75 years in the reference population is needed to further improve diagnostic accuracy. Beyond 80 years of age, there is the issue of survival bias, and there is limited information available regarding the generalisability of the

GLI equations in this population [30]. Therefore, caution is required when interpreting lung function in older individuals, and the need for more data in older subjects to develop updated age-appropriate criteria regarding the adequacy of test performance and to evaluate alternative measures of lung function. These improvements may broaden the generalisability of respiratory test results in geriatric practice.

Challenges

The GLI Network is not without its challenges. Despite its name, the GLI lacks data from large populations, namely those on the African continent, South Asia and India, and Latin America. The T_{LCO} equations are only available for Caucasians. Although spirometry reference equations were derived for the Asian population, studies have shown both cohort and migration effects on lung function in these populations [31, 32]. Several efforts have been made to collect and summarise data in these populations [31, 33, 34], and while these studies provide critical information regarding the generalisability of GLI in these populations, the conclusions have consistently been that prospective, high-quality data are needed in these populations, and that consideration of the effects of migration, both within the region and to western countries, is necessary to provide comprehensive recommendations for improved interpretation of results.

Although many regional respiratory societies have endorsed the GLI and individual laboratories have implemented the GLI spirometry equations, there are also many who have been reluctant to do so, often citing "myths" and misconceptions as reasons for this inaction [1]. Some argued that they cannot implement GLI-2012 because no reference values for transfer factor and static lung volumes are available, a criticism that is now largely outdated. Others argued that the lack of predicted values for peak expiratory flow and other flows means that they cannot interpret flow–volume curves. These myths regarding spirometry interpretation are generally now fully debunked in academic circles but need to be spread through education to the clinical "coalface"

At the time the GLI was established, privacy and data sharing rules and regulations were just emerging. Since all data were de-identified, there were limited logistical and operational hurdles to collecting and receiving data between academic institutions. This is very much no longer the case and, as the GLI Network evolved, so did the need for more rigorous data sharing policies and data management systems. When the GLI T_{LCO} Task Force was established, the infrastructure to collect and store the data was also updated. There have been several promising open-source projects for enabling privacy-sensitive data sharing [35]; however, these methods require an investment in infrastructure and information technology expertise at all data contributing sites. To address the scarcity of available technical solutions, the bioinformatics group at the Telethon Kids Institute (Kim Carter, Australia) built an intuitive, flexible and extensible data collection portal, called the Data Portal for Research (DPR), using open-source technologies (available from https://gitlab.com/kim.carter/dpr). Through DPR, it was possible to have contributors of data to the GLI sign up to the project online and, after approval, be provided access to the secure data upload portal. Data from each contributor are uploaded using a predefined data and metadata spreadsheet template, with all uploaded data checked against a defined data dictionary for validity (*e.g.* correct data type, appropriate range and missing data characters) before being made available for comparison with other uploaded data. Predefined analyses are run on each dataset, with the ability to compare and analyse all upload data across datasets securely through an intuitive and interactive graphical interface.

The future of the GLI Network

The GLI Network was formally established as an ERS Clinical Research Collaboration in 2016, and aims to develop a live repository of normative lung function data housed by the ERS. All current data contributors will be invited to give permission for data to be transferred to the repository. New data sharing agreements will be

Educational questions

1. The errors of using a "fixed ratio": when using a fixed ratio of FEV1/FVC, which of the following are correct?
   a. Airway obstruction is underestimated in the elderly (>70 years)
   b. Airway obstruction is overestimated in the elderly (>70 years)
   c. Airway obstruction is underestimated in adolescents
   d. Airway obstruction is overestimated in adolescents
2. The errors of using per cent of predicted: does the FEV1 for a person of the same height have the same LLN at ages 25 and 65 years?
   a. Yes
   b. No
3. GLI reference equations are now available for which lung function tests?
   a. Spirometry
   b. Respiratory muscle pressures
   c. T_{LCO}
   d. Lung volumes
   e. Blood gases
   f. Peak expiratory flow

sought, and data will be uploaded and hosted through an established infrastructure developed by the bioinformatics team at the Telethon Kids Institute. Data collection will be ongoing such that reference equations can be derived as new data become available for groups not previously represented. Importantly, the data repository has been established to facilitate longitudinal data, as well as having the potential to expand to include data from various disease groups. The GLI data repository will be available for researchers to access to answer novel physiological and methodological questions.

The GLI Network will also work with the European Lung Foundation (ELF) to improve resources for patients, educators and clinicians. Dissemination of training and education materials about interpretation of lung function tests results needs to go beyond the pulmonary function laboratory. The ELF is therefore developing videos and patient resources in multiple languages to help improve and standardise interpretation.

Can *Breathe* readers help?

Any centre that has collected (or is collecting) lung function data in healthy individuals anywhere in the world should consider contacting the GLI Network. Anyone who previously contributed is invited to give permission for their data to be included in the repository. For more information, visit the GLI website: www.lungfunction.org

Suggested answers

1. b and c.
2. b. FEV_1 % predicted values at the LLN decrease with advancing age.
3. a and c are currently correct. d is likely to be published in 2018.

Conflict of interest

None declared.

References

1. Stanojevic S, Quanjer P, Miller MR, *et al.* The Global Lung Function Initiative: dispelling some myths of lung function test interpretation. *Breathe* 2013; 9: 462–474.
2. Quanjer PH, Brazzale DJ, Boros PW, *et al.* Implications of adopting the Global Lungs Initiative 2012 all-age reference equations for spirometry. *Eur Respir J* 2013; 42: 1046–1054.
3. Rosenfeld M, Pepe MS, Longton G, *et al.* Effect of choice of reference equation on analysis of pulmonary function in cystic fibrosis patients. *Pediatr Pulmonol* 2001; 31: 227–237.
4. Stanojevic S, Wade A, Lum S, *et al.* Reference equations for pulmonary function tests in preschool children: a review. *Pediatr Pulmonol* 2007; 42: 962–972.
5. Subbarao P, Lebecque P, Corey M, *et al.* Comparison of spirometric reference values. *Pediatr Pulmonol* 2004; 37: 515–522.
6. Kirkby J, Aurora P, Spencer H, *et al.* Stitching and switching: the impact of discontinuous lung function reference equations. *Eur Respir J* 2012; 39: 1256–1257.
7. Quanjer PH, Weiner DJ. Interpretative consequences of adopting the global lungs 2012 reference equations for spirometry for children and adolescents. *Pediatr Pulmonol* 2013; 49: 118–125.
8. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159: 179–187.
9. Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
10. Beydon N, Davis SD, Lombardi E, *et al.* An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007; 175: 1304–1345.
11. Stanojevic S, Wade A, Cole TJ, *et al.* Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. *Am J Respir Crit Care Med* 2009; 180: 547–552.
12. Quanjer PH, Borsboom GJ, Brunekreef B, *et al.* Spirometric reference values for white European children and adolescents: Polgar revisited. *Pediatr Pulmonol* 1995; 19: 135–142.
13. Stanojevic S, Wade A, Stocks J, *et al.* Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008; 177: 253–260.
14. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med* 1992; 11: 1305–1319.
15. Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
16. Kuczmarski R, Ogden CL, Guo S, *et al. CDC Growth Charts*. Atlanta, National Center for Health Statistics, 2000.
17. Stanojevic S, Graham BL, Cooper BG, *et al.* Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 2017; 50: 1700010.
18. Bates DV, Christie RV. *Respiratory Function in Disease: an Introduction to the Integrated Study of the Lung*. Philadelphia, WB Saunders, 1964.
19. Miller MR. What defines abnormal lung function? *Thorax* 2007; 62: 1107.
20. Miller MR, Pincock AC. Predicted values: how should we use them? *Thorax* 1988; 43: 265–267.
21. Miller MR, Quanjer PH, Swanney MP, *et al.* Interpreting lung function data using 80% predicted and fixed thresholds misclassifies more than 20% of patients. *Chest* 2011; 139: 52–59.
22. WHO. *Good Health Adds Life to Years: Global Brief for World Health Day 2012*. Geneva, World Health Organization, 2012.
23. Boyd CM, Darer J, Boult C, *et al.* Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005; 294: 716–724.
24. Fried TR, Vaz Fragoso CA, Rabow MW. Caring for the older person with chronic obstructive pulmonary disease. *JAMA* 2012; 308: 1254–1263.
25. Marcus BS, McAvay G, Gill TM, *et al.* Respiratory symptoms, spirometric respiratory impairment, and respiratory disease in middle-aged and older persons. *J Am Geriatr Soc* 2015; 63: 251–257.
26. Miner B, Tinetti ME, Van Ness PH, *et al.* Dyspnea in community-dwelling older persons: a multifactorial geriatric health condition. *J Am Geriatr Soc* 2016; 64: 2042–2050.
27. Vaz Fragoso CA, Gill TM, McAvay G, *et al.* Respiratory impairment in older persons: when less means more. *Am J Med* 2013; 126: 49–57.
28. Quanjer PH, Hall GL, Stanojevic S, *et al.* Age- and height-based prediction bias in spirometry reference equations. *Eur Respir J* 2012; 40: 190–197.

29. Vaz Fragoso CA, McAvay G, Van Ness PH, *et al*. Phenotype of normal spirometry in an aging population. *Am J Respir Crit Care Med* 2015; 192: 817–825.
30. Miller MR, Thinggaard M, Christensen K, *et al*. Best lung function equations for the very elderly selected by survival analysis. *Eur Respir J* 2014; 43: 1338–1346.
31. Quanjer PH, Kubota M, Kobayashi H, *et al*. Secular changes in relative leg length confound height-based spirometric reference values. *Chest* 2014; 147: 792–797.
32. Coates AL, Wong SL, Tremblay C, *et al*. Reference equations for spirometry in the Canadian population. *Ann Am Thorac Soc* 2016; 13: 833–841.
33. Arigliani M, Canciani MC, Mottini G, *et al*. Evaluation of the Global Lung Initiative 2012 reference values for spirometry in African children. *Am J Respir Crit Care Med* 2017; 195: 229–236.
34. Lum S, Bountziouka V, Quanjer P, *et al*. Challenges in collating spirometry reference data for South-Asian children: an observational study. *PLoS One* 2016; 11: e0154336.
35. Carter KW, Francis RW, Carter KW, *et al*. ViPAR: a software platform for the Virtual Pooling and Analysis of Research Data. *Int J Epidemiol* 2015 [in press https://doi.org/10.1093/ije/dyv193].