

POSITION STATEMENT

Reference values for spirometry and their use in test interpretation: A Position Statement from the Australian and New Zealand Society of Respiratory Science

DANNY BRAZZALE,¹ GRAHAM HALL^{2,3,4} AND MAUREEN P. SWANNEY⁵

¹Respiratory Laboratory and Institute for Breathing and Sleep, Austin Hospital, Melbourne, Victoria, ²Paediatric Respiratory Physiology, Telethon Kids Institute, ³School of Physiotherapy and Exercise Science, Curtin University, ⁴Centre for Child Health Research, University of Western Australia, Perth, Western Australia, Australia, and ⁵Respiratory Physiology Laboratory, Christchurch Hospital, Christchurch, New Zealand

ABSTRACT

Traditionally, spirometry testing tended to be confined to the realm of hospital-based laboratories but is now performed in a variety of health care settings. Regardless of the setting in which the test is conducted, the fundamental basis of spirometry is that the test is both performed and interpreted according to the international standards. The purpose of this Australian and New Zealand Society of Respiratory Science (ANZSRS) statement is to provide the background and recommendations for the interpretation of spirometry results in clinical practice. This includes the benchmarking of an individual's results to population reference data, as well as providing the platform for a statistically and conceptually based approach to the interpretation of spirometry results. Given the many limitations of older reference equations, it is imperative that the most up-to-date and relevant reference equations are used for test interpretation. Given this, the ANZSRS recommends the adoption of the Global Lung Function Initiative (GLI) 2012 spirometry reference values throughout Australia and New Zealand. The ANZSRS also recommends that interpretation of spirometry results is based on the lower limit of normal from the reference values and the use of Z-scores where available.

Key words: interpretation, lung function, reference values, spirometry.

Abbreviations: ANZSRS, Australian and New Zealand Society of Respiratory Science; APSR, Asian Pacific Society of Respiriology; ARTP, Association of Respiratory Technology and

Physiology; ATS/ERS, American Thoracic Society/European Respiratory Society; COPD, chronic obstructive pulmonary disease; ECCS, European Community for Steel and Coal; FEV_{25-75%}, average forced expiratory flow between 25% and 75% of forced vital capacity; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; LLN, lower limit of normal; LMS, lambda, mu and sigma; NHANESIII, third National Health and Nutrition Examination Survey; TSANZ, Thoracic Society of Australia and New Zealand.

BACKGROUND

In February 2014, the Board of the Australian and New Zealand Society of Respiratory Science (ANZSRS) formed a working group to produce recommendations on the use of the Global Lung Function Initiative (GLI) 2012 spirometry prediction equations.¹ This group comprised the authors of this Position Statement, along with Dr Jeffrey Pretto (see *Acknowledgements*). These recommendations were based on the consensus view of the working group which was formed by review of existing literature and current international lung function guidelines, as relevant. The recommendations were reviewed and subsequently endorsed by the Board of the ANZSRS.

INTRODUCTION

Spirometry is the most commonly performed pulmonary function test and is performed in a wide variety of health care and research settings. Indications for the measurement of spirometry include diagnosis and monitoring of lung disease, evaluation of disability and impairment, research and public health for monitoring lung function or case-finding in at-risk groups.^{2,3} The interpretation of spirometry results is typically based on categorizing the results into three patterns: normal, obstructive or restrictive.⁴ When spirometry results indicate an obstructive problem, it is important to establish if the airway obstruction is reversible or not,

Correspondence: Danny Brazzale, Respiratory Laboratory and Institute for Breathing and Sleep, Austin Hospital, Level 1, Harold Stokes Building, Heidelberg, Melbourne, Vic. 3084, Australia. Email: danny.brazzale@austin.org.au

Received 22 April 2016; invited to revise 9 May 2016; revised 24 May 2016; accepted 26 May 2016 (Associate Editor: Chi Chiu Leung).

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

to guide diagnosis, pharmacological treatment or other management options.³ A restrictive pattern may prompt further investigation while normal results may be useful to exclude certain diagnoses.

Over the last 20 years, there has been a significant move towards standardization of the way in which spirometry and other lung function tests are performed and interpreted with recommendations published in international best practice guidelines.^{3–7} These guidelines have clearly defined equipment requirements, test performance procedures and interpretative strategies. However, despite providing lists of relevant reference value publications, these guidelines provide minimal direction about choosing the most appropriate reference values for interpreting the results of the lung function tests. In addition, these guidelines are now 10 years old and consequently reference values published since 2005 need to be considered.

The last two decades have also seen the emergence of a range of clinical guidelines that dictate how abnormal spirometry results are defined and the use of those results in managing individual patients.^{8–12} However, many of these strategies are based on expert consensus rather than direct evidence. For example, the interpretative approaches for identifying COPD vary significantly between major international societies and even within individual countries.^{11,12} One consequence of the variability in advice to clinicians has led to uncertainty in the best approach to confirm COPD from spirometry results.

SUMMARY OF PROBLEMS WITH CURRENT REFERENCE VALUES

Since the 1960s, there have been over 70 spirometry reference sets published in the literature with significant variability in the definition of a 'normal' population, the statistical approaches used and the ethnicity of the populations studied. There may also be a confounding cohort effect in some countries, where the lung function has improved over time due to changes in nutrition, exposure to smoking, the environment and socio-economic status.¹³ Given these issues, the pulmonary function community need to use the most up-to-date validated reference values for the interpretation of spirometric results.

A significant issue with older spirometry reference equations is that they were formulated for either adult or paediatric populations, with very few equations covering both children and adults. The transition between paediatric and adult respiratory services is a challenging period and introduces a number of complexities for the young person, their family and the respective health teams.¹⁴ One poorly documented aspect of this transition is the impact of changing reference equations between paediatric and adult equations. One approach has been to 'stitch' equations together such that manual changes within a service are not required. However, as recently documented, this can lead to significant inaccuracies in an individual's predicted lung function.^{15,16} The use of reference equations that span the life course of a patient's contact with health services and the standardization of the reference

equations would remove these problems and ensure that the most accurate representation of a patient's lung function at any particular age is maintained.

Another area of concern when evaluating patients' results with spirometry reference values is the effect of ethnicity (the term used throughout this review to describe racial background or physical characteristics). Identifying the correct approach to adjust spirometry reference values for ethnicity is poorly defined and inconsistently applied. Frequently, a percentage correction is used, such as a 12% reduction for spirometry (FEV₁ and FVC) if the subject is of non-Caucasian descent.¹⁷ While this approach may be appropriate for some people, the inherent variability of the population based on age, height and gender is not taken into account, therefore the use of a fixed percentage reduction is unlikely to be valid in all patients.⁴ Reference equations that cover the range of ethnic backgrounds of patients are required to accurately define the spirometry reference values for every ethnic group. It is recognized that this is not globally possible until data are available to generate reference equations for every ethnic population. The approach to individuals from parental mixed ethnicity is also a conundrum that needs further investigation. It is also recognized that other regional influences may give rise to differences in pulmonary function such as level of physical activity, nutrition and environmental factors.

As stated previously, international guidelines have provided little specific direction about the use of reference values.⁴ The most recent American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines have recommended the use of the Hankinson (NHANESIII)¹⁸ prediction equations in North America.⁴ These guidelines indicated that different reference equations^{19,20} were used in Europe and made no recommendations for the rest of the world. As a result, it is likely that there is significant variability in the reference sets used across Australia and New Zealand. The use of a single set of spirometry reference equations throughout Australasia would help optimize standardization of spirometry testing procedures and interpretation of results across all health facilities.

THE GLI 2012 REFERENCE VALUES

Since the 2005 ATS/ERS guidelines were published, significant advances have been made in the area of reference values with the publication of the GLI 2012 spirometry reference values.¹ The GLI 2012 equations have been endorsed by multiple national and international respiratory societies including ANZSRS, Thoracic Society of Australia and New Zealand (TSANZ) and Asian Pacific Society of Respiriology (APSR). The GLI started as a collaboration of researchers, respiratory physiologists and physicians who were concerned with the limitations of currently available spirometry reference equations. The success of the Asthma UK initiative to derive spirometry reference ranges in a Caucasian population aged from 3 to 80 years demonstrated that the concept of collating data from individual spirometry records was sound and could lead to significant advances in the prediction of spirometry

outcomes in patients of all ages.²¹ A working party was formed at the ERS conference in 2008, which subsequently received endorsement as an ERS Task Force. The brief of the GLI Task Force was to collate spirometry data from healthy individuals of all ethnic backgrounds and to derive all-age, multi-ethnic spirometry reference ranges.

The generosity of the global respiratory community to participate in the GLI efforts was unparalleled with data from 73 centres equating to over 160 000 individual spirometry records being submitted. Following assessment of paired spirometry and ethnicity information and other exclusions, equations were derived from a total of 74 187 spirometry records in individuals aged 3–95 years. The analysis of the spirometry data was performed using the lambda, mu and sigma (LMS) method, which allows for modelling of variability and skewness of data and uses splines to account for the interactive effects of age, height and gender.¹⁶ The resultant GLI spirometry equations provided continuous age–sex–height prediction equations for Caucasian, African-American and North-East and South-East Asian populations between the ages of 3 and 95 years.¹ The GLI also produced a set of equations for use in ethnicities where no specific equations were created (labelled ‘Other’), using the entire data.

Respiratory laboratories across Australia and New Zealand have struggled with selection of appropriate lung function reference ranges for patients that are from non-Caucasian backgrounds, primarily due to the paucity of reference equations in other ethnic populations. The advanced statistical modelling of the GLI 2012 spirometry reference equations demonstrated that the differences in predicted lung function between ethnic groups were stable across the age and height range for men and women.¹ An important outcome is that lung function reference ranges from previously unrepresented ethnic groups (such as Australian Aboriginal and Torres Strait and Pacific Islanders) can be derived from smaller data sets to create new LMS equation coefficients within the current GLI 2012 equations. Until these can be developed, it is recommended that the reference data for the Other GLI ethnic group are used for individuals of ethnic origins not identified within the GLI 2012 equations.¹

As the GLI 2012 equations have been derived from a very large population using multiple equipment types, the variability associated with the equipment type is minimal when compared with the biological variability from the subjects involved. The reference equations therefore are not only applicable to a range of ethnicities, but also to a broad base of instrumentation and method of measurement.

The appropriateness of the GLI 2012 spirometry reference equations to local, contemporary conditions was confirmed through the comparison of the GLI 2012 data to that of a collated data set from centres in Australia and New Zealand. Hall *et al.* collated spirometry data from >2000 Caucasian individuals across 14 centres and compared the predicted GLI 2012 values with the measured values.²² These authors demonstrated that the mean difference of Z-scores was <0.25 across all outcomes, equating to differences of <90 mL and 3% predicted for FEV₁. These findings have been extended to other multi-ethnic populations

in London suggesting that the GLI 2012 equations will be appropriate for the range of ethnic groups represented within the original study.²³ However, caution should be exercised in situations where individuals have migrated from developing countries or come from a significantly lower socio-economic background as recent results from Tunisia and India suggest that the GLI 2012 equations may be less accurate in these circumstances.^{24,25}

EFFECTS OF CHANGING TO GLI 2012

Since the release of the GLI 2012 reference values, there have been a number of publications examining the effect of adopting these equations on spirometry interpretation. When applied to a clinical data set, the difference in the mean predicted values for FEV₁, FVC and FEV₁/FVC between the GLI 2012 reference values and other commonly used equations^{18,19,21} tends to be small. In a sample of 2278 individuals aged between 5 and 85 years, the average predicted FEV₁ and FVC were almost identical when using the GLI 2012, Hankinson and Stanojevic equations, with a 200-mL difference in the mean predicted FEV₁ and FVC when the GLI 2012 equations were compared with the ECCS equations.²⁶

In a study by Brazzale *et al.*, the effect of changing to the GLI 2012 equations on the clinical interpretation of routine spirometry results were compared with the use of Hankinson *et al.*, Stanojevic *et al.* or ECCS spirometry equations.²⁶ The incidence of airflow obstruction was similar across the four equations with the rates of obstruction ranging from 28.5% for the Hankinson equations to 20.0% with the Stanojevic equations, while the GLI 2012 equations led to a diagnosis of airflow obstruction in 26.3% of patients. The rates of a reduced FVC varied more widely across the four different equations investigated (14.2–25.8%). Adopting the GLI 2012 equations resulted in lower rates of an abnormal FVC compared with the Hankinson and Stanojevic equations, but higher rates of an abnormal FVC compared with the ECCS equations. A study by Quanjer *et al.* found similar results in obstructive spirometry and a reduced FVC in both males and females across the entire age range.²⁷

A further study by Quanjer *et al.* investigated the effect of adopting GLI 2012 equations on spirometry interpretation in children and adolescents aged 6–18 years.²⁸ This study showed that the predicted values for FEV₁, FVC and FEV₁/FVC produced by the GLI 2012 equations were similar to the equations from Wang *et al.*²⁹ and Hankinson *et al.*¹⁸ within ethnic groups. The effect on test interpretation was that there would be minimal change when transitioning from the equations of Wang *et al.* and Hankinson *et al.* to the GLI 2012 equations; however, there would be significant changes moving from equations derived by Knudson *et al.*³⁰ (more airflow obstruction in both genders), Polgar and Varuni³¹ (lower rate of reduced FVC in girls) and Zapletal *et al.*³² (lower rate of reduced FVC in boys).

One important issue which needs to be considered when adopting the GLI 2012 equation is that age should be calculated to one decimal place to allow accurate calculation of the predicted values. Quanjer *et al.* reported that using age in whole years rather than

one decimal place introduced a bias which ranged from -8% to $+7\%$ in the predicted value.³³ This effect is more pronounced in children than adults; however, it is significant across the entire age range. Another important factor is the accurate measurement of height, rather than using stated height. It has been reported that errors in self-reported height can be as large as 6.9 cm.³⁴ Using the GLI 2012 equation, a 1% bias in height introduced biases in the predicted FEV₁ and FVC ranging from 2.1% to 2.4%.³³

INTERPRETATIVE APPROACHES WHEN USING GLI 2012

The ATS/ERS interpretative strategies for lung function tests provide guidance to determine whether the spirometric pattern is normal, obstructive or restrictive. The interpretation includes an assessment of test quality (acceptability and repeatability), the comparison of the patient's results to an appropriate reference population and consideration of the clinical question.

The ATS/ERS guidelines recommend that the interpretation of spirometry measurements use the lower limit of normal (LLN) to detect an abnormality. The LLN represents data below the lower fifth percentile from a large healthy reference group.

Using the ATS/ERS algorithm, spirometry results are assessed in order:

1. If the FEV₁/FVC ratio is below the LLN, an obstructive deficit is indicated.
2. If the FEV₁/FVC ratio \geq LLN and the FVC is $<$ LLN, a restrictive pattern is suggested, which should be confirmed by evaluating the total lung capacity.
3. If both FEV₁/FVC and FVC are above their respective LLNs, the spirometry is most likely to be within normal limits.

The final step in the interpretation process is to answer the clinical question, that is, the reason for referral for spirometry testing.

The ANZSRS support the recommendation that the interpretation of spirometry measurements use the LLN to detect an abnormality rather than a fixed cut-off. Unfortunately, while a single threshold may be easy to remember and apply, it is fraught with error and is not applicable to the entire population's age range. The FEV₁/FVC ratio varies with age, height and gender, and declines with age. Applying a fixed FEV₁/FVC cut-off value of <0.70 to define the presence of airway obstruction has been reported to lead to under-diagnosis of obstruction (false negatives) in the younger population and over-diagnosis of obstruction (false positives) in the older population.³⁵ Furthermore, evaluating spirometry data with 80% predicted and fixed cut-off points to determine if results are abnormal can lead to more than 20% of patients referred for pulmonary function to be misdiagnosed.³⁶ The ANZSRS recommends that the LLN is used to define the presence of lung function abnormalities. It is however important to consider that the LLN is based on statistical data and there may not be perfect agreement with clinical normality. Therefore, the clinical context of the test result must also be considered when interpreting results. A result below the LLN is more likely to represent true clinical

abnormality in a subject from a high-risk group or where the subject has clinically relevant signs or symptoms.

A simple way to present spirometry results and their relationship to LLN is to express the results as Z-scores both numerically and using a pictogram (see Figs 1–4). The Z-score represents how many SD the measured value is away from the mean predicted value (i.e. a Z-score of 0 represents the mean predicted value, while a Z-score of -1 would be one SD below the mean predicted value). This visual representation of data is easy to understand for all health care professionals. The shading on the scales clearly identifies the normal range, the areas close to the limits of the normal range and the area outside of the normal range. The Z-score for each variable is represented by an arrow or dot, which allows clinicians to quickly visualize which, if any, spirometric parameters are below the LLN range (Z-score < -1.64) indicating the presence of abnormality. The location of the arrow or dot also allows the clinician to assess how severe any deficit is, with a more negative Z-score indicating more severe abnormality. Another significant advantage of this mode of representation is that results of any measured respiratory function variable can be represented in this way, making comparison of different lung function outcomes quite straight-forward.

The most widely used severity classification for test interpretation is that recommended by the ATS/ERS guidelines.⁴ These recommendations have five different categories based on arbitrary cut-off values using FEV₁ % predicted. Recently, research has investigated other approaches, such as Z-scores, to assess the severity of spirometric abnormalities. A study by Quanjer *et al.* used a large pool of both clinical data and data from epidemiological studies to investigate this technique.³⁷ The study determined Z-score cut-off values to classify the severity of spirometric abnormalities, which correlated very well with the ATS/ERS cut-off values. Using Z-scores to determine the severity of spirometric abnormalities would eliminate the age and height biases which are associated with the percentage of predicted approach. This is an area of spirometry interpretation that has potential for further study prior to inclusion in clinical management guidelines.

The application of GLI 2012 reference equation and a statistically based approach to evaluation of spirometry measurements is demonstrated in the following examples. Using the report layout shown below (Figs 1–4), the clinician can either compare the measurements with the LLN or simply just view the Z-score.

Example 1 (Fig. 1): The pre-bronchodilator spirometry results for a 73.4-year-old Caucasian male with a height of 176.6 cm show a normal spirometric pattern. The measured FEV₁/FVC is 67% which is above the LLN of 62%, with the GLI 2012 Z-score being -1.01 . Therefore, the measured FVC is then evaluated and at 4.70 L (Z-score of 0.97), the FVC is also above the LLN of 2.98 L. Thus, this spirometry result is within the normal limits. In Figure 1, the dots on the Z-score pictogram clearly show that all values are within the normal range. Although the measured FEV₁/FVC is <0.7 , these spirometry results do not indicate an obstructive spirometric pattern because the LLN is 62% for this individual.

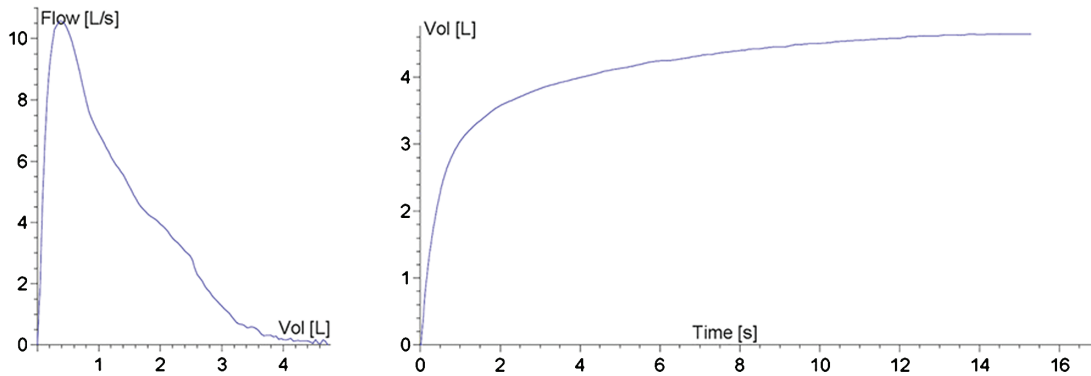
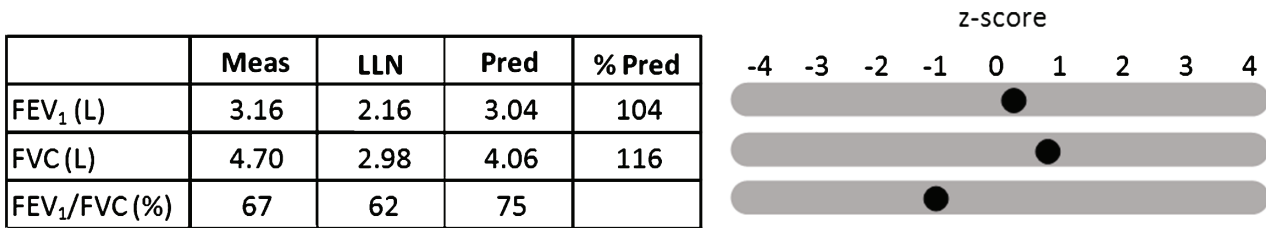


Figure 1 Spirometry results for a 73.4-year-old caucasian male (height of 176.6 cm) showing the measured values (Meas), lower limit of normal (LLN), predicted value (Pred), percent predicted value (%Pred) and Z-score for each parameter plotted on the bars. Both flow/volume and volume/time graphs are also shown.

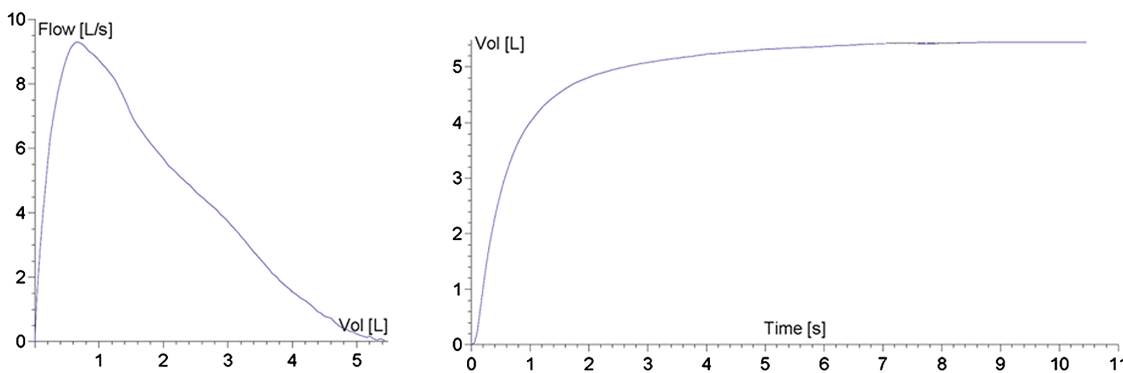
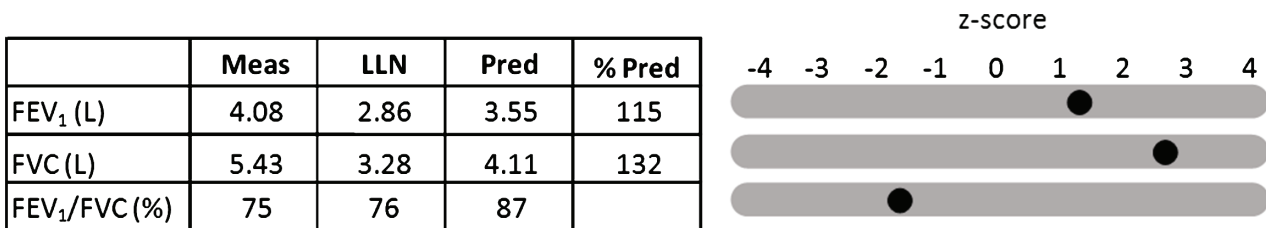


Figure 2 Spirometry results for a 22.4-year-old caucasian female (height of 168.0 cm) showing the measured values (Meas), lower limit of normal (LLN), predicted value (Pred), percent predicted value (%Pred) and Z-score for each parameter plotted on the bars. Both flow/volume and volume/time graphs are also shown.

Example 2 (Fig. 2): The pre-bronchodilator spirometry results for a 22.4-year-old Caucasian female with a height of 168.0 cm depict a borderline obstructive result. The measured FEV₁/FVC ratio at 75% (GLI 2012 Z-score of -1.71) is just below the LLN of 76%. The

measured FEV₁ of 4.08 L (Z-score of 1.27) is well above the LLN of 2.86 L. The minor reduction in FEV₁/FVC represents a borderline result and care needs to be exercised when results are close to the LLN. It is important to correlate with clinical information and

	Meas	LLN	Pred	% Pred	Post	% Change
FEV ₁ (L)	1.2	2.57	3.1	39	1.63	36
FVC (L)	3.23	3.37	3.99	81	3.65	13
FEV ₁ /FVC (%)	37	68	78		45	

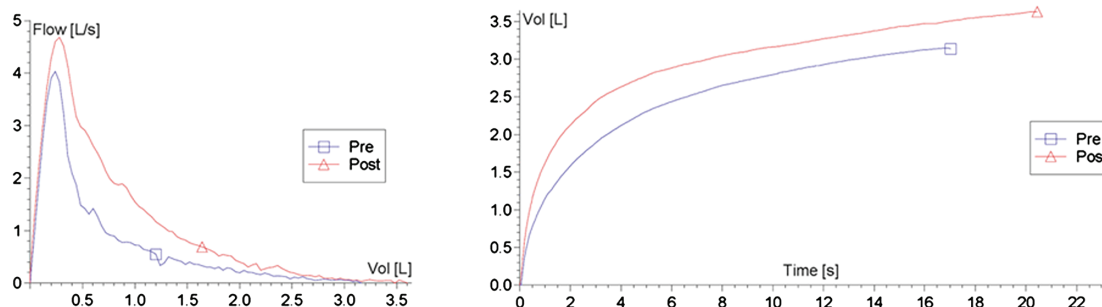
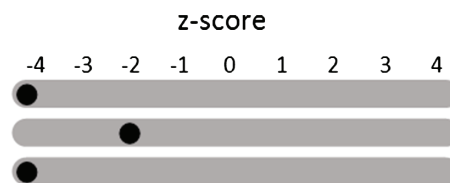


Figure 3 Spirometry results for a 63.6-year-old chinese male (height of 172.0 cm) showing the measured values (Meas), lower limit of normal (LLN), predicted value (Pred); percent predicted value (%Pred) and Z-score for each parameter plotted on the bars. Both flow/volume and volume/time graphs are shown. Post-bronchodilator (Post) and percent change (% Change) from measured baseline are also given (□, pre-bronchodilator; △, post-bronchodilator).

	Meas	LLN	Pred	% Pred
FEV ₁ (L)	2.97	3.30	4.19	71
FVC (L)	4.47	4.17	5.28	85
FEV ₁ /FVC (%)	66	69	80	

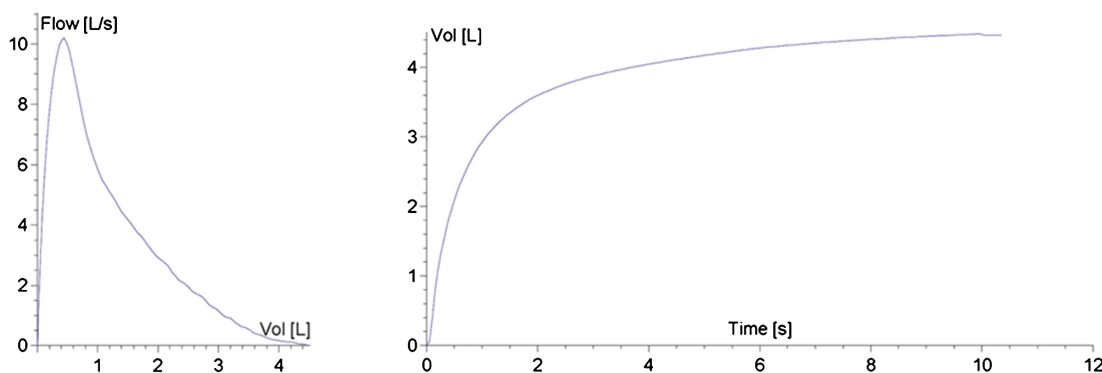
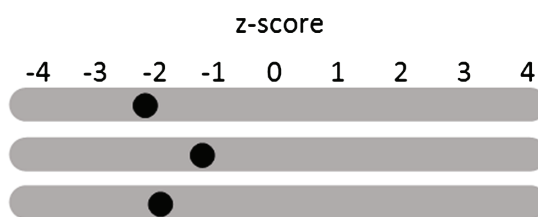


Figure 4 Spirometry results for a 45.3-year-old caucasian male (height of 180.2 cm) showing the measured values (Meas), lower limit of normal (LLN), predicted value (Pred); percent predicted value (%Pred) and Z-score for each parameter plotted on the bars. Both flow/volume and volume/time graphs are also shown.

pre-test probability of disease/dysfunction in borderline cases. Diagnosis should not be made based on lung function alone.

Example 3 (Fig. 3): The pre- and post-bronchodilator spirometry results for a 63.6-year-old Chinese male with a height of 172.0 cm clearly show an obstructive pattern. It was established that this individual was from North-East Asia for choosing the most relevant

reference set from the GLI 2012 equations. The FEV₁/FVC ratio of 37% (GLI 2012 Z-score of -5.46) is below the LLN of 68% and FEV₁ at 39% of the predicted value (Z-score of -5.50) is below the LLN of 2.57. These represent measurements well below their LLN and Z-scores of -3.0 as seen on the pictogram which represents the pre-bronchodilator results. This example also shows the spirometry results measured 15 min after

Salbutamol inhalation, and a significant bronchodilator response is evident with both FEV₁ and FVC improving by >12% and >200 mL, respectively.⁴ Although the baseline FVC is below the LLN, the post-bronchodilator value is above the LLN suggesting that co-existent pulmonary restriction is unlikely.

The final example (Fig. 4): Pre-bronchodilator spirometry results from a 45.3-year-old Caucasian male, height of 180.2 cm, show a mild obstructive pattern. The FEV₁/FVC ratio is 66% (GLI 2012 Z-score of -2.02) which is below the LLN of 69%. The measured FEV₁ of 2.97 L (Z-score of -2.24) is also below the LLN of 3.30 L and at 71% of the predicted value this indicates a mild obstructive pattern using the ATS/ERS guidelines. The measured FVC of 4.47 L is within normal limits.

POTENTIAL LIMITATIONS TO ADOPTING THE GLI 2012 SPIROMETRY EQUATIONS

It is important to consider potential limitations to the uptake of the GLI 2012 spirometry equations into clinical and research practice. The main issues are summarized below. For additional information, the reader is directed to an excellent educational paper by Stanovec *et al.*³⁸

Currently, the GLI 2012 equations offer the most comprehensive multi-ethnic spirometry equations. However, it must be acknowledged that there is a vast global ethnic diversity and that it is unlikely that any lung function reference equations will be able to cover the complete spectrum of ethnic groups seen within any one health service. This is highlighted by increasing global migration and children of ethnically diverse parents.

Within the Australian and New Zealand context, the GLI 2012 equations do not include Australian Aboriginal, Torres Strait Islander, Maori and Pacific Island populations and this remains a significant challenge for the Australasian community. For these groups, until specific GLI equations are produced, it would be reasonable to use the GLI 2012 Other equations. It should be noted that the ethnic variability in the predicted FEV₁/FVC ratio from the GLI 2012 reference equations is low with the largest difference of 2.9% being between Caucasian and South-East Asian males.¹ It is therefore likely that the use of the FEV₁/FVC GLI 2012 predicted values will minimize the potential misclassification of obstructive lung disease in patients from a range of ethnic backgrounds.

The ANZSRS recommends that each health service makes an informed choice on how the service plans to address the issue of ethnicity for their own patient populations. This could include either using equations considered to be most appropriate while acknowledging on their lung function reports that accurate reference equations for the ethnic population in question are unavailable, or use the GLI 2012 Other category for bi-racial patients and those from unrepresented ethnic groups while noting the potential problems with this approach on the reports.

The changing of any prediction equations will potentially impact the clinical results of previous tests. It will be critical for each clinical service to consider how it will approach this change. Comparison of absolute values from different visits, rather than comparing percentage of predicted values is the most appropriate way to deal with this issue. Medical, scientific and nursing staff within a clinical service should have a clear understanding of the changes and how these will be explained to patients as they attend for follow-up visits.

The GLI 2012 spirometry equations were developed to include spirometric parameters recommended for clinical use by the ATS/ERS spirometry guidelines: FEV₁, FVC and FEV₁/FVC.³ FEF_{25-75%} is also available, although not recommended in the ATS/ERS interpretative strategy. The use of FEF_{25-75%} and additional flow and/or volume outcomes for the clinical interpretation while common in some practices is not supported by successive national and international guidelines and has been demonstrated in three large independent studies not to add any value to the interpretation of the spirometry results.^{3,4,22,39,40}

An increasing number of manufacturers have incorporated the GLI 2012 equations into their existing software and/or hardware systems. The GLI group regularly updates information outlining which spirometry systems are GLI 2012-enabled (www.ers-education.org/guidelines/global-lung-function-initiative/manufacturers.aspx). Depending on the situation, applications are available that allow the GLI 2012 predicted values to be generated for an individual patient at the time of the clinical test, or for larger research data sets to be converted into predicted GLI 2012 outcomes. These applications can be found at the GLI website (www.lungfunction.org).

SUMMARY OF STATEMENT

The use of appropriate reference values is vital for valid interpretation of spirometric results. Given the large number of subjects, the stringent criteria used and the fact that the data are contemporary and use appropriate statistical analyses, the GLI 2012 spirometry prediction equations represent the most robust and scientifically valid equations available at this time. These equations have been endorsed by national and international respiratory societies and have been formally recommended for usage by the Association of Respiratory Technology and Physiology (ARTP). The ANZSRS formally recommends the use of the GLI 2012 spirometry prediction equations for all spirometries performed in clinical, screening, occupational health and safety and research settings. This is an important step in the standardization of spirometry across Australasia.

Given the significant amount of data revealing how lung function declines with age, the ANZSRS also formally recommends the use of LLN to define abnormality in spirometric results rather than the use of fixed cut-off values. Moreover, where possible, ANZSRS encourages the use of Z-scores to aid interpretation. These important steps will result in a reduction in misclassified spirometry results.

Recommendations

The following recommendations have been proposed by the ANZSRS:

1. ANZSRS recommends the adoption of the GLI 2012 spirometry reference values throughout Australia and New Zealand.
2. ANZSRS recommends that interpretation of spirometry results is based on the LLN from the reference values.
3. ANZSRS encourages the use of Z-scores where possible on lung function reports.

Acknowledgements

The authors would like to acknowledge the contribution of the late Dr Jeff Pretto (John Hunter Hospital, Newcastle, NSW) to this manuscript. Dr Pretto originally proposed that this manuscript should be written and contributed some preliminary ideas before his tragic and untimely death in March 2014. A great friend and colleague to many.

REFERENCES

- 1 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J *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**: 1324-43.
- 2 Pretto JJ, Brazzale DJ, Guy PA, Goudge RJ, Hensley MJ. Reasons for referral for pulmonary function testing: an audit of 4 adult lung function laboratories. *Respir. Care* 2013; **58**: 507-10.
- 3 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P *et al.* Standardisation of spirometry. *Eur. Respir. J.* 2005; **26**: 319-38.
- 4 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J *et al.* Interpretative strategies for lung function tests. *Eur. Respir. J.* 2005; **26**: 948-68.
- 5 Miller M, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten C, Gustafsson P. Standardization of spirometry, 1994 update. American Thoracic Society. *Am. J. Respir. Crit. Care Med.* 1995; **152**: 1107-36.
- 6 Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM *et al.* Standardisation of the measurement of lung volumes. *Eur. Respir. J.* 2005; **26**: 511-22.
- 7 MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur. Respir. J.* 2005; **26**: 720-35.
- 8 Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, Calverley PMA, Chavannes N, Dillard T, Fahy B *et al.* Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur. Respir. J.* 2004; **23**: 932-46.
- 9 BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997; **52**: 1.
- 10 Siafakas N, Vermeire P, Pride N, Paoletti P, Gibson J, Howard P, Yernault J, Decramer M, Higenbottam T, Postma D *et al.* Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur. Respir. J.* 1995; **8**: 1398-420.
- 11 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD 2013. [Accessed 17 Jul 2015.] Available from URL: <http://www.goldcopd.org>
- 12 Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: a consensus statement from the national lung health education program. *Chest* 2000; **117**: 1146-61.
- 13 Quanjer PH, Kubota M, Kobayashi H, Omori H, Tatsumi K, Kanazawa M, Stanojevic S, Stocks J, Cole TJ. Secular changes in relative leg length confound height-based spirometric reference values. *Chest* 2015; **147**: 792-7.
- 14 Towns SJ, Bell SC. Transition of adolescents with cystic fibrosis from paediatric to adult care. *Clin. Respir. J.* 2011; **5**: 64-75.
- 15 Kirkby J, Aurora P, Spencer H, Rees S, Sonnappa S, Stocks J. Stitching and switching: the impact of discontinuous lung function reference equations. *Eur. Respir. J.* 2012; **39**: 1256-7.
- 16 Cole TJ, Stanojevic S, Stocks J, Coates AL, Hankinson JL, Wade AM. Age- and size-related reference ranges: a case study of spirometry through childhood and adulthood. *Stat. Med.* 2009; **28**: 880-98.
- 17 Lung function testing: selection of reference values and interpretative strategies. *Am. Rev. Respir. Dis.* 1991; **144**: 1202-18.
- 18 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**: 179-87.
- 19 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur. Respir. J. Suppl.* 1993; **16**: 5-40.
- 20 Quanjer PH, Stocks J, Polgar G, Wise M, Karlberg J, Borsboom G. Compilation of reference values for lung function measurements in children. *Eur. Respir. J. Suppl.* 1989; **4**: 184S-261.
- 21 Stanojevic S, Wade A, Cole TJ, Lum S, Custovic A, Silverman M, Hall GL, Welsh L, Kirkby J, Nystad W *et al.* Spirometry centile charts for young Caucasian children: the Asthma UK Collaborative Initiative. *Am. J. Respir. Crit. Care Med.* 2009; **180**: 547-52.
- 22 Hall GL, Thompson BR, Stanojevic S, Abramson MJ, Beasley R, Coates A, Dent A, Eckert B, James A, Filsell S *et al.* The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. *Respirology* 2012; **17**: 1150-1.
- 23 Bonner R, Lum S, Stocks J, Kirkby J, Wade A, Sonnappa S. Applicability of the global lung function spirometry equations in contemporary multiethnic children. *Am. J. Respir. Crit. Care Med.* 2013; **188**: 515-6.
- 24 Ben Saad H, El Attar MN, Hadj Mabrouk K, Ben Abdelaziz A, Abdelghani A, Bousarssar M, Limam K, Maatoug C, Bouslah H, Charrada A *et al.* The recent multi-ethnic global lung initiative 2012 (GLI2012) reference values don't reflect contemporary adult's North African spirometry. *Respir. Med.* 2013; **107**: 2000-8.
- 25 Sonnappa S, Lum S, Kirkby J, Bonner R, Wade A, Subramanya V, Lakshman PT, Rajan B, Nooyi SC, Stocks J. Disparities in pulmonary function in healthy children across the Indian urban-rural continuum. *Am. J. Respir. Crit. Care Med.* 2015; **191**: 79-86.
- 26 Brazzale DJ, Hall GL, Pretto JJ. Effects of adopting the new global lung function initiative 2012 reference equations on the interpretation of spirometry. *Respiration* 2013; **86**: 183-9.
- 27 Quanjer PH, Brazzale DJ, Boros PW, Pretto JJ. Implications of adopting the Global Lungs Initiative 2012 all-age reference equations for spirometry. *Eur. Respir. J.* 2013; **42**: 1046-54.
- 28 Quanjer PH, Weiner DJ. Interpretative consequences of adopting the global lungs 2012 reference equations for spirometry for children and adolescents. *Pediatr. Pulmonol.* 2014; **49**: 118-25.
- 29 Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. *Pediatr. Pulmonol.* 1993; **15**: 75-88.
- 30 Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am. Rev. Respir. Dis.* 1983; **127**: 725-34.
- 31 Polgar G, Varuni P. *Pulmonary Function Testing in Children: Techniques and Standards*. Philadelphia, USA, Saunders Limited, 1971.
- 32 Zapletal A, Paul T, Samanek M. Significance of contemporary methods of lung function testing for the detection of airway obstruction in children and adolescents (author's transl). *Z. Erkr. Atmungsorgane* 1977; **149**: 343-71.
- 33 Quanjer PH, Hall GL, Stanojevic S, Cole TJ, Stocks J, Global LI. Age- and height-based prediction bias in spirometry reference equations. *Eur. Respir. J.* 2012; **40**: 190-7.

- 34 Brener ND, McManus T, Galuska DA, Lowry R, Wechsler H. Reliability and validity of self-reported height and weight among high school students. *J. Adolesc. Health* 2003; **32**: 281–7.
- 35 Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, Jensen RL, Falaschetti E, Schouten JP, Hankinson JL *et al.* Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008; **63**: 1046–51.
- 36 Miller MR, Quanjer PH, Swanney MP, Ruppel G, Enright PL. Interpreting lung function data using 80% predicted and fixed thresholds misclassifies more than 20% of patients. *Chest* 2011; **139**: 52–9.
- 37 Quanjer PH, Pretto JJ, Brazzale DJ, Boros PW. Grading the severity of airways obstruction: new wine in new bottles. *Eur. Respir. J.* 2014; **43**: 505–12.
- 38 Stanojevic S, Quanjer PH, Miller MR, Stocks J. The Global Lung Function Initiative: dispelling some myths of lung function test interpretation. *Breathe* 2013; **9**: 463–74.
- 39 Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25–75% and FEF75% does not contribute to clinical decision making. *Eur. Respir. J.* 2014; **43**: 1051–8.
- 40 Lukic KZ, Coates AL. Does the FEF25–75 or the FEF75 have any value in assessing lung disease in children with cystic fibrosis or asthma? *Pediatr. Pulmonol.* 2015; **50**: 863–8.