Effects of adopting the Global Lung Function Initiative 2017 reference equations on the interpretation of carbon monoxide transfer factor

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ABSTRACT The recently published Global Lung Function Initiative (GLI) carbon monoxide transfer factor (T_{LCO}) reference equations provide an opportunity to adopt a current, all-age, widely applicable reference set. The aim of this study was to document the effect of changing to GLI from commonly utilised reference equations on the interpretation of T_{LCO} results.

33 863 T_{LCO} results (48% female, 88% Caucasian, n=930 aged <18 years) from clinical pulmonary function laboratories within three Australian teaching hospitals were analysed. The lower limit of normal (LLN) and proportion of patients with a T_{LCO} below this value were calculated using GLI and other commonly used reference equations.

The average T_{LCO} LLN for GLI was similar or lower than the other equations, with the largest difference seen for Crapo equations (median: −1.25, IQR: −1.64, −0.86 mmol·min^{-1}·kPa^{-1}). These differences resulted in altered rates of reduced T_{LCO} for GLI particularly for adults (+1.9% *versus* Miller to −27.6% *versus* Crapo), more so than for children (−0.8% *versus* Kim to −14.2% *versus* Cotes). For adults, the highest raw agreement for GLI was with Miller equations (94.7%), while for children it was with Kim equations (98.1%). Results were reclassified from abnormal to normal more frequently for younger adults, and for adult females, particularly when moving from Roca to GLI equations (30% of females *versus* 16% of males).

The adoption of GLI T_{LCO} reference equations in adults will result in altered interpretation depending on the equations previously used and to a greater extent in adult females. The effect on interpretation in children is less significant.

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Introduction

Carbon monoxide transfer factor (T_{LCO}) is a widely used test of respiratory function [1] and plays a vital role in the assessment of gas exchange and the diagnosis and management of various respiratory diseases [2–6]. The accurate interpretation of T_{LCO} relies on the comparison with predicted values that are calculated from reference equations. However, the selection of appropriate reference equations can be problematic with at least 15 sets of equations published in the decade from 1995 to 2004 [7]. The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines from 2005 [7] provide little guidance regarding the choice of T_{LCO} reference equations, with the guidelines merely listing the most commonly used in North America and Europe.

In 2017 the Global Lung Function Initiative (GLI) published a new set of reference equations for T_{LCO} [8]. These were derived from a very large normal data set (9710 subjects) compared to previous equations. The data was obtained from multiple international sites, with strict selection criteria. To be included in the analysis, the data needed to be collected after the year 2000, on modern equipment and adhere to strict quality control requirements. This large volume of data was used to create reference equations using the lambda, mu and sigma (LMS) method, which allows modelling of variability and skewedness of data, accounts for the interactive effects of age, height and sex and uses splines to model the non-linear age effects across the life span. The GLI reference equations also span the age range from 5 to 85 years, avoiding the need to use separate paediatric and adult equations, as well as reducing the need to extrapolate reference equations in the elderly.

The strengths of the GLI T_{LCO} reference equations mean that they are most appropriate to use globally, which will lead to more consistent interpretation of T_{LCO} results across centres. However, this transition could impact the interpretation of T_{LCO} results in a clinical respiratory laboratory.

Such differences in the interpretation of spirometry have been well documented when those reference equations were updated [9–13]. In those studies, there were significant differences in the proportion of people classified as abnormal despite reasonable overall agreement across reference equations. To our knowledge, a similar analysis has not been performed for T_{LCO}. The increased complexity in the measurement of T_{LCO} compared with spirometry has the potential to create larger differences across reference equations, and hence a larger impact on T_{LCO} interpretation.

The aim of this study was to document the effect of changing to the GLI T_{LCO} reference equations from commonly utilised older reference equations on the interpretation of T_{LCO} results in a large clinical dataset.

Materials and methods

Data were obtained from clinical pulmonary function laboratory databases at three Australian teaching hospitals (Austin Hospital in Victoria, Concord Repatriation General Hospital in New South Wales and The Royal Children's Hospital in Victoria). All three are large university-affiliated tertiary referral centres involved in the management of a broad range of respiratory diseases. Local Ethics Committee approval was obtained from each of the three hospitals.

A search was conducted on each of the hospital's databases for all T_{LCO} results from 2008 until August 2018. Data were collected for patients aged 5 to 85 years. All testing was performed in accordance with the ERS/ATS guidelines [14]. Any test results not meeting the ERS/ATS guidelines were excluded.

The older reference equations used for comparison with the GLI equations for adults were those from Miller *et al.* [15], Roca *et al.* [16], Crapo and Morris [17] and European Community of Coal and Steel (ECCS) [18]. These reference equations were extrapolated to cover the range from 18 to 85 years. A separate analysis was performed with no age extrapolation (covering only the age range specified by each equation). For children, the comparisons with the GLI equations were made with the equations from Cotes *et al.* [19] and Kim *et al.* [20]. Data from both Caucasians and non-Caucasians were included in the analysis, with no race adjustment made for non-Caucasians.

The reference equations were used as published, with the exception of Roca, which contain a weight term for T_{LCO} and carbon monoxide transfer coefficient (K_{CO}) for females and alveolar volume (V_A) and K_{CO} for males. Due to the small weight range of the reference population, when these equations are applied to obese patients, the predicted values become non-physiological. A common practice to deal with this issue is to use the equations with a limitation on the maximum weight that is used to calculate the predicted values (limited to the maximum weight in the reference population). For example, the maximum weight in the reference population for females was 86 kg; so, for a female whose weight is above this value, a weight of 86 kg is used to calculate the predicted values.

Statistical analysis

The older reference equations were specifically for either adults or children and these data were analysed separately with patients <18 years of age assessed using the equations for children. The GLI equations that span the age range from 5 to 85 years were used for all patients. For each T_{LCO}, K_{CO} and V_A result the lower limit of normal (LLN) was calculated using each of the relevant reference equations. A measured value below the LLN was considered abnormally low. The proportion of patients below LLN for each of the relevant reference equations, as well as the number of patients that changed from a normal to abnormal classification (or vice versa) was calculated. The level of raw agreement between each of the older equations compared with the GLI equations was calculated based on the percentage of patients that were classified in the same manner (either both normal or both abnormal) using both equations. The level of agreement was also assessed with the kappa statistic.

Results

Patient characteristics

The patient characteristics are shown in table 1. Data from 33 863 patients were available for analysis after excluding data (approximately 7% not meeting ERS/ATS acceptability criteria). Of these patients, 4028 (11.9%) were non-Caucasian. With the clinical indication for measurement of T_{LCO} being less common in children, only 3% (n=930) of the patients were under 18 years of age. There was an even distribution of both sexes (48% female) and a wide distribution of height and weight in the dataset, with a tendency for the adult patients to be older and in the overweight range, based on BMI.

Adults

For the adult equations, the median difference (IQR) in the T_{LCO} LLN for GLI compared with the older equations was Crapo: −1.25 (−1.64–0.86), Roca: −1.02 (−1.33–0.67), ECCS: −0.35 (−0.62–0.07), Miller: 0.14 (−0.04–0.30) mmol·min^{-1}·kPa^{-1}. Figure 1 plots the mean LLN for each of the adult reference equations as a function of age, separated by sex. The GLI reference equations tend to produce a slightly lower LLN for a large portion of the age range for both sexes, particularly at a younger age, compared with all other equations. Above the age of approximately 70 years there is a tendency for the GLI equations to produce an LLN which is slightly higher than the LLN from the Miller and ECCS equations (fig. 1).

The proportion of adult males and females with a reduced T_{LCO} (below LLN) using each of the reference equations, as a function of age is illustrated in figure 2. Although the differences in the LLN were not large, they did result in altered rates of reduced T_{LCO} for adults (Miller: 34.2% (n=11 249), GLI: 36.1% (n=11 902), ECCS: 43.2% (n=14 219), Roca: 58.8% (n=19 370), Crapo: 63.7% (n=20 991)). The largest difference in rates of a reduced T_{LCO} for GLI equations occurs when compared with those of Crapo and Roca, particularly for females. There is also a large difference for younger females when comparing the GLI and ECCS equations. The closest agreement with the GLI equations for rates of reduced T_{LCO} is with the Miller equations.

The proportion of adult males and females who changed from an abnormally low T_{LCO} result to within the normal range, when moving from each of the older equations to the GLI equations is illustrated in

TABLE 1 Summary of patient demographics and carbon monoxide transfer factor (T_{LCO}) results for the entire patient group

	Adults	Children
Patients n	32 933	930
Male %	52.0	54.4
Non-Caucasian %	12.1	3.2
Age years	64.2 (52.9–73.1)	14.5 (11.3–16.3)
Height cm	166.0 (159.0–173.0)	159.0 (146.0–168.0)
Weight kg	79.0 (67.0–93.6)	50.2 (37.4–61.6)
BMI kg·m^{-2}	28.5 (24.6–33.3)	
Height for age z-score		−0.01 (−0.88–0.68)
Weight for age z-score		0.10 (−0.74–0.85)
T_{LCO} mmol·min^{-1}·kPa^{-1}	6.1 (4.7–7.7)	5.7 (4.4–7.3)
K_{CO} mmol·min^{-1}·kPa^{-1}	1.4 (1.1–1.7)	1.6 (1.4–1.8)
V_A L	4.4 (3.6–5.4)	3.6 (2.8–4.5)

Data are presented as median (interquartile range), unless otherwise stated. BMI: body mass index; K_{CO}: carbon monoxide transfer coefficient; V_A: alveolar volume.

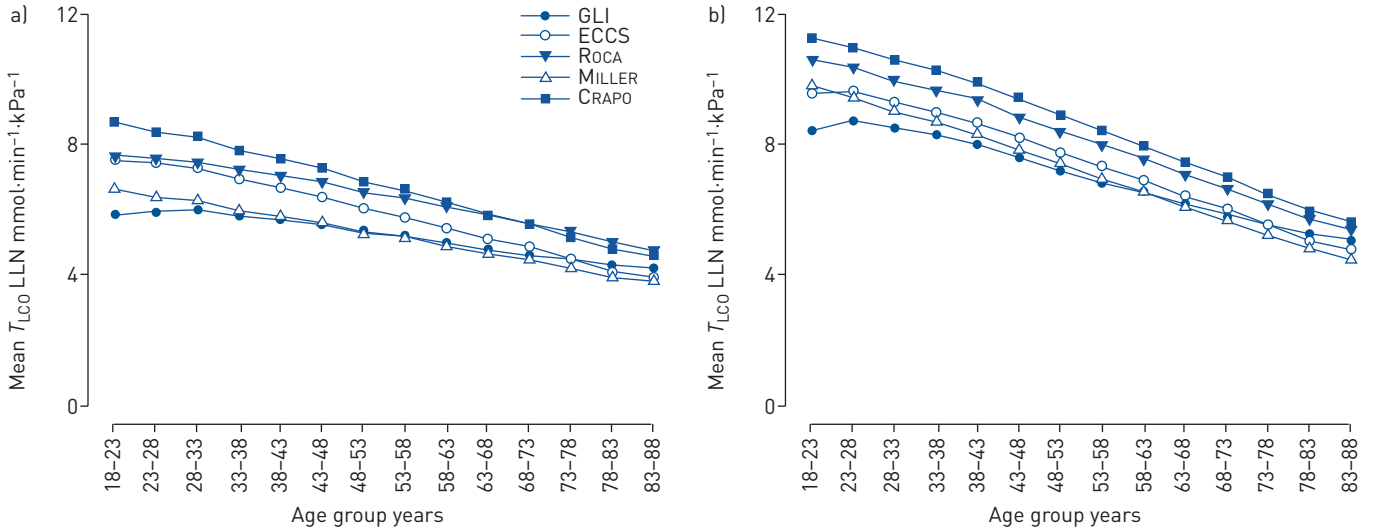

FIGURE 1 Mean carbon monoxide transfer factor (T_{LCO}) lower limit of normal (LLN) for each of the adult reference equations as a function of age, separated into (a) females and (b) males.

figure 3. Result classification changed (abnormal to normal) more frequently for adult females compared with males (for example reclassification occurred for 30% (n=4741) of females *versus* 16% (n=2779) of males when moving from Roca to GLI equations).

The largest proportion of patients changing category were younger rather than older adults. This pattern was most prominent for females when shifting from the Crapo and ECCS equations. As would be expected from the data in figure 2 there were a small number of older adults whose T_{LCO} result changed from within the normal range to abnormally low when moving to the GLI equations from those of Miller and ECCS (supplementary figure S1).

Paediatric

For the paediatric equations, the median difference (IQR) for GLI in the T_{LCO} LLN was Cotes: −0.53 (−0.63–0.39), Kim: 0.00 (−0.07–0.07) mmol·min^{-1}·kPa^{-1}. Figure 4 plots the mean LLN for each of the paediatric reference equations as a function of age, separated by sex. It can be seen that GLI reference equations, produce a slightly lower LLN for the entire age range for both sexes compared with the Cotes equations.

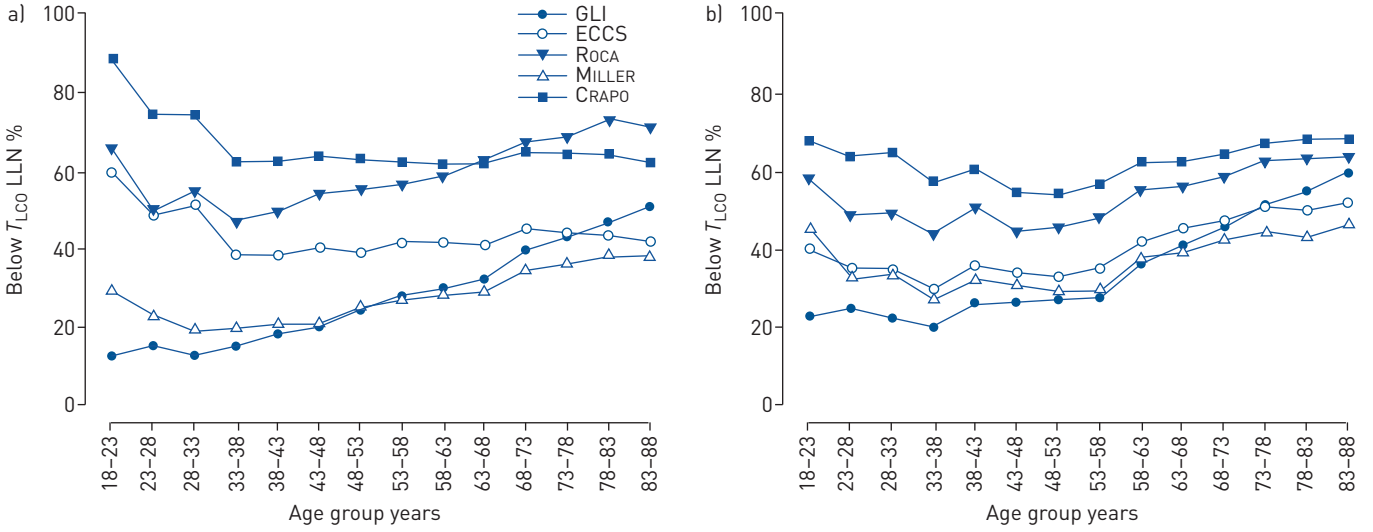

FIGURE 2 The proportion of (a) females and (b) males with a carbon monoxide transfer factor (T_{LCO}) below the lower limit of normal (LLN) using each reference equations, as a function of age for adults.

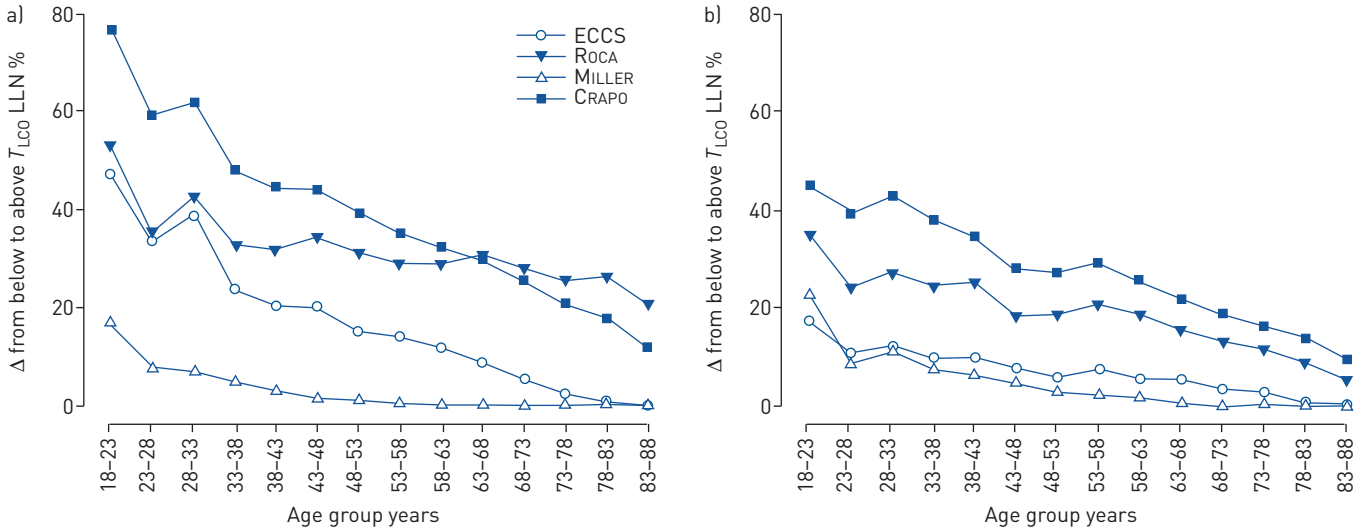

FIGURE 3 The proportion of (a) females and (b) males who changed from an abnormally low carbon monoxide transfer factor (T_{LCO}) result to within the normal range, when moving from each of the older equations to the Global Lung Function Initiative (GLI) equations. LLN: lower limit of normal.

Figure 5 demonstrates the proportion of males and females with an abnormally low T_{LCO} using each reference equation, as a function of age for children. The rates of reduced T_{LCO} for children were more similar across equations (GLI: 39.5% (n=367), Kim: 40.3% (n=375), Cotes: 53.7% (n=499)) than for adults. The GLI equations produced lower rates of a reduced T_{LCO} for both sexes compared with those from Cotes (44.3% (n=224) *versus* 57.9% (n=293) for boys, 33.7% (n=143) *versus* 48.6% (n=206) for girls). The proportion of boys and girls who changed from an abnormally low T_{LCO} result to within the normal range, when moving from each of the older equations to the GLI equations is illustrated in figure 6.

Agreement between equations

Table 2 shows the level of agreement of the GLI equations with the older equations in identifying abnormality. The overall raw agreement varied from 72.3% with Crapo equations in adults to 98.1% with the Kim equations in children. For adults, the highest level of agreement with the GLI equations for both sexes is with the equations from Miller, whereas the lowest level of agreement is with the Crapo equations (table 2). The level of agreement between the GLI equations and those of Roca, Crapo, and ECCS is lower for females than it is for males. For children, the level of agreement between the GLI equations and those of Cotes is lower than the equations from Kim for both sexes.

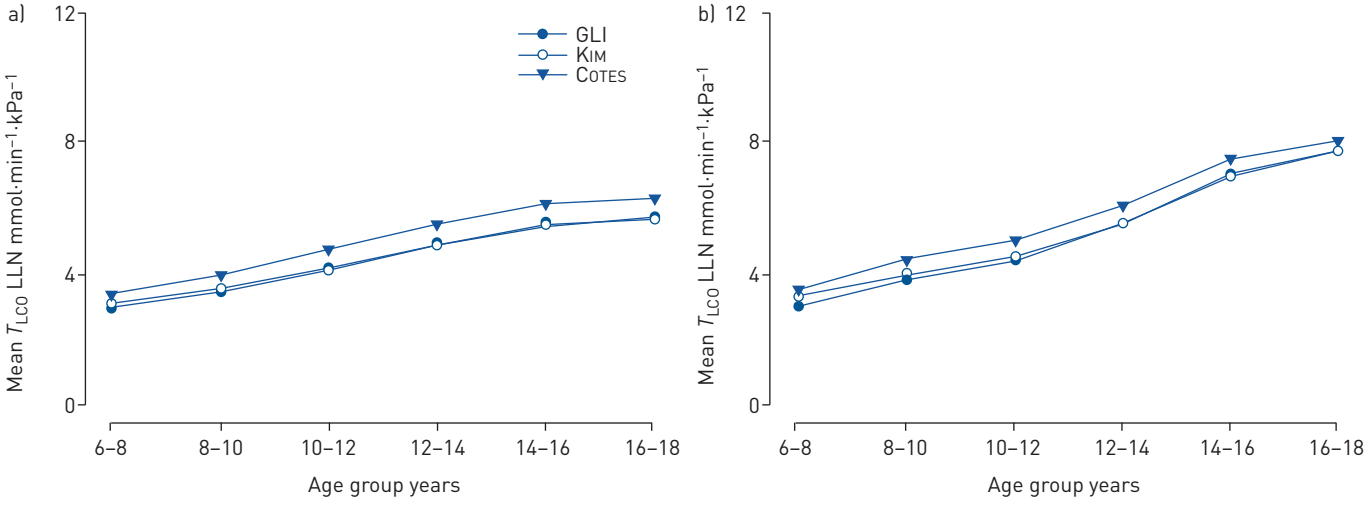

FIGURE 4 Mean carbon monoxide transfer factor (T_{LCO}) lower limit of normal (LLN) for each of the paediatric reference equations as a function of age, separated into (a) females and (b) males.

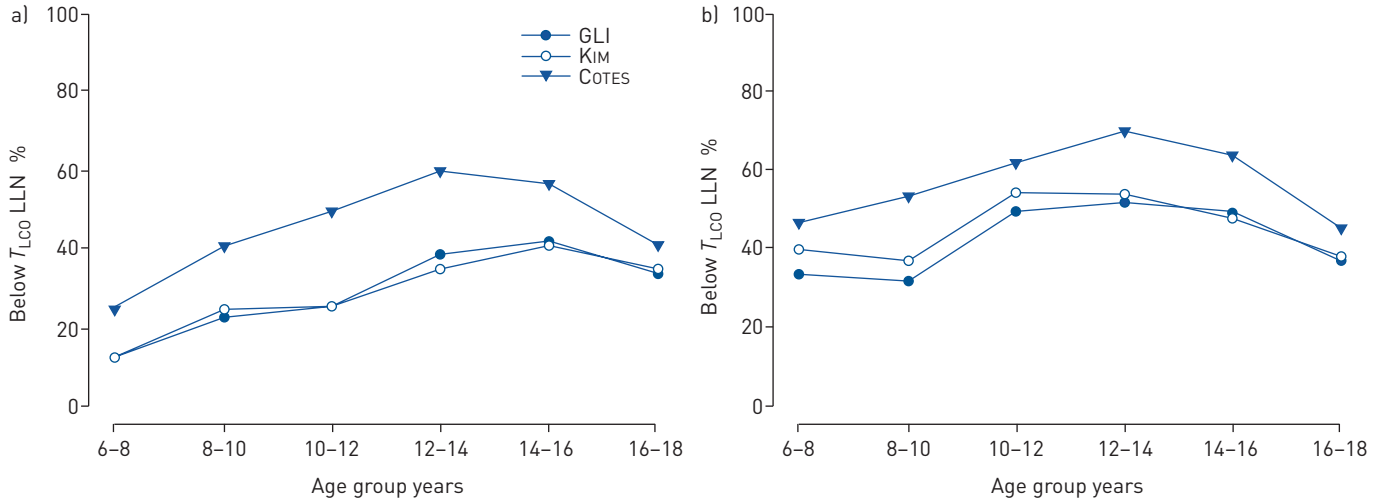

FIGURE 5 The proportion of females (a) and males (b) with an abnormally low carbon monoxide transfer factor (T_{LCO}) using each of the different reference equations, as a function of age for children. LLN: lower limit of normal.

In a separate analysis, the limits of agreement were calculated without any age extrapolation of the older equations. The results of this analysis were very similar to those seen with the extrapolated data (supplementary table S1).

Bland–Altman plots comparing the LLN for each of the older equations with the GLI are included in the supplementary material (supplementary figures S2 and S3 and supplementary table S2), showing the median difference (and 95% confidence intervals) between the older equations and GLI separated into males and females. These plots confirm that for adults the largest difference between equations occur when the LLN is larger, which would be seen in younger and taller people.

K_{CO} and V_A

The comparison with the GLI equations for adults shows that the LLN for K_{CO} is similar to those of Miller and ECCS, however, they tend to be smaller compared to those of Roca and Crapo, particularly for females (supplementary figures S4 and S5, table S3). The difference was more pronounced at a younger age and higher K_{CO} values. The comparison with the GLI equations for children shows that the LLN for K_{CO} are similar to the Kim equations but the values tend to be smaller compared with the Cotes equations (supplementary figures S6 and S7, table S4). These differences in the LLN result in altered rates of an abnormal K_{CO} with different equations, with the largest differences (and lowest agreements) occurring with the Crapo and Roca equations for adult females and the Cotes equations for children (supplementary figure S8, table S5).

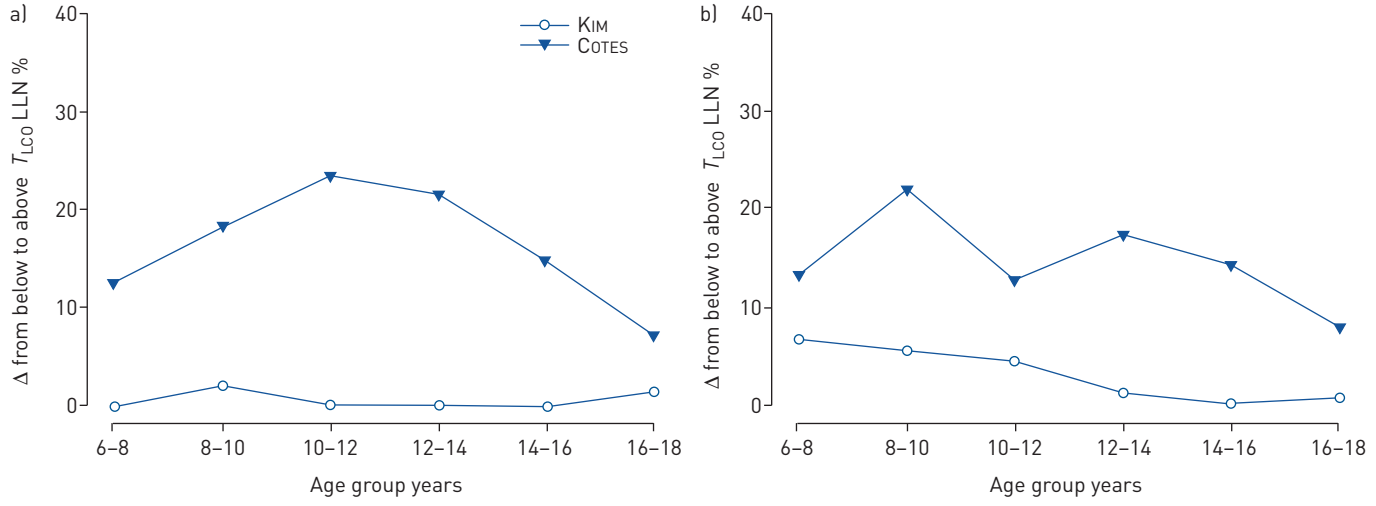

FIGURE 6 The proportion of (a) female and (b) male children who changed from an abnormally low carbon monoxide transfer factor (T_{LCO}) result to within the normal range, when moving from each of the older equations to the Global Lung Function Initiative (GLI) equations. LLN: lower limit of normal.

TABLE 2 Levels of agreement for a reduced carbon monoxide transfer factor (T_{LCO}) (below lower limit of normal) comparing Global Lung Function Initiative equations to each of the older reference equations

Equation *versus* GLI2017	Reduced T_{LCO} % raw agreement (κ)		
	All	Females	Males
Adults			
Miller	94.7 (0.88)	95.2 (0.89)	94.3 (0.88)
ECCS	90.5 (0.80)	87.5 (0.74)	93.3 (0.86)
Roca	77.2 (0.56)	70.0 (0.45)	83.8 (0.68)
Crapo	72.3 (0.48)	67.3 (0.41)	76.8 (0.56)
Children			
Kim	98.1 (0.96)	98.6 (0.97)	97.6 (0.95)
Cotes	85.8 (0.72)	85.1 (0.70)	86.4 (0.73)

κ: kappa statistic; ECCS: European Community of Coal and Steel.

The LLN for V_A comparison with the GLI equations yielded mixed results (supplementary figures S9–S12, tables S3 and S4). Values are similar to those of Miller, and for the Kim and ECCS equations for females but not males. Although the median difference was not large for the Roca equations there was a larger spread. No predicted V_A is available for the Crapo and Cotes equations. These differences in the LLN result in altered rates of an abnormal V_A with different equations, with the largest differences (and lowest agreements) occurring with the ECCS equations for adult males and the Kim equations for male children (supplementary figure S13, table S6).

Discussion

Our analysis shows significant differences in T_{LCO} interpretation using GLI reference equations compared with some commonly used older equations for adults. These differences in abnormality rates are smaller for children. Within these groups, the differences also alter with sex and age. The largest change in abnormality rate will be a reduction of approximately 33% for females if transitioning from the Crapo to the GLI equations. There will be a similar change for females if moving from the Roca equations. There will also be a reduction in abnormality rates (approximately 25%) for younger adult females when transitioning from the ECCS equations to the GLI equations and a similar change for younger adult males when moving from the Roca equations. The Bland–Altman plots comparing the T_{LCO} LLN for older equations with GLI equations (supplementary figures S2 and S3) suggest that for any given T_{LCO}, the change may be variable when switching equations and not easily predicted.

The recent publication of the GLI T_{LCO} reference equations is likely to cause many pulmonary function laboratory directors to re-appraise their choice of reference equations. Changing reference equations is problematic for any clinical laboratory, with characterisation of disease presence and severity potentially altered. Given that our data are from three large hospital laboratories, we feel that they provide an important overview of the effects on interpretation in a representative clinical population.

The observed change in T_{LCO} abnormality rates is not surprising. Similar to our study, a recent letter [21] identified a 1–21% increase in the number of patients who would qualify for clinical trials based on a T_{LCO} cut-off of ⩾30% predicted when using GLI compared with older equations, and the best agreement to be with the Miller equations. This strong agreement between the GLI and Miller equations is reassuring given that the Miller equations have previously been shown to be the best at predicting survival in a large group of patients [22]. This suggests that the GLI equations would be appropriate to use.

There are several explanations for the differences in abnormality rates between reference equations. Most of the older reference equations utilised data which were collected prior to 1993, before widespread standardisation of the T_{LCO} test technique. There may have also been discordance in the actual values quoted (*e.g.* mean *versus* highest value) and most of the data were collected using equipment which may have had different performance characteristics compared with modern equipment. In addition, the GLI reference equations utilised data after correction for equipment deadspace and test altitude above mean sea level, and used more complex statistical analyses.

Another potential explanation is that the population used to generate the reference equations is not representative of the clinical population. While validation of reference equations is possible by comparing

results from local normal subjects, the number required to identify any real differences may be up to 300 [23], which is not realistic for most respiratory function laboratories.

The levels of agreement between GLI equations and the older equations for classification of abnormality vary from 72.3% to 98.1%. These are lower than those seen with similar comparisons for spirometry equations [13]. This would be easily explained by the increased complexity of T_{LCO} measurement, with the requirement to measure additional variables such as inspired and expired gas concentrations.

Overall for adults, adopting GLI will tend to reduce abnormality rates for adults, particularly up to the age of 70 years. This calls to question whether patients were falsely being identified as having a reduced T_{LCO} using older equations. This may well be the case as there are several publications identifying an unexplained reduction in T_{LCO} as a common clinical scenario [24–26]. The adoption of the GLI T_{LCO} reference equations may result in fewer unnecessary clinical investigations following the identification of an isolated reduction in T_{LCO}.

The difference in abnormality rates between the older equations and the GLI equations is most evident in young adults. One potential explanation for this is the use of linear models over the entire adult range in the older equations. The GLI data suggest that there is a plateau in T_{LCO} from the age of approximately 18 to 25 years. Fitting a linear equation to this age range, when it is included with data from older adults may result in an overestimation of predicted values in young adults with the older equations.

In contrast, the GLI equations in both sexes above the age of 70 years produce higher rates of abnormality than the ECCS and Miller equations, with a small proportion of patients moving from within the normal range to abnormally low T_{LCO} (supplementary figure S1). Survival data has suggested that the GLI spirometry equations overestimate predicted values in the elderly, when compared with extrapolated data from other equations [27]. This raises the possibility that the elderly subjects who are able to participate in the GLI normal values study may not be truly representative of the normal elderly population.

The use of K_{CO} and V_A in T_{LCO} interpretation remains a controversial topic [7]. The levels of agreement for V_A between the older prediction equations and GLI tend to be higher than the levels of agreement for K_{CO} (supplementary tables S5 and S6). The levels of agreement for K_{CO} tend to match well the levels of agreement for T_{LCO} in the adult equations with the exception of the Crapo equations (table 2 and supplementary table S5). For children, there tends to be a difference in the levels of agreement between K_{CO} and T_{LCO}. The variability of agreement levels for these two parameters and the difference compared with the levels of agreement with T_{LCO} is reflective of the fact that the prediction equations are produced independently for each of the parameters.

Although there may be concern about the differences in interpretation compared with older equations, the GLI equations have numerous advantages. First, the GLI equations cover a wider age range than the older equations, reducing the need to extrapolate equations beyond the age in which the data were collected. Secondly, use of the GLI equations eliminate the need to switch from paediatric to adult equations. The issues with switching equations at a certain age are well documented for spirometry [28] and are also relevant for T_{LCO}. As previously mentioned, the other strength of the GLI equations is their scientific validity. All of these advantages suggest that the adoption of the GLI equations is likely to be widespread and rightly so.

The major weakness with the GLI T_{LCO} compared with the GLI spirometry equations is the lack of race-specific equations for non-Caucasians. This poses a significant practical issue for most laboratories; however, this issue is also relevant to the older reference equations which are currently used. The current analysis did not apply an adjustment for non-Caucasians, given that the most commonly used adjustment [29] is based on small numbers, and a single race and sex. Interpreting T_{LCO} results for non-Caucasians remains problematic and the creating race-specific T_{LCO} equations should be a high priority.

There are some limitations to the current analysis. The most obvious is the assumption that the LLN is sensitive enough to separate normal from abnormal. We acknowledge that the certainty of interpretation is reduced, and likelihood of altered classification increases when results are close to the LLN. In these circumstances, the test results are best interpreted with the use of additional information such as other test results, the clinical picture and pre-test probability. Despite this limitation, the LLN is the value that underpins interpretative strategies [7] and we believe that our approach is justified in describing likely effects of changing reference equations. Our analysis did not apply the Roca reference equations exactly as published, which may be considered a limitation. However, our approach of applying a weight limit to the Roca equations [16] prevented extrapolated non-physiological reference values. Without this weight limit, the difference in abnormality rates for females between the Roca and GLI equations would be even larger.

The 2017 GLI T_{LCO} equations provide a unique opportunity to enable accurate prediction of normal values, and their widespread uptake into clinical practice appears likely. Our analysis provides an all-age summary of changes that can be expected, and we believe this information will assist in adoption of these reference equations, facilitating further standardisation in the interpretation of this valuable diagnostic tool.

Conflict of interest: None declared.

References

1 Crapo RO. Pulmonary function testing. *N Engl J Med* 1994; 331: 25–30.
2 Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.
3 Galiè N, Humbert M, Vachiery J-L, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2015; 37: 67–119.
4 King TE Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 2005; 172: 268–279.
5 Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. *Curr Opin Rheumatol* 2008; 20: 340–346.
6 Vogelmeier CF, Criner GJ, Martinez FJ, *et al.* Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med* 2017; 195: 557–582.
7 Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
8 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.
9 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.
10 Quanjer PH, Weiner DJ. Interpretative consequences of adopting the global lungs 2012 reference equations for spirometry for children and adolescents. *Pediatr Pulmonol* 2014; 49: 118–125.
11 Sood A, Dawson BK, Henkle JQ, *et al.* Effect of change of reference standard to NHANES III on interpretation of spirometric 'abnormality'. *Int J Chron Obstruct Pulmon Dis* 2007; 2: 361–367.
12 Brazzale DJ, Upward AL, Pretto JJ. Effects of changing reference values and definition of the normal range on interpretation of spirometry. *Respirology* 2010; 15: 1098–1103.
13 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: 183–189.
14 MacIntyre N, Crapo RO, Viegi G, *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; 26: 720–735.
15 Miller A, Thornton JC, Warshaw R, *et al.* Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state. *Am Rev Respir Dis* 1983; 127: 270–277.
16 Roca J, Rodriguez-Roisin R, Cobo E, *et al.* Single-breath carbon monoxide diffusing capacity prediction equations from a Mediterranean population. *Am Rev Respir Dis* 1990; 141: 1026–1032.
17 Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981; 123: 185–189.
18 Cotes JE, Chinn DJ, Quanjer PH, *et al.* Standardization of the measurement of transfer factor (diffusing capacity). *Eur Respir J* 1993; 6: Suppl. 16, 41–52.
19 Cotes JE, Dabbs JM, Hall AM, *et al.* Lung volumes, ventilatory capacity, and transfer factor in healthy British boy and girl twins. *Thorax* 1973; 28: 709–715.
20 Kim Y-J, Hall GL, Christoph K, *et al.* Pulmonary diffusing capacity in healthy caucasian children. *Pediatr Pulmonol* 2012; 47: 469–475.
21 Wapenaar M, Miedema JR, Lammering CJ, *et al.* The impact of the new Global Lung Function Initiative TLCO reference values on trial inclusion for patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2019; 53: 1801895.
22 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.
23 Quanjer PH, Stocks J, Cole TJ, *et al.* Influence of secular trends and sample size on reference equations for lung function tests. *Eur Respir J* 2011; 37: 658–664.
24 Aduen JF, Zisman DA, Mobin SI, *et al.* Retrospective study of pulmonary function tests in patients presenting with isolated reduction in single-breath diffusion capacity: implications for the diagnosis of combined obstructive and restrictive lung disease. *Mayo Clin Proc* 2007; 82: 48–54.
25 Ansari A, Collier J, Mohsenifar Z. Isolated reduction in single-breath diffusion capacity in young, healthy, asymptomatic women. *Am J Med Sci* 1995; 310: 226–228.
26 Mohsenifar Z, Collier J, Belman MJ, *et al.* Isolated reduction in single-breath diffusing capacity in the evaluation of exertional dyspnea. *Chest* 1992; 101: 965–969.
27 Ward H, Cooper B, Miller MR. Validation of lung function prediction equations from patient survival data. *Eur Respir J* 2012; 39: 1181–1187.
28 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.
29 Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; 144: 1202–1218.