Global Lung Function Initiative equations improve interpretation of FEV1 decline among patients with cystic fibrosis

To the Editor:

The prognosis for individuals with cystic fibrosis has improved markedly over the last 50 years, with most countries now reporting that 50% of the population reach at least 35 years of age [1–3]. Despite this improvement, the average age at death is still in the late 20s and varies enormously between cystic fibrosis centres and countries [4]. To further improve the trajectory of lung disease, it is critical to identify patients that would benefit most from early intervention.

Current markers of disease progression rely on spirometric measures of lung function (forced expiratory volume in 1 s (FEV1)) and it is well recognised that choice of reference equation may have a dramatic effect on the apparent rate of decline in lung function [5, 6]. The recently published Global Lung Function Initiative (GLI) equations [7], which better explain age-related change in normal lung function, present an opportunity to investigate longitudinal trends in lung function in patients with cystic fibrosis. Cross-sectional analysis of data from the UK Cystic Fibrosis Trust Registry demonstrated important differences in interpretation of spirometry results between the internationally endorsed GLI equations [7], and those of Knudson et al. [8], Wang et al. [9] and Hankinson et al. [10]. While overall results summarised as % predicted FEV1 according to each equation differed by only a few per cent, individual patient results were quite discrepant, particularly in young children, those >50 years of age and adolescents. The discrepancies observed during adolescence are of particular concern since this population is recognised to be at risk of rapid progression of cystic fibrosis lung disease.

In this study, we aimed to investigate the impact of the GLI equations on estimates of population-level decline in % predicted FEV1 with age.

Data were extracted from the Toronto cystic fibrosis database containing 1023 subjects with 27868 measurements over 23 years (1990–2013) and the UK Cystic Fibrosis Registry containing 6043 subjects with 20013 measurements over 5 years (2007–2011). In the encounter-based Toronto registry, patients had an average of 49 observations (range 1–150), while in the annual-based UK registry, patients had an average of 4 observations (range 1–5). Patients were included irrespective of number of observations, transplant status, age at diagnosis or death. Spirometric outcomes were interpreted using % predicted FEV1 calculated from the GLI [5], Knudson [8] and Wang–Hankinson [9, 10] equations. These were chosen to reflect the current practice of many cystic fibrosis registries. Analyses were limited to Caucasian patients >6 years of age to permit appropriate comparison between equations. Patients >30 years of age or with FEV1 >130% predicted were excluded to minimise the impact of survival bias and reduce undue influence of outlier values.

A nonlinear, mixed-effects approach using a shape-invariant spline-curve model was used to simultaneously estimate the average change in lung function with age, while adjusting for subject-specific random intercepts and slopes, assuming that all patients follow the same underlying curve shape. The average change in lung function with age was fitted as a natural cubic spline where degrees of freedom were chosen to minimise the Bayesian information criterion. We compared the complexity (degrees of freedom) of the average lung function decline curve described by each of the three spirometry reference equations. Analysis was performed in the statistical program R (The R Project for Statistical Computing, Vienna, Austria) using the sitar package.

Selecting the simplest model with the best fit for each reference equations demonstrated that the pattern of FEV1 decline at population level differed according to the reference equation used (fig. 1). The GLI models were the simplest, with a steady and near-linear decline starting at younger ages, whereas the other equations required more complex models and suggest greater decline during adolescence and early adulthood. Similar patterns were observed in the Toronto (fig. 1a) and UK populations (fig. 1b). Overall, >85% of the variance was explained by each of the models. Thus, while the estimated pattern of lung function decline was influenced by reference equation, model fit was not.
The GLI equations demonstrated a near-linear decline throughout childhood with no acceleration or deceleration during adolescence. These findings suggest that the well-established adolescent decline described at a population level may, in part, be an artefact of the spirometry reference equations used, rather than reflecting the true clinical course. The ability to interpret rate of decline in lung function accurately is even more important for individual patients in whom inaccurate tracking of FEV1 may prompt unnecessary intervention, including invasive procedures and aggressive treatments. Equally, these findings suggest that current practice may be missing a critical opportunity for intervention earlier in childhood.

The GLI equations are seamless across all ages, thus avoiding artifactual changes that can occur when transitioning from paediatric to adult reference equations [11]. Unlike many paediatric spirometry equations, the GLI equations take both age and height into account, such that predicted values are higher in older than younger individuals of the same height. Thus, the GLI reference equations model growth appropriately during the adolescent period [12] and highlight the relative importance of early childhood in understanding the progression of cystic fibrosis lung disease. In addition the current study confirms that nonlinear growth models are appropriate to describe patterns of lung function decline.

The pattern of % predicted FEV1 decline differed according to the spirometry reference equation used. While such differences have been reported previously [5, 6], this is the first study to use the GLI equations, which model changes during adolescence more appropriately [12] and employ a nonlinear, mixed approach to analysis. The largest discrepancies were observed for the Knudson equations, which are a composite of three separate equations, each based on a relatively small sample. The Wang–Hankinson equations, which are based on larger samples with join points carefully chosen to minimise discontinuity between equations, match the GLI more closely. Nonetheless, use of these older equations may exaggerate the rate of decline during adolescence.

Our study population was inclusive of patients irrespective of clinical status; therefore, the observed pattern of lung function decline may not be comparable to previous studies. The analyses excluded subjects <6 years of age; however, lung function decline may start much earlier, emphasising the need for early markers of lung disease for this population. In addition, the analysis was limited to a spirometric outcome, FEV1, which itself may not be sensitive enough to detect early pathological changes.

Our decision to base models on % predicted values is in line with current clinical practice and widespread use in epidemiological studies. However, this may introduce an age, sex and height bias, especially when interpreting results from adults, which can be avoided by alternative ways of using FEV1 [13], including the use of z-scores [14], which can be readily calculated when using GLI equations. To further investigate the potential benefits of these alternative approaches when interpreting longitudinal changes, it will be essential to link changes in lung function to clinical outcomes within individuals. Whereas the clinical interpretation of change over time in % predicted FEV1 (including its inherent challenges) is familiar to the cystic fibrosis community, longitudinal changes in z-scores are less well understood and require further detailed analysis, which is beyond the scope of the current brief report.

**FIGURE 1** Overall pattern of % predicted forced expiratory volume in 1 s (FEV1) with age at the population level as defined by three spirometric reference equations: those of the Global Lung Function Initiative (GLI) [7], Wang–Hankinson [9, 10] and Knudson [8]. Data are presented for a) the Toronto cystic fibrosis database and b) the UK Cystic Fibrosis Registry. In the Toronto dataset, the GLI and Wang–Hankinson equations show a steady rate of decline in childhood, whereas the Knudson equations show periods of accelerated decline in adolescence. In the UK dataset, both the Wang–Hankinson and Knudson equations show periods of accelerated decline in adolescence, with the GLI equations showing a steady decline starting in childhood.
These findings challenge previously held beliefs about population trends in disease progression in patients with cystic fibrosis, particularly the rapid FEV1 decline during adolescence. It is crucial that we better understand the nature and relationship of disease progression, as inaccurate tracking of lung function will make targeted intervention for at-risk individuals less effective.

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Adolescent FEV1 decline in cystic fibrosis may be an artefact of the spirometry reference equations used http://ow.ly/J0com

Sanja Stanojevic1, Diana Bilton2, Alexandra McDonald1, Janet Stocks3, Paul Aurora3,4, Ammani Prasad1, Tim J. Cole3 and Gwyneth Davies3,4

1Hospital for Sick Children, Toronto, ON, Canada. 2Royal Brompton Hospital, London, UK. 3UCL Institute of Child Health, London, UK. 4Great Ormond Street Hospital for Children NHS Trust, London, UK.

Correspondence: Sanja Stanojevic, Division of Respiratory Medicine, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, M5G 1X8, Canada. E-mail: Sanja.Stanojevic@sickkids.ca

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References