Interpretation of Pulmonary Function Tests in Children: choosing and using a reference equation

PATS and ERS Webinar April 2022
Di Gray, University of Cape Town, South Africa
Conflict of interest

• Research funding: the Wellcome Trust
Objectives

• Highlight the importance of improving access to lung function testing in children
• Discuss the challenges in interpretation of lung function testing with focus on spirometry in African children
• Provide some guidance for clinicians and researchers in choosing and using reference equations for paediatric spirometry
Spirometry in children: useful, doable, accessible

• Provides objective measure of lung function
• Informs diagnosis of respiratory disease
• Used to track progression of disease and response to treatments
• Commonly used as outcome for measure for clinical trials and epidemiological studies
• FEV1 associated with clinical outcome
• Feasible in children as young as 3 years
• Access to testing improving across Africa
Reference equations are important

- To distinguish health from disease
- To determine changes over time, considering predictors that change over time
- Ideally based on data collected from large number of healthy people from the same populations as the person tested
- Reference data from African countries lacking
Paediatric an Adult African Spirometry (PAAS)

An urgent need for African spirometry reference equations: the Paediatric and Adult African Spirometry study

R. Masekela, G. L. Hall, S. Stanojevic, B. Sartorius, R. MacGinty, H. Benn Saad, Y. Trabelsi, F. Messan, M. Arigiani, A. Kettfi, D. Gray, on behalf of the Paediatric and Adult African Spirometry (PAAS) collaborators

- Collation of published spirometry collected in healthy children and adults in Africa
- 4750 individuals (5-85 years), from North, South, East, West and Central Africa

Need for high quality prospectively collected lung function data in healthy African populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>North Africa mean ± SD</th>
<th>West Africa mean ± SD</th>
<th>East Africa mean ± SD</th>
<th>Central Africa mean ± SD</th>
<th>Southern Africa mean ± SD</th>
<th>Total mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>2.8 ± 0.9</td>
<td>1.9 ± 0.6</td>
<td>1.3 ± 0.3</td>
<td>1.6 ± 0.4</td>
<td>2.2 ± 0.7</td>
<td>2.4 ± 1.0</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.4 ± 1.2</td>
<td>2.4 ± 0.7</td>
<td>1.5 ± 0.3</td>
<td>1.9 ± 0.4</td>
<td>2.5 ± 0.8</td>
<td>2.9 ± 1.2</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.0</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>GLI African-American FEV₁ Z-score</td>
<td>0.99 ± 1.36</td>
<td>−2.25 ± 1.16</td>
<td>0.10 ± 0.88</td>
<td>−0.16 ± 0.79</td>
<td>−0.12 ± 0.98</td>
<td>0.35 ± 1.57</td>
</tr>
<tr>
<td>GLI African-American FVC Z-score</td>
<td>0.91 ± 1.38</td>
<td>−1.79 ± 1.24</td>
<td>0.16 ± 0.85</td>
<td>−0.09 ± 0.83</td>
<td>−0.15 ± 0.98</td>
<td>0.35 ± 1.50</td>
</tr>
<tr>
<td>GLI African-American FEV₁/FVC Z-score</td>
<td>0.16 ± 1.12</td>
<td>−1.07 ± 1.56</td>
<td>−0.10 ± 0.95</td>
<td>−0.17 ± 0.71</td>
<td>0.05 ± 0.89</td>
<td>−0.03 ± 1.17</td>
</tr>
<tr>
<td>GLI Caucasian FEV₁ Z-score</td>
<td>−0.12 ± 1.37</td>
<td>−3.18 ± 1.00</td>
<td>−1.10 ± 0.82</td>
<td>−1.36 ± 0.74</td>
<td>−1.28 ± 0.91</td>
<td>−0.75 ± 1.52</td>
</tr>
<tr>
<td>GLI Caucasian FVC Z-score</td>
<td>−0.26 ± 1.36</td>
<td>−2.83 ± 1.11</td>
<td>−1.10 ± 0.79</td>
<td>−1.36 ± 0.78</td>
<td>−1.35 ± 0.94</td>
<td>−0.82 ± 1.45</td>
</tr>
<tr>
<td>GLI Caucasian FEV₁/FVC Z-score</td>
<td>0.25 ± 1.11</td>
<td>−0.86 ± 1.49</td>
<td>0.01 ± 0.94</td>
<td>−0.06 ± 0.70</td>
<td>0.14 ± 0.87</td>
<td>0.09 ± 1.13</td>
</tr>
</tbody>
</table>

GLI = Global Lung Initiative; SD = standard deviation; DRC = Democratic Republic of Congo; FEV₁ = Forced expiratory flow in 1 sec; FVC = forced vital capacity.
South Africa: PAAS 2

Number of people approached for testing N= 4223

Included tests N=3676

Total Excluded N= 547

Reasons for exclusion:
- Failed medical screening questions (130)
- Pulmonary function tests failed quality control (138)
- Current or past smoker (157)
- Data missing (150)
- Z-score greater than +/- 5 (18)
- Excluded due to ethnicity/age (4)

Table 1. Characteristics of the study population (KwaZulu-Natal and Western Cape province, South Africa).

<table>
<thead>
<tr>
<th></th>
<th>Black African (n=2116)</th>
<th>Coloured (n=343)</th>
<th>Mixed Ethnicity (n=693)</th>
<th>Indian (n=524)</th>
<th>Total (n=3676)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex - Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=1200 (56.6%)</td>
<td>153 (44.6%)</td>
<td>404 (58.3%)</td>
<td>326 (62.2%)</td>
<td>2083 (56.7%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 years</td>
<td>1128 (53.3%)</td>
<td>212 (61.8%)</td>
<td>440 (63.5%)</td>
<td>243 (46.4%)</td>
<td>2023 (55.0%)</td>
</tr>
<tr>
<td>≥ 25 years</td>
<td>988 (46.7%)</td>
<td>131 (38.2%)</td>
<td>253 (36.5%)</td>
<td>281 (53.6%)</td>
<td>1653 (45.0%)</td>
</tr>
<tr>
<td>Weight for age Z-score</td>
<td>0.04 (0.41)</td>
<td>0.10 (0.66)</td>
<td>0.09 (0.47)</td>
<td>0.12 (0.56)</td>
<td>0.07 (0.48)</td>
</tr>
<tr>
<td>Height for age Z-score</td>
<td>-0.27 (0.84)</td>
<td>0.08 (0.87)</td>
<td>-0.40 (1.12)</td>
<td>-0.25 (0.95)</td>
<td>-0.26 (0.92)</td>
</tr>
<tr>
<td>BMI for age Z-score</td>
<td>0.99 (1.28)</td>
<td>0.71 (1.15)</td>
<td>0.90 (1.03)</td>
<td>1.01 (1.28)</td>
<td>0.95 (1.29)</td>
</tr>
<tr>
<td>Connick index</td>
<td>0.51 (0.03)</td>
<td>0.52 (0.04)</td>
<td>0.50 (0.03)</td>
<td>0.52 (0.03)</td>
<td>0.51 (0.03)</td>
</tr>
<tr>
<td>Stunting*</td>
<td>110 (5.2%)</td>
<td>5 (1.5%)</td>
<td>64 (9.2%)</td>
<td>37 (7.1%)</td>
<td>216 (5.9%)</td>
</tr>
</tbody>
</table>

Province

<table>
<thead>
<tr>
<th></th>
<th>KwaZulu-Natal</th>
<th>Western Cape</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1260 (59.6%)</td>
<td>856 (40.4%)</td>
</tr>
<tr>
<td></td>
<td>236 (68.8%)</td>
<td>107 (31.2%)</td>
</tr>
<tr>
<td></td>
<td>306 (44.2%)</td>
<td>387 (55.8%)</td>
</tr>
<tr>
<td></td>
<td>517 (98.7%)</td>
<td>7 (1.3%)</td>
</tr>
<tr>
<td></td>
<td>2319 (63.1%)</td>
<td>1357 (36.9%)</td>
</tr>
</tbody>
</table>

PAAS 2 Results

Best fit:
- Black and mixed-race South Africans: GLI Other
- Caucasian South Africans: GLI White
- Indian South Africans: GLI SE Asian

FEV1 Z-score for each ethnic group using each of the GLI reference equations
PAAS 2 Results

FVC Z-score for each ethnic group using each of the GLI reference equations

Best fit:
- Black and mixed-race South Africans: GLI Other
- Caucasian South Africans: GLI White
- Indian South Africans: GLI SE Asian
Angola, Democratic Republic of Congo (DRC) and Madagascar


Michele Angiliani1, Mario C. Canciani1, Giovanni Motti2, Michele Altomare2, Andrea Magnolato3, Sofia Vanda Loa Clemente6, Leon Tehillo6, Paola Cogo1, and Philip H. Quanjer1,3,6

1Department of Clinical and Experimental Medical Sciences, Unit of Pediatrics, University Hospital of Udine, Udine, Italy; 2International Health Cooperation Project, University Campus Bio-Medico, Rome, Italy; 3“Sapienza” University of Rome, Rome, Italy; 4University of Treviso, Treviso, Italy; 5Hospital Divina Providenza, Luanda, Angola; 6Service de Pédiatrie, Centre Hospitalier Moment and Centre de Formation et d’Appli Sanitaire, Kinshasa, Democratic Republic of the Congo; and 7Department of Pulmonary Diseases and 8Department of Paediatrics-Pulmonary Diseases, Erasmus Medical Centre, Erasmus University, Rotterdam, the Netherlands

- Spirometry in 1082 children 6-12.8 years: 306 Angola, 377 DRC, 399 Madagascar.
- Compared GLI 2012 African-American, NHANES (African American)

GLI African better fit than NHANES
Nutrition and SES impacting lung function:
Children with zBMI <-2 lower zFEV1 and zFVC

Population Characteristics and Lung Function (GLI 2012 African) by Country

<table>
<thead>
<tr>
<th></th>
<th>Angola (n = 306)</th>
<th>DR Congo (n = 377)</th>
<th>Madagascar (n = 399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys, %</td>
<td>50</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>In public school, n (% boys)</td>
<td>94 (50)</td>
<td>191 (53)</td>
<td>147 (50)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>9.8 (1.9)*</td>
<td>9.5 (1.6)</td>
<td>8.7 (1.5)</td>
</tr>
<tr>
<td>Sitting/standing height</td>
<td>0.48 (0.04)*</td>
<td>0.50 (0.02)*</td>
<td>0.52 (0.02)*</td>
</tr>
<tr>
<td>zHeight</td>
<td>−0.28 (1.30)*</td>
<td>0.32 (1.30)*</td>
<td>−1.22 (1.13)*</td>
</tr>
<tr>
<td>zBMI</td>
<td>−0.64 (2.16)*</td>
<td>−0.20 (1.10)*</td>
<td>−1.07 (1.08)*</td>
</tr>
<tr>
<td>zFEV1</td>
<td>−0.32 (0.74)*</td>
<td>−0.16 (0.79)*</td>
<td>0.10 (0.89)*</td>
</tr>
<tr>
<td>zFVC</td>
<td>−0.38 (0.80)*</td>
<td>−0.09 (0.83)*</td>
<td>0.16 (0.84)*</td>
</tr>
<tr>
<td>zFEV1/FVC</td>
<td>0.10 (0.78)*</td>
<td>0.17 (0.71)</td>
<td>−0.10 (0.95)</td>
</tr>
</tbody>
</table>
Cameroon

Spirometric reference equations for Cameroonian aged 4 to 89 years derived using lambda, mu, sigma (LMS) method

• 625 children and adolescents (290 males, 335 females), 1152 adults (552 males, 600 females); 5-88 years
• Data collected 2014-2018
• Children better fit than adults with GLI 2012 - ?generational effect
Zimbabwe


Tafadzwa Madanhire1,2, Rashida A. Ferrand3,4, Engi F. Attila5, Elogy N. Sibanda2, Simba Rusakaniko1 and Andrea M. Rehman6

- 712 children (344 girls, mean age: 10.5 years (SD 1.81))
- Primary school children, urban and peri-urban Harare schools

- Best fit: GLI 2012 African-American (except FEV1/FVC)
- Better fit than Polgar
Summary

• Until recently spirometric reference equations derived from healthy African populations have been lacking

• Efforts to develop robust all age international reference standards for spirometry (Global Lung function Initiative) have afforded the chance to harmonise spirometry interpretation globally, but lacks African data

• Recent African studies of healthy spirometry data have shown variable fit with GLI equations – highlighting the complexity of defining precise global healthy lung function trajectories
Interpretation of Pulmonary Function Tests in Children

Sanja Stanojevic PhD
GLI Network
ERS CRC Co-Chair
Conflicts of Interest

• Research funding for Vertex Pharmaceuticals
• Consulting fees from Chiesi Farmaceuticals
• Funding from ERS to for GLI Task Forces and Network
Objectives

• Describe current approaches to interpretation of pulmonary function test results
• Highlight the factors that influence normal growth and development of the lungs
• Discuss the advantages and disadvantages of using multi-ethnic reference equations for lung function
Measurement of lung function is important...

What is Normal?
It depends..

Choice of 34 equations for spirometry in same commercial equipment!

Over 200 outcome variables for spirometry and plethysmography WITHIN each module, derived from different equations according to age and outcome!
Does it matter which reference equation we choose?
Tracking of Individual Results

% Predicted

Kirkby et al. ERJ 2012
Tracking of Individual Results

Absolute Values
Global Lung Function Initiative

- A network of physiologists, clinicians, statisticians, manufacturers
- Aims to develop robust all-age multi-ethnic reference equations for lung function tests
- Based on collaborative sharing of existing data resource
Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations


Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians

Sanja Stanojević,1,2 Brian L. Graham,3 Brendan G. Cooper,4 Bruce R. Thompson,5 Kim W. Carter,6,7 Richard W. Francis5,7 and Graham L. Hall5,8,9 on behalf of the Global Lung Function Initiative TCO working group10

Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry

Graham L. Hall,1,2 Nicole Filipow,2 Gregg Ruppel,2 Tolu Okitika,2 Bruce Thompson,2 Jane Kirkby,2 Irene Steenbruggen,3,4 Brendan G. Cooper,2 Sanja Stanojević3 on behalf of the contributing GLI Network members2

<table>
<thead>
<tr>
<th>Test</th>
<th>Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td>2008-2012</td>
<td>Published 2012</td>
</tr>
<tr>
<td>T&lt;sub&gt;L,CO&lt;/sub&gt;</td>
<td>2013-2017</td>
<td>Published 2017</td>
</tr>
<tr>
<td>Lung Volumes</td>
<td>2016-2019</td>
<td>Published 2021</td>
</tr>
<tr>
<td>Fe&lt;sub&gt;NO&lt;/sub&gt;</td>
<td>2018-2020</td>
<td>Anticipated 2022</td>
</tr>
<tr>
<td>FOT</td>
<td>2018-2020</td>
<td>Data collection</td>
</tr>
<tr>
<td>Multiple Breath Washout</td>
<td>2020-2022</td>
<td>Data collection</td>
</tr>
<tr>
<td>CPET</td>
<td>2022-2024</td>
<td>Project Initiated</td>
</tr>
</tbody>
</table>

www.lungfunction.org
Lung function rapidly increases in childhood, declines slowly in adulthood.
Tracking of Individual Results

% Predicted GLI

GLI equations track continuity
Patient details

- Accurate measures of height and age
- Sex and gender
- Ancestry/ethnicity
- Current medications/activities prior to test (e.g., smoking)
How do we use reference equations?
% predicted

- Observed/Predicted*100
- Assumes single value (100%) represents normal
- How far an individual observation is from the predicted value

Most widely used method to interpret PFT results

2.7 Liters
Female
17 years old
165 cm
78% predicted

Quanjer et al., ERJ 2014
Where does 80% predicted come from?

This assumes 1 SD of the between-subject variability is 10%
Between-subject variability varies with age
Between-subject variability varies with age
The 5th and 95th percentile limits (-1.645 and +1.645 z-scores) of the healthy population can be used to identify individuals with unusually low or high results, respectively.
2.7 Liters
Female
20 years old
165 cm
78% predicted
-1.8 z-scores
Race and Ethnicity

2.7 Liters
Female
20 years old
165 cm
African ancestry

78% predicted
-1.8 z-scores

New York Times
August 14 2019

Myths about physical racial differences were used to justify slavery — and are still believed by doctors today.
GLI Ethnic Groups

• ‘Caucasian’/White European ancestry
  • Europe, Israel, Australia, USA, Canada, Mexican Americans, Brazil, Chile, Mexico, Uruguay, Venezuela, Algeria, Tunisia

• African American

• South East Asian
  • Thailand, Taiwan and China (including Hong Kong) south of the Huaihe River and Qinling Mountains

• North East Asian
  • Korea and China north of the Huaihe River and Qinling Mountains
GLI Ethnic Groups

- ‘Caucasian’/White European ancestry
  - Europe, Israel, USA, Canada, South Africa, Argentina, Uruguay, Chile, Brazil, Mexico, Peru
- African American
- South East Asian
  - Thailand, Taiwan, China south of the Huaihe River and Qinling Mountains
- North East Asian
  - Korea and China north of the Huaihe River and Qinling Mountains

What about the rest of the world?
GLI ‘other’

- Represents an average of the 4 ethnic groups
  - Biased towards the White European population
- Represents a way to standardize interpretation of measurements
- Requires less reliance on ‘limits of normal’
Ethnicity is a Social Construct

• How ethnicity is defined varies across the world
• People of similar geographic ancestry living in different parts of the world can have different exposures and lived experiences
• Within a geographical area people of the same ‘ethnicity’ can be very different (genetic admixture/exposures)
• People from many regions of the world are not represented in the GLI equations
Impact of Genetic Ancestry?

- Kumar *et al* (*NEJM* 2010)
  - Significant relationship between degree of admixture with African genes and lung volumes

- Brehm *et al* (*JACI* 2012)
  - As proportion of African ancestry ↑ in Puerto Rican children, FEV$_1$ and FVC ↓, independently of socio-economic status, health care access, or key environmental or lifestyle factors
Ethnic differences in FEV$_1$ mirror body proportions

Lum et al., ERJ 2014
Disparities in Pulmonary Function in Healthy Children across the Indian Urban–Rural Continuum

Samatha Sonnappa1,2,3, Sooky Lum1, Jane Kirkby1, Rachel Bonner1, Angela Wade4, Vinita Subramanya3, Padmanabha T. Lakshman3, Babitha Rajan,5 Shalini C. Nooyi3, and Janet Stocks1
Influences on lung and airway growth

- Socioeconomic Status
- Structural Racism
- Genetic Ancestry Admixture Specific Variants
- Nutrition
- Environment (e.g., altitude, pollution)
- Epigenetics
- Standing Height
- Health Behaviours (e.g., smoking, access to care)
- Age, Sex

Stocks et al Lancet Resp Med 2013
### Complete Blood Count

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>3.8</td>
</tr>
<tr>
<td>RBC</td>
<td>4.47</td>
</tr>
<tr>
<td>HGB</td>
<td>14.5</td>
</tr>
<tr>
<td>HCT</td>
<td>42.0</td>
</tr>
<tr>
<td>MCV</td>
<td>94.1</td>
</tr>
<tr>
<td>MCH</td>
<td>32.5</td>
</tr>
<tr>
<td>MCHC</td>
<td>34.5</td>
</tr>
<tr>
<td>RDW</td>
<td>14.6</td>
</tr>
<tr>
<td>PLT</td>
<td>217</td>
</tr>
<tr>
<td>PLT Smear</td>
<td></td>
</tr>
<tr>
<td>NE%</td>
<td>Adequate</td>
</tr>
<tr>
<td>LY%</td>
<td></td>
</tr>
<tr>
<td>MO%</td>
<td></td>
</tr>
<tr>
<td>EO%</td>
<td></td>
</tr>
<tr>
<td>BA%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Normochromia</td>
<td>Yes</td>
</tr>
<tr>
<td>Normocytopsis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Notes:**
- Adequate counts are within normal range.
- Values are in thousands per microliter (10^3/ul) for WBC, RBC, and PLT.
- HGB is measured in grams per liter (gm/l), HCT in percentage (%), and MCV, MCH, MCHC, RDW, PLT, NE%, LY%, MO%, EO%, BA%, Other in different units.
- Normochromia and Normocytopsis are present.
Disease

GLI African-American

GLI ‘other’

Health

FEV$_1$
Challenges

• What is normal?
  • Lung size and function differs between people living in different parts of the world
  • Do these differences represent disease, or early warning signs of later sequelae?

• Global equations or Population specific
  • Global represents a reference population and wider limits of normal
    • Less precision
  • Population specific better reflect the population being tested
    • Can normalize disparities
    • Are prone to sampling bias if study populations are small and not representative
What should you use in your clinic?

• Choose a robust physiological standard
• Interpret lung function z-score in relation to the clinical picture
• Avoid strict cut-offs to make a diagnosis
• Use your patient as their own control in deciding management
• Know your question or the answer may make no sense!
• Which reference equation?
  • GLI 2012
  • ‘other’
  • best fit based on prospectively collected healthy data (>300 subjects)
Future work

• How do we define normal?
• Anchor interpretation to more sensitive markers of lung disease
• Anchor interpretation to clinically meaningful endpoints
• Re-think the use of ‘cut-off’s of lung function to guide binary clinical decisions
  • Eligibility for employment and treatments
  • Eligibility for referral (e.g. transplant)
• Improved ways to track progression of lung disease over time