Selecting Reference Values
Are you Abnormal??

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Where Do ‘Predicted’ Values Come From?

• Representative sample of healthy subjects (non-smokers, etc.)

• Drawn from the general population (ideally)

• Exclude those with respiratory disease
  • past and present medical history
  • physical examination
  • chest x-ray findings
How Are ‘Predicted’ Values Derived?

• Regression (linear or other) by group
  • Male/Female
  • Child/Adult
  • Ethnicity

• Independent variables
  • Age
  • Height

• Variables included usually based on
  • statistical significance
  • explained variability ($R^2$)
  • ease of use, simplicity
  • comparability to other methods
What is Your Predicted Normal?
What reference values are you using?

- Knudson (1976)
- Knudson (1983)
- Morris
- Crapo
- Polgar
- NHANES III (Hankinson, et. al., 1999)*
- New GLI All Age?

*ATS-ERS cited preferred set of reference equations
Factors Affecting Lung Volumes & Flow Rates

- Height
- Age
- Sex
- Race

These measurements are very critical since the predicted normal values (reference values) are based on these.

Weight does **NOT** affect predicted normals!
Measure without shoes
Verify age with the birth date
Men have larger lung volumes than women.

Blacks & Asians have lower predicted values than Caucasians.
What is considered abnormal?
**Percentiles**

- Statistically acceptable even if data is skewed (can be estimated from regression model if data approximates a normal distribution)

- Lower Limit of Normal = Predicted value - $1.645 \times \text{SEE}$ (one-tailed)
Lower Limit of Normal (LLN)

• Threshold below which a value is considered abnormal (Of a normal population--95% will be above and 5% will be below the LLN)

“Rules of thumb”:
- 80% of predicted for FVC & FEV1
- 70% for actual FEV1/FVC ratio
- ?????????
GOLD Classification of COPD severity based on Post FEV1*

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV1/FVC &lt; 0.70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I:</td>
<td>FEV1 ≥ 80% predicted</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Stage II:</td>
<td>50% ≤ FEV1 &lt; 80% predicted</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Stage III:</td>
<td>30% ≤ FEV1 &lt; 50% predicted</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Stage IV:</td>
<td>FEV1 &lt; 30% predicted or FEV1 &lt; 50% predicted plus chronic respiratory failure</td>
</tr>
<tr>
<td>Very Severe</td>
<td></td>
</tr>
</tbody>
</table>

GOLD Controversy

• Global Initiative for Obstructive Lung Disease (GOLD): NHLBI, NIH, WHO
  • Recommends FEV$_1$/FVC < 70% (after bronchodilator) as diagnostic of COPD obstruction*

• Most studies show FEV$_1$/FVC falls with age (and may be influenced by gender, height and ethnicity)

• 70% cut-off results in increased **false negatives** and **false positives** with potential for misclassification
GOLD Misclassification

Mottram CD Ruppel’s Manual of Pulm Func 10th 2012
Fixed Cut-points?

- “Using 80% predicted and fixed thresholds for interpreting PFTs can lead to substantial clinical misclassification of disease that affects >20% of patients.”

CHEST 2011; 139(1):52–59
2005 ATS-ERS Recommended Spirometry Reference Set

• NHANES III
  - National Health and Nutrition Examination Survey
  - 7,429 asymptomatic, lifelong nonsmoking participants
  - 8 to 80 y.o.

Spirometric Reference Values from a Sample of the General U.S. Population

JOHN L. HANKINSON, JOHN R. ODENCRUNTZ, and KATHLEEN B. FEDAN

Linear Regression

Other Regressions

**ATS-ERS Interpretation**

<table>
<thead>
<tr>
<th>Degree of severity</th>
<th>FEV₁ % pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Moderate</td>
<td>60–69</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>50–59</td>
</tr>
<tr>
<td>Severe</td>
<td>35–49</td>
</tr>
<tr>
<td>Very severe</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>

% pred: % predicted.
http://www.lungfunction.org/

Founded in 2008
GLI Objectives

- Establishment of a formal ERS/ATS task force
- Establishment of a web site to facilitate communication between participants
- Collation and cleaning of the raw data from existing studies.
- Development of a study design/ statistical methods
• Development and validation of updated reference equations
• Recommendations for future normative data collection
• Dissemination of results
• Development of a long-term strategy for database management and update of equations
Organizations Supporting the GLI

- European Respiratory Society
- American Thoracic Society
- Australian and New Zealand Society of Resp Science
- Asian Pacific Society of Respirology
- Thoracic Society of Australia and New Zealand
- American College of Chest Physicians
- American Association of Respiratory Care
Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations

Eur Respir J 2012; 40: 1324–1343

“All-Age Approach”
Multi-ethnic reference values for spirometry for the clinical lung function laboratory

160,000 data pts from 72 centers in 33 countries

97,759 records of healthy nonsmokers (55.3% females) aged 2.5–95 yrs.

Reference equations were derived for healthy individuals aged 3–95 yrs for Caucasians (n=57,395), African–Amercans (n=3,545), and North (n=4,992) and South East Asians (n=8,255).

<table>
<thead>
<tr>
<th>Group</th>
<th>Males N</th>
<th>Age range yrs</th>
<th>Females N</th>
<th>Age range yrs</th>
<th>Total N</th>
<th>Age range yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>25827</td>
<td>2.5–95</td>
<td>31568</td>
<td>2.5–95</td>
<td>57395</td>
<td>6.1–87</td>
</tr>
<tr>
<td>African–American</td>
<td>1520</td>
<td>6–85</td>
<td>2025</td>
<td>6.1–87</td>
<td>3545</td>
<td>3–79</td>
</tr>
<tr>
<td>North East Asian</td>
<td>1414</td>
<td>16–91</td>
<td>3578</td>
<td>16–88</td>
<td>4992</td>
<td>7.4–89.7</td>
</tr>
<tr>
<td>South East Asian</td>
<td>3095</td>
<td>3.3–86</td>
<td>5160</td>
<td>3.2–92</td>
<td>8255</td>
<td>6.5–87</td>
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<tr>
<td>Total</td>
<td>31856</td>
<td></td>
<td>42331</td>
<td></td>
<td>74187</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age range yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iran</td>
<td>1</td>
<td>5–85</td>
</tr>
<tr>
<td>Oman</td>
<td>1</td>
<td>6–65</td>
</tr>
<tr>
<td>North East Asia</td>
<td>2</td>
<td>15.3–91</td>
</tr>
<tr>
<td>South East Asia</td>
<td>4</td>
<td>3.3–88</td>
</tr>
<tr>
<td>North Africa</td>
<td>2</td>
<td>6–78</td>
</tr>
<tr>
<td>Caucasian</td>
<td>14</td>
<td>2.5–95</td>
</tr>
<tr>
<td>Other</td>
<td>199</td>
<td>6.2–93</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>2.5–95</td>
</tr>
</tbody>
</table>

#: total sample included 97,759 subjects.
North vs South East Asian
Race/Ethnicity

The subjects being tested should be asked to identify their own race/ethnic group

• 2005 ATS-ERS Interpretation

• Race???????
• **Ethnic adjustment factors**
  
  • Black subjects by 12% for total lung capacity TLC, FEV1 and FVC
  
  • A race/ethnic adjustment factor of 0.94 is also recommended for Asian-Americans

Eur Respir J 2005; 26: 948–968
• 1,068 healthy nonsmoking subjects

• Multiply the Caucasian predicted values by \textbf{0.88} for Asian-Americans

CHEST 2010; 137(1):138–145
2005 ATS/ERS Recommendations

- All parameters (FVC, etc.) taken from single source whenever possible (NHANES III in US)

- Race-specific equations should be used; adjustment factors may be used

- Extrapolation should be avoided; if used, a statement of such should be included.

- Equations with explicit LLN are preferred; 5th percentile recommended.
Calculating Percentage of Predicted Normal

\[
\text{Measured value} \times 100 = \% \text{ of predicted}
\]

Example: 30 year old white male with measured FVC of 4.80 liters and predicted FVC of 4.97 liters

\[
\frac{4.80}{4.97} \times 100 = 96.6\%
\]
“I think you should be more explicit here in step two.”
Spirometry Demo

Patient takes a deep breath and blows as hard as possible into tube

Clip on nose

Technician monitors and encourages patient during test

Machine records the results of the spirometry test