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Spirometry: Reference values of Global Lung Initiative (GLI)

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1. Summary

Beside the known reference values of the European Coal and Steel Community (ECSC) and others, the software module "Spirometry" as part of the cardiopulmonary platform "custo diagnostic" has been providing the reference values of the Global Lung Initiative (GLI) since version custo diagnostic 4.4.

The reference values according to GLI boast the following benefits: The underlying selection of subjects is more representative regarding age, gender and health status than those of previous reference values. Thus, due to the comprehensive overall collective (nearly 100,000 subjects) a smooth transition between childhood and adulthood (age between 3 and 95 years) has been achieved. Furthermore, the mathematical methods for determining predicted average values have been optimized and consequently their validity regarding statistic deviations has been increased.

In the present custo diagnostic news, the backgrounds will be explained which have made it necessary to introduce new reference values. By using examples, the strengths and weaknesses of GLI and ECSC will be compared to each other and discussed. Finally, the implementation of GLI reference values in custo diagnostic will be outlined.

2. Introduction

Spirometry is an important and commonly used examination method worldwide for assessing lung function. In the course of a pulmonary function test, respiratory flow rates and lung volumes are measured and displayed graphically in a spirogram. The aim of spirometry is to diagnose the kind and severity of a pulmonary disease, to monitor the progress of the disease and to document therapy success. When a disease has been detected, the focus is at first on differentiating between the two main groups of lung diseases:

- the obstructive lung disease caused by narrowed airways such as asthma or COPD.
- the restrictive lung disease caused by reduced elasticity of the lungs and/or the thorax.

To assess the pulmonary function of a patient, defined measures are derived from the respiratory flow rate and the lung volume. The most important diagnostic measures of spirometry are Vital Capacity (VC), Inspiratory Vital Capacity (IVC), Forced expiratory Vital Capacity (FVC) and Forced Expiratory Volume, the ability to exhale within one second (FEV1). The result is indicated in liters and normalized to body temperature and the completely water-saturated environmental pressure (BTPS – body temperature, pressure saturated).

These volume- and time-dependent measures are individual and depend on gender, body height, age and the ethnicity as well as the health condition of the examined person. To compare the measurement results of a patient with the average values of a representative collective, reference values (predicted values) are consulted. The reliability of these predicted values is of major importance for the assessment of a patient's condition, for it depends on them if the situation of a patient has to be classified as healthy or pathological.
3. Reference values of the European Community for Coal and Steel (ECCS) compared to those of the Global Lung Initiative (GLI)

While there are clear guidelines and standards for the practical performance of a pulmonary function test, defined by the expert associations (such as German Respiratory Society, European Respiratory Society, American Thoracic Society), there is a significant range as far as the selection of reference values is concerned, provoking intensive discussions among experts again and again. Since the 1970s, the reference values of the European Community for Coal and Steel (ECCS) have often been used in Germany and across Europe in order to assess pulmonary function. A calculation formula for each lung-specific measure has been derived from a large number of measured values. From this formula, again predicted values for each measure have been determined (Lehnert et al. 2015).

The reference values according to ECCS have been considered the gold standard for a long time, although the limitations have been well known. According to Marek & Marek 2009 these are the following:

- The examined collectives were based on healthy, primarily non-smoking subjects
- The documentation of biometric data was partly incomplete
- The increase in height and age of the population

For this reason, the European Respiratory Society (ERS) founded the Global Lung Function Initiative (GLI), with the aim to create and establish new reference values for lung function. In 72 centers from 33 countries measurement results have been fed into the database of GLI in which there are quality-tested measurement data from almost 100,000 healthy, non-smoking subjects aged between 3 and 95 years (see also http://www.lungfunction.org). Consequently, this covers a significantly larger age group than the ECCS data. Furthermore, a higher part of women (55.3 %) and other ethnic groups beside the Caucasian population have been taken into account, compared to ECSC. Based on comprehensive measurement data, formulas have been developed with which individual expected values for the different functional parameters can be calculated (Quanjor et al. 2012).

The introduction of the new GLI reference values affects all application areas of pulmonary function diagnostics and they are also applied in the evaluation of studies, the assessment of lung function data in preventive care as well as in the assessment of occupational diseases (Lehnert, et al. 2015).

4. Particularities of reference values according to GLI

The approach of GLI is characterized by the following innovations and a number of differences (see also Table 1) with respect to the predicted values of ECCS:

- The choice of the population underlying the predicted values of GLI is considerably more comprehensive and broader than that of ECCS.
The equation for determining the predicted average values is more precise
There is a smooth transition from childhood to adulthood

So far, the common ECCS practice has been to consider a lung function value as pathological if it is less than 80% of the predicted value. However, this seems to be reasonable only for patients up to the age of 40. The lower limit deciding on the assessment "normal" or "pathological" (also called Lower Limit of Normal (LLN)) is for example below 70% of the old predicted value for 80-year-old people, so this was wrongly considered as pathological in the past. According to these data, the limit between "normal" and "pathological", expressed in percentages of the predicted value, depends on age. This is why a parameter was searched which describes this limit independently of age. This is the so-called "z-score" indicating how far the measured value deviates from the average value and the lower limit of normal (LLN), independent of age and gender.

Table 1: Differences between GLI and ECCS predicted values (acc. to: Criée et al., 2015)

<table>
<thead>
<tr>
<th>Comparison criterion</th>
<th>ECCS</th>
<th>GLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC and FEV₁ in middle to higher age</td>
<td>Up to 10% lower than GLI</td>
<td>Up to 10 % higher than ECSC</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Is not considered</td>
<td>Is considered</td>
</tr>
<tr>
<td>Dispersion of measured values</td>
<td>Is not considered</td>
<td>Varies according to age:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 15-45 years low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- &gt;45 years increasing</td>
</tr>
<tr>
<td>Limit values</td>
<td>Static, as a rule 80% below predicted value is considered pathological</td>
<td>Dynamic, due to separate calculation of normal value and lower limit of normal (LLN)</td>
</tr>
<tr>
<td>Reference equations</td>
<td>&quot;easier&quot;</td>
<td>&quot;more complex&quot; (see also <a href="http://www.lungfunction.org">www.lungfunction.org</a>)</td>
</tr>
</tbody>
</table>

In order to diagnose an obstructive ventilation disorder, an individual predicted average value for the FEV₁/FVC ratio of the examined person is derived. If the ratio of the determined parameters FEV₁ and FVC is below the LLN, the diagnosis will be classified as clinically suspicious or pathological and will give rise to further diagnostic procedures.

If the scatter range of normal values is to be considered, percentiles will be found which establish a relationship between the examination result and its statistic normal distribution in percentage steps. LLN and percentiles can be correlated, so the 5% percentile has been stipulated as the pathological limit of LLN (corresponding to a z-score of -1.645). In the guideline for spirometry (Criée et al, 2015) the severity classification is not recommended in percent of predicted value anymore as it used to be, but a classification according to the z-score. As a criterion for decision in serial examinations GLI recommends GLI the 2.5th percentile as LLN. As a criterion for clinical assessment of ill persons the 5th percentile is considered acceptable as LLN. The use of LLN as criterion for decision differs from the so-far common practice where e.g. an obstructive ventilation disorder was detected when the FEV₁/FVC ratio was inferior to 0.7. A fix limit of 0.7 does not take into account the considerable physiological dependence of the FEV₁/FVC ratio on the age of
the examined person. Significant differences in the clinical assessment are to be expected particularly in young and old persons (see also Fig. 1).

![Graph](image)

**Figure 1:** Comparison between diagnosing obstruction by using a fix FEV1/FVC ratio (blue line) and the use of an age-adjusted lower limit of normal (LLN, red line). *Source: Mannino et al. 2007*

### 5. Performance of a spirometry and important measures

The current guideline for spirometry (Crieé et al., 2015) describes in detail how spirometry is to be performed in practice. The creation of a meaningful flow-volume curve by the spirometer requires well-trained personnel as well as motivated cooperation of the examined person. Certain quality criteria have to be taken into account as well. Usually, at least three successive measurements are carried out which comply with the quality criteria of the American Thoracic Society (Miller et al. 2005). The best trial will be evaluated. The most important measures of spirometry are listed in table 2.
### Table 2: Important measures of spirometry

<table>
<thead>
<tr>
<th>Measure</th>
<th>Abbr.</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital capacity</td>
<td>VC</td>
<td>The maximum lung volume that can be exhaled after maximum inspiration (3.3 to 4.9 liters of air).</td>
</tr>
<tr>
<td>Inspiratory Vital Capacity</td>
<td>IVC</td>
<td>The lung volume which can be inspired at once after maximum expiration (approx. 3.5 liters of air).</td>
</tr>
<tr>
<td>Forced expiratory Vital Capacity</td>
<td>FVC</td>
<td>The lung volume that can be forcibly exhaled in one breath after maximum inspiration.</td>
</tr>
<tr>
<td>One-second capacity (Forced Expiratory Volume)</td>
<td>FEV1</td>
<td>The volume of air that can be maximally exhaled in one second after maximum inspiration (at least 70 percent of Vital Capacity).</td>
</tr>
<tr>
<td>Maximum respiratory flow rate (Peak Expiratory Flow)</td>
<td>PEF</td>
<td>Describes the strongest airflow exhaled from the lungs at the beginning of strong expiration (max. 600 l/min)</td>
</tr>
<tr>
<td>Mean respiratory flow rate (75%, 50%, 25%) (Maximal Expiratory Flow)</td>
<td>MEF (75%, 50%, 25%)</td>
<td>Expiratory flow at 25/50/75% of FVC. It is the maximum expiratory flow rate at 25/50/75% of vital capacity in the thorax, which means when 75/50/25% of vital capacity have already been exhaled.</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>TV</td>
<td>Corresponds to the volume of air inhaled or exhaled. With normal breathing and under resting conditions this is approximately 0.5 liters of air.</td>
</tr>
<tr>
<td>Inspiratory Reserve Volume</td>
<td>IRV</td>
<td>This is the volume that can be additionally inhaled after normal inspiration (approximately 3 liters of air).</td>
</tr>
<tr>
<td>Expiratory Reserve Volume</td>
<td>ERV</td>
<td>This is the volume that can be additionally exhaled after normal expiration (approximately 1.7 liters of air).</td>
</tr>
</tbody>
</table>

The patient inhales and exhales through a mouthpiece on the spirometer. An experienced, trained medical assistant gives clear instructions which the patient has to follow as exactly as possible. The strict and disciplined adherence to the instructions is important because otherwise measurement results could be wrong and as a consequence, conclusions as to treatment could be incorrect, too. The examination thus depends heavily on a good cooperation of the patient. The variables age, height, gender and ethnic group have to be identified for the registration of standard values and thus for the determination of a correct pulmonary function examination according to GLI. In addition, the lower limit of normal values (LLN) are corrected in terms of age for all ethnic groups.

### 6. Further functions of spirometry in custo diagnostic

As part of a pulmonary function test, the following measures are taken into account when selecting GLI predicted values: FVC, FEV1, FEV1/FVC, FEF25%-75%, FEF75%FVC, FEV0,75, FEV0,75/FVC, MEF25%FVC.
6.1 Delay

It happens again and again that in pulmonary function measurements the patients start the forced expiration with delay. This is why the zero point on the time axis has to be adapted accordingly in order not to falsify the calculation of FEV1. This adaptation is made by means of a back calculation in which a new zero point is determined. The relevant criteria for a new calculation of the zero point on the time axis are: Expiratory volume <5% or already expired volume in the first second below 150ml.

Figure 2: Normal measurement (blue line) and measurement with clearly recognizable delay (red line)

6.2 Notice in case of shallow tidal breathing

Prior to performing a breathing maneuver, the user can set how many tidal breaths the test person has to do before the breathing maneuver. The system gives a hint if tidal breathing is insufficient and asks the patient to inhale and exhale more deeply.

Figure 3: Notice when tidal breathing is insufficient

6.3 Notice in case of three reproducible measurements (5% rule)

As soon as the patient has performed three reproducible measurements, a notice appears that the series of measurements can be terminated. The German Airway League and the ATS recommend performing at least 3 comparable measurements in order to be able to make a statement as to quality and cooperation of the patient. After each measurement, first a check is made whether there are already 3
measurements. If this is the case, the relation of the values FVC, FEV1 and PEF to each other will be verified, whether they are within the set limits. The limits for FVC and FEV1 are at a value of 5%. If the ratios of the 3 best measurements are within the defined limits, the progress monitoring display will appear indicating that the series of measurements can be terminated now. These 3 best measurements can be printed both for the reference measurements and for the spasmylosis measurements.

There are 3 reproducible measurements now. The series of measurements can be terminated.

Hints as to the settings for this function can be found in chapter 7.5 (a: Reproducibility).

6.4 Further particularities of lung function with custo diagnostic

6.4.1 Calculation of the spirometric lung age

If the patient's age is included in the formula for calculating FEV1, the lung age can be determined by comparing predicted values. The FEV1 decreases with growing age. For example, the FEV1 of a 75-year-old is only about 70% of the FEV1 of a 25-year-old. It is important to consider that the lung age cannot be determined for each predicted author - when the formula for FEV1 does not depend on age.
6.4.2 Miller's Prediction Quadrant

The Miller’s Prediction Quadrant is a simple prognostic tool indicating the probability for the existence of an abnormality and its severity. The diagram is subdivided in four quadrants: obstructive disease, restrictive diseases, obstructive / restrictive disease or normal. The measurement results are shown in each quadrant, according to the prediction.

Figure 6: View of measurement results in the Miller's prediction quadrant.

6.4.3 Implementation of ATS specifications (American Thoracic Society)

The results of the breath test are displayed as flow-volume curve. The advantage of this view is that the patient’s cooperation can be evaluated immediately and it becomes immediately evident if there is a ventilation disorder. In order to improve comparability of several measurements carried out with the same patient for example, the American Thoracic Society has requested a precisely defined form for the flow-volume curve, the so-called 2:1 view.

Here, 2 liters are shown on the y-axis and 1 liter on the x-axis. This 2:1 view can be selected in custo diagnostic and be printed (see Fig.7).
A further specification according to ATS is that the expiratory volume-time diagram is displayed over a period of 6 seconds (see Fig. 8). This specification is also implemented in custo diagnostic.

For quality management, ATS requests that the date, the calibration result and the person having performed the calibration are protocolled each time a spirometer (Miller et al., 2005) is calibrated. This information is recorded and saved in custo diagnostic, together with the volume of the calibration pump, and can be called up and printed under the option "Calibrations" at any time.
7. Novelties in spirometry from custo diagnostic version 4.5.1 or higher

The integration of GLI as predicted author has been implemented in maximum compliance with the guidelines. Beside the known color scheme for reference (blue) and spasmolysis measurement (red), the colors for displaying LLN (green) and for the z-score (green/ orange) have been added. Below, the authors guide through an exemplary spirometry according to GLI in order to explain the novelty.

7.1 Carry out measurement

When carrying out an examination, ECSC provides a predicted value curve that helps to detect if a patient is within or outside the standard range. This predicted value curve is constructed on the basis of PEF and MEF\textsubscript{75, 50, 25}. These values are not relevant in GLI, however, in other software there is sometimes an envelope curve based on PEF. This is due to the aspect “orientation” but is, as this envelope curve is based on another predicted author, misleading and the guideline authors even recommend not using this procedure because the combination of two predicted authors in one examination results in a validity that is limited, difficult to interpret and doubtful. However, it is allowed to create an orientation guide out of the course of an imaginary line resulting from FVC and the limit of FEF\textsubscript{25-75}. Measurements whose line charts are above or within the corridor of LLN bars can be considered as acceptable (see Fig. 9). As soon as at least 2 reproducible measurements have been achieved, the corresponding hint will appear and the examination can be terminated.

![Figure 9: Predicted curve drawn from FVC and FEF25-75 with LLN bars](image)

7.2 Display measurement result

The measurement results are displayed in various manners, dependent on the phase of examination. In the reference measurement, the bars below the flow-volume curve show the results for FEV\textsubscript{1}, FVC and FEV\textsubscript{1}/FVC. The blue arrows mark the results of the reference measurement. Beside the predicted values and the achieved measured values and their percentage deviations, the results for the z-score are indicated in the measured value table.
If the z-score is in the predicted range, each result will be marked with a green square. If it is below the LLN (which means below -1.645) this will be highlighted with an orange square. The presentation of the results of spasmolysis measurement is comparable to the reference measurement, it just uses other colors (red) (see Fig. 10).

![Fig. 10: Representation of results of reference and spasmolysis measurement with GLI](image)

### 7.3 Automatic report

It is a new feature of custo diagnostic that the software provides the physician with a comprehensive overview of measurement results of the spirometric examination and that the criteria of evaluation are explained. The user can select four different options for creating a report (see Fig. 11):

- Standard¹
- COPD acc. to GOLD
- Acc. to guideline (only GLI)
- occupational medicine (only GLI)

For each selected option the patient-specific results are calculated and displayed.

![Fig. 11: Options for creating reports](image)

¹ Proposal as before, with 70% rule for FEV1/FVC and 80% rule for IVC and FVC
The clinical assessment of a spirometry is based on the patient-specific predicted values and/or on their deviation from them. If for example the measurement result for FEV1 (FVC) is between 40% and 60% of the predicted value, there is suspicion of a moderately severe obstruction (restriction).

When assessing according to occupational medical aspects, the limits are moved further towards the top and there is a moderately severe obstruction (or restriction) if FEV1 (and/or FVC) is between 55% and 85% of the predicted value. These report explanations support the physician in evaluating a patient according to the guidelines. They can be called up for the report (predicted author: GLI) under "Options" >> "Explanations" and also provide hints for COPD limit values according to GOLD (see Fig.12), in addition to the clinical and occupational-medical evaluation.

**Fig. 12: Report explanation according to guideline of predicted author GLI**

### 7.4 Extension of printing options

Printing options have been revised and extended. The following new functions have been added:

- Report evaluation (clinical, occupational medicine and acc. to GOLD) can also be printed.
- In progress monitoring and for the "Total evaluation employers' mutual insurance association" it is now possible to print the Miller's prediction quadrant and the FVC chart according to ATS.
- The results from a provocation test can now also be printed.
7.5 Extension of setting options

a) Reproducibility

The menu item "Settings" has been extended by some functions. Under "Menu/Functions" the criteria for reproducibility of a measurement can be viewed and be easily adapted if necessary. The following illustration shows which parameters are relevant here (see Fig.13).

![Check measurements for repeatability](image)

**Fig. 13: Setting options for the criteria of reproducibility**

b) View of measured values and determination of the best measurement

In the menu item "Diagnostics" >> "Parameter", the user can select the parameters to be displayed on the screen. It is possible to select a maximum of 7 parameters and the selection can be made separately for each predicted author. In addition, it is possible to set according to which parameter the "best measurement" is determined. The parameters IVC, FVC, FEV1 as well as the sum of FEV1 and FVC can be selected. The last one has proved to be particularly significant (see also Fig. 14).

![Selection for measurement values](image)

**Fig. 14: Options for view of measured values and for determination of best value**
c) Flow-volume curve

In the menu item "Diagnosics" >> "Parameter", the view of the flow-volume curve can be set. It is possible to select the view according to ATS (2:1 view) or with automatic scaling. If automatic scaling is selected, the scaling of x axis will be adapted according to FVC (see also table opposite and Fig.15).

<table>
<thead>
<tr>
<th>Volume FVC [L]</th>
<th>Scaling x axis [L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>0-4</td>
</tr>
<tr>
<td>3-5</td>
<td>0-6</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>0-8</td>
</tr>
</tbody>
</table>

Fig. 15: Setting options for the flow-volume curve

8. Practical suggestions for interpreting spirometry

Among the methods for pulmonary function testing, spirometry has an outstanding position because it is easy to conduct and because ventilation disorders can be well excluded. Of course, the lack of evidence for a ventilation disorder must not result in a general exclusion of a lung function disorder. Furthermore, spirometry only provides a snap-shot of a fluctuating ventilation function which is partly due to a disease.

The international task force of ATS/ERS has published a simplified flow for implementing a pulmonary function test for clinical practice. VC, FEV1, FEV1/VC and TLC are the relevant parameters here. A normal relative one second capacity (FEV1/VC) excludes a ventilation disorder when otherwise normal vital capacity (VC) is given (Bösch & Crie, 2013).

In order to further exclude a pulmonary vascular disorder, diffusion testing is required which also helps differentiate a restriction and can indicate the existence of emphysema or bronchial asthma if there is an obstruction.
9. Conclusion

At the end of the year 2012, the common taskforce of the European Respiratory Society (ERS)/"Global Lung Initiative" published new reference value recommendations for spirometry which came into being after 5 years of work on the basis of evaluations of comprehensible study material. More than 97,000 spirometry measurements of healthy non-smokers (55.3% women) were evaluated, the examination including more than 57,000 Caucasians (incl. Europeans). It was a major finding that the most important spirometric parameters such as forced vital capacity (VC) and one second capacity (FEV1) were approx. 10% higher in the middle to late stage of life than according to the previous reference value recommendations. This means that the frequently used practice to consider a lung function test as pathological if it is less than 80% of the predicted value (e. g. ECCS), is only justifiable for patients up to the age of 40. The lower limit deciding on the assessment "normal" or "pathological" (also called Lower Limit of Normal LLN), is for example inferior to 70 % of the previous predicted value in 80-year-old patients. This used to be wrongly considered as pathological. As the limit between "normal" and "pathological" according to these data, expressed in percentages of the predicted value, depends on age, a parameter has been searched which indicates this limit independently of age. This is the so-called "z-score" indicating how far the measured value is situated from the average value and from the lower normal limit (also called Lower Limit of Normal – LLN), independent of age and gender.

A side effect of the reference values according to GLI is the confirmation by older normal values that the definition of COPD according to GOLD guidelines is wrong from a pathophysiological point of view because the dependence on age has not been taken into account. This results in overestimation of COPD diagnoses in the older population (Airway League, 2015).
The software "Spirometry" as part of custo diagnostic implements the specifications according to GLI and ATS in compliance with the guidelines.

"Finally, it is important to mention that the validity of the individual examinations depends to a high degree on the performance and/or the cooperation of the patients and can be increased by good information flow regarding the clinical conditions, anamnesis and further cardiopulmonary examination results" (Bösch & Criée, 2013, S.164).

Yours sincerely,

custo med team

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