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White Paper

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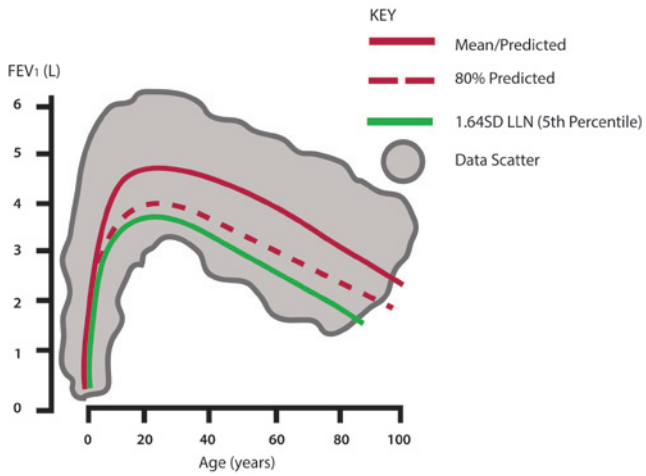
Defining the Lower Limits of Normal (LLN) in Spirometry

The use of percent predicted when assessing lung function is widely used and an 80% 'cut-off' for a lower limit of normal (LLN) is commonly utilised and considered during diagnosis and monitoring of respiratory disease. However, the 80% of predicted 'cut-off' for what may be considered 'normal' is not based on any scientific foundation and has been considered as statistically invalid[3].

As many authors in the past have shown[1,2,4,] scatter plots of data of respiratory parameters such as FEV1 show in healthy non-smokers, a proportional change of scatter as the value declines with age. As such, a LLN should follow the same pattern. When looking at the raw data scatter (Graph 1) using 80% predicted LLN shows a progressively increasing LLN as age increases with no statistical reasoning. Implementing this as a marker of abnormality, would create a large percentage of false-positive results in both young and elderly subjects. Additionally, with an ever increasing ageing population, this could be regarded as a potential problem when diagnosing and monitoring respiratory disease.

Graph 1. The decline of a statistical 1.64SD LLN compared with an 80% predicted LLN.

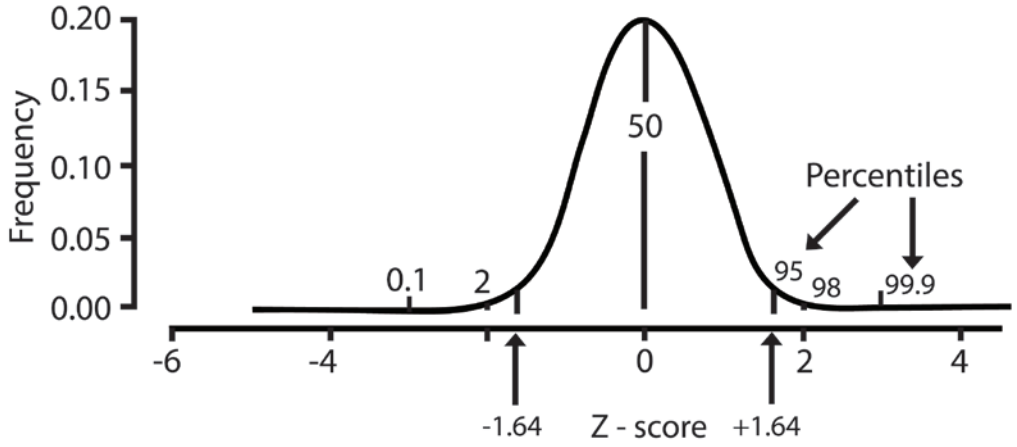
The comparison of the observed and predicted values which determines whether the difference between the measurements is compatible with the scatter distribution about the predicted value, is strongly recommended. Such a method needs to:



- Determine how normal a result is.
- Measure how far the result is from the mean (predicted) value.
- Express it in terms of the number of standard deviations (SD) from that mean (figure 1)

Thus, enabling clearer statistical weighting and rationale during a time of no clinically proven categorisation of severity of disease as opposed to an arbitrary 80% LLN.

Figure 1. A bell-curve representing the LLN of 1.64 SD accepting a false positive of 5% and a lower false positive of 2.5% if LLN was increased to 1.96 SD.



- Figure 1 shows the prevalence of data that exceeded or fell below a predicted value (Z-score of 0) from the chosen regression equation.
- Both the ERS and ATS have endorsed the LLN as 1.645 SD below the mean value applying the 5th percentile LLN.
- The 'Z-score' or Standard Residual (SR) show the number of standard deviations a result is from the mean value.
- By implementing a recognised LLN of 1.64 SD, observations lower than -1.64 would occur in only 5% of the reflected population.
- Implementing a 1.96 SD LLN would imply that this was only observed in 2.5% of the 'healthy' reference population.
- Using this as a statistical marker for abnormality of a result in the absence of any other scientifically proven method, could have a beneficial effect in assisting with respiratory diagnosis and monitoring as well as showing strong application in research clinical trials for patient outcomes and recruitment when boundaries or 'cut-off' markers are used.

Table 1 shows that subject (a) had a measured FEV1 which would be considered 'normal' when implementing an 80% LLN, but shows that this result would be considered 'abnormal' as it is in the 5th percentile of their population normality. Conversely, subject (b) shows an FEV1 of 75% predicted but is within a statistical LLN (90th percentile) based on their given population normality.

Table 1.

Height (cm)	Age (Yrs)	FEV1 Obs (L)	FEV1 Pred (L)	FEV1 80% Pred (L)	Z-score
(a) 185	39	3.48	4.36	3.48	-1.72
(b) 177	70	2.34*	3.12	2.49	-1.52

Nb. *Subject (b) achieved 75% predicted FEV1 but still fell within a statistical LLN Z-score (not less than -1.64).

It is worth serious consideration the recommendation to implement the use of Z-score (SR) when considering diagnosis, monitoring and treating respiratory conditions. A non-proven LLN of 80% predicted for what is considered a 'normal' result may prove to be costly for both patient and practice.

References:

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