

Observation on **ATS/ERS 2019** and **ATS/ERS 2021** guidelines

Premise

MIR spirometers are presented as *fully compliant* with the ATS/ERS 2019 and ATS/ERS 2021 guidelines. This definition is *acceptable from a commercial standpoint*; however, from a technical perspective, it should be understood as *full compliance within the scope of the type of spirometers we manufacture*. Indeed, the guidelines include technical requirements that do not specifically concern portable devices, which are the focus of our production.

Practical example: According to the diagnostic classification proposed by the ATS/ERS 2021 guidelines, our spirometers provide data on the degree of airflow obstruction (based on the FEV₁ Z-score), but not on restriction (which is based on *Total Lung Capacity TLC*). This is because direct measurement of TLC requires more complex equipment, such as body plethysmographs or gas dilution systems, which are not compatible with the compact design that characterize our portable technology.

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Compliance with ATS/ERS 2019 – 2021 guidelines

Starting from **release 2.1.9 of MIR Spiro**, the **adjustments required by the ATS/ERS 2019 and ATS/ERS 2021** guidelines will be implemented. In this way, all devices in the **Standard Line** will be **compliant when used with the software**. In the case of **MiniSpir**, since it is a software-based device, **compliance will also be ensured at the device level**.

Devices in the Plus Line will be compliant **both when operating in synergy with the MIR Spiro software and when used in Stand-Alone mode**.

The following sections describe the implemented compliance features.

1. Modification of the criteria for displaying the “significant BD” message from 12% and 200 mL to only a 10% variation

The **significant BDR** (significant bronchodilator response) indicates the minimum improvement that must be achieved to determine that the patient has shown a clinically significant response to a bronchodilator. Identifying a significant BDR is used to assess whether bronchial obstruction is reversible or not: a significant response indicates reversible obstruction, whereas the absence of a significant response is typical of a partially or non-reversible obstruction.

In practice, during a spirometry test:

1. An initial measurement is performed.
2. The patient is administered a bronchodilator drug (e.g., salbutamol).
3. After a standard waiting period (10–15 minutes), spirometry is repeated.
4. If the variation in values meets the criteria established by the guidelines, it is defined as a significant BDR, i.e., a clinically meaningful response to the bronchodilator.

This evaluation is important for obstructive airway diseases, such as asthma and COPD.

Specifically, it helps to distinguish between a reversible obstruction (typical of asthma) and a not fully reversible obstruction (more common in COPD). In restrictive diseases, such as pulmonary fibrosis, the bronchodilator test has no diagnostic relevance, since restriction does not improve with bronchodilator drugs.

ATS/ERS 2005	ATS/ERS 2019	ATS/ERS 2021
To define a response as clinically significant, both of the following criteria had to be met: • Increase $\geq 12\%$ (improvement calculated as a percentage relative to the baseline value). • Increase ≥ 200 mL (improvement calculated as an absolute change relative to the baseline value).	No changes from the 2005 guidelines.	Simplification of the criterion (the dual condition is no longer required): • Increase $\geq 10\%$ (improvement calculated only as percentage relative to the predicted value).

Note that in the ATS/ERS 2005 guidelines, the criterion referred to the baseline value (the value measured before bronchodilator administration), whereas in the ATS/ERS 2021 guidelines, it refers to the predicted value (the expected value based on the patient's anthropometric data). This change makes the criterion simpler and more universally applicable.

Reference: Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. **Bronchodilator responsiveness testing, pp. 9–11.** *Eur Respir J* 2022; 60: 2101499.

2. Inclusion in the GLI reference equations of four new formulas related to VC, IC, IRV, and ERV

Up to the ATS/ERS 2005–2019 guidelines, the interpretation of spirometry relied on **national or regional reference equations** (e.g., NHANES III in the United States and ECSC in Europe), which, however, resulted in **outcomes that were difficult to compare across populations**. Moreover, these equations primarily covered **dynamic spirometric parameters such as FEV₁, FVC, and FEV₁/FVC**.

To overcome this fragmentation, in 2008 the **Global Lung Function Initiative GLI** project was launched. It collected measurements from populations heterogeneous in age, sex, height, and ethnic group, developing universal and standardized predictive equations.

The GLI equations, **recommended by the ATS/ERS 2019 and mandated by the ATS/ERS 2021, still depend on the ethnic group of reference** (e.g., Caucasian, African, North-East Asian, South-East Asian, or Other/Mixed). Therefore, the **ATS/ERS 2023** introduced the option to use the new **GLI race-neutral** equations, which **eliminate the dependence of predicted values on ethnicity**. However, this approach remains under debate within the scientific community. At present, the GLI race-neutral predicted values have also been implemented in the MIR software.

ATS/ERS 2005	ATS/ERS 2019	ATS/ERS 2021
Use of regional reference equations, with a recommendation for NHANES III in North America and no specific recommendation for Europe, despite the widespread use of ECSC, which provide predicted values significantly lower than GLI.	- National/regional equations still accepted, although with a growing preference for GLI. - Focus on dynamic parameters (FEV₁, FVC, FEV₁/FVC).	Mandatory use of GLI equations, since diagnostic interpretation is based on the Z-score calculated from these equations. - Application of GLI equations for both dynamic parameters (FEV₁, FVC, FEV₁/FVC) and static volumes (VC, IC, IRV, ERV).

Dynamic parameters refer to the flows and volumes measured during a maximal and rapid expiration or inspiration, whereas static volumes refer to the volumes measured during slow breathing.

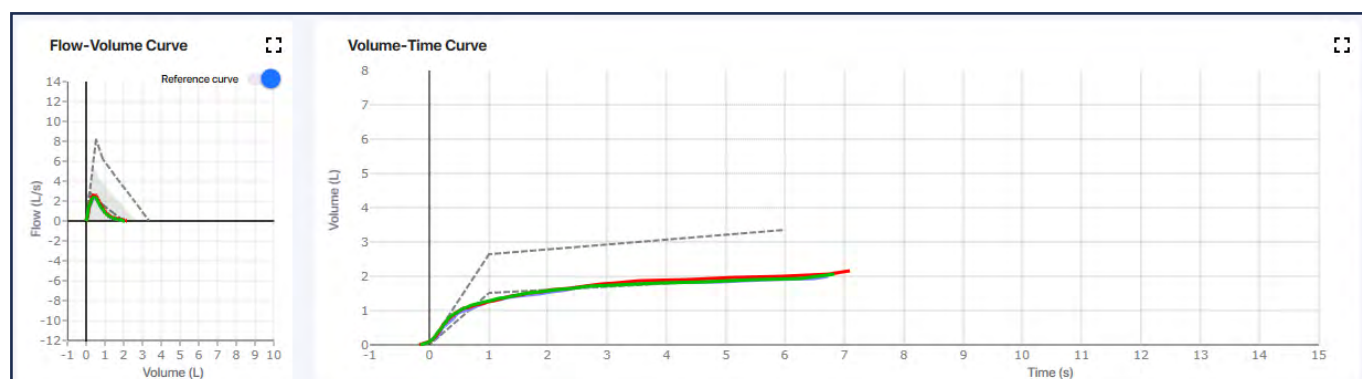
Reference: Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. **Comparison of measured values to a healthy population, pp. 2–9.** *Eur Respir J* 2022; 60: 2101499.

3. Flow/volume graph from -1 L and volume/time graph from -1 s

According to the ATS/ERS 2019 guidelines, **real-time visualization of both the flow/volume curve and the volume/time curve is required**. The operator must visually inspect the execution of each maneuver to ensure its quality before proceeding with subsequent maneuvers.

Accordingly, the following specifications have been defined for graph representation:

- **Volume/time curve: the graphical representation must begin either at the point of maximum inspiration or 1 second before Time 0 T_0 , whichever occurs first.** The maneuver should continue until the end of the plateau or the beginning of inspiration. This allows the **Back-Extrapolated Volume BEV** – the volume of air exhaled before the actual start of the curve (i.e., before T_0) – to be clearly displayed, helping to verify whether the maneuver was initiated correctly.
- **Flow/volume curve: the expiratory flow must be plotted upward, and the expiratory volume must be plotted to the right. The ratio between the flow and volume scales must be 2:1**, meaning that 2 L/s of flow and 1 L of volume correspond to the same graphical distance on their respective axes. **The graphical representation may include a -1 L margin on the volume axis to allow visualization of the curve's closure**, improving overall readability and quality control of the trace.



Reference: Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Display*, pp. E74-E75; *FEV₁ and FVC Maneuver*, pp. E79-E80. *Am J Respir Crit Care Med* 2019; 200: E70-E88.

4. Addition of a selection button between ATS/ERS 2019 and 2021 guidelines

The ATS/ERS 2021 guidelines do not fully replace those of ATS/ERS 2019. The former define interpretative and diagnostic updates, whereas the latter remain the reference for the technical standardization of spirometry. The option to select the reference version allows the operator to apply the interpretative approach most appropriate to the clinical context while consistently maintaining the technical requirements for test performance.

This option ensures:

- **Choice of reference equations:** ATS/ERS 2019 still allows the use of national or regional equations, in addition to GLI, whereas ATS/ERS 2021 prescribes the exclusive use of GLI equations. Allowing this selection enables the operator to decide which set of predicted values to use as a reference, depending on the clinical context or local practice.

- **Historical continuity and compatibility with existing databases:** many hospitals and clinical studies still follow protocols based on ATS/ERS 2019 to maintain consistency with historical datasets. Restricting interpretation to the 2021 guidelines would make new results not directly comparable with previous ones.

5. Addition of two columns in the reports for the display of LLN and Z-score values

The ATS/ERS 2021 guidelines replace the **classification of obstruction severity**, which in the ATS/ERS 2019 was based on the percent predicted value (% predicted) of FEV₁ (divided into five levels with thresholds of 70%, 60%, 50%, and 35%), introducing instead a **system based on Z-score values**. However, since % predicted does not provide uniform gradations across different ages, **the scale has been reformulated using Z-scores with threshold values of -2, -2.5, -3, and -4**.

The threshold values correspond to the following degrees of severity:

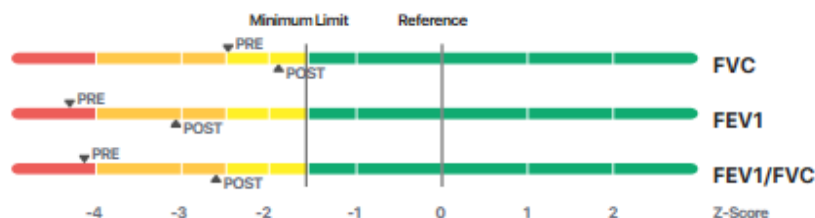
ATS/ERS 2005	ATS/ERS 2019	ATS/ERS 2021
• Based exclusively on the % predicted value of FEV₁. • LLN approximated to 80% of the predicted value. • Severity of obstruction classified as: ◦ Mild: FEV₁ > 70% ◦ Moderate: 60–69% ◦ Moderate-to-severe: 50–59% ◦ Severe: 35–49% ◦ Very severe: < 35%	• No changes from the 2005 guidelines. • Introduction of the statistical concept of LLN (5th percentile).	• Classification based on Z-scores. • Severity of obstruction classified as: ◦ Mild: -1.65 to -2.5 ◦ Moderate: -2.51 to -4.0 ◦ Severe: < -4.1 • Definition of LLN as Z = -1.645 (5th percentile). • Requirement to display LLN and Z-score in reports.

Parameters	PRED	LLN	PRE	%PRED	Z-Score
FVC (L)	2,66	1,96	2,16	81,20	-1,17
FEV1 (L)	2,08	1,50	1,32	63,46	-2,13
FEV1/FVC (%)	78,60	66,30	61,10	77,74	-2,25
PEF (L/s)	5,58	2,93	2,71	48,57	-1,79
ELA (Years)	71	-	95	134	-
FEF2575 (L/s)	1,76	0,79	0,65	36,93	-1,98
FET (s)	6,00	-	7,03	117,17	-
FVC (L)	2,66	1,96	1,86	69,92	-1,90
FEV1/VC (%)	78,60	66,30	—	-	-
FEV6 (L)	2,66	1,96	2,12	79,70	-1,27
FEV1/FEV6 (%)	78,60	66,30	62,30	79,26	-2,12
FEF25 (L/s)	5,19	2,67	2,32	44,70	-1,87
FEF50 (L/s)	2,83	1,58	0,75	26,50	-2,74

Reference: Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. **Severity of lung function impairment, pp. 13–15.** Eur Respir J 2022; 60: 2101499.

6. Introduction of the pictogram

To facilitate data interpretation, a pictogram has been introduced to allow a graphical visualization of the severity of functional impairment according to the thresholds defined by the guidelines.



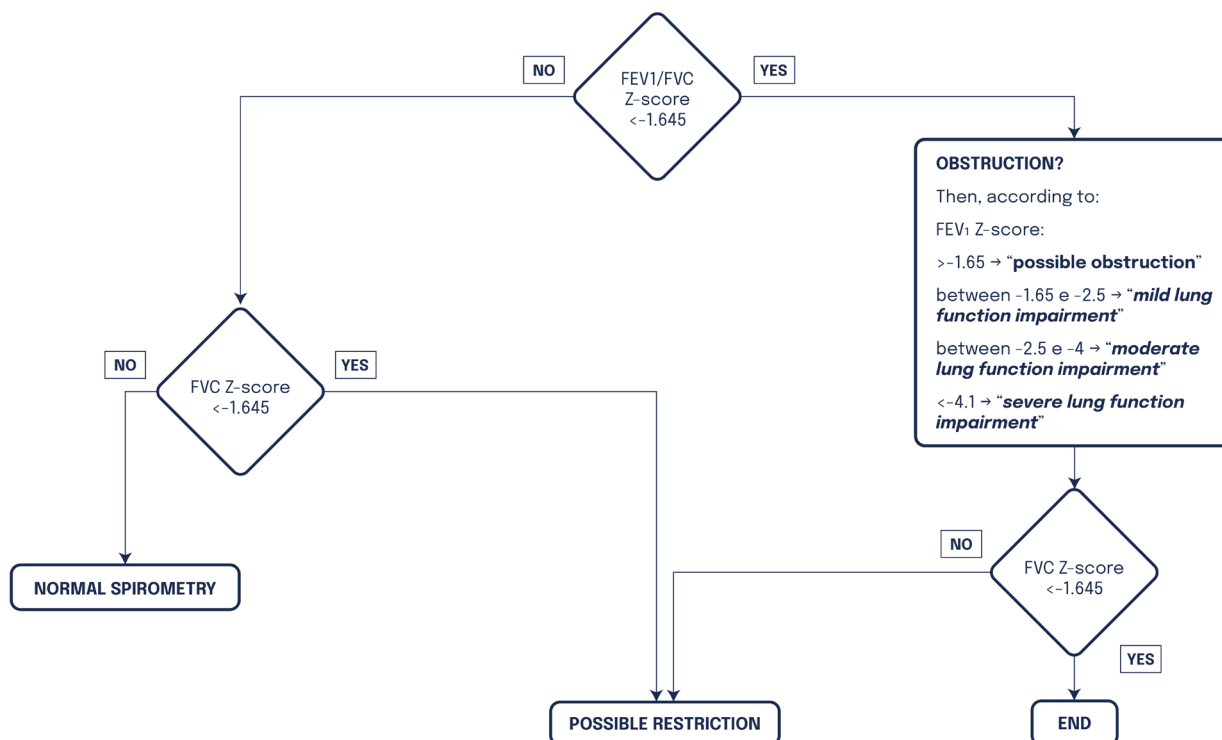
Each **horizontal bar** corresponds to a **spirometric parameter** (FVC, FEV₁, and FEV₁/FVC) and the **colored bands** indicate **different severity grades**:

- **Green:** Normal (Z-score > -1.645)
- **Yellow:** Mild (-1.65 to -2.5)
- **Orange:** Moderate (-2.51 to -4.0)
- **Red:** Severe (Z-score < -4.1)

Arrows indicate the **position of the measured Z-score value**:

- **Arrows above the band** indicate the **PRE value** (pre-bronchodilator)
- **Arrows below the band** indicate the **POST value** (post-bronchodilator)

Below the pictogram, in the center, the label “**Z-Score**” is displayed, indicating that the reference scale is the standardized one, in accordance with the ATS/ERS 2021 guidelines. Through the pictogram, the diagnostic process can therefore be interpreted as follows:



7. Introduction of the Quality Control Grade in accordance with the ATS/ERS 2019 guidelines

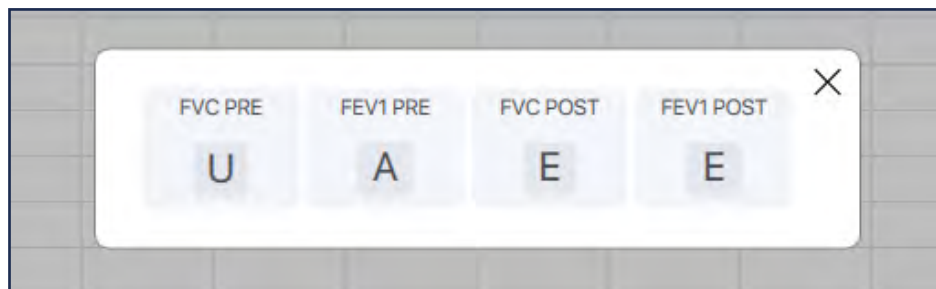
The ATS/ERS 2019 guidelines introduce a **grading system to indicate the level of acceptability and repeatability of spirometric maneuvers**. The system assigns a letter between A, B, C, D, E, and F, where **grade A represents the highest level of acceptability**, and **grade F indicates unusable data**. An additional grade, **U (Usable)**, has also been introduced to denote **measurements that are usable but not acceptable according to technical standards**.

In particular, for subjects older than 6 years:

- **Grades A-B:** difference between the two largest FEV₁ or FVC values < 0.150 L
- **Grades C-E:** repeatability between 0.200 and >0.250 L
- **Grade F:** no usable measurements

ATS/ERS 2005	ATS/ERS 2019	ATS/ERS 2021
• Introduction of the concept of acceptability and repeatability. • Evaluation performed for each individual maneuver. • Repeatability limit for FEV₁ and FVC ≤ 0.150 L for all subjects, with no age distinction, resulting in the exclusion of many pediatric tests classified as "not acceptable."	• Introduction of the grading system A, B, C, D, E, F, U. • Evaluation performed on the set of pre- and post-bronchodilator maneuvers, separately for FEV₁ and FVC. • Repeatability limits for FEV₁ and FVC differentiated by age: ◦ > 6 years: ≤ 0.150 L ◦ ≤ 6 years: ≤ 0.100 L or ≤ 10% of the highest value.	No changes from the 2019 guidelines.

In addition, the MIR Spiro software will include a notification pop-up that, upon achieving three consecutive FVC tests with the highest acceptability grade (AA) – meaning FVC = A and FEV₁ = A – will indicate that the session can be considered acceptable and completed.



Reference: Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. **Grading the Quality of the Test Session, p. E83.** Am J Respir Crit Care Med 2019; 200: E70–E88.