Nasal nitric oxide measurement for the diagnosis of primary ciliary dyskinesia: summary of the European Respiratory Society technical standard

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Shareable abstract (@ERSpublications)
There is a standardised approach for sampling, analysis and reporting of nasal NO measurements for the diagnosis of PCD across all age groups and for all types of devices in common use. Harmonising practice is necessary for reliable interpretation. https://bit.ly/4j7c66k

Cite this article as: Marangu-Boore D, Lucas JS, Beydon N. Nasal nitric oxide measurement for the diagnosis of primary ciliary dyskinesia: summary of the European Respiratory Society technical standard. *Breathe* 2025; 21: 240230 [DOI: 10.1183/20734735.0230-2024].

Received: 23 Sept 2024
Accepted: 26 March 2025

Abstract

Nasal nitric oxide (nNO) measurement is important in the primary ciliary dyskinesia (PCD) diagnostic pathway because levels are consistently very low in most patients. Machine type, environmental factors, respiratory manoeuvres and report interpretation are fundamental considerations when performing nNO testing. A European Respiratory Society Task Force recently published standards for testing which we summarise and discuss in this article. There are two main types of nNO machines: chemiluminescence and electrochemical analysers. Chemiluminescence analysers are highly accurate, reliable, real-time and have been validated in multicentre studies but are less portable and more expensive to purchase and maintain in comparison to electrochemical devices. Several factors may influence nNO levels and need to be addressed during patient preparation for testing. Factors including acute viral infections and nose bleeds may contribute to falsely low nNO levels, whereas high ambient NO levels may falsely increase nNO. Tidal breathing, breath-hold and exhalation against resistance are the three main respiratory manoeuvres used in nNO sampling and require a minimal, modest and high level of patient cooperation respectively. Finally, standardised reporting of nNO testing and the correct interpretation helps clinicians to formulate an appropriate clinical plan towards an accurate PCD diagnosis.

Educational aims

This article is aimed at those involved in diagnosing and managing primary ciliary dyskinesia patients. It provides an educational summary, and full details are available in the Task Force Technical Standard document. The reader will be able to:

- Acknowledge differences between chemiluminescence and electrochemical techniques in nasal nitric oxide (nNO) measurement and their respective pros and cons.
- Identify internal and external factors that influence nNO measurement during patient preparation.
- Know the basic steps of the three common respiratory manoeuvres used to perform nNO measurement.
- Know which respiratory manoeuvres to use based on the patient's comprehension and cooperation.
- Interpret the results of nNO measurement in conjunction with the clinical presentation and the results of other tests to help decide whether confirmatory diagnostic testing is required.

Introduction

Measurement of nasal NO (nNO) is important in the work-up for diagnosis of primary ciliary dyskinesia (PCD) [1–7]. Most PCD diagnostic tests require specialised laboratories and are time consuming. However,

TABLE 1 Pros and cons of chemiluminescence and electrochemical analysers.

Chemiluminescence		Electrochemical
+ + +	High accuracy	+ +
+ + +	Real-time display which allows selection and validation of the results from NO curves	+
+ + +	Stable plateau/regular peaks identified without a fixed sample collection minimum time requirement[#]	+
+ +	Consistent training and standard operating procedures provided by manufacturers	+ +
+ + +	Rigorously tested and not lacking published, validated cut-off values	+
+ +	Need rigorous operator training and expertise	+ +
+ + +	Simple to use	+ + +
+	Requires no calibration or preventative maintenance	+ + +
+	Cost effective for low-volume sites; less expensive to purchase and maintain	+ + +
+	Smaller and portable	+ + +

+ + +: clearly superior to the other technique; + +: non-important difference or depends on the brand of electrochemical device; +: clearly inferior to the other technique. [#]: Uninterrupted sampling for a fixed time can be problematic in young children due to interrupted flow (sniffing/crying) or difficulty maintaining the desired manoeuvre for the fixed duration of the test.

nNO can be measured by appropriately trained individuals in clinics, providing instant results which, in conjunction with the clinical presentation and the results of other tests, allow decisions to be made about the need for more complex, confirmatory tests. Previous standards have provided details for nNO measurements using chemiluminescence analysers for school-aged children and adults [8, 9]. A European Respiratory Society (ERS) Task Force recently developed a technical standard that is child-centred to support earlier diagnosis of PCD, including in pre-school children [1]. We summarise considerations for testing subjects of different ages and using different devices.

What are the differences between the two techniques used to measure NO?

Oral exhaled nitric oxide fraction (F_{ENO}), originating from lower airways or lungs, as well as nasal production of NO can be measured using the two types of machine, utilising chemiluminescence or electrochemical techniques. Chemiluminescence is the emission of light because of a chemical reaction. In the case of NO measurement, an instantaneous reaction between sampled NO and ozone generated in the machine results in the emission of electromagnetic radiation in the form of photons, which is proportional to the continuously sampled NO molecules [10]. Examples of chemiluminescence analysers include the CLD 88 sp (Eco Medics AG, Duernten, Switzerland), Sievers NOA 280i (Zysense, North Carolina, USA), NIOX FLEX (discontinued) (NIOX Group Plc, Oxford, UK), LR 2000 (Logan Research, Rochester, UK) and NOX EVA 4000 (discontinued) (Seres, Aix-en-Provence, France). In contrast, the electrochemical technique is a chemical reaction between NO that has accumulated in a chamber during the sampling and that is put in contact with active sensing materials (known as amperometric sensors) able to quantify the NO [10, 11]. The NIOX MINO (discontinued) and NIOX VERO (both NIOX Group, Oxford, UK), FeNO+ (MCG Diagnostics, Minnesota, USA) and Sunvou-CA2122 Nano Coulomb Breath Analyser (Sunvou Medical Electronics Co., Ltd., Jiangsu, China), are examples of electrochemical analysers.

Chemiluminescence and electrochemical machines have distinct pros and cons that are summarised in table 1 [1]. Although the American Thoracic Society and ERS guidelines recommend that nNO measurements are performed using chemiluminescence machines [6, 7, 9], results from a global survey of PCD centres indicated that electrochemical analysers are more frequently used, especially outside North America [12]. This trend may be increasing because of the simpler, cost-effective and more portable characteristics of electrochemical analysers. Furthermore, our knowledge on the comparison between measurements performed with both techniques is limited. Research in these areas is crucial [1].

What factors influence the nasal NO level?

Several patient and environmental factors may influence the nNO measurements obtained (figure 1), hence optimal patient assessment is key. A careful clinical history and assessment of the upper airways is needed before testing. Airway infections can lower nNO levels, and the ERS Task Force suggested delaying nNO testing for 2–4 weeks following an infective upper or lower airway exacerbation [1, 7, 12, 13]. At least

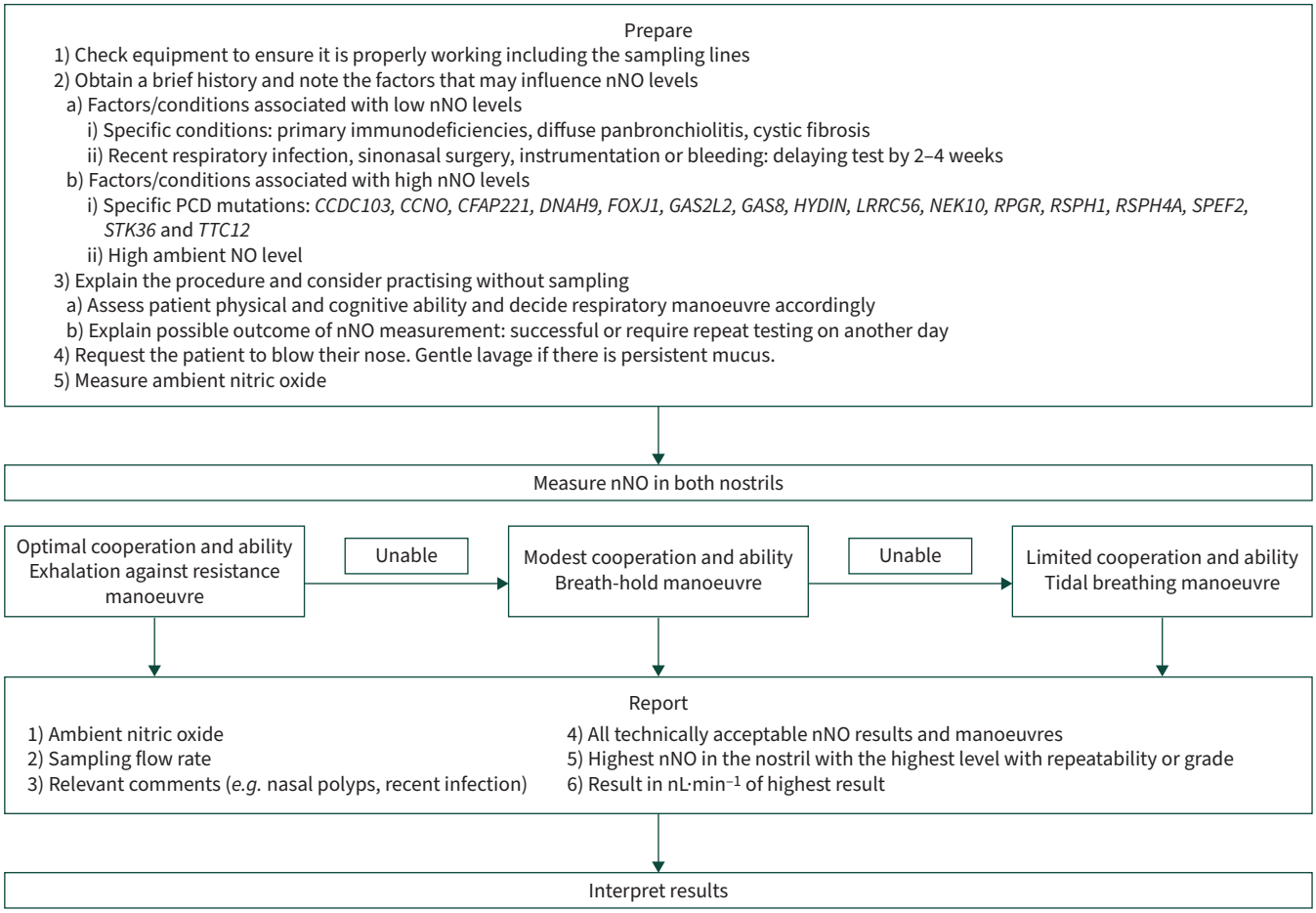

FIGURE 1 Suggested approach to measuring nasal nitric oxide (nNO) in patients for the diagnosis of primary ciliary dyskinesia (PCD).

four weeks after recovery from nasal/sinus surgery has been suggested before undertaking nNO testing [7]. In most specialist sites, cystic fibrosis must be excluded before performing nNO measurements.

Before testing, the physician should check that the patient has no exacerbation of symptoms suggestive of respiratory tract infection in the recent weeks. They should explain the procedure, and the patient asked to blow their nose. For patients who are not able to adequately clear their nasal passages gentle saline lavage may be helpful, taking care not to injure the mucosa. Moreover, nasal brushing or biopsy should be performed after nNO measurement to avoid bleeding since haemoglobin may tightly bind NO, reducing the level of nNO measured. Finally, high ambient NO can overestimate the nNO level and should be recorded and subtracted from all measurements made (especially when above 20 ppb).

If for any reason testing proceeds despite these factors and the measurements are low, testing should be repeated on a separate day. Patients with identified or suspected nasal obstruction with low nNO levels should be referred to an otorhinolaryngologist for assessment [1]. Sampling lines must be observed during the procedure to detect a possible obstruction.

Which respiratory manoeuvres can we use to measure nasal NO?

There are three respiratory manoeuvres commonly used to sample nNO from nostrils according to the level of cooperation of the patient and their ability. The manoeuvres are repeated twice in each nostril to study the intra- and inter-nostril repeatability. The preferred methods – exhalation against resistance and breath-hold – involve closing the velum to isolate the nasal cavities from the lower airway, which contains low levels of NO, thus preventing dilution of nasal NO. Among these, exhalation against resistance is considered the gold standard as it provides feedback on both the sustained exhalation and velum closure [1, 7–9, 14–17].

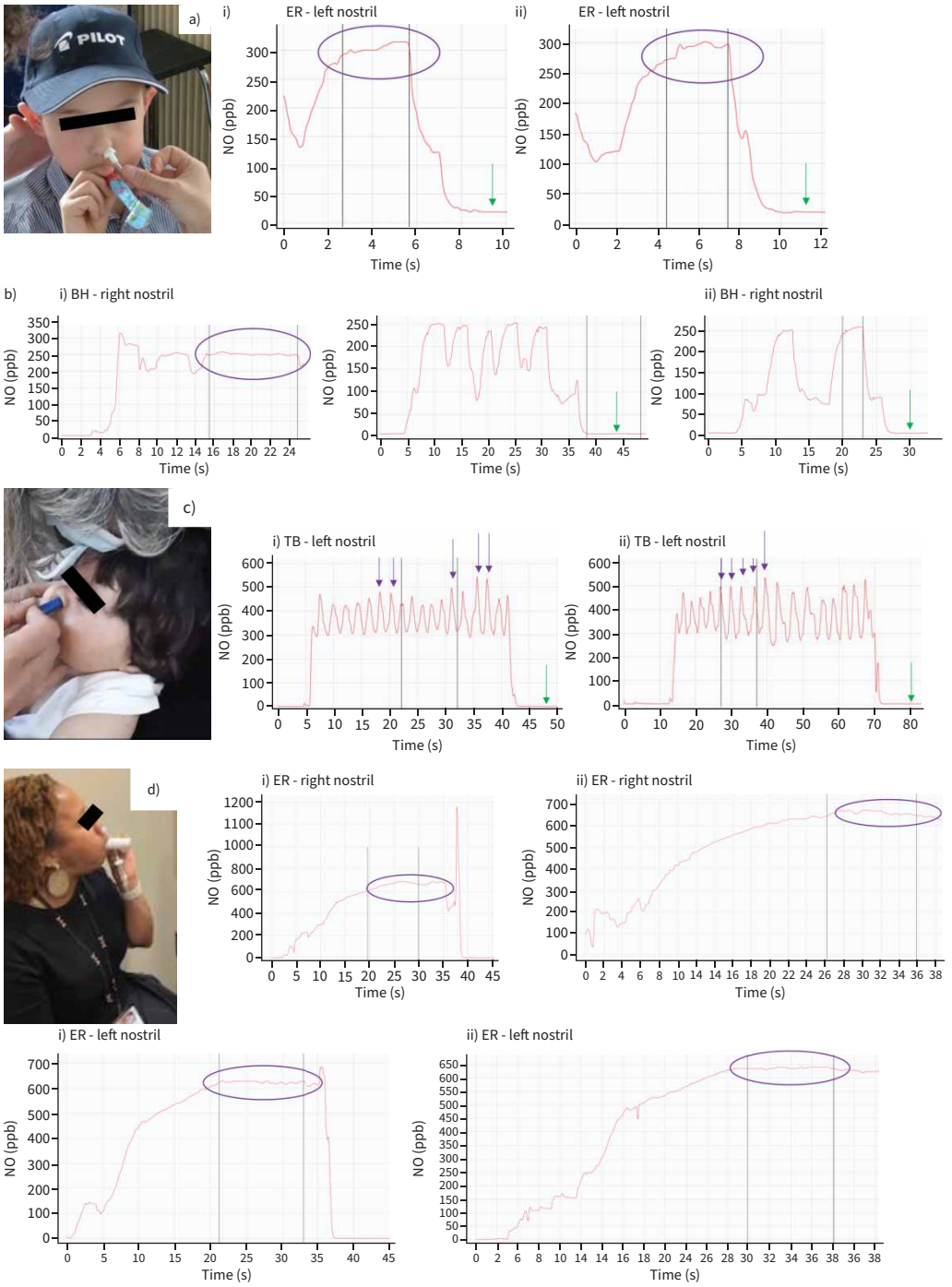

FIGURE 2 Respiratory manoeuvres used to perform nasal nitric oxide (nNO) measurement based on patient cooperation and ability. a) The photo shows nNO measured in an eight-year-old boy using the exhalation against resistance (ER) manoeuvre by blowing a party blower. The white olive is inserted in his left nostril and held in place by the respiratory technician, while his parent provides support to the back of his head with the boy sitting upright. Adjacent to the image of the child are two readings of left nostril NO measurements taken using the exhalation against resistance manoeuvre on a chemiluminescence analyser. On the first attempt, note the plateau circled in purple between the vertical lines is acceptable, >3 s showing a mean nNO of 304 ppb=100 nL·min^{-1}. The NO tracing on the second attempt is also acceptable with a plateau of 3 s recording a mean nNO of 292 ppb=96 nL·min^{-1}. These results are repeatable with ⩽10% variation in the left nostril. The green arrows show ambient NO levels measured at the end of testing of each of the left nostril measurements, approximately 22 ppb. Ambient NO levels above 20 ppb must be factored when calculating the final standardised nNO level. Here, the highest plateau value is 304−22=282 ppb. b) The tracings show right

nostril NO measurements taken using the breath-hold (BH) manoeuvre on a chemiluminescence analyser. On the first attempt, an acceptable plateau circled in purple between the vertical lines of >3 s is reached. The mean nNO is 251 ppb=82 nL·min^{-1}. The NO tracing on the second attempt is also acceptable with a plateau of 3 s recording a mean nNO of 253 ppb=83 nL·min^{-1}. These results are repeatable with <10% variation in the right nostril. The green arrows show low ambient NO levels measured at the end of testing of each of the right nostril measurements, almost 0 ppb. The final best result nNO in the right nostril is 83 nL·min^{-1}. c) The photo shows nNO measured using the tidal breathing (TB) method in an infant sleeping on her mother's lap. The blue olive is inserted in the left nostril and is held in place by the mother. Adjacent to the image of the infant are two readings of left nostril NO measurements taken during tidal breathing on a chemiluminescence analyser. On the first attempt, note the five reproducible (within 20%) maximal peaks shown by purple arrows that are not consecutive but acceptable showing a mean nNO of 375 ppb=124 nL·min^{-1}. The NO tracing on the second attempt shows five reproducible peaks (purple arrows) recording a mean nNO of 370 ppb=122 nL·min^{-1}. The green arrows show ambient NO levels measured at the end of testing of each of the left nostril measurements, low at 0 ppb. d) The photo shows nNO measured using the ER technique in an adult. The grey olive is inserted in the right nostril. Adjacent to the image of the adult are two tracings of right nostril NO measurements taken using the ER manoeuvre on a chemiluminescence analyser. Prior to patient nNO measurement, the sampling flow rate measured on this machine was 0.352 L·min^{-1} and the ambient NO was 2.956 ppb. On the first attempt, note the plateau circled in purple between the vertical lines is acceptable at 10 s (>3 s) showing a mean nNO of 660 ppb=232 nL·min^{-1}. The NO tracing on the second attempt is also acceptable with a plateau of 10 s recording a mean nNO of 657 ppb=231 nL·min^{-1}. Note the change in scale on the *y*-axis (nNO). These results are repeatable with ⩽10% variation in the right nostril. We also show two tracings of the left ER-nostril NO measurements taken in the same adult. Both results are acceptable. The plateaus circled in purple between the vertical lines are 10 s and 8 s respectively (>3 s) and show a mean nNO of 624 ppb=220 nL·min^{-1} in the first attempt; and 638 ppb=224 nL·min^{-1} in the second attempt. The variability between the right and left NO measurements is ⩽10%. The ambient NO being <20 ppb is not factored in the calculation of the final result. The highest result from the highest nostril is used in the calculation of the final result (660 ppb). The final standardised value is (660 ppb×0.352 L·min^{-1})=232 nL·min^{-1} which is above the cut-off of 77 nL·min^{-1} for ER-nNO measurements. Reproduced with permission from Nicole Beydon and Diana Marangu. The adult nNO measurements were performed at the National Institutes of Health courtesy of Andrew Lipton and Gita Bhandari-Giri.

Exhalation against resistance

The exhalation against resistance manoeuvre is performed using a mouth resistor at 5–10 cm H_2O or a party blower/noisemaker (a blow-out toy horn taped closed at the distal end). After taking a deep inhalation, ideally using a chemiluminescence device, the patient slowly exhales against the resistance until a plateau is reached for ⩾3 s with ⩽10% variation (*i.e.* the difference between the highest and lowest value) [18]. Using a chemiluminescence analyser the NO tracing is viewed real-time, and the optimal plateau determined manually (figure 2a and 2d). When an electrochemical machine is used, a slow oral exhalation is performed for a duration set by the device which must be ⩾10 s. If connected to appropriate software, an electrochemical device such as the NIOX VERO can display a NO tracing, which is not real-time but can be used to manually select a plateau. Without ability to visualise the curve the result from the device can be accepted, but this is a limitation of measuring using these devices [1].

Breath-hold

The breath-hold manoeuvre requires the patient's ability to voluntarily close the velum. The patient is instructed to inhale to total lung capacity. Velum closure is achieved while holding their breath by closing the glottis and performing a Valsalva manoeuvre. Carbon dioxide in the free nostril should be zero if measured, and nasal NO measurements performed while carbon dioxide is high must be discarded [9]. The breath-hold manoeuvre is considered an alternative technique in patients who fail to optimally exhale against resistance and shows similar repeatability to exhalation against resistance if velum closure is achieved [14–20]. Criteria for plateau, repeatability and duration of the manoeuvre are similar to those used for the ER method (figure 2b).

Tidal breathing

The tidal breathing manoeuvre is a non-velum closure method that is feasible in infants and younger children aged <5 years and in adults with poor lung function who cannot hold their breath [14–17, 19–21]. Due to dilution of the air sampled in the nose with air coming from the lower airway, the final result using this method is always lower than the value obtained using velum closure methods (expected 64% (interquartile range: 54–80) that of nNO measured with velum close) [19]. Less than 15% of children

TABLE 2 Report, pitfalls and interpretation of nasal nitric oxide (nNO) measurement

Minimum parameters that need to be included in a nNO measurement report
Analyser model
Sampling rate
Ambient NO
Respiratory manoeuvre used
Two repeatable nNO results from the right nostril
Two repeatable nNO results from the left nostril
Intra-nasal repeatability: ideally exhalation against resistance/breath-hold manoeuvres ⩽10% variation; tidal breathing ⩽20%
Inter-nostril variability: ideally exhalation against resistance/breath-hold manoeuvres ⩽10% variation; tidal breathing ⩽30%
Any technical or other noteworthy comments
Final result (parts per billion, ppb) = highest result from highest nostril (MINUS ambient NO level if >20 ppb)
Final standardised value (nL·min^{-1}) = final result (ppb)×sampling rate of analyser (L·min^{-1})
Pitfalls
False-positive and false negative results can occur in a confirmed PCD patient
Ambient NO level
If the ambient NO level >20 ppb, estimate its effect on the result by subtracting the ambient NO from the patient's NO
If the final result is:
Well above the cut-off, it can be accepted
Close to the cut-off, the measurement should be repeated on another day
Interpretation of nasal NO results
Consider the respiratory manoeuvre, type of analyser and patient age
Exhalation against resistance and breath-hold manoeuvres using either chemiluminescence or electrochemical devices:
The cut-off is 77 nL·min^{-1} with sampling close to 0.3 L·min^{-1}
If nNO <77 nL·min^{-1}:
Ideally perform tidal breathing to exclude a false positive result
Tidal breathing manoeuvre:
Age 1–2 years: the cut-off is 30 nL·min^{-1}
Age >2 years: the cut-off is 44 nL·min^{-1} for mean peaks using a chemiluminescence device
Age >2 years: the cut-off is 40 nL·min^{-1} for mean of 30 s of tidal breathing for all types of devices
For any nNO < cut-off:
Consider repeating the nNO measurement
Further diagnostic testing for PCD is indicated

PCD: primary ciliary dyskinesia.

aged 2–7 years actively cooperate during nNO sampling using velum closure methods [20]. Conversely, it is possible to obtain a measurement in at least 95% of children aged <6 years using the tidal breathing manoeuvre (figure 2c) [17, 18]. With a chemiluminescence device, the mean of three to five peaks manually chosen during regular breathing is calculated. These peaks do not have to be consecutive but should be within 20% or 10 ppb, whichever is greater [18]. If an electrochemical analyser is used, it is only possible to report the result estimated by the machine which is lower than the chemiluminescence result because the former analyser averages sampled nNO while the latter measures the peak values.

To sum up, tidal breathing, breath-hold and exhalation against resistance manoeuvres are the three commonly used methods for nNO sampling requiring minimal, modest and high levels of patient cooperation and ability respectively. The chosen manoeuvre(s) should be undertaken twice in both nostrils in order to evaluate repeatability (figure 2).

What details should be included in the result report?

It is important for the physician to be aware of the minimum information that needs to be included in a nNO measurement report. This information includes technical issues and environmental conditions, all

Laboratory details
Patient demographic information

NASAL NITRIC OXIDE REPORT

Device model:

	Measure 1	Measure 2	% Difference
Date			
Time			
Method			
nNO–Left nare (ppb)			
nNO–Right nare (ppb)			
Internasal difference (%)			
Ambient NO (ppb)			
Sampling rate (L/min)			

Highest nNO reported minus ambient NO if > 20 ppb

Highest nNO (nL/min)	
Quality Grade	
Reference	

PICADAR Score:

Clinical Comments:

For example: respiratory tract infection status, medications at the time of testing

Technical Comments:

For example: deviations from the standard operating procedures, client cooperation

Physician Report:

FIGURE 3 Example of a reporting form for recording nasal nitric oxide (nNO) measurements.

results obtained in both nostrils along with their repeatability, and a final result of nNO measurement in ppb which is calculated as the highest result from the highest nostril minus ambient NO level (mandatory if ambient NO >20 ppb) as shown in table 2. The final standardised nNO value in nanolitres per minute is calculated by multiplying the final result in ppb with the sampling rate of the analyser expressed in litres per minute [22]. To illustrate the calculation, with an ambient NO of 50 ppb, if the final averaged nNO concentration is 450 ppb−50 ppb=400 ppb, using a machine sampling at a rate of 0.33 $L \cdot min^{-1}$, then the final standardised value is 400×0.33=132 $nL \cdot min^{-1}$. To allow between-result comparisons, the sampling rate should be recorded as a subscript of nNO. For example, exhalation against resistance $nNO_{0.33}$=400 ppb or exhalation against resistance $nNO_{0.33}$=132 $nL \cdot min^{-1}$ (table 2 and figure 3).

The confidence for some measurements is higher than for others: *e.g.* exhaled against resistance using a chemiluminescence analyser, with good intra- and inter- nasal repeatability is reliable; tidal breathing, using an electrochemical device without repeatability is less dependable. The Task Force therefore graded the various scenarios in the main document [1].

Nasal NO alone is not a definitive diagnostic tool, as false negative and false positive results can occur. Several factors must be considered when interpreting nNO results with special attention for those influencing nasal NO level (figure 3). First, we emphasise that if the ambient NO is >20 ppb, one should estimate its effect on the result by subtracting the ambient NO from the patient's NO as previously described. If the final nNO measurement is significantly above the cut-off, then it can be accepted. However, if the final nNO result is close to the cut-off (or an accurate result is needed for research purposes), the test should be repeated on another day. Second, the type of respiratory manoeuvre determines the cut-off value used in interpreting the results (table 2). For exhalation against resistance and breath-hold manoeuvres using chemiluminescence or electrochemical devices, the cut-off nNO value for a PCD diagnosis is 77 $nL \cdot min^{-1}$ with a sampling rate of 0.33 $L \cdot min^{-1}$ [22]. It is to be noted that this cut-off established by multicentre studies for the chemiluminescence technique is not confirmed for the electrochemical technique. If the result measured is <77 $nL \cdot min^{-1}$, a tidal breathing manoeuvre may be performed to exclude a false positive result (the tidal breathing value should be lower than the velum close value) [18, 19]. There is limited data for the nNO diagnostic cut-off for a PCD diagnosis using the tidal breathing manoeuvre. Experts from the ERS Task Force suggest the following age-specific cut-offs in favour of a PCD diagnosis; for children aged 1–2 years, 30 $nL \cdot min^{-1}$ with a sampling rate of 0.33 $L \cdot min^{-1}$; for children aged >2 years, 44 $nL \cdot min^{-1}$ for a mean of 3–5 peaks when using a chemiluminescence device, or 40 $nL \cdot min^{-1}$ for mean of 30 s of tidal breathing for all types of devices [1].

Nasal NO for children aged <12 months should not be used clinically because the levels are inherently very low in this age group [13, 21]. In brief, ambient NO, the respiratory manoeuvre, the type of device and the age of the patient are among the various factors that should be considered when interpreting nNO results. Nasal NO is not diagnostic of PCD, and symptomatic individuals with levels below the cut-off should undergoing further diagnostic testing in a specialist diagnostic centre. Furthermore, some individuals with PCD have normal nNO levels, and if clinical suspicion is high, further PCD tests (*e.g.* PCD genetics panel, transmission electron microscopy) should be conducted [6].

Limitations of the technical standard

The ERS technical standard has a few limitations. There is a paucity of data comparing exhalation against resistance and breath-hold techniques and large multicentre studies using electrochemical technique to validate a cut-off with this technique are lacking [1]. In addition, there is no validated cut-off applicable to adult subjects if a higher sampling flow is used (the standard recommends approximately 0.3 $L \cdot min^{-1}$) [22, 23]. Data on nNO measurements for children younger than 4 years of age is scarce [1]. Research in these areas is urgently needed.

Conclusion

Nasal nitric oxide measurement is a fast, non-invasive and accurate test in the PCD diagnostic armamentarium. We summarise the recent ERS task force technical standard to guide physicians and technicians involved in nNO testing. Specifically, we highlight the considerations related to the type of devices, aspects on environmental factors, the respiratory manoeuvres used, reporting, interpretation and limitations. Further research is needed to increase the evidence base of these technical standards.

Key points

- Chemiluminescence analysers are highly accurate, reliable and have been validated in multicentre studies but are less portable and more expensive to purchase and maintain in comparison to electrochemical devices.
- Inherent patient factors including acute viral infections may contribute to falsely low nNO levels, whereas external factors, in particular high ambient NO concentrations, may falsely increase nNO levels.
- Tidal breathing, breath-hold and exhalation against resistance are the three common respiratory manoeuvres used in nNO sampling requiring minimal, modest and high levels of patient understanding and cooperation respectively.
- Standardised reporting of nNO measurement and correct interpretation informs the next clinical steps in the diagnosis of primary ciliary dyskinesia.

Self-evaluation questions

1. In comparison to chemiluminescence devices, electrochemical analysers are more:
    a) Accurate
    b) Portable
    c) Reliable
    d) Expensive
    e) Validated in multicentre studies

2. Which of the following situations can lead to false negative results in nNO testing?
    a) Acute viral respiratory infections
    b) Cystic fibrosis
    c) Fresh blood in the nose
    d) High ambient nitric oxide level
    e) Nasal polyps
3. A 2-year-old presents at your centre for nNO testing. She has been treated with an antibiotic for acute otitis media with rhinitis in the past week. What would be the best action?
    a) Perform the measurement today
    b) Perform the measurement only if the mirror test is positive
    c) Reschedule the test in ⩾3 months
    d) Reschedule the test in ⩾4 weeks
    e) Postpone the test until the child is 5 years old
4. Regarding nNO measurement shown in the photograph in figure 2a, what is/are the characteristic/s of the respiratory manoeuvre used?
    a) Requires tidal breathing against resistance
    b) Gives significantly higher results when NO is measured by a chemiluminescence analyser compared to an electrochemical device
    c) Cannot be checked by real-time NO curve when an electrochemical machine is used
    d) Is ideal for measurements in infants
    e) Is considered unsuccessful if nNO minus ambient nNO is > 77 $nL \cdot min^{-1}$ (at 0.33 $L \cdot min^{-1}$ sampling rate)
5. nNO measured with chemiluminescence analyser 0.33 $L \cdot min^{-1}$ sampling flow, an ambient NO of 49 ppb, during exhalation against resistance, with <10% intra-nasal variation and <10% inter-nostril variation was 281 ppb. Which of the following statements is/are true?
    a) The child does not have primary ciliary dyskinesia
    b) The nNO output is 100 $nL \cdot min^{-1}$
    c) The ambient NO level is within the normal range
    d) The child should be evaluated on another occasion
    e) The intranasal repeatability should be <5%

Acknowledgements: We wish to thank all the members of the ERS Task Force on nasal nitric oxide measurement in children for the diagnosis of primary ciliary dyskinesia for their contribution to the technical standard on which this summary is based. The Task Force comprised: Murielle Colas, Stephanie Davis, Thomas Ferkol, Eric Haarman, Amanda Harris, Claire Hogg, Emma Kilbride, Panayiotis Kouia, Claudia Kuehni, Kim Nielsen, Philipp Latzin, June Marthin, Catherine Pendergrast, Phil Robinson, Nisreen Rumman, Matthew Rutter and Woolf Walker. Diana Marangu-Boore was a junior ERS member on the Task Force; Jane Lucas and Nicole Beydon were the Task Force Chairs.

Conflict of interest: D. Marangu-Boore declares no conflict of interest with the content of this Review. J.S. Lucas reports research and equipment grants paid to her institution from AAIR Charity, LifeArc, Medical Research Council, National Institute for Health Research, and Great Ormond Street Hospital Children's Charity, outside the submitted work. N. Beydon and J.S. Lucas were co-chairs of the Task Force for a technical standard for nasal nitric oxide to diagnose primary ciliary dyskinesia.

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Suggested answers

1. b) Portable
2. d) High ambient nitric oxide level
3. d) Reschedule the test in ⩾4 weeks
4. c) Cannot be checked by real-time NO curve when an electrochemical machine is used
5. d) The child should be evaluated on another occasion