reporting complications of mechanical ventilation. More importantly, the entire process—development of the VAE performance protocol, publication of this protocol in *AnnalsATS*, and the follow-up process—represents an important era in the evolution of performance metrics and clinician accountability in critical care. The combined voice of professional societies representing pulmonary/critical care clinicians as partners with governmental regulatory agencies resulted in the development of performance metrics to be used in clinical accountability programs. Just as importantly, they developed a dynamic partnership so that clinicians remain involved in the evolution and refinement of performance metrics and accountability in the future. This partnership is crucial for ensuring that performance metrics have the highest likelihood of driving improved care for our patients, now and in the future.

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Nasal Nitric Oxide Is an Important Test in the Diagnostic Pathway for Primary Ciliary Dyskinesia

Robust diagnosis of primary ciliary dyskinesia (PCD) is important if patients are to receive appropriate specialist management before irreversible deterioration of lung function occurs. Early diagnosis also enables patients and their families to receive appropriate genetic counseling, disease-specific management of ear and rhino-sinus disease, and screening for PCD-associated problems (e.g., cardiac problems) (1, 2). The association of extremely low levels of nasal nitric oxide (nNO) in PCD has been recognized for over 15 years, and measurement of nNO is increasingly used as a screening test for PCD in Europe (1). The manuscript by Leigh and coworkers in this edition of *AnnalsATS* (3) provides an important advance in the use of nNO for clinical and research purposes. Their data confirm that nNO is a reliable investigation for PCD in the North American population and setting, including identification of "atypical" patients with PCD who might otherwise be missed due to normal ciliary ultrastructure. The authors provide evidence that a standardized protocol using different NO analyzers can be used to reliably differentiate patients with PCD from patients without PCD and from healthy children, in geographically dispersed centers. They have additionally developed cutoff values using data from their large study population, which can now be validated in other populations.

There is no "gold standard" diagnostic test to identify all PCD phenotypes, and diagnostic workup requires access to a number of specialist investigations. Previously, ciliary ultrastructure analyzed by electron microscopy (EM) was considered diagnostic, but there is an increasing literature on normal ciliary ultrastructure, at EM resolution, in PCD. This

indicates that PCD will be missed in centers where diagnosis depends solely on EM (2, 4). It is also recognized that certain EM defects previously considered diagnostic might on occasion represent secondary changes that resolve on repeat testing (4, 5). In Europe, assessment of ciliary beat frequency (CBF) and pattern (CBP) by high-resolution, high-speed video microscopy (HSVm) is recommended as a functional test for PCD (1, 6). If HSVm analysis is abnormal, re-differentiation of basal epithelial cells at an air–liquid interface (ALI) in cell culture enables reassessment of ciliary function and ultrastructure to differentiate primary from secondary dyskinesia (1). Alternatively, immunoflorescent (IF) staining of ciliary proteins can support diagnosis of PCD (7). EM, HSVm, ALI-culture, and IF all require a high degree of expertise in addition to expensive equipment and infrastructure. These techniques are therefore restricted to a few highly specialized centers, limiting easy access to diagnostic testing (8). Diagnosis supported by bi-allelic mutations in genes known to be associated with PCD is promising; currently genotyping detects only 50–65% of patients (2), but as new genes are rapidly identified this will become increasingly sensitive.

The evidence provided by Leigh and coleagues (3) is therefore to be welcomed by clinicians, researchers, and in particular families who are unable to travel to a highly specialized center. It is to be hoped that the U.S. Food and Drug Administration and other regulatory authorities will approve nNO analyzers for clinical use given the evidence that nNO is a reliable screening test for PCD and that valid measurements can be taken at sites geographically distant from a diagnostic center using standardized protocols. Leigh and coworkers report a cutoff value for nNO of 77 nL/min providing sensitivity of 0.98 and specificity greater than 0.999. This cutoff value was validated across six other sites, identifying 70 of the 71 (98.6%) participants with confirmed PCD. A previous study used a cutoff for nNO of 105 parts per billion and reported a specificity of 88%, a sensitivity of 100%, and a positive predictive value of 89% for correctly diagnosing PCD (9).

While there are now substantial data to demonstrate that nNO measurement is helpful in guiding the diagnostic pathway, we need to recognize limitations of this measurement. Standardized methods (10) to measure nNO are not appropriate for younger children, precisely the age group that need targeting for diagnostic measurement. Tidal measurements allow levels to be measured in young infants, although there is limited experience in this younger age group (1, 11, 12).

Patients with other with upper and lower airway diseases have been reported to have reduced nNO levels, although usually not as low as in PCD; such diseases include cystic fibrosis, nasal polyps and chronic sinusitis. A few groups have recently reported normal levels of nasal NO in a minority of patients with PCD (1, 11, 13). These studies highlight that patients with a history strongly suggestive of PCD should not be excluded from further diagnostic evaluation on the basis of nNO, and also that, while providing an excellent screening test, nNO is not diagnostic and low levels should trigger referral to a highly specialized diagnostic center.

A priority for researchers is to understand the cause of the extraordinarily low nNO observed in PCD (14). From a clinical perspective, the next hurdle to overcome is the lack of regulatory approvals of nNO analyzers for PCD diagnosis, as well as the cost and therefore availability of devices. Until recently, the only commercially available analyzers for measuring nNO were nonportable desktop analyzers, which are extremely expensive. More reasonably priced portable machines (15) are now available, although they are not yet fully validated nor approved for clinical use. Manufacturers should be encouraged to develop, validate, and seek approvals for user-friendly, reasonably priced nNO analyzers. This will lead to a step change in the diagnosis of PCD by reliably identifying patients for referral to specialist diagnostic centers.

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