RESEARCH LETTER

The dangers of widespread nitric oxide screening for primary ciliary dyskinesia

ABSTRACT

Primary ciliary dyskinesia (PCD) is underdiagnosed and requires complex testing at specialist diagnostic centres. Measurement of nasal nitric oxide (nNO) has good sensitivity and specificity screening for PCD, but is currently usually measured at PCD centres rather than prior to referral. Proposals to include NO testing for asthma diagnoses could widen access to PCD screening if nasal mode analysers are available. Data from 282 consecutive referrals to our PCD diagnostic centre (31 PCD positive) were used to model predictive values for nNO testing with varying pretest probability and showed that predictive values were good in the referral population, but extending screening to more general populations would result in excessive false positives that may overwhelm diagnostic services. Although nNO remains a useful test, a 'normal' result with classical clinical history should still be considered for further testing.

Proposed asthma diagnosis guidelines from the UK National Institute for Health and Care Excellence include the expansion of exhaled nitric oxide (NO) from a research tool into routine care.[1] This could lead to improved availability of nasal NO (nNO) screening for primary ciliary dyskinesia (PCD).

Exceptionally low nNO differentiates PCD from other respiratory diseases[2] and measurement is recommended as a screening test in symptomatic patients prior to diagnostic testing by high-speed video analysis (HSVA) of ciliary beating, transmission electron microscopy (TEM) of cilial ultrastructure or genetic tests.[3] HSVA and TEM require expensive infrastructure and dedicated scientists; testing is focused in a geographically disparate centre making access for patients difficult. Local screening by measurement of nNO is therefore attractive; however, our data reiterate the importance of continuing rigorous patient selection in applying screening tests (pretest probability). Classical features suggestive of PCD include persistent wet cough, upper airway disease, neonatal respiratory distress and persistent rhinitis.[4]

We analysed nNO levels in 282 consecutive eligible referrals (aged 6–79 years) at our national PCD diagnostic centre (June 2006–December 2013) (see online supplementary methods for details of nNO measurement and PCD diagnosis).[4] Thirty-one out of 282 were PCD positive (11%). A previously published threshold of 77 nL/min[5] was used; a level below this was considered a 'positive test'. Sensitivity in our population was 93.6% (95% CI 78.5% to 99.0%) and specificity was 84.1% (95% CI 78.9% to 88.4%) (table 1). Therefore, in our population the positive predictive value (PPV) was 42.6% (95% CI 30.2% to 54.5%) and negative predictive value (NPV) was 99.1% (96.6% to 99.9%); so approximately 6/10 patients with a positive test did not have PCD. However, predictive values were dependent on the prevalence of the disease in the tested population (figure 1). Previous data from children have suggested that the prevalence of PCD within those with recurrent wet cough is 5%,[6] which would give a PPV of 23.6% and NPV of 99.6%; therefore, this group should be targeted for testing. A recent systematic review of 989 patients with non-cystic fibrosis bronchiectasis found that 9% had PCD, which is a similar proportion to those referred to our service.[7] Therefore, this is a population that could possibly be targeted for screening as long as other clinical features are present. PCD prevalence is around 1:10 000 in the general population,[8] which would reduce the PPV to less than 0.1%, rendering general population screening useless. Additionally, non-specialist centres need to understand how to interpret results; different cut-off values have been used that will result in varying accuracy metrics (table 1). Fractional exhaled NO is also lower in PCD than healthy/disease controls; however, it is less accurate than nNO[9] and its use is not recommended by current PCD diagnostic guidelines.[10]

Table 1 Sensitivity, specificity, PPV and NPV for different screening thresholds used across published studies on nNO diagnostics,[2] but analysed against our data (n=282)

	120 nL/min (%)	77 nL/min (%)	40 nL/min (%)	20 nL/min (%)
Sensitivity	100 (88.8 to 100)	93.6 (78.6 to 99.2)	93.6 (78.6 to 99.2)	77.4 (58.9 to 90.4)
Specificity	68.9 (61.1 to 73.1)	84.1 (78.9 to 88.4)	94.4 (90.8 to 96.9)	97.6 (94.9 to 99.1)
PPV	27.4 (19.5 to 36.6)	42 (30.2 to 54.5)	67.4 (51.5 to 80.9)	80.0 (61.4 to 92.3)
NPV	100 (97.8 to 100)	99.1 (96.7 to 99.9)	99.2 (97.0 to 99.9)	97.2 (94.4 to 98.9)

95% CIs in brackets.
nNO, nasal nitric oxide; NPV, negative predictive value; PPV, positive predictive value.

These results are significant for several reasons. First, a NPV of 99.1% confirms that nNO >77 nL/min is excellent for excluding PCD, although cases of PCD with normal nNO are well documented.[2] Second, although a PPV of 42% makes nNO a poor diagnostic test in isolation, use prior to referral could reduce referrals and patient burden/healthcare costs associated with travel to a distant centre for complex diagnostics; indeed, 211 of our 282 patients would have had PCD correctly 'excluded' by nNO screening. Patients with a particularly strong history would warrant formal testing even with nNO >77 nL/min. Importantly, if nNO is used as a screening test in populations without classical symptoms of PCD, the number of false-positive cases will overwhelm diagnostic services.

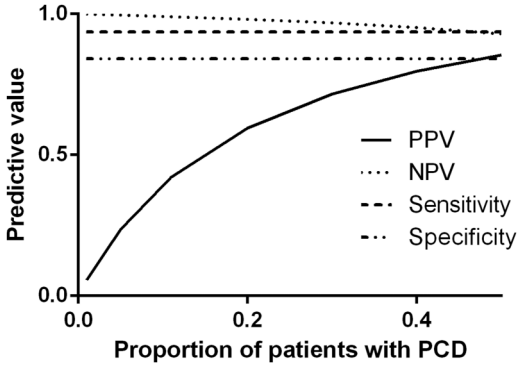

Figure 1 Relationship between PPV and NPV and the pretest probability of PCD (proportion of patients with PCD in the tested population). Sensitivity and specificity shown to illustrate that these are test specific and do not vary with disease prevalence. NPV, negative predictive value; PCD, primary ciliary dyskinesia; PPV, positive predictive value.

PCD is underdiagnosed but increasing awareness and structured diagnostic referral pathways are helping tackle this.[3] Wider nNO use would rely on screening only those with classical symptoms of PCD and adequate competency-based training of those taking/interpreting nNO readings. Our measurements used a 'gold standard' breath-hold method with chemiluminescence analyser. Alternative breathing manoeuvres reduce discriminatory value[2] and portable machines without a 'real-time' nNO trace risk not taking plateau nNO readings. As NO analysers become more widespread, the opportunity for nNO screening at centres without PCD diagnostics is potentially useful if used in correctly selected patients.

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Contributors AH and KG conducted patient testing, LB collated and analysed data, SAC analysed data and drafted the manuscript with JSL.

Competing interests None declared.

Ethics approval Southampton and South West Hampshire Research Ethics.

Provenance and peer review Not commissioned; externally peer reviewed.

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2015-208056).

To cite Collins SA, Behan L, Harris A, *et al*. *Thorax* Published Online First: [*please include* Day Month Year] doi:10.1136/thoraxjnl-2015-208056

Received 11 November 2015
Revised 14 January 2016
Accepted 25 January 2016

Thorax 2016;**0**:1–2.
doi:10.1136/thoraxjnl-2015-208056

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