**Title:** The controversies and difficulties of diagnosing primary ciliary dyskinesia (PCD)

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We welcome the correspondence from Lavie and Amirav1, highlighting the difficulties diagnosing PCD, and the role of high-speed video analysis (HSVA). As members of the European Respiratory Society (ERS) PCD Diagnostic Task Force2 and/or large PCD Centres, we agree that HSVA has an important role which is not recognized by the ATS PCD Diagnostic Guideline3. This risks a large proportion of false negative ‘missed’ diagnoses and a sizable number of false positive cases; we make additional important observations.

We agree with Lavie that nasal nitric oxide (nNO) should not be used in isolation to make a diagnosis, nor to exclude PCD. This risk of ‘false negatives’ is clearly described in the literature (reviewed in2). ERS Guidelines therefore suggest that both nNO and HSVA should be entirely normal before deciding that further investigation is not warranted2. We all have patients who proceeded to further testing because clinical history was strong or HSVA was abnormal despite normal nNO, and then had a diagnosis confirmed by transmission electron microscopy (TEM) or genetics (e.g. *CCDC103, DNAH9* or *RSPH1* mutations). Contrary to Lavie and Amirav, neither ATS nor ERS guidelines would exclude the diagnosis of PCD in patients with a compatible history and diagnostically low nNO despite normal HSVA, without proceeding to further tests including TEM and genetics.

Similarly to Lavie, we were surprised that the ATS guideline specifically suggests *not* assessing ciliary beat pattern. Dyskinesia is a key feature of the condition and can be accurately detected by HSVA4. According to ERS Guidelines, repeatedly dyskinetic cilia or abnormal beat pattern following reanalysis following culture, with normal genetics and TEM, indicates PCD is ‘highly likely’2; patients should follow a PCD treatment plan2. This recognizes that TEM and genetics will each be normal in 20-30%2 of patients who truly have PCD (false negative) and that HSVA will detect most of these patients who require specialist PCD care. Until HYDIN, DNAH11 and GAS8 were discovered as PCD genes, the patients were recognized by abnormal HSVA, and until all genetic causes are identified, HSVA is needed. It also acknowledges that even repeatedly abnormal HSVA may be falsely positive, therefore ERS Guidelines recommended that patients are not labelled as definitely having PCD based on HSVA alone2,4. Importantly HSVA provides an accurate result on the day of testing which can be used to counsel patients and commence treatment whilst awaiting confirmatory TEM and genetics4.

There are a large number of PCD genes and because of their size, variants are common; not infrequently, patients without PCD have bi-allelic variants of unknown significance in PCD-related genes. The specificity of genetic testing is severely reduced, and many individuals could be incorrectly diagnosed with PCD (false positive) unless the mutations are confirmed pathogenic. It is therefore essential to ensure that the genotype is compatible with the ciliary phenotype using TEM, immunofluorescence labelling and/or HSVA, as well as with the clinical phenotype2.

Importantly, there is no perfect way to identify patients for diagnostic testing based on clinical assessment. Lavie outlines the approach proposed by the ATS Guideline, using a four point clinical symptoms score. Having two of four clinical features provides specificity (0.72) ensuring that the diagnostic service only see the most likely cases, but we suggest it has insufficient sensitivity for screening (0.8), meaning that 20% of PCD patients are not tested and will therefore never be correctly diagnosed5. The ERS Guideline provides a flexible approach (‘patients with several typical features’2), or suggests a clinical predictive score called PICADAR, which has good sensitivity and specificity (cut off 4; 0.97, specificity 0.48)6. Thereby, PICADAR may correctly identify 97% who require further testing, whilst not inappropriately overwhelming diagnostic services since approximately 50% of patients will turn out to have PCD. Both scores need validating in primary care settings.

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