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## High-Speed Videomicroscopy Analysis Presents Limitations in Diagnosis of Primary Ciliary Dyskinesia

*To the Editor*:

In response to the letter by Dr. Lavie and Dr. Amirav highlighting the use of high-speed videomicroscopy analysis (HSVA) in a patient with suspected primary ciliary dyskinesia (PCD) (1), we stand by the American Thoracic Society (ATS) PCD diagnostic guideline recommendation. This recommendation specifically states that clinicians should avoid using HSVA as a replacement diagnostic test for transmission electron microscopy (TEM) and/or extended genetic panel testing (2). Although we appreciate the authors' opinion and argument for the use of HSVA as a diagnostic tool in PCD, we have concerns about their anecdotal evidence and reference to publications with methodologic bias.

First, they reference a publication reporting near-perfect sensitivity and specificity of HSVA testing for PCD (3). In this article, randomly selected HSVA case interpretations from blinded experts, at three separate centers in England, are retrospectively analyzed for diagnostic accuracy. This publication has numerous methodologic biases (explained in a recently published letter [4]) that affect data interpretation and likely inflate the diagnostic accuracy. No other publication has examined the diagnostic accuracy of HSVA against PCD genetic testing. Thus, the true diagnostic accuracy of HSVA in the era of PCD genomics remains unclear, but it is likely lower than the values described in that article.

No single diagnostic test can exclude PCD. TEM and genetic testing individually miss approximately 30% of PCD diagnoses. The authors claim that in one case, normal HSVA "helped to determine a diagnosis of PCD in this patient as being highly unlikely," even though the patient had a strong PCD phenotype and repeatedly low nasal nitric oxide (nNO) values. Defects in at least six known PCD-associated genes (*HYDIN*, *CCDC164*, *DNAH9*, *GAS8*, *CCNO*, and *MCIDAS*) result in normal or nondiagnostic HSVA, and more common genes (*DYX1C1*, *RSPH1*, and *RSPH4A*) have unexpected beat patterns for their corresponding axonemal defects, making HSVA nondiagnostic in these cases as well. Despite the well-recognized possibility of PCD with normal HSVA, the authors do not present any TEM or genetic testing results in their case and dismiss this patient from further PCD therapies. Their decision to ignore the repeatedly low nNO values as a consequence of sinus surgeries is concerning, as nNO levels typically increase in non-PCD patients after sinus surgery (5). The ATS PCD guidelines were prioritized to avoid this scenario, in which patients with PCD are dismissed because of false-negative results on a single diagnostic test.

Finally, the authors claim the "simplicity of use and expeditious results" of HSVA should prompt the ATS to reconsider its PCD diagnostic guidelines. However, there is nothing simple about HSVA studies, as they remain nonstandardized in both sample preparation and beat pattern interpretation. Moreover, to avoid secondary causes of dyskinesia giving false-positive results, the European Respiratory Society PCD guidelines also strongly recommend regrowth of ciliary samples at the air–liquid interface before HSVA analysis (6). This arduous, weeks-long regrowth process requires highly specialized laboratory expertise and refutes the claim of "expeditious results," leading to an immediate PCD diagnosis. Most important, no studies have shown that HSVA can be reliably and accurately performed outside of a few expert centers (2).

The ATS PCD diagnostic guidelines are rooted in science with rigorous methodology. Although not perfect, they represent the most rigorous review and analysis of scientific publications on PCD diagnosis and prioritize limiting false-negative diagnoses in which patients will suffer without proper, long-term PCD therapies. Until prospective, well-designed, multicenter studies are completed, the ATS guideline committee cannot recommend HSVA as a clinical diagnostic test for PCD. ■



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## Reply to Shoemark *et al.* and to Shapiro *et al.*

*To the Editor*:

We thank Shoemark and colleagues and Shapiro and colleagues for their thoughtful comments in response to our research letter (1). Shoemark and colleagues represent the European Respiratory Society in its positive position about the value of high-speed video microscopy (HVM) in primary ciliary dyskinesia (PCD), and Shapiro and colleagues represent the American Thoracic Society (ATS) in its negative stand with regard to its worth. How can one bridge this Atlantic Ocean difference in guidelines?

We believe that as with any conflict, the solution lies somewhere in the middle and largely depends on individual perspectives. Furthermore, even with guidelines, physicians should use their common sense and clinical judgment and make their decisions individually on a case-by-case basis (2).

Although the reason for the referral of our case was to determine whether the patient had PCD, the question that arose given the results of the HVM was, would there be any value in pursuing further tests in the evaluation, and would further testing, such as genetic and transmission electron microscopy (TEM) evaluations, make a clinical difference and change the management strategy or clinical decisions? We believe that given the HVM results, the decision to not pursue this further was the correct one. First, both genetic microscopy and TEM are susceptible to a high rate of false-negative results. Second, an abnormal TEM would not assist us, as our patient has chronic rhinosinusitis, in which case secondary TEM abnormalities would be highly likely. And lastly, the few pathogenic genes that were suggested as candidates for normal HVM findings (by Shapiro and colleagues) have either a severe or complete lack of cilia (e.g., CCNO and MCIDAS) or have an altered (albeit subtly) ciliary beat pattern (e.g., HYDIN, CCDC164, DNAH9, and GAS8) (3–9). With normal HVM performed in expert hands, these genetic mutations would have been very unlikely.

Despite the fact that both the ATS and European Respiratory Society guidelines advocate a combination of tests for PCD diagnosis rather than a single test, the ATS contradicts itself in its algorithm when it suggests that there is no need to pursue more testing when a single test (nasal nitric oxide) is abnormal for clinical diagnostic purposes in a patient with a compatible clinical presentation (*see* the ATS guidelines in Figure 1). The ATS explicitly states that further pursuit of more tests in these cases is justified only "for prognostic purposes, for further understanding of the disease, and to suggest potential future therapeutic considerations" (10).

As we noted in our research letter, had we followed the ATS guideline and stopped the evaluation after obtaining an abnormal nasal nitric oxide result, we would have incorrectly diagnosed PCD in our patient.

We stand behind our support for performing HVM in the diagnosis of suspected PCD. The evidence for the use of HVM is not limited to anecdotal reports but rather is derived from several studies that demonstrated its value in PCD (11). We understand that HVM has not been in common use in the United States in the past, and we acknowledge the limitations of the test and lack of standardization. However, we believe that rejecting it as a whole is unjustified. Our center has available devices, available



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