# ABOUT THE AUTHOR

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Dr. Kevan Mehta completed medical school in the United Kingdom, general pediatrics residency and pediatric respirology fellowship at the University of Toronto, and an additional fellowship in pediatric sleep medicine and severe asthma with Sick Kids Hospital in Toronto. Since that time, he has worked as a pediatric respirologist and pediatric sleep medicine physician, first at Sick Kids Hospital and now with McMaster Children's Hospital, in addition to a busy community pediatric sleep clinic in west Toronto. His current practice includes treating children with all types of respiratory conditions including asthma, interstitial lung disease, primary ciliary dyskinesia, sleep apnea, and long-term ventilation. In addition to his clinical work, Dr. Mehta has an active interest in medical education and his research work relates to use of ventilation for children with sleep disordered breathing and long-term ventilation needs due to complex medical illnesses.

# PRIMARY CILIARY DYSKINESIA: A REVIEW

## PATHOPHYSIOLOGY

Primary ciliary dyskinesia (PCD) is a disease involving the cilia of the body. First identified as Kartagener's syndrome (a constellation of findings of chronic sinusitis, bronchiectasis, and situs inversus), the genetic basis has been increasingly uncovered over time. It is now recognized as an autosomal recessive condition due to a mutation in one of several dozen genes, and more is still being discovered as we continue to have ever-expanding access to genetic sequencing technology. These mutations can affect different parts of the creation, structure, or effector mechanisms of the cilia, with the common result being the impairment of ciliary function. Thus, the primary pathology in PCD is immotile or reduced motility of the cilia in various organs, which leads to the principal manifestation of impaired muco-ciliary clearance in the respiratory tract. These cilia are responsible for the constant movement of mucus upwards, often termed the muco-ciliary escalator, to prevent mucus stasis and eliminate the natural collection of airway debris. When this fails, it provides a nidus for bacterial growth, leading to both chronic bacterial colonization and acute bacterial respiratory exacerbations, defined as an acute worsening of respiratory symptoms. In relation to other manifestations, rotary cilia play a role in embryonal development and lateralization of the organs; hence the possibility of situs inversus/ambiguus developing in PCD. Normal ciliary movement is also required for spermatozoan motility, leading to infertility in males with PCD; females can also experience impaired fertility and higher rates of ectopic pregnancy due to reduced ciliary function in the fallopian tubes.

The respiratory cilia are arranged in a so-called 9+2 fashion, where nine paired microtubules form the outer structure, and a central pair are in the middle. The outer doublets have outer and inner dynein arms, that have enzymes for ATP hydrolysis, responsible for converting chemical energy into motility. Radial spokes connect the outer doublets to the central pair for structural stability. Approximately 200 cilia per cell are able to beat directionally in sync, coordinated with cilia in adjacent cells, to generate a "wave" of upward motion (**Figure 1**). Mutations causing PCD have been identified in each of these parts, indicating the complexity of these tiny structures.

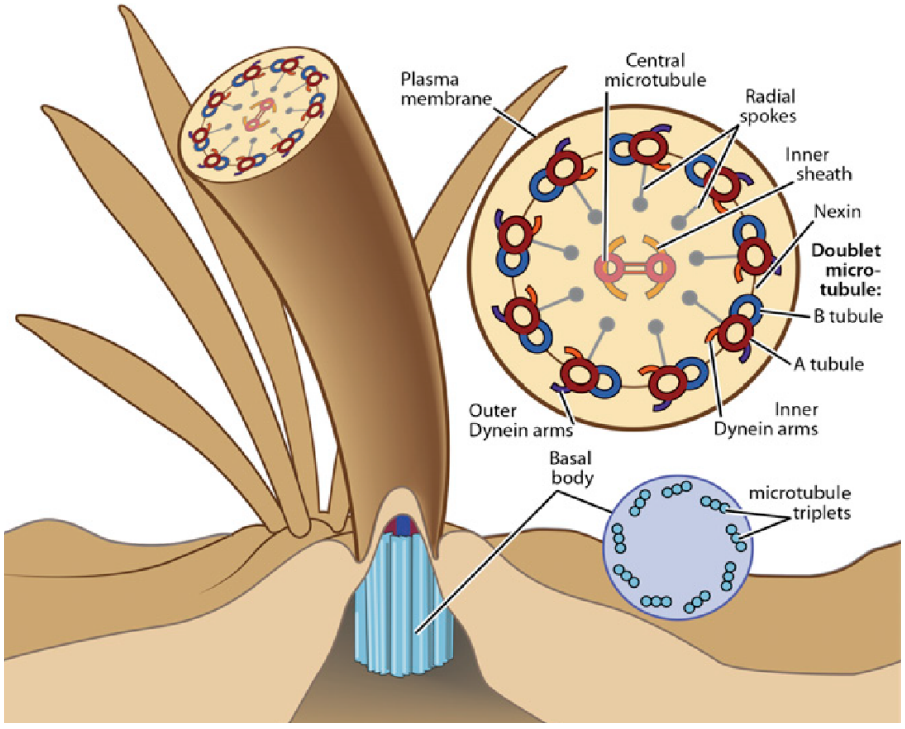


*Figure 1. Normal motile cilia (9 + 2) configuration; adapted from Knowles, M. R.,et al, 2013*

## Epidemiology

The true incidence and prevalence of PCD is unclear owing to the difficulty in establishing a firm diagnosis. Surveys in Norway and Japan have estimated an incidence of 1 per 10,000-20,000 live births[1]. There are also areas of higher incidence due to the genetic characteristics of the population. For instance, in Bradford, United Kingdom, which has a predominantly South Asian population with less genetic variation, incidence rates of about 1 per 2265 have been identified[2]. The true incidence/prevalence rates can also depend on how PCD is diagnosed: up to 70% of patients with likely PCD will have an identifiable genetic mutation while 10-20% of patients with PCD are reported to have normal ciliary ultrastructure on electron microscopy[3].

## Clinical Features

PCD can be missed for many years, as children will present with chronic, intermittently acute, symptoms that require a high index of suspicion from a clinician to connect and form the whole clinical picture (**Table 1**). In retrospect, neonatal distress is present in over 80% of children with PCD, even when born at term, and is often diagnosed as transient tachypnea of the newborn (TTN) or sometimes neonatal pneumonia[4].

**These infants will then suffer from chronic nasal congestion and discharge, with almost 100% developing a persistent, daily wet cough. Through their early childhood years, they will frequently get recurrent acute-on-chronic otitis media, each episode often treated individually without clinicians realizing there may be a connection between them.** They will also begin to present with repeated respiratory infections/exacerbations, treated as asthma and/or pneumonias, again in discrete episodes that may not be connected. These patients may have normal or non-specific findings on chest x-rays, even between illnesses. In one study, children without a laterality defect had a median age of diagnosis of 6 years of age.[9] This means that school age children can present with nasal congestion, cough, sinus issues, etc. and potentially have an underlying diagnosis of PCD that needs to be considered. Sinus issues are also common but with variable onset, as each set of sinuses develop at different ages in young children, leading to chronic sinusitis. By the time these patients reach late adolescence/adulthood, they invariably will have bronchiectasis if not diagnosed early and provided preventative care. It is important to ensure cystic fibrosis (CF) is excluded as an alternative condition causing chronic cough and recurrent respiratory exacerbations in children. In addition to these features, laterality defects are common in patients with PCD (situs inversus or ambiguuus). In adults, infertility may be a presenting symptom, with some patients being diagnosed after they or their partner have struggled to conceive.

## Diagnosis

Controversy exists over the gold-standard method of diagnosis in PCD. Previously, electron microscopy or high-speed video microscopy were considered the diagnostic test of choice. More recently, as the many genetic mutations for PCD have been increasingly elucidated, many guidelines now suggest using a multi-gene panel as the initial diagnostic step. While the microscopic investigation of cilia does not leave one at risk of missing an undescribed/untested mutation, it requires a skilled operator to collect the nasal ciliary biopsy, a capable technician to prepare the sample, advanced equipment, and a knowledgeable pathologist to analyze the sample. Suitable samples for electron microscopy are reported to be collected approximately 60-80% of the time but still with the possibility of false positives/negatives, while genetic testing is thought to now have more than 80% sensitivity. Furthermore, there are debates over the advantages

| When to Suspect PCD (at least 2 of 4 of the following features): |
|---|
| • Unexplained neonatal respiratory distress, especially in term infants |
| • Year-round daily cough starting before 6 months of age |
| • Year-round daily nasal congestion beginning before 6 months of age |
| • Organ laterality defect |

*Table 1. Symptoms that may be indicative of PCD; Adapted from Shapiro et al, 2018*

and disadvantages between the microscopy methods: some structural defects can be absent or hard to identify on electron microscopy, but high-speed video microscopy will show impaired function. Conversely, the moving image on high-speed video microscopy can be difficult to interpret conclusively, while electron microscopy produces static images more easily reviewed. All forms of diagnostic testing can lead to false negatives, making definitive diagnosis challenging (**Figure 2**).

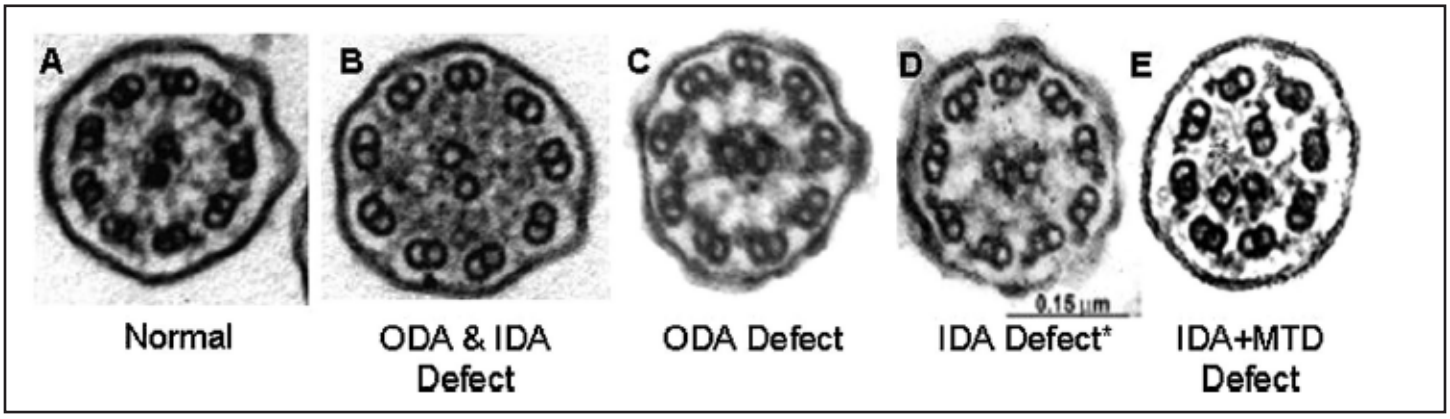


*Figure 2. Electron microscopy findings in primary ciliary dyskinesia Shapiro, A. J.et al, 2015*

There are other tools that can aid in the diagnosis of PCD. For children who are able to perform pulmonary function, nasal nitric oxide may be used as a screening tool, with a level below 77 nl/min showing a sensitivity of about 98% and specificity of 99% for PCD. This method has the advantages of being quick, returning results immediately, and being non-invasive. However, it is not typically used for a definitive diagnosis, with either microscopy and/or genetic testing being subsequently utilized to confirm the diagnosis of PCD. Nasal nitric oxide differs from exhaled nitric oxide. It requires a specific device and a cooperative child (usually having the same criteria as needed for the performance of spirometry). There is some controversy over the best technique, but most well-accepted techniques require the patient to exhale forcefully via the mouth against resistance for several seconds while a tube secured in the nose is connected to the measurement device; some will measure during tidal breathing or breath holding as well. (**Figure 3**). The key is to achieve soft palate closure so nitric oxide concentration from the lungs does not affect that of the nasal cavity/sinuses, which is what is being measured.

*Figure 3. Pediatric patient using nasal nitric oxide; Davis, Stephanie D., Ernst Eber, and Anastassios C. Koumbourlis, eds. Diagnostic tests in pediatric pulmonology: Applications and Interpretation. Springer, 2014.*

In older children and adults, a sputum culture is also sometimes utilized as a partially useful screening tool. While non-specific, the presence of certain bacteria like *Pseudomonas aeruginosa* is unusual in a patient without impaired muco-ciliary clearance issues or immunodeficiency, and so it can help to raise the suspicion of PCD, among other potential conditions. More commonly, sputum cultures in children with PCD are found to have *Hemophilus influenzae, Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. Mycobacterial cultures showing the presence of non-tuberculous mycobacterium can also point towards an underlying diagnosis (**Figure 4**).

## AMERICAN THORACIC SOCIETY DOCUMENTS

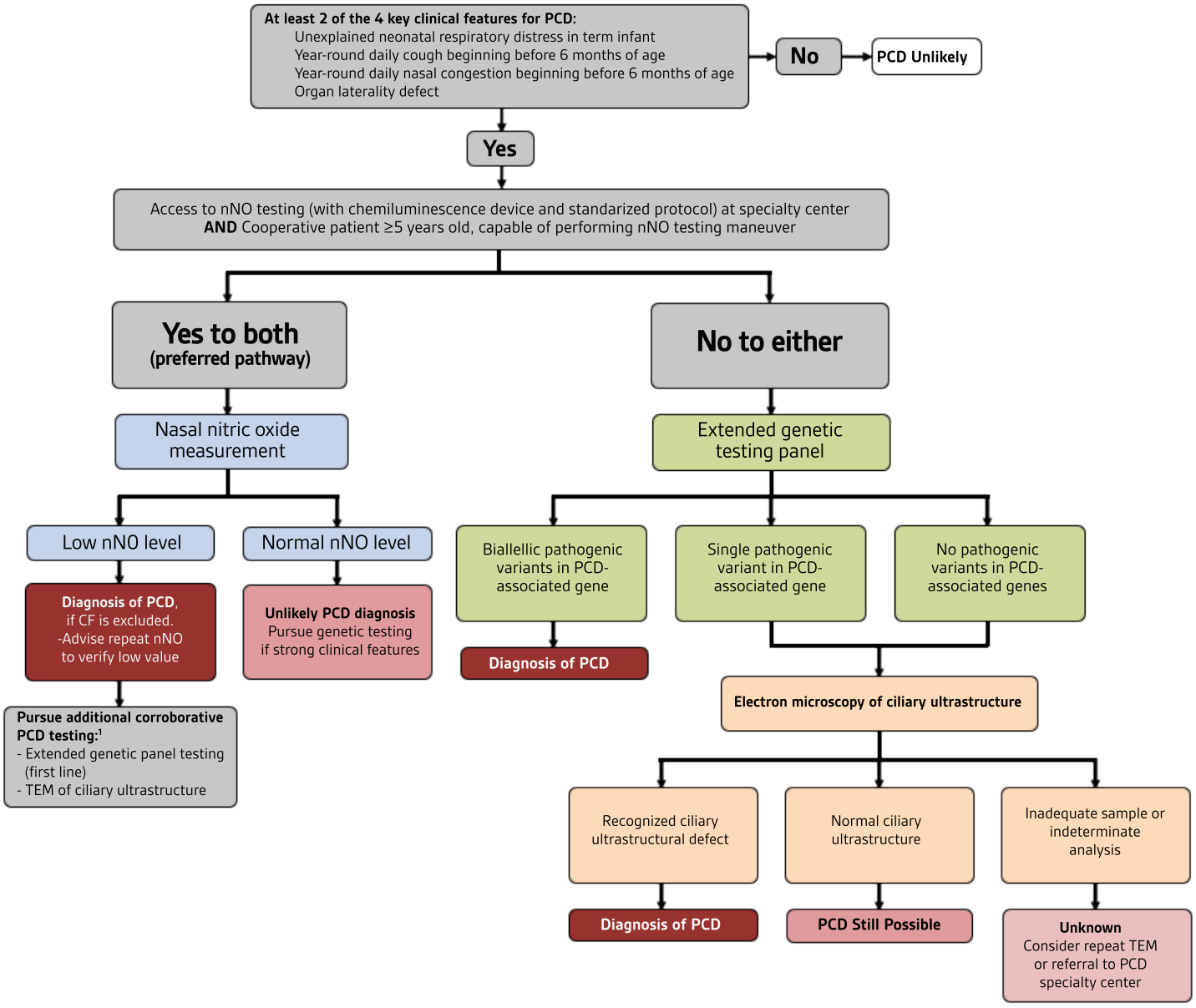


*Figure 4. Suggested diagnostic algorithm for evaluating the patient with suspected primary ciliary dyskinesia ; adapted from Shapiro, A. J. et al, 2018*

## Management

The approach to patients with PCD focuses significantly on **preventative** care. Many of the treatments utilized extrapolate evidence from other muco-ciliary clearance disorders, primarily cystic fibrosis. First and foremost, patients should be monitored on a regular basis: this includes clinical review, throat swab (infants) or sputum (older, capable children) surveillance cultures, and pulmonary function (in those able to perform); mycobacterial cultures are also collected at regular intervals given the higher incidence of non-tuberculous mycobacteria in patients with PCD and the possibility of this affecting isolation status and treatment. A key indicator for current health status and risk of progression is the forced expiratory volume in one second (FEV1), which is typically done at every visit; these children will generally have an established baseline FEV1 with deviations from this leading to investigations and treatments as clinically indicated. If measured early in the disease process, the FEV1 and spirometry is often normal, as it is well known that FEV1 is not a very sensitive measure for early disease and/or damage.[10] A new test, the multiple breath washout (MBW) test, is showing promise at being more sensitive for early change but is not widely available, as it is mainly a research tool currently. The most common abnormality, if present, is a reduced FEV1 with an obstructive pattern, like that seen in asthma (which is why it can sometimes be misdiagnosed as asthma). As the data continues to emerge it is thought that these patients start with similar spirometry as their peers early in life and deteriorate faster (than natural age-related loss), but this can be somewhat mitigated with early diagnosis and management.[11] Added emphasis is given to immunizations in these children, especially influenza and pneumococcal vaccines. Mucolytic (e.g. inhaled dornase-alpha) and osmotic agents (e.g. inhaled hypertonic saline) are also frequently employed in preventative care for children with PCD, determined by their severity and progress. Daily chest physiotherapy is also recommended to aid mucus clearance: infants are often started on percussion chest physiotherapy with progression to airway-based techniques appropriate to the child's developmental age, eventually utilizing positive expiratory pressure devices. Patients demonstrating exacerbations should be treated promptly and effectively to minimize airway damage and risk of bronchiectasis; specific antibiotics are usually started based on the patient's known microbiology from their surveillance cultures while awaiting results from a culture taken at the time of the exacerbation, and adjusted, if necessary. Patients with PCD are prone to develop respiratory bacteria with antibiotic resistance, which greatly impacts antibiotic choice. Depending on the severity of the exacerbation, the majority are treated with oral antibiotics as outpatients, while a proportion of these children will require admission and intravenous antibiotics for more significant illness. They may also be prescribed inhaled antibiotics on a routine basis, using the same guidelines as children with cystic fibrosis, to reduce exacerbations from pathogenic bacteria that have colonized the airway. Additionally, there is a role for anti-inflammatory therapies, such as macrolide antibiotics, in preventative care for some children with PCD, with evidence similar to that of cystic fibrosis emerging in people with non-CF bronchiectasis.[5]

In those having more significant disease, chest computerized tomography (CT) scans may be required to characterize degree of lung disease/bronchiectasis and guide the intensity of therapy; there is generally no recommendation for routine CT scanning in all patients with PCD. In children, it is advisable that these CT scans take place in a centre with pediatric expertise to ensure: the most appropriate CT protocols are used (to gather the correct sequences, minimize radiation exposure, etc.), access to safe sedation if required, and suitable radiologist interpretation. Those with severe disease may be candidates for partial lung resection (localized disease) or lung transplantation (end-stage diffuse disease).

Given the complex and chronic nature of care for these patients, it is recommended that they are seen in a centre with appropriate expertise and multidisciplinary care. The healthcare team for these children may include physicians of many sub-specialties, nurses, nurse practitioners, respiratory therapists, physiotherapists, dietitians, social workers, and others to ensure a holistic approach to the child with PCD.

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