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TITLE:
Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review

ABSTRACT:
Primary ciliary dyskinesia (PCD) is a genetically heterogeneous, rare lung disease resulting in chronic oto-sino-pulmonary disease in both children and adults. Many physicians incorrectly diagnose PCD or eliminate PCD from their differential diagnosis due to inexperience with diagnostic testing methods. Thus far, all therapies used for PCD are unproven through large clinical trials. This review article outlines consensus recommendations from PCD physicians in North America who have been engaged in a PCD centered research consortium for the last 10 years. These recommendations have been adopted by the governing board of the PCD Foundation to provide guidance for PCD clinical centers for diagnostic testing, monitoring, and appropriate short and long-term therapeutics in PCD patients. Pediatr Pulmonol. 2016;51:115–132. © 2015 The Authors. Pediatric Pulmonology Published by Wiley Periodicals, Inc.

INTRODUCTION:
Primary ciliary dyskinesia (PCD) is a genetically heterogeneous, rare lung disease causing chronic oto-sino-pulmonary disease and irreversible lung damage that may progress to respiratory failure.1, 2, 3 Recently, significant progress has been made in PCD diagnosis,4 yet few physicians outside of highly experienced PCD centers are skilled in recognizing the characteristic clinical phenotype and interpreting diagnostic tests.5, 6, 7, 8, 9 Patients often receive false-positive or false-negative PCD diagnoses, as physicians are unaware of the pitfalls commonly encountered with ciliary electron microscopy,10, 11 PCD molecular genetic panels,12, 13 ciliary motility studies,14, 15, 16 and nasal nitric oxide testing.17, 18 Furthermore, PCD is often missed when respiratory symptoms are present in patients with other complex diseases involving cilia, such as heterotaxy and various genetic syndromes.19, 20, 21, 22 From a therapeutic perspective, there are no prospective, randomized clinical trials on monitoring or treating PCD. Thus, physicians treating PCD adapt therapeutic approaches used for other chronic respiratory diseases, such as cystic fibrosis (CF) and non-CF bronchiectasis. Differences in various phenotypic parameters among PCD, CF, and non-CF bronchiectasis suggest that extrapolating therapies may not be appropriate for PCD management in some circumstances.23, 24, 25, 26

Because of the uncertainty surrounding diagnosis and management of PCD, physicians from the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) created this consensus statement to guide new North American PCD clinical centers endorsed by the PCD Foundation. The GDMCC includes clinicians at nine academic centers in North America that have systematically evaluated over 1,000 patients suspected of having PCD and performed longitudinal studies of pediatric patients with a confirmed diagnosis of PCD. The GDMCC also works closely with the PCD Foundation on research and clinical PCD projects. This consensus statement is evidence based where possible, and addresses key clinical PCD issues, but it is not the product of GRADE recommendations.27 Through telephone conferences, email communications, and in person meetings, eight pediatric pulmonologists, two adult pulmonologists, and two otolaryngologists from North America undertook to: (1) describe the PCD clinical phenotype, (2) establish standard PCD diagnostic recommendations, (3) recommend PCD clinical care and long-term monitoring schedules, and (4) outline clinical therapies used to manage PCD. After a literature review (using Pubmed and Embase), drafts were created and circulated iteratively to participating physicians with discussion of feedback and suggestions over sequential telephone conferences and electronic communications. Participating GDMCC physicians and the PCD Foundation governing board unanimously approved this consensus statement.

PCD CLINICAL PHENOTYPE:
Clinical symptoms in PCD affect the entire respiratory tract; the majority of symptoms occur on a chronic, daily basis and start soon after birth (Table 1). At least 80% of newborn babies with PCD develop neonatal respiratory distress despite a full-term gestation, with increased work of breathing, tachypnea, and prevalence of upper and middle lobe atelectasis on chest

radiographs.28 Most PCD patients are well immediately after birth, but develop respiratory distress at 12–24 hr of life (as opposed to other causes of respiratory distress in term neonates (e.g., transient tachypnea of the newborn—TTN), which often present in the first few hours after birth). A small proportion of PCD patients are discharged home on day 1 of life but are then hospitalized with respiratory distress within the first few weeks of life. Often misdiagnosed with TTN or pneumonia, PCD infants frequently require supplemental oxygen for days to weeks. When neonatal respiratory distress appears, particularly with situs inversus totalis or other situs anomalies, PCD should be investigated.
At least 80% of PCD patients also have year-round, daily nasal congestion (or chronic sinusitis in older children and adults), which appears in early infancy and does not resolve with changes of season or between viral infections. Nasal polyps can occur in PCD,29 and nearly all PCD patients demonstrate severe pansinusitis on computed tomography (CT) scan.4

Persistent, year-round, daily cough from early infancy is present in nearly 100% of PCD patients.4 The cough is usually wet and productive, even in infancy, yet occasionally patients report dry cough. The cough can partially improve with antibiotic therapy, but does not resolve with therapy or changes of season. Conversely, episodic cough alternating with symptom-free periods is unlikely to be from PCD.
A spectrum of organ laterality defects occur with PCD, including situs inversus totalis (SIT—mirror-image arrangement) and situs ambiguus (SA—arrangement falls somewhere between normal and mirror image; Fig. 1). SA may be associated with complex congenital heart disease (known as heterotaxy), yet mild cardiac septal defects can also occur with PCD. SIT occurs in slightly less than 50% of PCD patients,30 whereas SA occurs in at least 12% of PCD.19 Subtle laterality defects (e.g., intestinal malrotation, interrupted inferior vena cava, or polysplenia) may be undetected in PCD patients without further imaging studies, such as abdominal ultrasound, spleen scan, or echocardiogram. In patients with chronic oto-sino-pulmonary disease and any organ laterality or cardiac defect, PCD should be considered.
Recurrent otitis media (ROM) with chronic middle ear effusion affects at least 80% of children with PCD, particularly in the first year of life.31 Complications of ROM may include multiple sets of pressure equalization tubes, conductive hearing loss, speech/language delay, or need for hearing aids.32 Chronic middle ear disease is quite common in the general pediatric population; thereby, ROM alone is insufficient to warrant further PCD testing. The absence of ROM goes against, but does not rule out, a diagnosis of PCD.
Recurrent pneumonia or bronchitis is common in PCD; however, some infants will lack this history due to frequent antibiotics for nasal discharge and otitis media. By preschool age, up to 80% of PCD patients have recurrent lower respiratory tract infections.4 Bronchiectasis, predominantly affecting the middle and lower lobes,33 is an age-related finding in PCD, with 50% of children having bronchiectasis by 8 years of age and nearly universal presence in adults.34, 35 In adults with PCD, the combination of bronchiectasis and chronic sinusitis may be the most readily identifiable PCD-related features because adults with PCD may not be able to recall age of onset of early childhood symptoms.
Finally, infertility occurs in nearly 100% of adult males with PCD, while females with PCD also have reduced fertility. The structure in both sperm tails and the fimbriae of fallopian tubes are almost identical to those in respiratory cilia. Thus, males with PCD have diminished fertility through reduced sperm motility,36 while females with PCD have increased risk of ectopic pregnancy from abnormal fallopian transit of oocytes.37

All of the above features may not be seen in each individual patient with PCD; however, most patients have 3 or more of the above features. The combination of multiple distinct clinical features of PCD (neonatal respiratory distress, chronic wet cough with recurrent lower respiratory infections and bronchiectasis, chronic nasal drainage with pansinusitis, recurrent otitis media particularly in childhood, laterality defect, and male infertility) markedly increases the likelihood of a PCD diagnosis.

Respiratory Epithelial Biopsy With Electron Microscopy ::: Diagnostic Tests ::: APPROACH TO DIAGNOSING PCD:
Respiratory epithelial biopsy with EM processing for ultrastructural examination of ciliary axonemes is a proven technique for PCD diagnosis39 and is recommended as part of a panel of diagnostic tests for PCD. Disease causing EM defects in the outer dynein arms,40 outer and inner dynein arms,41 inner dynein arms with microtubule disorganization,42 radial spokes,43 or central

apparatus44, 45 provide confirmation of PCD diagnosis (Fig. 2). However, EM studies with normal ciliary ultrastructure do not rule out PCD, as certain PCD gene mutations can result in normal ultrastructure,10, 38, 46 or subtle abnormalities (particularly those involving the central apparatus and radial spokes) that are not readily recognized on EM.47, 48 Additionally, repeat biopsies that fail to demonstrate any respiratory cilia could represent an oligociliary defect causing PCD.49, 50

It is estimated that EM will detect approximately 70% of all PCD cases,4 but in centers inexperienced with EM processing and interpretation, this percentage will be notably less. Centers lacking extensive experience with ciliary EM processing and interpretation should strongly consider referring patients to a PCD Foundation clinical center for PCD investigations. At least 20–50 clear ciliary cross-sections are required for a diagnostic EM study, and diagnostic abnormalities should be consistently demonstrated on cross sectional images from multiple different cilia to be considered disease causing. Physicians may try nasal corticosteroids, nasal saline lavages, or systemic antibiotics for persistent nasal symptoms interfering with biopsies, but these practices are unproven and may not improve biopsy yield. Furthermore, it is essential that biopsies are collected when patients are at their baseline health, as secondary changes in ciliary ultrastructure can occur during respiratory exacerbations.15 Thus, biopsies should be delayed until at least 2 weeks after full recovery from an illness. For absence of inner dynein arms in isolation, repeat biopsy and EM studies are always required to verify that this pathologic change persists and therefore is more likely genetic (primary) and not from secondary causes.11 One may also consider repeat biopsies to verify the universality and permanence of findings suggestive of central apparatus, radial spoke, or inner dynein arm with microtubule disorganization defects. Patients with EM studies consistent with PCD should be referred to a PCD Foundation Clinical Center for confirmation.

Nasal Nitric Oxide Measurement ::: Diagnostic Tests ::: APPROACH TO DIAGNOSING PCD:
Measurement of nasal nitric oxide (nNO) by chemiluminescence analyzer is recommended as part of a panel of diagnostic tests for PCD in adults and children ≥5 years old.18 This test is sensitive, rapid, non-invasive, and results are immediately available. Nasal NO values are more reliable in school aged children and adults because these patients can cooperate with blowing into a resistor. Tidal breathing techniques for nNO measurement in children <5 years old are currently being investigated,17 but PCD diagnostic cutoff values for tidal techniques are not currently available. Unfortunately, chemiluminescence devices are limited to research settings in North America, but they are gaining acceptance as a clinical tool in various countries across Europe, through efforts by the BESTCILIA PCD consortium.51 Handheld electrochemical nNO analyzers are affordable and portable, but with only limited prospective study in PCD,52, 53 these devices are not currently recommended for PCD testing.
Nasal nitric oxide values are extremely low in PCD.54, 55 Using a nNO cutoff value <77 nl/min, one will detect PCD, resulting from ciliary axonemal defects or mutations in DNAH11, with sensitivity and specificity of 98% and >99%, respectively, if CF has been ruled out (Figure 3).18 Values well above this cutoff level significantly decrease the likelihood of PCD. However, clinicians still must consider PCD when confronted with an appropriate clinical phenotype for PCD and nNO values above 77 nl/min, as forms of PCD with nNO values above this cutoff have rarely been reported.56, 57 Very low nNO levels (below 77 nl/min) can occur during acute viral respiratory infections and in approximately 30% of patients with cystic fibrosis; therefore, nNO testing must be performed when the patient has fully recovered from a viral illness and after diagnostic testing to rule out cystic fibrosis.58 Other conditions can also result in nNO levels below PCD cutoff values (i.e., HIV,59 panbronchiolitis,60 non-atopic sinusitis61). Lastly, nNO device operators must be well trained and use standard operating protocols to avoid false results.18

Functional Ciliary Beat/Waveform Analysis With High Speed Videomicroscopy ::: Diagnostic Tests ::: APPROACH TO DIAGNOSING PCD:
Ciliary biopsy with examination of cilia waveform by high speed videomicroscopy can provide confirmation of PCD, and this test is recommended as part of a panel of PCD diagnostic tests, but only in centers highly experienced with this technology.62 Functional ciliary analysis is difficult to perform correctly, and considerable experience is necessary to avoid false-positive and false-negative results. Biopsies should only be performed when patients are in their baseline state of health. Repeat biopsies are required to assure abnormal beat patterns are not due to secondary processes, such as viral illness,63 tobacco or environmental exposures,64 poor biopsy

specimen,16 or improper biopsy processing.14 Some European centers also maintain biopsied epithelial cells in culture for weeks, at an air-liquid interface, to remove influence of secondary insults.15 There are no prospective studies examining inter-rater agreement for functional ciliary analysis. Currently, there are no American centers that can reliably perform this testing, yet several skilled European centers regularly employ this test.

Immunofluorescence Testing for Ciliary Proteins ::: Diagnostic Tests ::: APPROACH TO DIAGNOSING PCD:
Immunofluorescence testing (IF) using antibodies to detect missing dynein arm proteins along the ciliary axoneme can help confirm PCD as part of a panel of PCD diagnostic tests.65, 66 Through staining of specific ciliary proteins (DNAH5, DNAI2, DNALI1, and RSPH4A/RSPH1/RSPH9), which are essential for overall dynein arm and radial spoke head assembly, IF can detect various outer dynein arm, inner dynein arm, and radial spoke defects, even when other (often less integral) ciliary protein deficiencies are the primary cause of PCD.42, 67, 68, 69, 70, 71, 72 Although IF is currently limited to a few centers, it has been shown equivalent to EM analysis for detecting outer dynein arm defects, caused by DNAH5, in a small (n = 16), blinded study.66 Additionally, IF diagnostic results do not seem to be affected by secondary insults.73 Further investigations are required to evaluate the sensitivity and specificity of IF against other PCD diagnostic tests.

PCD Genetic Testing ::: Diagnostic Tests ::: APPROACH TO DIAGNOSING PCD:
Genetic testing for disease-causing mutations associated with PCD is recommended as part of a panel of diagnostic PCD tests. There are currently 33 known genes associated with PCD (Table 4), with new genes being discovered at a rapid pace.8, 12, 13, 74 Almost all of these genes follow autosomal recessive inheritance (with exception of two rare, X-linked syndromic genes RPGR and OFD1—see section on “Diseases that co-exist with PCD”); therefore, two disease-causing mutations must occur in the same PCD gene for a diagnosis. No documented cases of digenic inheritance (heterozygous mutations in two different PCD genes), unequivocally associated with human PCD, exist thus far. Currently, the most comprehensive commercial PCD genetic panel tests 19 PCD genes through next generation sequencing (NGS), at a cost of $1,990, and detects approximately 50% of PCD cases.75 Genetic testing costs for other commercial NGS panels range from $1,500 to $4,500 and often include full cystic fibrosis transmembrane regulator (CFTR) protein analysis.76, 77, 78 Results may contain genetic variants of unknown significance, and a genetic diagnosis may not be clearly established. Thus, genetic counselling is recommended. Any patients with genetic studies that provide unclear diagnostic information should be referred to a PCD Foundation Clinical Center for further investigations.

Tests Not Recommended for PCD Diagnosis ::: APPROACH TO DIAGNOSING PCD:
Several older diagnostic tests are no longer recommended for PCD evaluation (Table 5), including nasal saccharin testing,79 ciliary beat frequency calculation,62, 80 and visual assessment of ciliary motion without high speed recording devices. Each of these tests has significant limitations, which can lead to frequent false positive or false negative results, especially in uncooperative children; thus, these tests are not appropriate for PCD diagnosis. Radioaerosol mucociliary clearance testing is potentially useful to rule out PCD.81, 82 Although this test remains limited to a few expert centers, requires a level of patient cooperation suitable for children >7 years old, and cannot distinguish secondary ciliary dysfunction, it may help to rule out PCD with a normal result.

Other Chronic Respiratory Conditions to Consider ::: APPROACH TO DIAGNOSING PCD:
The clinical symptoms associated with PCD often overlap with other common pediatric and adult respiratory diseases (Table 6). Each of these other diseases should be considered in patients with chronic oto-sino-pulmonary symptoms; however, investigations should only be pursued when the clinical picture suggests their presence. Thus, PCD is not a diagnosis of exclusion.
Sweat testing or cystic fibrosis genetic testing are recommended when evaluating patients for PCD, as both diseases can present with similar phenotypes83 and produce nNO levels below the PCD diagnostic cutoff of 77 nl/min.58 Immunodeficiency can also present similarly to PCD,84 and in patients with suspected PCD, laboratory studies investigating immunodeficiency are necessary. Preliminary study of nNO in certain humoral immunodeficiencies has shown normal values well above 77 nl/min,85 but further study is required to know if all forms of immunodeficiency produce normal nNO levels.

Pulmonary aspiration, with or without gastroesophageal reflux, can cause chronic respiratory symptoms in adults and children, including cough, wheeze, bronchitis, or pneumonia.86, 87 Thus in patients with possible PCD, a thorough feeding history is essential. A history of chronic cough from asthma can also resemble PCD in young children, especially with frequent viral infections from daycare exposures. Additionally, chronic nasal congestion from allergic rhinitis can seem similar to PCD rhinosinusitis. However, PCD nasal disease is present year-round and does not resolve with seasonal change, as often occurs with allergic rhinitis. Lastly, protracted bacterial bronchitis (PBB) is a disorder of preschool aged children causing >3 weeks of wet cough with lower airway bacterial infection and airway neutrophilia.88 In general though, the characteristic, year-round, daily, often wet or productive cough of children with PCD usually distinguishes them from these other conditions.

Diseases that Co-Exist With PCD ::: APPROACH TO DIAGNOSING PCD:
PCD can rarely co-exist with other rare disorders (Table 7). Retinitis Pigmentosa (an inherited cause of blindness from retinal ciliary dysfunction) and Orofaciodigital Syndrome (including mental retardation, craniofacial abnormalities, macrocephaly, digital anomalies, and cystic kidneys) are X-linked disorders involving ciliary genes, RPGR and OFD1, respectively.21, 89 Although these account for a very small minority of PCD cases, there may be further overlap of retinal and respiratory cilia.90, 91 Thus, retinal examination is recommended in individuals with PCD due to gene mutations in RPGR, clinical visual disturbances, or a family history of Retinitis Pigmentosa, whereas PCD patients with OFD1 phenotypes should be referred for genetic consultation.
Various diseases caused by genetic disorders of non-motile cilia can result in cystic kidneys, cystic or cholestatic liver, skeletal malformations, developmental delay, hydrocephalus, blindness, or deafness. These include Joubert Syndrome, Bardet–Biedl syndrome, Usher Syndrome, Jeune Syndrome, polycystic kidney disease, and others. The overlap of these non-motile ciliopathies with respiratory cilia dysfunction is unusual, and poorly understood at present,90, 92, 93 but increased rates of bronchiectasis are found in polycystic kidney disease.94 Therefore, consultation with a geneticist or other subspecialists is recommended when patients with possible PCD have features of non-motile ciliary dysfunction.
PCD can also co-exist with other rare diseases through close proximity of disease causing mutations at the same chromosomal locus (Table 7). Cri du Chat syndrome can occur with PCD due to a large deletion on chromosome 5p and a point mutation in DNAH5 on the remaining chromosome.22 Glanzmann Thrombasthenia (associated with ITGB3) can occur with PCD (associated with CCDC103) through mutations in the neighboring genes on chromosome 17.95 Alternatively, PCD can co-exist with other rare diseases through disease-causing mutations which are not in close genetic proximity; such as cystic fibrosis due to mutations in CFTR (Chr7q) with PCD due to mutations in DNAH11 (Chr7p),96 and Miller Syndrome due to mutations in DHODH (chr 16) with PCD due to mutations in DNAH5 (Chr5).97

Recent publications have also shown respiratory ciliary dysfunction in patients with mild forms of congenital heart disease, not meeting cardiology definitions for SA or heterotaxy.98 Thus, physicians should ask about chronic oto-sino-pulmonary symptoms in all patients with congenital heart disease to screen for possible PCD and test as indicated.

Pulmonary Care and Monitoring ::: CLINICAL CARE AND LONG-TERM MONITORING:
Long-term follow-up should be in a PCD Foundation clinical center or an accredited cystic fibrosis center that has a comprehensive, multidisciplinary team approach to care. Outpatient visits with a pulmonologist experienced in management of chronic suppurative lung disease, such as cystic fibrosis, are recommended 2–4 times annually (Table 8). Surveillance cultures of expectorated sputum or oropharyngeal cough swabs are recommended two to four times annually in all PCD patients.1 Although the most common airway pathogens in children with PCD are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, surveillance cultures should be processed in the same manner as cystic fibrosis cultures, including examination for Pseudomonas aeruginosa and other Gram negative organisms, as well as non-tuberculosis mycobacterial (NTM) organisms.1, 4 Culture results should guide antibiotic therapy during future respiratory exacerbations. When PCD patients are not responding to culture-directed antibiotics, physicians should consider additional NTM and fungal cultures, allergic bronchopulmonary aspergillosis testing (ABPA) testing (IgE levels ± evidence of aspergillus specificity) and bronchoscopy with bronchoalveolar lavage fluid cultures to guide antimicrobial therapy.

Spirometry using ATS/ERS criteria99 is suggested two to four times annually to follow disease progression in PCD. Although spirometry may not be the most sensitive test of pulmonary function in PCD, it is the most available testing method in pediatric and adult centers. With further validation, other tests of pulmonary function, such as multiple breath washout, may be useful in PCD.100, 101

Chest radiography should be performed at diagnosis and during respiratory exacerbations, as indicated. Otherwise, chest radiography should be performed every 2–4 years in stable patients, in order to monitor disease progression. The decision to use serial CT scans for monitoring PCD disease progression should be decided on a case by case basis, and the lowest possible radiation doses should be used. However, a chest CT scan is generally recommended at least once after diagnosis to detect bronchiectasis, which may encourage better compliance to airway clearance in patients and parents who are aware of this finding. Chest CT can be considered when children are old enough to cooperate (and avoid sedation), and images will be of sufficient quality to diagnose bronchiectasis, or sooner depending on clinical symptoms.33, 34 Some centers perform chest CT scans on PCD patients every 5 years, but there is no evidence that this improves clinical outcomes,102 and cumulative radiation doses need to be considered for PCD patients.
Infection control policy is essential for clinical care in PCD, and general hospital infection control policies should be followed where PCD patients receive care. Patients with resistant organisms on sputum culture should be specifically targeted for infection control in all clinical areas. Although there is no evidence for cross contamination of respiratory organisms among PCD patients, it is logical to assume this may occur, as it does in similar diseases.103 More stringent infection control policies have the potential to cause psychosocial harm to patients and families,104 and thus should be avoided in PCD. However, this recommendation may be adjusted if there is clear evidence for risks that outweigh potential harm.

Otolaryngology Care and Monitoring ::: CLINICAL CARE AND LONG-TERM MONITORING:
Pediatric PCD patients should visit a pediatric otolaryngologist at least once to twice annually, while adult patients should have otolaryngology care, as needed. An initial audiology assessment in all PCD patients is suggested at diagnosis, with subsequent evaluations coordinated through their otolaryngologist. The major otolaryngology concern in PCD patients is the nearly universal conductive hearing loss due to persistent otitis media with effusion (OME).105 Hearing abnormalities often improve in adolescence, but in some cases, continue into adulthood. Pressure equalization tubes (PET) are advocated for children with PCD who have hearing deficits or speech delay and middle ear effusions. Although several systematic reviews have cast doubt on the utility of PET in OME,106, 107 these studies are not necessarily generalizable to a PCD population, where individuals are expected to have greater portion of their prelingual life with conductive hearing loss. In studies assessing hearing in children with PCD post-PET placement, hearing normalized in 80–100% of participants.32, 108, 109 In another study examining surgical treatment with PET versus medical management alone in PCD, children with PET had larger hearing improvements post-operatively than those treated with medical therapy.108

All patients undergoing PET insertion should be counselled on the likelihood of multiple insertions, post-operative otorrhea, and the possibility of a permanent tympanic membrane perforation (up to 50% in one study).110 Additionally, patients with PET are typically seen by their otolarygologist every 3–6 months while the tubes remain in place.107 Although some physicians avoid PET in PCD for fear of prolonged post-operative otorrhea, studies show that post-operative otorrhea in PCD is no worse than the general population111 and is easily controlled with topical therapies.109 Persistent otorrhea can be attributed to biofilm formation, especially in children with longer lasting PET112; however, given the poor eustachian tube function and multiple PET insertions, acquired cholesteatoma should also be considered as a potential cause of persistent otorrhea in PCD.
Otolaryngologists should also monitor for chronic rhinosinusitis (CRS) in PCD patients. CRS is estimated to affect over 50% of patients with PCD31 and nasal endoscopy (as permitted by age) can be used to identify polyps which may be exacerbating already poor mucociliary clearance. Nasal polyposis has been observed in up to 15% of PCD patients.29, 113 Although CRS is not generally life threatening, it substantially affects quality of life.114 Daily saline irrigation has been demonstrated as safe and beneficial in patients with CRS.115 Anecdotally, in PCD patients, saline nasal irrigations are beneficial, but studies demonstrating their efficacy are lacking. Given the

minimal side effect profile and likelihood for benefit, nasal irrigations are generally encouraged for symptomatic CRS relief in PCD. The effects of saline irrigation are likely increased after functional endoscopic sinus surgery (ESS), as the saline solution will more easily reach the sinus mucosa through post-surgical ostia. Thus, ESS is often performed in PCD patients and may improve lower respiratory tract disease in some patients.116 Antibiotics and nasal steroids may be used in acute on chronic exacerbations of rhinosinusitis; however, a recent review showed lack of consensus on the treatment of CRS in children with PCD,113 and there are no randomized, controlled, or long-term prospective CRS studies in PCD.

Routine Therapies in PCD ::: PRINCIPLES OF TREATMENT:
Airway clearance through daily chest physiotherapy is highly recommended in PCD.117 Unlike cystic fibrosis, cough clearance is preserved in PCD.118 Thus, airway clearance is expected to be quite beneficial in PCD and should be a cornerstone of long-term therapy. Daily cardiovascular exercise should also be strongly encouraged, as poor exercise capacity is linked to decreased pulmonary function in PCD,119 and exercise may improve mucus clearance.120

Antibiotics should be given for acute respiratory exacerbations in PCD. Acute changes in cough, sputum production, respiratory rate, or work of breathing are likely reliable markers of a respiratory exacerbation in PCD (as demonstrated in non-CF bronchiectasis121), and oral antibiotics are recommended for mild exacerbations. Most physicians use a broad-spectrum oral antibiotic (amoxicillin plus clavulinic acid or an equivalent cephalosporin) to target the common respiratory pathogens in children with PCD. Typically, at least 2–3 weeks of oral antibiotics are recommended in PCD, based upon other disorders with similar pathophysiology (protracted bacterial bronchitis,122 cystic fibrosis,123 and non-CF bronchiectasis124). More severe exacerbations, or those failing oral therapy, may require parenteral antibiotics. Antibiotic choice should be guided by past respiratory cultures. Despite a lack of published evidence, inhaled antibiotics are also an option for acute PCD respiratory exacerbations, but these are usually reserved for patients with Pseudomonas aeruginosa infection. Eradication of initial positive Pseudomonas airway culture also seems prudent in PCD, although no evidence supports this practice. Non-CF bronchiectasis guidelines make similar suggestions for Pseudomonas eradication.125, 126 Although Burkholderia cepacia has not been reported in PCD, recovery of this organism should prompt eradication practices.
Finally, PCD patients should receive recommended vaccinations per local schedules. Annual influenza127 and pneumococcal vaccinations (per the Advisory Committee on Immunization Practices)128, 129 are recommended in PCD. In the first year of life, monthly (seasonal) immunoprophylaxis against respiratory synctial virus can be considered for infants with PCD, and more specifically for infants with complicated respiratory courses requiring prolonged oxygen supplementation.

Therapies to Consider on a Case by Case Basis in PCD ::: PRINCIPLES OF TREATMENT:
Chronic suppressive inhaled antibiotics can be used on an individual basis in PCD patients. Inhaled aminoglycoside and beta-lactam antibiotics are recommended for chronic respiratory infections (particularly those associated with Pseudomonas aeruginosa) in non-CF bronchiectasis,125, 130, 131 and several months of inhaled aminoglycosides or colistin in Pseudomonas colonized adults with non-CF bronchiectasis result in decreased hospitalization and improved respiratory symptoms.132, 133, 134 However, there are no studies of inhaled antibiotics in children with non-CF bronchiectasis or PCD.
Chronic suppressive oral antibiotics, including trimethoprim-sulfamethoxazole, macrolides, or other agents, can be used on a case by case basis in PCD. Chronic macrolide therapy in PCD is currently under prospective investigation by the BESTCILIA consortium in Europe.51 When using chronic macrolide therapy, sputum culture surveillance for non-tuberculous mycobacterium infection is indicated.135 Prospective clinical study of chronic macrolides in adults and children with non-CF bronchiectasis shows decreased respiratory exacerbations and improved lung function,136, 137, 138 but increased emergence of macrolide resistant respiratory organisms. The long-term significance of macrolide resistance is unclear.139 Small case reports of chronic macrolide therapy in PCD also demonstrate some benefits, although not as robust as those in non-CF bronchiectasis.140, 141, 142, 143 Remote studies on trimethoprim-sulfamethoxazole in chronic bronchitis also suggest benefit, but this agent has not been studied in PCD.144, 145

Inhaled hyperosmolar agents can be used on a case-by-case basis in PCD. These agents promote cough clearance and alter mucus rheology to favor increased cough clearance. However, a recent meta-analysis reported unclear long-term benefits of hyperosmolar agents in non-CF bronchiectasis.146 Hypertonic saline (3% to 7% concentration) has not been studied in PCD. Trials comparing inhaled hypertonic saline to isotonic saline show limited positive effects in non-CF bronchiectasis.147 When physicians use inhaled hypertonic saline in PCD, it is essential that they instruct patients in proper equipment sterilization. Inhaled dry powder mannitol has also been studied in non-CF bronchiectasis, but outcomes are inconclusive.146, 148 Mannitol has not been studied in PCD.

DNase (dornase-alfa or Pulmozyme®) can be used on an individual basis in PCD. Although there are no prospective trials of DNase in PCD, studies of DNase in adults with non-CF bronchiectasis show no clinical benefits in one study149 and increased frequency of respiratory exacerbations with worsened lung function in another study.150 Several case reports of DNase in PCD suggest possible benefit when used for both short and long-term periods.151, 152, 153 Larger, prospective clinical studies of DNase in children and young adults with PCD are required before the potential negative effects of this medication can be dismissed.

Lastly, inhaled bronchodilators can be used on a case-by-case basis in PCD. In limited study, long-acting bronchodilators (with inhaled corticosteroids) in non-CF bronchiectasis do not show clinical efficacy. In PCD, bronchodilators show mixed results, with one study demonstrating significant improvement in lung function after a single bronchodilator dose,154 whereas another study showed unchanged lung function after 6 weeks of regular bronchodilators.155

Therapies Not Routinely Recommended in PCD ::: PRINCIPLES OF TREATMENT:

Inhaled corticosteroids are not routinely recommend in PCD and should be reserved for PCD patients with associated asthma or airway reactivity. Inhaled corticosteroids are also discouraged in non-CF bronchiectasis without airway reactivity.156 Similarly, intravenous immunoglobulin (IVIG) is not recommended for routine use in patients with PCD. Immunodeficiency rarely exists with PCD,157, 158 and most PCD patients have normal immune function. PCD patients with documented dysfunction of vaccine responses or other aspects of humoral immunity may benefit from IVIG therapy. Isolated IgA or IgG subclass disorders do not justify IVIG therapy.

Lobectomy is not routinely suggested as therapy in PCD. The decision to perform lobectomy in PCD requires multi-disciplinary discussion between pulmonologists, intensivists, and surgeons. In the post-operative period, airway clearance is limited by pain and immobility, and PCD patients are at risk of pulmonary deterioration. Although lobectomy may be beneficial in rare cases of PCD with severe, localized bronchiectasis, it should be considered with caution. Similarly, lung transplantation can be considered in PCD patients with advanced pulmonary disease, but situs anomalies may surgically complicate this procedure.159, 160

Summary ::: PRINCIPLES OF TREATMENT:

PCD is a rare disorder; consequently, only a limited number of centers have extensive experience in the diagnosis and management of PCD. Research over the past decade has led to a revolution in diagnostic approaches, including nNO and genetic testing. Nevertheless, many PCD patients are still undiagnosed or misdiagnosed. To date, only limited studies have addressed management of PCD, and there have been no large, randomized clinical trials to direct therapy. Therefore, this review article includes consensus recommendations from PCD physicians in North America for diagnosis, monitoring and management of PCD.