Diagnosis, Monitoring, and Treatment of Primary Ciliary Dyskinesia: PCD Foundation Consensus Recommendations Based on State of the Art Review

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Summary. 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.

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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.[1–3] 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.[5–9] 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,[14–16] 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.[19–22] 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.[23–26]

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

ABBREVIATIONS:	
ABPA	allergic bronchopulmonary aspergillosis
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
CRS	chronic rhinosinusitis
CT	computed tomography
EM	electron microscopy
ESS	endoscopic sinus surgery
GDMCC	Genetic Disorders of Mucociliary Clearance Consortium
IDA	inner dynein arm
IF	immunofluorescence testing
IVIG	intravenous immunoglobulin
MTD	microtubule disorganization
N-DRC	nexin-dynein regulatory complex
NGS	next generation sequencing
nNO	nasal nitric oxide
NTM	non-tuberculosis mycobacterium
ODA	outer dynein arm
OME	otitis media with effusion
PBB	protracted bacterial bronchitis
PCD	primary ciliary dyskinesia
PET	pressure equalization tubes
ROM	recurrent otitis media
SIT	situs inversus totalis
SA	situs ambiguus
TTN	transient tachypnea of the newborn

TABLE 1— Age-Related Prevalence of Clinical Features in Primary Ciliary Dyskinesia[1]

PCD clinical feature	Youngest age when feature present in >50% of PCD	Youngest age when feature present in >80% of PCD
Neonatal respiratory distress	12 hr of life[2]	24 hr of life[2]
Organ laterality defects (SIT or SA)	Neonatal to school age	—
Recurrent otitis media with effusion	Infancy	Infancy
Year-round, daily cough	Infancy	Infancy
Year-round, daily nasal congestion	Infancy	Infancy
Chronic pansinusitis	Preschool[3]	School age
Recurrent lower respiratory infections	Infancy	Preschool
Bronchiectasis	School age	Adult
Male infertility	—	Adult

SIT, situs inversus totalis; SA, situs ambiguus.
[1]Adapted from Knowles et al.[4]
[2]Reference.[28]
[3]Pansinusitis is seen in almost all patients with PCD who have sinus imaging studies, but these studies are not done often in pre-school age children.

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]
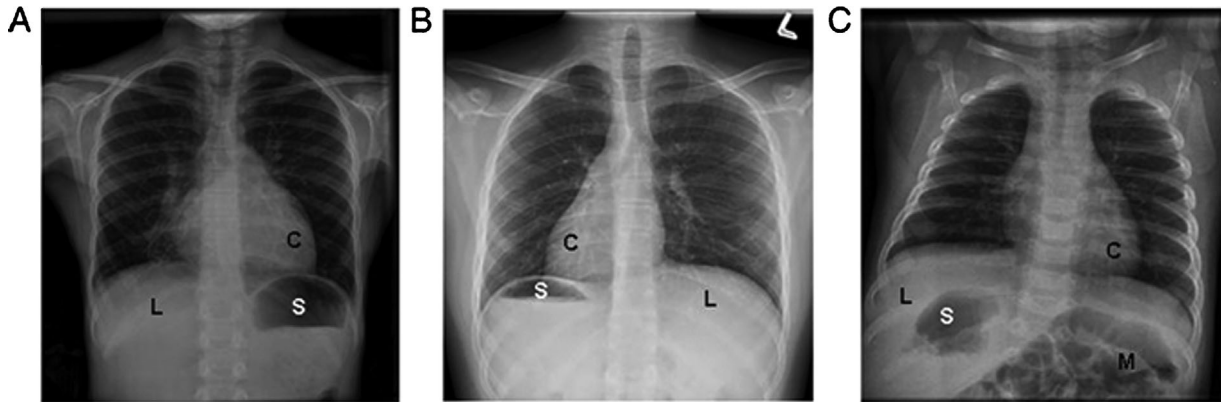
Fig. 1. Examples of various laterality defects on radiology imaging in PCD. Different situs arrangements found in PCD, including (A) a participant with situs solitus, or normal organ arrangement, with left cardiac apex, left-sided stomach bubble, and right-sided liver; (B) a patient with situs inversus totalis (SIT), or mirror-image organ arrangement, with right cardiac apex, right-sided stomach bubble, and left-sided liver; (C) a patient with situs ambiguus (SA), with left cardiac apex, right-sided stomach bubble, right-sided liver, and intestinal malrotation; This patient also had right-sided polysplenia visualized on a CT scan. C, cardiac apex; S, stomach; L, liver; M, intestinal malrotation. Reproduced with permission from CHEST.[19]

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.

APPROACH TO DIAGNOSING PCD

Diagnostic Tests

The first step in diagnosing PCD is evaluation for clinical features of PCD as outlined in the prior section. The diagnosis of PCD requires clinical phenotypic features in conjunction with diagnostic testing. A number of tests can be used to support the diagnosis of PCD, and often a panel of tests are required to confirm a PCD diagnosis (Table 2). As PCD can result from various defects in ciliary biogenesis, structure, function, or organization, no single test captures all PCD defects. For instance, patients with biallelic *DNAH11* mutations have a classic clinical phenotype and low nasal nitric oxide levels, but normal electron microscopy (EM) ultrastructure with only subtle changes on ciliary waveform analysis.[10] Patients with biallelic mutations in *RSPH1* demonstrate later onset of clinical symptoms, subtle EM defects, and slight changes in ciliary waveform, with borderline (and in some cases normal) nasal nitric oxide levels.[38] Consequently, a panel of the following PCD diagnostic tests are recommended, and

with a greater number of positive tests, there is a higher likelihood of definite PCD.

Diagnostic PCD algorithms will differ per patient location (where some tests will not be readily accessible) and upon local expertise of the institution performing the PCD investigation. Furthermore, age of the patient may dictate which PCD testing should be initially pursued. In neonates and children <5 years old, nasal nitric oxide values are not as reliable; thus diagnostic testing in this age group usually includes ciliary biopsy for electron microscopy and/or genetic studies in North America, versus ciliary biopsy for high speed videomicroscopy analysis in Europe. In children over 5 years old and adults, who can cooperate with the required maneuvers for nasal nitric oxide measurement, a low nasal nitric oxide value coupled with an appropriate clinical phenotype may be adequate for a clinical diagnosis of PCD, followed by ciliary biopsy for electron microscopy or high speed videomicroscopy and/or genetic studies, as needed. Minimal PCD diagnostic criteria have been proposed by the GDMCC (Table 3). For all patients given a diagnosis of PCD by clinicians outside of PCD Foundation Clinical Centers, at least one visit to a PCD Foundation Clinical Center is recommended to officially confirm the diagnosis. For patients followed in centers without PCD expertise, a PCD Foundation Clinical Center referral for diagnostic investigation is highly recommended.

Respiratory Epithelial Biopsy With Electron Microscopy

Respiratory epithelial biopsy with EM processing for ultrastructural examination of ciliary axonemes is a proven technique for PCD diagnosis[39] and is recommended as part

TABLE 2— Recommended Diagnostic Testing Methods for Primary Ciliary Dyskinesia

Test recommended for PCD diagnosis	Potential for false positive results	Potential for false negative results
Nasal nitric oxide measurement	Low[1]	Low[2]
Ciliary biopsy with electron microscopy	Variable[3]	Variable[4]
PCD genetic testing panels	Low[5]	Moderate[6]
Functional ciliary beat/waveform analysis with high speed videomicroscopy	Variable[7]	Moderate[8]
Immunofluorescence testing	Unknown	Unknown

[1]As long as cystic fibrosis has been excluded. Risk of false positive result is increased during viral respiratory infection, epistaxis, and non-atopic sinusitis. Testing should be performed at baseline health status and repeated if there is any question about health status.
[2]Reference.[18]
[3]The risk of false positive result is moderately increased with secondary changes from infectious processes or pollutant exposures, improper specimen handling and processing, or inexperience with electron microscopy interpretation.[4]
[4]Several PCD-causing genetic mutations can result in normal electron microscopy[10] or subtle changes which are not readily apparent.[38]
[5]Misinterpretation of genetic panel result (e.g., variants of unknown significance or single mutations in two different PCD genes interpreted as "diagnostic").
[6]Genetic panel testing may miss large insertions, deletions, and mutations in novel genes, since approximately 30% of PCD do not have identifiable mutations in the currently known PCD associated genes, but this risk should decrease with broader range of genetic analysis provided by NGS panels.
[7]With a high risk for false positive results from secondary insults on a single test. To limit this risk, many centers now perform three ciliary biopsies at separate clinical visits for repeat high speed videomicroscopy analysis.
[8]Subtle waveform defects will be missed in centers without extensive experience.

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 apparatus[44,45] 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

TABLE 3— Recommended PCD Diagnostic Criteria by Age

Newborns (0–1 month of age)
    Situs inversus totalis and unexplained neonatal respiratory distress at term birth plus at least one of the following:
    Diagnostic ciliary ultrastructure on electron micrographs
    Biallelic mutations in one PCD-associated gene
    Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
Children (1 month to 5 years)
    Two or more major PCD clinical criteria (see below) plus at least one of the following (nasal nitric oxide not included in this age group, since it is not yet sufficiently tested):
    Diagnostic ciliary ultrastructure on electron micrographs
    Biallelic mutations in one PCD-associated gene
    Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
Children 5–18 years of age and adults
    Two or more major PCD clinical criteria (see below) plus at least one of the following:
    Nasal nitric oxide during plateau <77 nl/min on 2 occasions, >2 months apart, with cystic fibrosis excluded
    Diagnostic ciliary ultrastructure on electron micrographs
    Biallelic mutations in one PCD-associated gene
    Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions

Major clinical criteria for PCD diagnosis*
1) Unexplained neonatal respiratory distress (at term birth) with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for >24 hr.
2) Any organ laterality defect—situs inversus totalis, situs ambiguous, or heterotaxy.
3) Daily, year-round wet cough starting in first year of life or bronchiectasis on chest CT.
4) Daily, year-round nasal congestion starting in first year of life or pansinusitis on sinus CT.
*Other diagnostic possibilities should have been considered, such as cystic fibrosis and immunodeficiencies, and diagnostic tests performed to rule out those disorders, as clinically indicated.
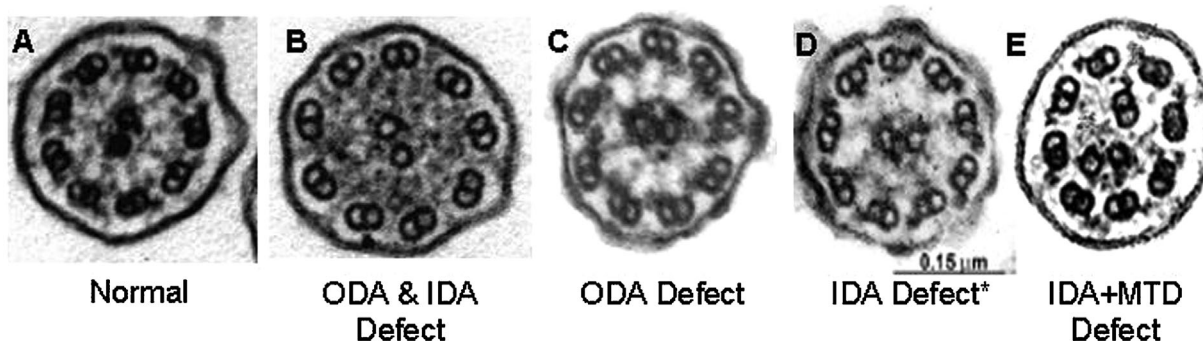
Fig. 2. Electron microscopy findings in primary ciliary dyskinesia. Diagnostic ciliary electron microscopy findings in primary ciliary dyskinesia. Normal ciliary ultrastructure (A), Outer and inner dynein arm defect (B), Outer dynein arm defect (C), Inner dynein arm defect alone* (D), Inner dynein arm defect with microtubule disorganization (E). * Inner dynein arm defects alone are quite rare as a cause of PCD and usually due to secondary artifact. Adapted from Leigh et al.[164]

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

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 sinusitis[61]). 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

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
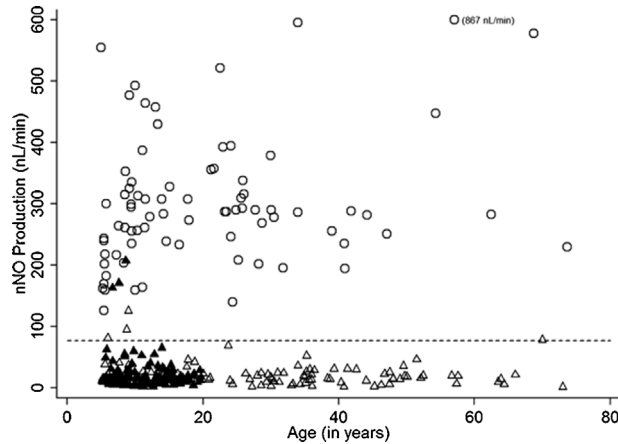
Fig. 3. Nasal nitric oxide in primary ciliary dyskinesia and healthy controls. Scatter plot of nasal nitric oxide (nNO) values (linear scale; nl/min) versus age for individuals with primary ciliary dyskinesia (PCD, with cystic fibrosis ruled out) and healthy control subjects with nNO cutoff of 77 nl/min. All nNO values from healthy control subjects (open circles) were well above the cutoff of 77 nl/min and most of the nNO measurements in subjects with PCD and ciliary ultrastructure defects (open triangles, single measurements; solid triangles, repeated measurements) were below the cutoff. Findings are similar in disease controls, including asthma and COPD (data not shown). The three solid triangles above the cutoff are repeated measurements in the same individual with PCD. Reproduced with permission from the American Thoracic Society. Copyright © 2015 American Thoracic Society. The *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.[18]

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

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.[42,67–72] 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

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.[76–78] 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

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

The clinical symptoms associated with PCD often overlap with other common pediatric and adult

TABLE 4—PCD Genetics

PCD genes	Prevalence in PCD	Ciliary structural defect	Detected on current commercial PCD NGS panels
NME8	+	Partial ODA defect	Yes
DNAH5	++++	ODA defect	Yes
DNAI1	+++	ODA defect	Yes
DNAI2	++	ODA defect	Yes
DNAL1	+	ODA defect	Yes
CCDC114	++	ODA defect	Yes
CCDC103	++	ODA ± defect	Yes
DNAAF1	++	ODA and IDA defect	Yes
DNAAF2	++	ODA and IDA defect	Yes
DNAAF3	+	ODA and IDA defect	Yes
LRRC6	++	ODA and IDA defect	Yes
HEATR2	+	ODA and IDA defect	Yes
RPGR	+	Normal	Yes
OFD1	+	Normal	Yes
DNAH11	+++	Normal	Yes
CCDC39	+++	IDA defect + MTD defect	Yes
CCDC40	+++	IDA defect + MTD defect	Yes
RSPH9	+	Central pair defect or normal	Yes
RSPH4A	++	Central pair defect or normal	Yes
RSPH1	++	Central pair defect or normal	
RSPH3	+	Central pair defect or normal	
CCNO	+	Oligocilia (residual axoneme normal)	
MCIDAS	+	Oligocilia (residual axoneme abnormal)	
DNAH8	+	Not available	
CCDC151	++	ODA defect	
ARMC4	++	ODA defect	
DYX1C1	+	ODA and IDA defect	
C21orf59	+	ODA and IDA defect	
ZMYND10	++	ODA and IDA defect	
SPAG1	++	ODA and IDA defect	
HYDIN	+	Normal	
CCDC164 (DRC1)	+	Mostly normal (N-DRC defect)	
CCDC65 (DRC2)	+	Mostly normal (N-DRC defect)	

+, genetic mutations causing <1% of all PCD; ++, genetic mutations causing 1–4% of all PCD; +++, genetic mutations causing 4–10% of all PCD; ++++, genetic mutations causing >15% of all PCD; IDA, inner dynein arm; IDA + MTD, inner dynein arm defect with microtubule disorganization; N-DRC, nexin-dynein regulatory complex; ODA, outer dynein arm.

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 phenotypes[83] and produce nNO levels below the PCD diagnostic cutoff of 77 nl/min.[58] Immunodeficiency can also present similarly

TABLE 5—Tests NOT Recommended for Diagnosing Primary Ciliary Dyskinesia

Tests NOT recommended for primary ciliary dyskinesia diagnosis	Potential for false positive results	Potential for false negative results
Nasal saccharin testing	Very high[1]	Very high[1]
Radioaerosol mucociliary clearance tests	High[2]	—
Ciliary beat frequency alone (CBF)	High[3]	High[3]
Ciliary motion analysis without high speed videomicroscopy	Very high[4]	Very high[4]

[1]This test is subjective and involves a high degree of cooperation by the patient. In children <5–7 years old, the feasibility of this test will be low due to poor patient cooperation.
[2]This test can result in false positive PCD diagnoses, as detected abnormalities in mucociliary clearance lack specificity, and may be due to secondary causes.
[3]In proven cases of PCD, CBF can be low, normal, or high, leading to false positive and false negative results.[80]
[4]Visual assessment of ciliary motion without high speed video-recording devices will lead to frequent false positive and false negative results.

TABLE 6— Other Chronic Respiratory Conditions to Consider When Considering a Diagnosis of PCD

Chronic condition	Methods of evaluation
Cystic fibrosis	Sweat chloride testing or cystic fibrosis genetic testing
Immunodeficiency	Quantitative measurement of immunoglobulins, lymphocytes, complement levels, antibody responses to vaccines, and complete blood counts. Consultation with a board certified Immunologist is also recommended
Asthma	Clinical history, pulmonary function testing, and asthma medication trials. Although one normally expects asthma-related cough to be dry in nature, it can seem wet to parents when accompanied by viral respiratory infections. Obstructive defects on pulmonary function testing can be seen with both PCD and asthma, and bronchodilator responsiveness is not exclusive to asthma and does not exclude a diagnosis of PCD
Pulmonary aspiration	Clinical feeding history followed by swallowing assessment and intervention only when pulmonary aspiration seems likely
Allergic rhinitis	Clinical history of seasonal symptoms, allergy testing, and trials of nasal corticosteroids and antihistamines, which should greatly improve allergic rhinitis symptoms. PCD nasal disease shows minimal (if any) improvement with these interventions
Protracted bacterial bronchitis	Clinical history of 3 weeks of wet cough in pre-school aged children, with resolution of cough after 14 days of amoxicillin plus clavulinic acid.[122] The cough usually does not return after a subsequent 2-week period off antibiotics

to PCD,[84] and in patients with suspected PCD, laboratory studies investigating immunodeficiency are necessary. Preliminary study of nNO in certain humoral immuno-deficiencies 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 gastroesopha-geal 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 conges-tion 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

PCD can rarely co-exist with other rare disorders (Table 7). Retinitis Pigmentosa (an inherited cause of blindness from retinal ciliary dysfunction) and Orofacio-digital Syndrome (including mental retardation, cranio-facial 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 muta-tions 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

TABLE 7— Other Diseases Co-Segregating With PCD

Associated rare disorder	Level of PCD association	Method of PCD overlap	Specific gene affected
Situs ambiguus and heterotaxy	At least 12% of PCD	Shared common genes	Any PCD gene encoding for ODA, IDA, or ODA + IDA proteins (ex: DNAH5, DNAH11, CCDC39/40, LRRC6, DNAAF1/2/3)[19]
Retinitis pigmentosa	Multiple unrelated cases reported; <1% of PCD	Shared common gene mutation	RPGR[21,91,161,162]
Orofaciodigital syndrome (sibling males with mental retardation and macrocephaly)	1 sibling-pair reported; <1% of PCD	Shared common gene mutation	OFD1[89]
Cri du chat syndrome	2 unrelated cases reported	Mutation in close proximity to PCD gene	Chr 5p deletion including DNAH5[22]
Glanzmann thrombasthenia	1 sibling-pair reported	Mutation in close proximity to PCD gene	Chr 17q haplotype that includes CCDC103 and ITGB3[95]
Cystic fibrosis	1 case reported	Mutations in two different genes	Chr 7 including region with DNAH11 and CFTR via uniparental isodisomy[96]
Miller syndrome	1 sibling-pair reported	Mutations in two different genes	Biallelic mutations in DNAH5 (Chr 5) for PCD and DHODH (Chr 16) for Miller syndrome[97]
Common variable immunodeficiency	1 sibling-pair and 2 unrelated cases reported	Unknown	1 sibling-pair with homozygous DNAH11 mutations and low IgM and S.pneumoniae titers after booster.[157] 2 unrelated cases; 1 with outer dynein arm defect and low IgG titers[157], and 1 with Kartagener Syndrome, abnormal ciliary ultrastructure, and low IgG, IgM, Tetanus and S.pneumoniae titers after booster.[158]
Polycystic kidney disease	1 case reported	Unknown	Unknown[92]
Familial mediterranean fever	1 case reported	Unknown	MEFV-R202Q polymorphism on Chr 16p13.3 and unknown PCD gene[163]
Other non-motile ciliopathies (Joubert, Bardet-biedl, Usher, Jeune syndromes, and others)	No definite cases reported	Unknown	Unknown

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.

CLINICAL CARE AND LONG-TERM MONITORING

Pulmonary Care and 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 criteria[99] 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

TABLE 8— Suggested Schedule of Investigations and Clinical Care in Primary Ciliary Dyskinesia

Clinical visits
  Pulmonology: 2–4 times/year
  Otolaryngology: 1-2 time/year in children, as needed in adults
  Audiology: at diagnosis and as needed per otolaryngology
  Reproductive medicine: As clinically needed
Long-term surveillance
  Chest radiography: every 2–4 years
  Chest computed tomography: consider at least once after 5–7 years old (when sedation not required and images are of highest quality)[1]
  Airway microbiology cultures: 2–4 times/year
  Non-tuberculosis mycobacterial cultures: every 2 years (and with unexplained clinical decline)
  Pulmonary function testing: 2–4 times/year
  ABPA testing: IgE levels ± evidence of aspergillus specificity at diagnosis, with new onset wheezing, unexplained clinical decline
Preventative therapies
  Airway clearance: daily
  Nasal sinus lavage: daily (when pertinent)
  Standard vaccinations: per local schedule
  Influenza vaccine: annually[2]
  13-valent pneumococcal vaccine: per ACIP guidelines[3]
  23-valent pneumococcal vaccine: per ACIP guidelines[4]
  RSV immunoprophylaxis: consider monthly in first winter[5]

[1]And as clinically indicated on a case by case basis.
[2]After 6 months old, including household members.
[3]ACIP guidelines.
[4]ACIP guidelines.
[5]Specifically consider in infants with complicated respiratory courses, including prematurity, prolonged mechanical ventilation, prolonged need for supplemental oxygen, need for home supplemental oxygen, or frequent respiratory illnesses.

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

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 otolaryologist 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 population[111] and is easily controlled with topical therapies.[109] Persistent otorrhea can be attributed to biofilm formation, especially in children with longer lasting PET[112]; 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 PCD[31] 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.

PRINCIPLES OF TREATMENT

Routine Therapies in PCD

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 bronchiectasis[121]), 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 bronchiectasis[124]). 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 influenza[127] 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

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.[132–134] 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,[136–138] 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.[140–143] 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 study[149] 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.[151–153] 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

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

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.

drafts of this document and provided input in areas needing clarification.

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