HHS Public Access

Author manuscript

Expert Opin Orphan Drugs. Author manuscript; available in PMC 2016 March 16.

Published in final edited form as:

Expert Opin Orphan Drugs. 2015 March 1; 3(1): 31–44. doi:10.1517/21678707.2015.989212.

Genetics, diagnosis, and future treatment strategies for primary ciliary dyskinesia

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Abstract

Introduction—Primary ciliary dyskinesia (PCD) is a genetically heterogeneous recessive disorder resulting in chronic oto-sino-pulmonary disease. While PCD is estimated to occur in 1 in 20,000 individuals, fewer than 1,000 patients in the US have a well-established diagnosis.

Areas Covered—We provide an overview of the clinical manifestations of PCD, describe the evolution of diagnostic methods, and critique the literature on management of PCD.

Expert Opinion—Although interest in clinical studies in non-CF bronchiectasis has increased in recent years, some of whom enroll patients with PCD, the literature regarding therapy for PCD as a distinct entity is lacking, as the numbers are small, and there have been no sub-analyses published. However, with improved screening and diagnostic methods, the development of clinical and research consortiums, and actively enrolling registries of PCD patients, the environment is conducive to perform longitudinal studies of disease course and therapeutic studies to alter that course.

Keywords

bronchiectasis; genotype; Kartagener syndrome; nasal nitric oxide; phenotype; primary ciliary dyskinesia

1. Introduction

Primary ciliary dyskinesia (PCD) [OMIM #244400] is a genetically heterogeneous recessive disorder of motile cilia resulting in neonatal respiratory distress, chronic oto-sino-pulmonary disease, and male infertility; organ laterality defects are present in approximately 50% of individuals[1–5]. Initially recognized in 1933, the triad of chronic sinusitis, bronchiectasis, and situs inversus was termed Kartagener syndrome[6]. It was not until 1976 when Afzelius described the cilia in these patients as being immotile due to defective ciliary ultrastructure[7] that some understanding of the etiology of the syndrome was obtained. Subsequent studies

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Competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

have revealed that cilia have a stiff, or even vigorous, but always uncoordinated and ineffective beat consistent with dyskinesia, rather than complete immotility. The term “primary” distinguishes it from secondary or acquired (i.e. non-genetically determined) ciliary defections associated with infection and inflammation.

Limitations imposed by hitherto inadequate diagnostic methods have made it difficult to determine the true prevalence of PCD. Based on population surveys of situs inversus and bronchiectasis in Norway and Japan, the incidence of PCD is estimated at 1 per 10,000–20,000 births[8, 9]. In the US, there are fewer than 1,000 patients with a well-established diagnosis of PCD[5]. The development and validation of nasal nitric oxide (nNO) as a screening test for PCD[10] and continued discoveries of PCD causing mutations have improved diagnostic certainty[5]. At this time, there is no therapy specific for PCD; rather therapies are extrapolated from other suppurative lung diseases such as cystic fibrosis (CF) and non-CF bronchiectasis.

1.1 Cilia structure and function in health and disease

Cilia classification *in vivo* is based on function, creating two categories: motile and sensory. Normal motile cilia contain 9 outer doublets and a central pair (Figure 1). The outer doublets are composed of microtubules of α- and β-tubulin monomers, and possess outer and inner dynein arms along their length, which contain enzymes for ATP hydrolysis, producing ciliary movement. Stability is provided by the nexin links connecting the outer doublets and by the radial spokes that extend from the doublets to the central pair. Mutations of genes that encode any of these components, or those are involved in the cilia assembly mechanism, result in clinical disease. Specialized motile cilia, which lack a central pair, move in a rotatory fashion and are responsible for organ lateralization during embryogenesis, hence organ laterality defects are associated with some (approximately 50%) patients with PCD.

A single non-motile sensory cilium is present in most cells of the body and contains specialized proteins and receptors, which sense the local environment. This gives the sensory cilia an important role in signaling pathways and planar cell polarity. Mutations in genes involved in the assembly and function of the sensory cilia result in disorders such as Bardet-Biedl syndrome, retinitis pigmentosa, Joubert syndrome, nephronophthisis, and autosomal dominant polycystic kidney disease. For the purposes of this review, we will not further address these clinical entities.

2. Diagnosis (Figure 2)

A consistent clinical phenotype should prompt a referral to a specialized center for further testing. See next section, but briefly, these include neonatal respiratory distress, persistent cough or recurrent pneumonias from birth, recurrent difficult otitis media, and/or unexplained bronchiectasis in adulthood. The presence of situs inversus or ambiguous, or male infertility and female subfertility in association with the above are particularly suggestive of the likelihood of PCD. Unlike CF, digestive tract abnormalities (pancreatic insufficiency, liver disease, malnutrition) are not usually a feature of PCD. While some features can be seen in isolation in the general population (even situs inversus alone), persistence of hallmark clinical features is highly suggestive of PCD. Because PCD

diagnostic testing is expensive and requires expertise, identification of clinical manifestations of PCD is critical to initiate further diagnostic evaluation at specialized centers. Other etiologies of bronchiectasis, including CF, primary immune deficiencies, and alpha1-antitrypsin deficiency, should be ruled out. Since motile cilia are present throughout the respiratory tract (the conductive airways, paranasal sinuses, middle ear), the clinical features of PCD reflect defects in the primary innate defense mechanism of mucociliary clearance, which confers much of the morbidity of PCD on patient's quality of life (cough with recurrent infections). Laterality defects result from defects in the embryonic nodal motile cilia during embryogenesis. Manifestations of PCD are evident at birth and persist through the individual's lifetime (Table 1).

2.1 Clinical presentation

Neonatal respiratory distress, often described as transient tachypnea of the newborn or neonatal pneumonia, is seen in over 80% of term neonates with PCD. Infants have tachypnea, increased work of breathing, and may even need supplemental oxygen or positive pressure ventilation[11–13]. This phenomenon implies that cilia in the airways are necessary for the clearance of fetal fluid from the lungs.

Daily wet cough, chronic nasal congestion, and recurrent otitis media are nearly universally present in PCD patients[11, 14]. Recurrent otitis media can result in hearing loss and speech delays. Chronic sinusitis is seen more often in older children and adults as compared to young children secondary to lack of radiographic imaging[5]. Atelectasis and lobar collapse, particularly of the middle and lower lobes, is seen in infants and young children with PCD[11, 14, 15]. Bronchiectasis is universally present in adults with PCD; young children with PCD can have airway wall thickening and bronchiectasis visible on high resolution chest CT[15–17]. Evidence of airflow obstruction may be evident on spirometry[18], even in young children[19].

Microbial pathogens in PCD tend to parallel those seen in CF. While *Haemophilus influenza*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* dominate the pulmonary bacteriology of children with PCD, *Pseudomonas aeruginosa* is seen in teens and young adults[11, 20]. Chronic *Pseudomonas* tends to present at a later age as compared to CF, and *S. pneumoniae* is seen more often in PCD than in CF. Similar to CF, some patients culture more than one type of bacteria from the same sample. The prevalence of non-tuberculous mycobacterium (NTM) in adult PCD patients is about 15% and is somewhat lower in PCD children, similar to what is seen in CF[20]. These observations underscore the need to monitor sputum microbiology (including NTM) on a regular basis (at least twice a year).

Cilia also play a critical role in cardiac development and organ lateralization[21–23]. Situs inversus totalis occurs in about 50% of PCD patients. Situs ambiguous occurs in about 12% of PCD patients, and manifestations include polysplenia (left isomerism), asplenia (right isomerism), duplication of the inferior vena cava, and complex congenital heart disease[24–26]. The risk of structural congenital heart disease in PCD patients with situs ambiguous is at least 200-fold higher than the general population with heterotaxy[25].

Due to dysmotility of the spermatozoa flagella, nearly all males with PCD are infertile. There are rare reports of men with PCD who have fathered children with[27] and without fertility assistance[28]. PCD females have impaired ciliary function within the fallopian tubes, which delays ovum transit and can result in ectopic pregnancies or infertility[29].

2.2 Nitric oxide measurements for screening and diagnosis

The saccharine test was the first screening test for PCD, but due to the lack of specificity and the development of more accurate diagnostic methods, there is no role for this testing in the diagnosis of PCD. The observation in the early 1990s that nitric oxide levels in exhaled nasal air is lower than that of healthy or disease controls was fortuitous, and has led in recent years to the development of measures of nasal NO as a diagnostic test[30]. Nasal nitric oxide (nNO) is appropriate to screen for PCD in patients with a compatible clinical phenotype and in whom testing has excluded CF[20, 31]. In PCD, nNO values are typically 10–20% of normal (20.7 nl/min) but individuals with *RSPH1* mutations can have higher nNO (98.3 nl/min)[32]. Using a standardized protocol, a disease specific cutoff of 77nl/min has a sensitivity of 98% and a specificity of >99.9%. The positive predictive value is influenced by age and prevalence, underscoring the importance of obtaining a detailed clinical phenotype[3]. While the test requires some equipment and technical training/expertise, it is easy to perform down to about age 5 years, and is non-invasive[10]. Nasal NO has replaced the saccharine test as a reliable screening method.

2.3 Ciliary ultrastructure and ciliary beat

Assessment of ciliary ultrastructure using electron microscopy (EM) has long been considered the PCD diagnostic standard, but this method is limited for several reasons. At least 30% of patients with PCD have normal ultrastructure[33, 34]. Furthermore, the challenges of obtaining an adequate sample, the technical skill required for sample processing, and the experience necessary to correctly interpret the images impose additional limitations. As many as 15 to 20% of patients referred to the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) with a diagnosis of PCD based on EM findings did not have PCD[5], underscoring the importance of this testing occurring in specialized centers.

Assessment of ciliary motility, including beat frequency and waveform analysis, in experienced hands, can be a useful adjunct to diagnose PCD, particularly if the patient has complete immotility or gross dysmotility of all cilia. Some forms of PCD have subtle or no evidence of abnormal beat or waveform. Secondary ciliary dyskinesia can result from infection and inflammation, increasing the rate of false positive diagnoses when using biologic assessments of ciliary structure and function. Thus, relying on ciliary structural and functional analyses alone, as has traditionally been the practice, does not provide enough specificity nor sensitivity for the diagnosis of PCD.

2.4 Genetics (Table 2)

The number of genes and mutations identified as causative for PCD has exploded in recent years, allowing a shift away from a biological method of diagnosing the disease and towards a more definitive method of diagnosis (Table 2)[34]. Over 65% of PCD patients have biallellic mutations identified in one of the 32 published PCD genes[5]. Continued identification of

genetic mutations that result in PCD will provide better understanding of the genotype-phenotype relationship and more clearly define the phenotypic spectrum of disease. For examples, mutations in genes that code for proteins in the ODA complexes result in situs abnormalities; this is not seen with mutations in radial spoke head protein genes due to the unaffected nodal cilium (which lacks the central pair, and thus retains the normal rotatory function important for normal L-R asymmetry). Individuals with mutations in *RSPH1* have a milder clinical phenotype and higher nNO measures as compared to other PCD patients[32]. A recent publication notes the presence of PCD in patients Cri du Chat Syndrome (CdCS) who are hemizygous for a *DNAH5* mutation due to the 5p segmental deletion attributed to CdCS on the opposite chromosome[35].

3. Disease management

Randomized clinical trials in the PCD population are lacking, and publications of therapies in PCD mainly consist of case reports. Studies of non-CF bronchiectasis often do not indicate if patients with PCD are included, or if they were, how the diagnosis was made. Children with non-CF bronchiectasis are not generally included in non-CF studies. Thus, therapies for PCD are largely extrapolated from other diseases with defective mucociliary clearance, such as cystic fibrosis (CF) and non-CF bronchiectasis. For the purposes of this review, we will address and discuss existing as well as novel treatments that have been studied in the published literature, and review how these treatments might be useful in PCD. The assumption is made that while PCD is a disease associated with defective ciliary function, there are no other complications related to systemic manifestations, and that treatments shown to be useful in CF and non-CF bronchiectasis may therefore be extrapolated to PCD.

The three major focus areas to date are: airway clearance, infection control, and minimizing inflammation. Unlike the situation in CF where approaches have been studied to rectify the basic defect in the disease using gene therapy, and more recently molecular modulators, no such novel strategies have yet been tested in PCD.

3.1 Airway clearance: Devices and pharmacologic approaches (Table 3)

Normal mucociliary clearance, a critical component of airway host defense, occurs when the coordinated beating of motile cilia propel the airway surface liquid toward larger airways, expelling infectious and non-infectious particles out of the lungs. Alterations in the airway surface liquid, such as dehydration as seen in CF, and ineffective ciliary beating as seen in primary ciliary dyskinesia, markedly impair this process, leading to clinical disease[36–38]. This leaves mucus, irritants, and infection in the airways, resulting in increased inflammation and scarring, ultimately causing bronchiectasis. Therefore, it is imperative to augment airway clearance and avoid cough suppressing medications[1].

There are a variety of devices and methods available for airway clearance with no clear superiority shown for one over others. Intra-thoracic oscillatory devices generate oscillating positive pressure through a mouthpiece, resulting in vibrations that shake the mucus off the airway walls and intermittent elevation of endobronchial airway pressures that stent the airways open for more effective clearance. Airflow accelerations during exhalation mobilize

the freed mucus into the larger airways[39, 40]. Some of these devices connect to a nebulizer, allowing patients to inhale a medication and generate oscillations on exhalation. High frequency chest compression using vest therapy generate extra-thoracic oscillations at variable frequencies and intensities, which are transmitted to the airways[39, 41]. Other methods of airway clearance avoid the use of devices and include manual chest physiotherapy, postural drainage, autogenic drainage, active cycle breathing, and exercise[41–43]. Use of one method does not preclude use of another method, even in combination[44]. At this time, there is no clear evidence that one device or method is superior to another,[45, 46] although one study in children with PCD found that exercise was a more potent bronchodilator than inhaling a β2-agonist[47].

Another method of removing airway secretions is through airway hydration via aerosolized therapies, particularly when secretions are inspissated. In an early pilot study including solely PCD patients, aerosolized uridine-5′-triphosphate (UTP), which acts to increase chloride secretion (and thus water) across airway epithelia, significantly increased airway clearance as measured using clearance of radiolabeled particles during cough. Although an increase in ciliary beat would not be expected in PCD (unlike in healthy controls), UTP increased chloride conduction into the airway via an alternative channel, altering the liquid and mucin content within airway secretions, thus facilitating cough clearance[48]. Along similar lines, several studies have tested whether isotonic saline (0.9%) or hypertonic saline (3 or 7%) improves airway clearance in non-CF bronchiectasis. A small study in non-CF bronchiectasis patients demonstrated improved clearance after nebulizing isotonic saline prior to chest physiotherapy[49]. Prior to research demonstrating improved airway clearance in CF patients after nebulizing hypertonic saline, evidence emerged that nebulizing hypertonic saline was beneficial in non-CF bronchiectasis. Nebulizing hypertonic saline 7% resulted in significantly reduced sputum viscosity, increased ease of expectoration, and therefore, increased sputum volume expectorated as compared to isotonic saline. Small but significant improvements in lung function were also described[50]. After three months, individuals with non-CF bronchiectasis using hypertonic saline daily had decreased antibiotic use, lower health care utilization, and improved quality of life measures. There was continued improvement in sputum viscosity, ease of expectoration, and lung function[51]. In contrast, other studies have found no difference in exacerbation frequency, sputum colonization, lung function or quality of life after nebulizing hypertonic saline 6% or isotonic saline for 12 months[52]. As an example of why this might be, hypertonic saline is thought to disrupt the interactions between IL-8 and glycosaminoglycans. This makes IL-8 more susceptible to degradation, thereby limiting the concentrations of this pro-inflammatory cytokine within the airway[53]. The differing impact of hypertonic saline[54] may relate to individual variation in airway IL-8 levels as well as the underlying cause of the bronchiectasis. Based on two studies which found significantly higher levels of IL-8 in sputum expectorated from children with PCD as compared to children with CF[55, 56], PCD patients may have a greater potential to derive benefit from inhaled hypertonic saline, and deserves further study in this population.

Recombinant human DNase I (rhDNase, dornase alfa) provides significant benefit in CF[57], leading some to propose benefit in non-CF bronchiectasis. In the setting of infection, neutrophils accumulate in the airways and undergo necrosis; DNA and actin are released and

increase sputum viscosity[58–60]. Recombinant human DNase I cleaves extracellular DNA, decreasing the DNA concentration, and thereby decreasing sputum viscosity. There are several case reports noting improvement in pulmonary symptoms in PCD patients with both intermittent[61] and chronic use[62, 63]. Although PCD airway secretions contain elevated DNA concentrations[55], it is not to the same degree as CF. Importantly, a randomized control trial found that dornase alfa provided no benefit and potentially cause harm when used by idiopathic bronchiectasis patients[64]. It is unclear how many well-phenotyped PCD patients were enrolled in this study. For the present, inhaled dornase alpha is not recommended for patients with non-CF bronchiectasis, including PCD.

Inhaled mannitol increases mucociliary and cough clearance in patients with asthma, bronchiectasis, and CF by creating an osmotic drive for water to move into the airway and hydrate secretions[65]. In cell culture, mannitol increases ciliary beat frequency[66]. This therapy may be beneficial in PCD patients through improved cough clearance as it is unlikely to improve ciliary beat without correcting the underlying structural defect. In a recent publication of non-CF bronchiectasis patients, inhaled dry powder mannitol (400 mg twice daily) over 52 weeks did not decrease annual exacerbation rates (primary outcome) nor improve FEV1 but did increase the time to exacerbation and improved quality of life measures[67]. Overall, it was well tolerated with similar mild and moderate adverse event frequency to the placebo arm; the treatment arm had less frequent severe adverse events as compared to the control arm.

N-acetylcysteine (NAC) is a sulfhydryl compound that depolymerizes mucus in vitro by breaking the disulfide bonds, decreasing sputum viscosity. Because inhaling NAC can result in bronchospasm in patients with hyperresponsive airways and it possess a distasteful sulfur smell, it is typically taken orally. Unfortunately, there is no evidence that oral NAC reaches therapeutic concentrations in airway secretions[68]. Additionally, a small study of oral NAC in PCD patients found no improvement in clinical status or lung function[69].

Because nNO is low in PCD and NO plays a key role in host defense and up-regulation of ciliary motility, arginine, a precursor to nitric oxide (NO) synthesis, was postulated to have a therapeutic role in PCD. Despite encouraging preliminary data of nasal ciliary motility[70], arginine did not normalize airway nitric oxide concentrations nor improve lung function[71].

3.2 Infection control

Recommendations from the European Respiratory Society and British Thoracic Society suggest that clinicians monitor airflow mechanics (spirometry) and collect respiratory cultures, including those for NTM, regularly (every 3 to 6 months) in patients with PCD[1, 72]. Specimens should be processed in the same manner as CF sputum, given the similar microbial pathogens[11, 20]. Nebulizer equipment and airway clearance devices should be cleaned and disinfected according to CF guidelines.

3.21 Acute anti-microbial therapy—Manifestation of a bronchiectasis exacerbation includes an increase in sputum volume or change in sputum viscosity; an increase in sputum purulence; and an increase in cough, wheeze, and dyspnea[72]. Sputum should be sent for culture but should not delay initiation of antibiotics, whether oral or intravenous[72]. Prior

sputum culture results can help guide antibiotic choice. Management of the various microbes that usually occur in bronchiectasis including PCD (gram negatives, resistant Staph, fungi, and NTM) is beyond the scope of this article, and the reader is referred to published guidelines[72–74]. In general, there is little evidence supporting combination antibiotic therapy in the absence of *P. aeruginosa*. There is some controversy as to whether combination antibiotics are necessary in patients colonized with *P. aeruginosa.* The addition of inhaled tobramycin to oral ciprofloxacin during exacerbations improved microbial outcomes, but clinical outcomes were no different than treating with oral ciprofloxacin alone[75]. The optimal length of antibiotic treatment is unknown; the BTS guidelines recommending 14 days of treatment is based on grade D evidence[72].

3.22 "Preventive" (chronic) anti-microbials—There is no firm evidence as to when to initiate such treatment, but clinical experience suggests that inhaled antibiotics for prophylaxis should be considered in cases requiring repeated courses of oral antibiotics[76], particularly if adequate airway clearance is being performed. It is unlikely that patients who are non-compliant with airway clearance will regularly use inhaled antibiotics. The use of rotational oral antibiotics for long-term outpatient therapy is not recommended routinely[72]. In the US, tobramycin, aztreonam, and colistin are available in a nebulized form, although are not FDA approved for use in non-CF bronchiectasis as yet. Ciprofloxacin (liposomal and powder preparations), gentamicin, and liposomal amikacin are being tested in clinical trials in international studies. Inhaled tobramycin is both tolerable and beneficial in stable adult non-CF bronchiectasis patient with chronic *Pseudomonas* infection[77–79]. The benefit of inhaled aztreonam[80], colistin[81], and gentamicin[82] is less clear (Table 3). Two phase 2 clinical trials of inhaled ciprofloxacin have shown tolerability with significant reductions in total bacterial load and longer time to first exacerbation[83, 84].

3.3 Anti-inflammatory approaches

Previously extrapolated from CF literature, the use of macrolides to decrease airway inflammation in idiopathic bronchiectasis has recently been examined in several studies. The EMBRACE trial in New Zealand found that azithromycin 500 mg taken three days per week reduced exacerbation frequency in adults with idiopathic bronchiectasis who experienced at least one exacerbation in the preceding year. The number of individuals who cultured *Pseudomonas* or who carried a diagnosis of PCD is unknown[85]. In idiopathic bronchiectasis patients with at least two exacerbations in the previous year, the BLESS trial demonstrated that twice daily erythromycin ethylsuccinate significantly reduced exacerbations in all enrolled patients and in the pre-specified subgroup with baseline *Pseudomonas* airway infection[86]. Daily azithromycin 250 mg reduced infectious exacerbation in patients with at least three lower respiratory infections in the preceding year in the BAT trial[87]. Three and one PCD patient were enrolled in the BLESS and BAT trials respectively. In contrast to CF, most of the non-CF bronchiectasis patients cultured bacteria other than *P. aeruginosa*, suggesting that the mechanism of azithromycin may be both anti-inflammatory and anti-microbial. Patients should not receive chronic oral macrolides unless they have been tested and proven to *not* have sputum colonized or infected with NTM[5]. Overall, it appears that chronic use of a macrolide provides benefits in patients with non-CF bronchiectasis, including patients with PCD. Not all patients with PCD should automatically be prescribed

macrolides. In addition to those that may sporadically or chronically expectorate NTM, there are those in whom the potential for side effects (cardiac or gastrointestinal) may exceed the benefits described above, and there are patients with a good quality of life in whom macrolides can be considered in the future.

The use of inhaled corticosteroids, beta-agonists, leukotriene inhibitors, and oral corticosteroids should be considered in individuals with overlapping atopic disease[72, 88]. There is no clear evidence that use of these agents benefits all patients with PCD[5, 72, 74]. However, since asthma and allergies are common, they can be present in addition to PCD. Before adding beta-agonists to a treatment regimen, it should be noted that PCD patients can have spirometry measures that meet ATS criteria for repeatability but improve steadily due to cough clearance. If the patient has not reached a plateau during the pre-bronchodilator testing, one may erroneously assume that there is a post-bronchodilator response rather than attributing improvement to continued cough clearance.

Statins have effects beyond reducing cholesterol levels, including reducing inflammation and modulating the innate and adaptive immune systems. A recent publication demonstrated improvement in the Leicester Cough Questionnaire, a quality of life measurement instrument, in non-CF bronchiectasis patients after 6 months of atorvastatin. Further study is needed to determine if long-term statin use can also reduce exacerbations[89].

It is critical to avoid exposure to inflammatory triggers. Patients and family members who smoke should receive smoking cessation counseling. Routine immunizations including influenza, pneumococcus, and pertussis should be encouraged[1, 5].

3.4 Other management methods

Since PCD is a disease that affects cilia throughout the entire lung, lobectomy should be carefully considered and is rarely indicated. Patients in whom lobectomy should be considered include those with severe localized bronchiectasis with recurrent febrile relapses despite aggressive therapy and those with uncontrolled severe hemoptysis[90]. PCD patients with end stage lung disease are candidates for lung transplantation. A small number have been successfully performed in PCD patients, both with and without situs inversus[91].

3.5 Upper airway disease

The management of ear and nose disease is similar to the management of lung disease. Sinus rinses augment clearance of mucus from the nasal passages and sinuses[1]. Antibiotic rinses have been used to treat persistent bacterial colonization in PCD. Nasal steroids can be helpful in patients with significant allergic rhinitis and sinusitis. In patients with sinus disease refractory to medical management, functional endoscopic sinus surgery is helpful, particularly if there is aggressive postsurgical treatment to maintain adequate drainage[92]. Tympanostomy tube placement is controversial. Although tubes may improve hearing[93], otitis media can improve during the teen years, and tubes may result in persistent otorrhea[94]. Because conductive hearing loss due to chronic otitis media can result in speech and language development delay, audiology assessments, hearing aids, and adjunctive therapies should be encouraged[1].

4. Conclusion

In conclusion, primary ciliary dyskinesia is a genetically heterogeneous recessive disorder of motile cilia which results in chronic oto-sino-pulmonary disease. Diagnostic methods have advanced to now include nNO as a screening test in individuals with a compatible clinical phenotype and other known causes of bronchiectasis and chronic oto-sino-pulmonary disease have been excluded. Ciliary ultrastructural abnormalities as seen on electron microscopy and videomicroscopy are useful adjunctive diagnostic modalities as the genetic mutations involved in PCD are further identified. Management of PCD is primarily extrapolated from studies in cystic fibrosis and non-CF bronchiectasis. The foundation of managing disease in PCD includes airway clearance, infection control, and reduction of inflammation. With the development of clinical and research consortiums and actively enrolling registries of PCD patients, the environment is conducive to initiate longitudinal studies of disease course as well as therapeutic trials to alter disease course.

5. Expert Opinion

The method of diagnosing PCD has dramatically changed over the past decade. Through large cross-sectional studies, the clinical phenotype of PCD has been refined with better definitions and new knowledge, for example, the high prevalence of neonatal respiratory distress in PCD, and the association with complex congenital heart disease. It is now known that mutations that preserve the ciliary central apparatus do not result in situs abnormalities, and that PCD individuals with situs ambiguous are more likely to have complex congenital heart disease. Nasal NO has proven to be an excellent screening test for PCD. However, like sweat chloride in CF, nNO levels in PCD can include false positives as well as false negatives, underscoring the importance of determining the genetic mutations. The diagnosis of PCD had hinged on the visualization of ciliary ultrastructural defects on EM, an imperfect diagnostic method. At least 30% of individuals with PCD have normal ciliary ultrastructure (*DNAH11* and *CCDC65* mutations). Other mutations result in ultrastructural defects in only a subset of cilia; this may not be appreciated without the skill and expertise in sample processing and image interpretation. Elucidating genetic mutations for all patients with PCD is rapidly becoming a reality. The number of known PCD causing genes has more than doubled in the past three years, and a PCD research genetic panel is under development through the GDMCC.

Treatment of PCD patients lacks evidence and standardization. Many patients receive sub-optimal management including lack of sputum cultures and pathogen directed antibiotic therapy. The Bronchiectasis Severity Index (BSI) can help clinicians identify patients, including those with PCD bronchiectasis, who are at high risk of developing bronchiectasis complications and therefore, may benefit from intensification of therapies such as adding inhaled antibiotics or oral macrolides[95].

Working together, the GDMCC and the PCD Foundation have developed the PCD Foundation Clinical and Research Center Network (CRCN), which includes the eight original GDMCC sites, four new sites, and nine affiliate sites. The goal of the CRCN is to provide a reliable diagnosis; consistent high-quality, appropriate care; and comprehensive

data collection through the PCD registry[96]. BESTCILIA is a research consortium comprised of ten European clinical centers and two US clinical centers with the goal of improving the clinical practice in PCD care through standardized care protocols and diagnostic testing as well as observational and randomized control trials[97]. The development and validation of a PCD quality of life instrument[98, 99] leaves researchers well-poised to capitalize on patient participation in the CRCN and PCD registry with longitudinal studies to more accurately describe disease course and randomized control studies to alter this course.

Therapeutic studies directly assessing the benefit of hypertonic saline, azithromycin, or even dornase alfa are potential initial research directions. Looking to the future, given the success with modulatory therapeutics for CF, it is conceivable that genetic modulators could improve or fully correct ciliary defects in PCD. Extrapolating from the chronic bronchitic COPD phenotype, roflumilast may decrease the airway inflammation seen in PCD. A new orphan drug candidate, NM001 (Lynovex®; NovaBiotics) is a mucolytic agent being tested in CF, and potentially other chronic lung diseases. When considering these types of therapeutic trials, it is critical to choose the correct primary outcome. Exacerbation rate was a sound outcome in the macrolide studies, given that exacerbations manifest with increased inflammation and macrolides are presumably acting as an anti-inflammatory agent. A quality of life measurement was used in the atorvastatin trial and reached significance. However, quality of life measures and exacerbation frequency have not yielded the same outcomes in the inhaled antibiotic studies.

PCD is a genetically heterogenous disease with a variety of mutations in numerous genes resulting in a shared phenotype, sparing no race or ethnic group. Despite general perceptions, PCD lung disease may not necessarily be mild. A delay in recognizing PCD features and formal diagnosis can result in the development and progression of irreversible lung disease. In CF, early identification and diagnosis leads to early treatment and frequent monitoring to decrease morbidity and mortality. Although CF and PCD are both recessive disorders that result in bronchiectasis and sinusitis, the underlying pathogenesis differs. While the CF model is appropriate for disease follow up and development of a clinical network of disease expertise, PCD is not the same as CF, and management is not identical[100]. This is evidence in prior studies of UTP, which demonstrated improved airway clearance in PCD patients but no benefit in CF patients. Without further PCD patients to test the therapy, there was little incentive for pharmaceutical companies to pursue drug development. Improved identification and more accurate diagnosis of PCD provides a large cohort of PCD patients who are eager to participate in research with the goal of improving clinical care.

Acknowledgments

Thanks to Dr. Michael R. Knowles and Dr. Maimoona Zariwala for their guidance and support, to all of the GDMCC investigators and study coordinators for their hard work, and to the PCD patients for their participation.

MLD is supported by US National Institute of Health (NIH) – National Heart, Lung, and Blood Institute K12 (1K12HL119998-01) and ORDR (U54HL096458). The Genetic Disorders of Mucociliary Clearance Consortium (U54HL096458) is part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN), supported through collaboration between the NIH Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Science (NCATS), and the National Heart, Lung & Blood Institute

(NHLBI). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial disclosure

P Noone has participated in industry sponsored studies for Gilead, Insmed and Aragigm Pharmaceuticals.

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Article Highlights

- Primary ciliary dyskinesia is a genetically heterogeneous recessive disorder of motile cilia that results in chronic oto-sino-pulmonary disease as well as organ laterality defects and congenital heart disease.
- Nasal nitric oxide is a useful screening test in individuals with a compatible clinical phenotype and in whom other known cause of chronic oto-sino-pulmonary disease have been excluded.
- Although useful, biologic diagnostic methods, such as assessment of ciliary ultrastructure using electron microscopy and visualization of ciliary motility using videomicroscopy, are limited by technical skill and availability of equipment.
- Continued identification of genetic mutations causing PCD provides a more definitive diagnostic method. Over 65% of PCD patients have biallelic mutations identified in one of the 30 published PCD genes.
- The foundation of managing disease in PCD includes airway clearance, infection control, and reduction of inflammation. Use of the Bronchiectasis Severity Index can help identify individuals at high risk of complications from their bronchiectasis who may benefit from intensification of therapies.
- With the development of clinical and research consortiums and actively enrolling registries of PCD patients, the environment is conducive to initiate longitudinal studies of disease course as well as therapeutic trials to alter disease course.

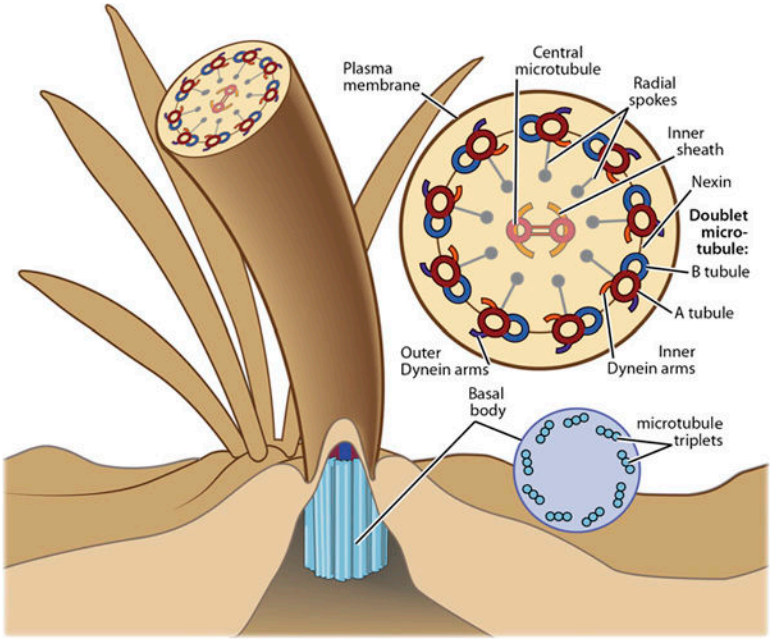

Figure 1. Normal motile cilia (9+2) configuration

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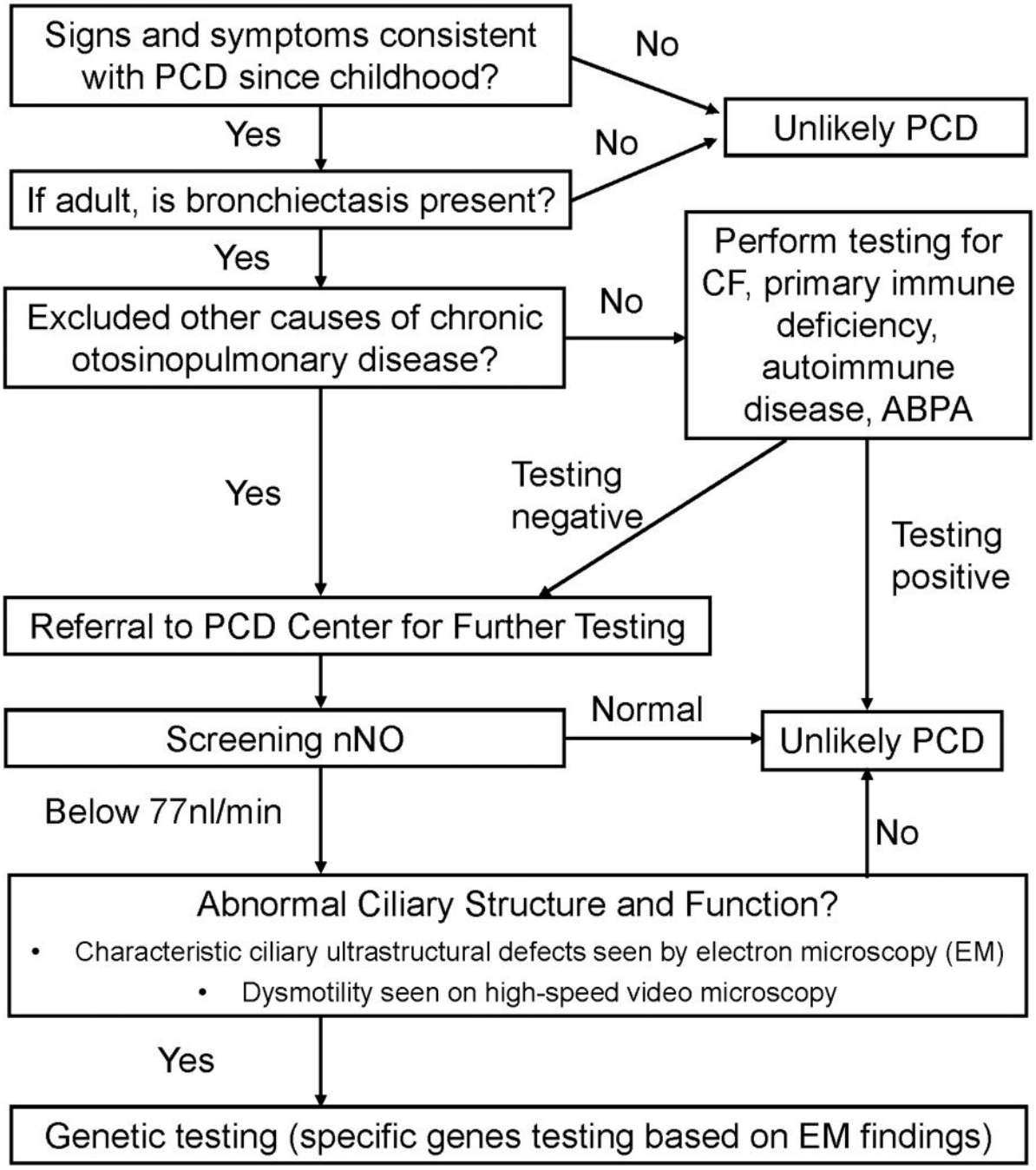

Figure 2.
Diagnostic algorithm for PCD diagnosis

Table 1

Clinical Features of Primary Ciliary Dyskinesia

Location of Dysfunctional Cilia	Features
Embryonic Node	Laterality defects
	Congenital heart disease
Nose & Sinus	Year-round, daily nasal congestion
	Pan-sinusitis
Eustachian Tubes	Chronic or recurrent otitis media
	Transient hearing loss
Trachea & Bronchi	Year-round, daily wet cough
	Unexplained neonatal respiratory distress
	Recurrent lower respiratory infections
	Bronchiectasis
Reproductive Tract	Infertility
	Ectopic pregnancy

Table 2

Mutations in Genes that Cause Human Primary Ciliary Dyskinesia[34]

Gene	Chromosomal Location	Axonemal Component	Ciliary Ultrastructure in Subjects with Biallelic Mutations	Laterality Defects Present	Gene MIM#
DNAH5	5p15.2	ODA dynein HC	ODA defect	yes	603335
DNAI1	9p21-p13	ODA dynein IC	ODA defect	yes	604366
DNAI2	17q25	ODA dynein IC	ODA defect	yes	605483
DNAL1	14q24.3	ODA dynein LC	ODA defect	yes	610062
CCDC114	19q13.32	ODA DC	ODA defect	yes	615038
CCDC151	19p13.2	ODA transport component	ODA defect	yes	615956
ARMC4	10p12.1-p11.23	ODA transport component	ODA defect	yes	615408
TXNDC3 (NME8)	7p14-p13	ODA dynein IC/LC	Partial ODA defect (66% cilia defective)	yes	607421
DNAAF1 (LRRC50)	16q24.1	Cytoplasmic DA preassembly factor	ODA+IDA defect	yes	613190
DNAAF2 (KTU)	14q21.3	Cytoplasmic DA preassembly factor	ODA+IDA defect	yes	612517
DNAAF3 (C19orf51)	19q13.42	Cytoplasmic DA preassembly factor	ODA+IDA defect	yes	614566
CCDC103	17q21.31	Cytoplasmic DA attachment factor	ODA+IDA defect	yes	614677
HEATR2	7p22.3	Cytoplasmic DA preassembly or transport	ODA+IDA defect	yes	614864
LRRC6	8q24	Cytoplasmic DA preassembly or transport	ODA+IDA defect	yes	614930
C21orf59	21q22.1	Cytoplasmic DA assembly or adaptor for transport	ODA+IDA defect	yes	615494
SPAG1	8q22	Cytoplasmic DA preassembly or transport	ODA+IDA defect	yes	603395
DYX1C1	15q21.3	Cytoplasmic DA preassembly factor	ODA+IDA defect	yes	608706
ZMYND10	3p21.3	Cytoplasmic DA assembly	ODA+IDA defect	yes	607070
CCDC39	3q26.33	N-DRC	IDA defect + Axonemal disorganization	yes	613798
CCDC40	17q25.3	N-DRC	IDA defect + Axonemal disorganization	yes	613799
CCDC164 (DRC1)	2p23.3	N-DRC	Nexin link missing; axonemal disorganization in small proportion of cilia	no	615288
RSPH4A	6q22.1	RS component	Mostly normal, CA defects in small proportion of cilia	no	612647
RSPH9	6p21.1	RS component	Mostly normal, CA defects in small proportion of cilia	no	612648
RSPH1	21q22.3	RS component	Mostly normal, CA defects in small proportion of cilia	no	609314

Gene	Chromosomal Location	Axonemal Component	Ciliary Ultrastructure in Subjects with Biallelic Mutations	Laterality Defects Present	Gene MIM#
HYDIN	16q22.2	CA component	Normal, very occasionally CA defects	no	610812
DNAH11	7p21	ODA dynein HC	Normal	yes	603339
CCDC65 (DRC2)	12q13.12	N-DRC	Normal	no	611088
MCIDAS	5q11.2	multiciliated cell differentiation	Oligocilia	no	614086
CCNO	5q11.2	multiciliated cell differentiation	Oligocilia	no	607752
DNAH8	6p21.2	ODA dynein HC	Unknown	Unknown	60337
RPGR	Xp21.1	Unknown	Mixed	no	312610
OFD1	Xq22	Unknown	Unknown	no	300170

DA: dynein arm; ODA: outer dynein arm; IDA: inner dynein arm; CA: central apparatus; RS: radial spoke; HC: heavy chain; LC: light chain; IC: intermediate chain; DC: docking complex; N-DRC: nexin-dynein regulatory complex.

Expert Opin Orphan Drugs. Author manuscript; available in PMC 2016 March 16.

Table 3

Summary of Therapeutic Trials in non-CF Bronchiectasis

Author	Study	N	Intervention	Duration	Primary Outcome	Result
O'Donnell et al. 1998[64]	Randomized	349	Aerosolized rhDNase 2.5mg versus placebo	24 weeks	Incidence of exacerbations and mean % change in FEV1	rhDNase increased exacerbations and decreased FEV1
Barker et al. 2000[78]	Randomized	74	Tobramycin solution for inhalation (300 mg) twice daily versus placebo	4 weeks	Change in *P aeruginosa* density from baseline	Reduction in *P aeruginosa* bacterial density
Drobnic et al. 2005[79]	Randomized crossover	30	Aerosolized tobramycin 300 mg twice daily versus placebo	6 months	Number of exacerbations and number of hospitalizations	No difference in exacerbations but fewer individuals on tobramycin needed admission and those who were admitted had a shorter duration of hospitalization.
Murray et al. 2011[82]	Randomized	65	Gentamicin 80 mg nebulized twice daily versus placebo	12 months	Sputum bacterial density, sputum purulence, lung function, exercise capacity, LCQ, SGRQ, exacerbation frequency	Reduced sputum bacterial density and purulence; increased exercise capacity; fewer exacerbations and increased time to first exacerbation; improvement in LCQ and SGRQ. No change in sputum volume or lung function.
Serisier et al. 2013[83]	Randomized	42	Dual release ciprofloxacin for inhalation versus placebo nebulized once daily for up to 3 treatment cycles of 28 days	24 weeks	Change in sputum *P aeruginosa* bacterial density to end of treatment cycle 1	Reduction in *P aeruginosa* bacterial density
Wilson et al. 2013[84]	Randomized	60	Ciprofloxacin dry powder for inhalation (32.5 mg) twice daily versus placebo	28 days of therapy and 56 days of follow up	Bacterial density in sputum	Significant reduction in total bacterial load
Barker et al. 2014[80]	Randomized	540	Aztreonam for inhalation solution 75 mg three times per day versus placebo (E-flow nebulizer)	16 weeks	Change in QOL-B-RSS	No difference in QOL-B-RSS
Haworth et al. 2014[81]	Randomized	144	Colistin 1 million IU versus placebo (saline 0.45%) via I-neb twice daily	6 months	Time to exacerbation	No difference. Subanalysis showed benefit in the individuals compliant with colisitin therapy.
Wong et al. 2012[85]	Randomized	141	Azithromycin 500 mg three days per week versus placebo	6 months	event based exacerbations, change in FEV1, and change in SGRQ	Exacerbation rate decreased. No change in FEV1 or SGRQ
Altenburg et al. 2013[87]	Randomized	83	Azithromycin 250 mg daily versus placebo	12 months	Exacerbations over 12 months	Decreased exacerbations
Serisier et al. 2013[86]	Randomized	117	Twice daily erythromycin ethylsuccinate 400 mg versus placebo	12 months	Annualized mean rate of protocol defined pulmonary exacerbations	Decreased exacerbations
Mandal et al. 2014[89]	Randomized	60	Atorvastatin 80 mg daily versus placebo	6 months	Reduction in cough using Leicester Cough Questionnaire	Improved cough on quality of life scale (LCQ).

LCQ: Leicester Cough Questionnaire; SGRQ: St. George Respiratory Questionnaire; QOL-B-RSS: Quality of Life-Bronchiectasis Respiratory Symptoms Score