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.

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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
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, and nearly all PCD patients demonstrate severe pansinusitis on computed tomography (CT) scan. PCD clinical feature

| 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[^2]                                   |
| Bronchiectasis                              | School age                                      | Adult                                           |
| Male infertility                            | —                                               | Adult                                           |

[^1]: Adapted from Knowles et al.[^3]

[^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.

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

- SIT, situs inversus totalis; SA, situs ambiguus.
- Adapted from Knowles et al.[^3]
- Reference.[^28]

[^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.

Diagnosis and Management of PCD

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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. Patients with biallelic mutations in *RSPO1* 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. 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 and is recommended as part...
of a panel of diagnostic tests for PCD. Disease causing EM defects in the outer dynein arms, outer and inner dynein arms, inner dynein arms with microtubule disorganization, radial spokes, or central apparatus 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, or subtle abnormalities (particularly those involving the central apparatus and radial spokes) that are not readily recognized on EM. Additionally, repeat biopsies that fail to demonstrate any respiratory cilia could represent an oligociliary defect causing PCD. It is estimated that EM will detect approximately 70% of all PCD cases, 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 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<sup>1</sup>                      | Low<sup>2</sup>                      |
| Ciliary biopsy with electron microscopy                                                          | Variable<sup>3</sup>                | Variable<sup>4</sup>                |
| PCD genetic testing panels                                                                      | Low<sup>5</sup>                      | Moderate<sup>6</sup>                |
| Functional ciliary beat/waveform analysis with high speed videomicroscopy                        | Variable<sup>7</sup>                | Moderate<sup>8</sup>                |
| Immunofluorescence testing                                                                      | Unknown                              | Unknown                              |

<sup>1</sup>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.

<sup>2</sup>Reference.<sup>18</sup>

<sup>3</sup>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.<sup>4</sup>

<sup>4</sup>Several PCD-causing genetic mutations can result in normal electron microscopy<sup>10</sup> or subtle changes which are not readily apparent.<sup>38</sup>

<sup>5</sup>Misinterpretation of genetic panel result (e.g., variants of unknown significance or single mutations in two different PCD genes interpreted as “diagnostic”).

<sup>6</sup>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.

<sup>7</sup>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.

<sup>8</sup>Subtle waveform defects will be missed in centers without extensive experience.

### 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<sup>*</sup>

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.

<sup>*</sup>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.

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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. 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. 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. 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, 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. Handheld electrochemical nNO analyzers are affordable and portable, but with only limited prospective study in PCD, these devices are not currently recommended for PCD testing.

Nasal nitric oxide values are extremely low in PCD. 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). 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. 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. Other conditions can also result in nNO levels below PCD cutoff values (i.e., HIV, panbronchiolitis, non-atopic sinusitis). Lastly, nNO device operators must be well trained and use standard operating protocols to avoid false results.

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. Functional ciliary analysis is difficult to perform correctly, and considerable experience is necessary to avoid false-positive and false-negative results. Biopsies should only be performed when
patients are in their baseline state of health. Repeat biopsies are required to assure abnormal beat patterns are not due to secondary processes, such as viral illness,\textsuperscript{63} tobacco or environmental exposures,\textsuperscript{64} poor biopsy specimen,\textsuperscript{16} or improper biopsy processing.\textsuperscript{14} Some European centers also maintain biopsied epithelial cells in culture for weeks, at an air-liquid interface, to remove influence of secondary insults.\textsuperscript{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.\textsuperscript{65,66} Through staining of specific ciliary proteins (DNAH5, DNAI2, DNALI1, and RSPH4A/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.\textsuperscript{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.\textsuperscript{66} Additionally, IF diagnostic results do not seem to be affected by secondary insults.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{79} ciliary beat frequency calculation,\textsuperscript{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.\textsuperscript{87,88} 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 conditions such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and bronchiectasis. These conditions often present with similar symptoms, such as chronic cough, recurrent respiratory infections, and abnormal lung function tests. Therefore, it is crucial to differentiate these conditions from PCD in order to provide appropriate medical care. In cases where symptoms are nonspecific, genetic testing can help confirm the diagnosis.
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 and produce nNO levels below the PCD diagnostic cutoff of 77 nl/min. Immunodeficiency can also present similarly.

**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                                           |
| DNH11     | +++               | Normal                   | Yes                                           |
| CCDC39    | +++               | IDA defect + MTD defect  | Yes                                           |
| CCDC40    | +++               | IDA defect + MTD defect  | Yes                                           |
| RSPF9     | +                 | Central pair defect or normal | Yes                                     |
| RSPF4A    | ++                | Central pair defect or normal | Yes                               |
| RSPF1     | ++                | Central pair defect or normal | Yes                                     |
| RSPF3     | +                 | Central pair defect or normal | Yes                                     |
| CCNO      | +                 | Oligocilia (residual axoneme normal) | Yes                                      |
| MCIDA5    | +                 | Oligocilia (residual axoneme abnormal) | Yes                                     |
| DNAH8     | +                 | Not available            |                                               |
| CCDC151   | ++                | ODA defect               |                                               |
| ARM4C     | ++                | ODA defect               |                                               |
| DXY1C1    | +                 | 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.

**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<sup>1</sup>               | Very high<sup>1</sup>               |
| Radioaerosol mucociliary clearance tests                     | High<sup>2</sup>                    | —                                   |
| Ciliary beat frequency alone (CBF)                           | High<sup>3</sup>                    | High<sup>3</sup>                    |
| Ciliary motion analysis without high speed videomicroscopy   | Very high<sup>4</sup>               | Very high<sup>4</sup>               |

<sup>1</sup>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.

<sup>2</sup>This test can result in false positive PCD diagnoses, as detected abnormalities in mucociliary clearance lack specificity, and may be due to secondary causes.

<sup>3</sup>In proven cases of PCD, CBF can be low, normal, or high, leading to false positive and false negative results.<sup>80</sup>

<sup>4</sup>Visual assessment of ciliary motion without high speed video-recording devices will lead to frequent false positive and false negative results.

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to PCD, and in patients with suspected PCD, laboratory studies investigating immunodeficiency are necessary. Preliminary study of nNO in certain humoral immunodeficiencies has shown normal values well above 77 nL/min, but further study is required to know if all forms of immunodeficiency produce normal nNO levels.

Pulmonary aspiration, with or without gastroesophageal reflux, can cause chronic respiratory symptoms in adults and children, including cough, wheeze, bronchitis, or pneumonia. Thus in patients with possible PCD, a thorough feeding history is essential. A history of chronic cough from asthma can also resemble PCD in young children, especially with frequent viral infections from daycare exposures. Additionally, chronic nasal congestion from allergic rhinitis can seem similar to PCD rhinosinusitis. However, PCD nasal disease is present year-round and does not resolve with seasonal change, as often occurs with allergic rhinitis. Lastly, protracted bacterial bronchitis (PBB) is a disorder of preschool aged children causing >3 weeks of wet cough with lower airway bacterial infection and airway neutrophilia. 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 Orofaciodigital Syndrome (including mental retardation, craniofacial abnormalities, macrocephaly, digital anomalies, and cystic kidneys) are X-linked disorders involving ciliary genes, RPGR and OFD1, respectively. Although these account for a very small minority of PCD cases, there may be further overlap of retinal and respiratory cilia. 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, but increased rates of bronchiectasis are found in polycystic kidney disease. 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 DNAHS on the remaining chromosome. Glanzmann Thrombasthenia (associated with ITGB3) can occur with PCD (associated with CCDC103) through mutations in the neighboring genes on chromosome 17. Alternatively, PCD can co-exist with other rare diseases through disease-causing mutations which are not in close genetic proximity; such as cystic fibrosis due to mutations in CFTR (Chr7q) with PCD due to mutations in DNAH11 (Chr7p), and Miller Syndrome due to mutations in DHODH (Chr16) with PCD due to mutations in DNAHS (Chr5).

Recent publications have also shown respiratory ciliary dysfunction in patients with mild forms of congenital heart disease, not meeting cardiology definitions for SA or

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

| Chronic condition                  | Methods of evaluation                                                                 |
|------------------------------------|---------------------------------------------------------------------------------------|
| Cystic fibrosis 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 clavulanic acid. The cough usually does not return after a subsequent 2-week period off antibiotics. |
heterotaxy. 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. 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. 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 and evidence of aspergillus specificity), and bronchoscopy with bronchoalveolar lavage fluid cultures to guide antimicrobial therapy.

**Spirometry** using ATS/ERS criteria 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. Chest radiography should be performed at diagnosis and during respiratory exacerbations, as indicated. Otherwise, chest radiography should be performed every

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**TABLE 7—Other Diseases Co-Segregating With PCD**

| Associated rare disorder | Level of PCD association | Method of PCD overlap | Specific gene affected |
|--------------------------|--------------------------|-----------------------|-----------------------|
| Situs ambiguous 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) |
| Retinitis pigmentosa | Multiple unrelated cases reported; <1% of PCD | Shared common gene mutation | RPRGR |
| Orofaciodigital syndrome (sibling males with mental retardation and macrocephaly) | 1 sibling-pair reported; <1% of PCD | Shared common gene mutation | OFDI |
| Cri du chat syndrome | 2 unrelated cases reported | Mutation in close proximity to PCD gene | Chr 5p deletion including DNAH5 |
| Glanzmann thrombasthenia | 1 sibling-pair reported | Mutation in close proximity to PCD gene | Chr 17q haplotype that includes CCDC103 and ITGB3 |
| Cystic fibrosis | 1 case reported | Mutations in two different genes | Chr 7 including region with DNAH11 and CFTR via uniparental isodisomy |
| 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 |
| 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. 2 unrelated cases; 1 with outer dynein arm defect and low IgG titers, and 1 with Kartagener Syndrome, abnormal ciliary ultrastructure, and low IgG, IgM, Tetanus and S.pneumoniae titers after booster |
| Polycystic kidney disease | 1 case reported | Unknown | Unknown |
| Familial mediterranean fever | 1 case reported | Unknown | MEFV-R202Q polymorphism on Chr 16p13.3 and unknown PCD gene |
| Other non-motile ciliopathies (Joubert, Bardet-biedl, Usher, Jeune syndromes, and others) | No definite cases reported | Unknown | Unknown |

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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. Some centers perform chest CT scans on PCD patients every 5 years, but there is no evidence that this improves clinical outcomes, 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. More stringent infection control policies have the potential to cause psychosocial harm to patients and families, 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). 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, 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. 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.

All patients undergoing PET insertion should be counselled on the likelihood of multiple insertions, postoperative otorrhea, and the possibility of a permanent

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**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) |
|                                 | 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)
- Influenza vaccine: annually
- 13-valent pneumococcal vaccine: per ACIP guidelines
- 23-valent pneumococcal vaccine: per ACIP guidelines
- RSV immunoprophylaxis: consider monthly in first winter

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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.

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tympanic membrane perforation (up to 50% in one study). Additionally, patients with PET are typically seen by their otolaryngologist every 3–6 months while the tubes remain in place. 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 and is easily controlled with topical therapies. Persistent otorrhea can be attributed to biofilm formation, especially in children with longer lasting PET; 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 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. Although CRS is not generally life threatening, it substantially affects quality of life. Daily saline irrigation has been demonstrated as safe and beneficial in patients with CRS. 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. 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, 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. Unlike cystic fibrosis, cough clearance is preserved in PCD. 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, and exercise may improve mucus clearance.

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), and oral antibiotics are recommended for mild exacerbations. Most physicians use a broad-spectrum oral antibiotic (amoxicillin plus clavulanic 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, cystic fibrosis, and non-CF bronchiectasis). 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. 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 and pneumococcal vaccinations (per the Advisory Committee on Immunization Practices) are recommended in PCD. In the first year of life, monthly (seasonal) immunoprophylaxis against respiratory syncitial 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, and several months of inhaled aminoglycosides or colistin in *Pseudomonas* colonized adults with non-CF bronchiectasis result in decreased hospitalization and improved respiratory symptoms. 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. When using chronic macrolide therapy, sputum culture surveillance for non-tuberculous mycobacterium infection is indicated. Prospective clinical study of chronic
macrolides in adults and children with non-CF bronchiectasis shows decreased respiratory exacerbations and improved lung function, but increased emergence of macrole resistant respiratory organisms. The long-term significance of macrolide resistance is unclear. Small case reports of chronic macrolide therapy in PCD also demonstrate some benefits, although not as robust as those in non-CF bronchiectasis. Remote studies on trimethoprim-sulfamethoxazole in chronic bronchitis also suggest benefit, but this agent has not been studied in PCD.

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. 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. 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. Mannitol has not been studied in PCD.

DNase (dornase-alpha 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 and increased frequency of respiratory exacerbations with worsened lung function in another study. Several case reports of DNase in PCD suggest possible benefit when used for both short and long-term periods. 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, whereas another study showed unchanged lung function after 6 weeks of regular bronchodilators.

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. Similarly, intravenous immunoglobulin (IVIG) is not recommended for routine use in patients with PCD. Immunodeficiency rarely exists with PCD, 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.

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.

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REFERENCES

1. Davis SD, Ferkol TW, Rosenfeld M, Lee HS, Dell SD, Sagel SD, Millia C, Zariwala MA, Pittman JE, Shapiro AJ, et al. Clinical features of childhood primary ciliary dyskinesia by genotype and ultrastructural phenotype. Am J Respir Crit Care Med 2015;191:316–324.

2. Magnin ML, Cros P, Beydon N, Mahloul M, Tamalet A, Escudier E, Clement A, Le Pointe HD, Blanchon S. Longitudinal lung function and structural changes in children with primary ciliary dyskinesia. Pediatr Pulmonol 2012;47:816–825.

3. Marthin JK, Petersen N, Skovgaard LT, Nielsen KG. Lung function in patients with primary ciliary dyskinesia: a cross-sectional and 3-decade longitudinal study. Am J Respir Crit Care Med 2010;181:1262–1268.

4. Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. Am J Respir Crit Care Med 2013;188:913–922.

5. Leigh MW, O’Callaghan C, Knowles MR. The challenges of diagnosing primary ciliary dyskinesia. Proc Am Thorac Soc 2011;8:434–437.

6. Hosie P, Fitzgerald DA, Jaffe A, Birman CS, Morgan L. Primary ciliary dyskinesia: overlooked and undertreated in children. J Paediatr Child Health 2014;50:952–958.

7. Lucas JS, Leigh MW. Diagnosis of primary ciliary dyskinesia: searching for a gold standard. Eur Respir J 2014;44:1418–1422.

8. Zariwala MA, Knowles MR, Leigh MW. Primary ciliary dyskinesia. 2007 Jan24 [updated 2015 Sep 3] In: Pagon RA, Adam MP, Amemiya A, Bird TD, et al., editors. GeneReviews™. Seattle (WA): University of Washington, Seattle; 1993–2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK11222/.

9. Boon M, Jorissen M, Proesmans M, De Boeck K. Primary ciliary dyskinesia, an orphan disease. Eur J Pediatr 2013;172:151–162.

10. Knowles MR, Leigh MW, Carson JL, Davis SD, Dell SD, Ferkol TW, Olivier KN, Sagel SD, Rosenfeld M, Burns KA, et al. Mutations of DNAH11 in patients with primary ciliary dyskinesia with normal ciliary ultrastructure. Thorax 2012;67:433–441.

11. O’Callaghan C, Rutman A, Williams GM, Hirst RA. Inner dynein arm defects causing primary ciliary dyskinesia: repeat testing required. Eur Respir J 2011;38:603–607.

12. Kim RH, A Hall D, Cutz E, Knowles MR, Nelligan KA, Nykamp K, Zariwala MA, Dell SD. The role of molecular genetic analysis in the diagnosis of primary ciliary dyskinesia. Ann Am Thorac Soc 2014;11:351–359.

13. Berg JS, Evans JP, Leigh MW, Omar H, Bizon C, Mane K, Knowles MR, Weck KE, Zariwala MA. Next generation massively parallel sequencing of targeted exomes to identify genetic mutations in primary ciliary dyskinesia: implications for application to clinical testing. Genet Med 2011;13:218–229.

14. Jackson CL, Goggin PM, Lucas JS. Ciliary beat pattern analysis below 37 degrees C may increase risk of primary ciliary dyskinesia misdiagnosis. Chest 2012;142:543–544; author reply 544–5.

15. Hirst RA, Rutman A, Williams G, O’Callaghan C. Ciliated air-liquid cultures as an aid to diagnostic testing of primary ciliary dyskinesia. Chest 2010;138:1441–1447.

16. Thomas B, Rutman A, O’Callaghan C. Disrupted ciliated epithelium shows slower ciliary beat frequency and increased dyskinesia. Eur Respir J 2009;34:401–404.

17. Mateos-Corral D, Coombs R, Grasemann H, Ratjen F, Dell SD. Diagnostic value of nasal nitric oxide measured with non-velum closure techniques for children with primary ciliary dyskinesia. J Pediatr 2011;159:420–424.

18. Leigh MW, Hazucha MJ, Chawla KK, Baker BR, Shapiro AJ, Brown DE, Lavange LM, Horton B, Qajish B, Carson JL, et al. Standardizing nasal nitric oxide measurement as a test for primary ciliary dyskinesia. Ann Am Thorac Soc 2013;10:574–581.

19. Shapiro AJ, Davis SD, Ferkol T, Dell SD, Rosenfeld M, Olivier KN, Sagel SD, Millia C, Zariwala MA, Wolf W, et al. Laterality defects other than situs inversus totalis in primary ciliary dyskinesia: insights into situs ambiguous and heterotaxy. Chest 2014. 146:1176–86.

20. Shapiro AJ, Tolleson-Rinehart S, Zariwala MA, Knowles MR, Leigh MW. The prevalence of clinical features associated with primary ciliary dyskinesia in a heterotaxy population: results of a web-based survey. Cardiol Young 2014;25:752–9.

21. Moore A, Escudier E, Roger G, Tamalet A, Pelosse B, Marlin S, Clément A, Geremek M, Delaisi B, Bridoux AM, et al. RPGR is mutated in patients with a complex X linked phenotype combining primary ciliary dyskinesia and retinitis pigmentosa. J Med Genet 2006;43:326–333.

22. Shapiro AJ, Weck KE, Chao KC, Rosenfeld M, Nygren AE, Knowles MR, Leigh MW, Zariwala MA. Cri du chat syndrome and primary ciliary dyskinesia: a common genetic cause on chromosome 5. J Pediatr 2014;165:858–861.

23. Lucas JS, Carroll M. Primary ciliary dyskinesia and cystic fibrosis: different diseases require different treatment. Chest 2014;145:674–676.

24. Cohen-Cymberknoh M, Simonovský N, Hiller N, Gileles Hillel A, Shoseyov D, Kerem E. Differences in disease expression between primary ciliary dyskinesia and cystic fibrosis with and without pancreatic insufficiency. Chest 2014;145:738–744.

25. Paff T, van der Schee MP, Daniels JM, Pals G, Postmus PE, Sterk PJ, Haarman EG. Exhaled molecular profiles in the assessment of cystic fibrosis and primary ciliary dyskinesia. J Cyst Fibros 2013;12:454–460.

26. Horvath I, Loukides S, Wodehouse T, Csizser E, Cole PJ, Khaitonov SA, Barnes PJ. Comparison of exhaled and nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia. Thorax 2003;58:68–72.

27. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ, Group GW. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.

28. Mullaney T, Manson D, Kim R, Stephans D, Shah V, Dell S. Primary ciliary dyskinesia and neonatal respiratory distress. Pediatrics 2014;134:1160–1166.

29. Campbell R. Managing upper respiratory tract complications of primary ciliary dyskinesia in children.Curr Opin Allergy Clin Immunol 2012;12:32–38.

30. Afzelius BA. A human syndrome caused by immotile cilia. Science 1976;193:317–319.

31. Sommer JU, Schafer K, Omran H, Olbrich H, Wallmeier J, Blum A, Hornmann K, Stuck BA. ENT manifestations in patients with primary ciliary dyskinesia: prevalence and significance of otorhinolaryngologic co-morbidities. Eur Arch Otorhinolaryngol 2011;268:383–388.

32. el-Sayed Y, al-Sarhani A, al-Essa AR. Otological manifestations of primary ciliary dyskinesia. Clin Otolaryngol Allied Sci 1997;22:266–270.

33. Kennedy MP, Noone PG, Leigh MW, Zariwala MA, Minnix SL, Knowles MR, Molina PL. High-resolution CT of patients with primary ciliary dyskinesia. AJR Am J Roentgenol 2007;188:1232–1238.
Diagnosis and Management of PCD

1. Brown DE, Pittman JE, Leigh MW, Fordham L, Davis SD. Early lung disease in young children with primary ciliary dyskinesia. Pediatr Pulmonol 2008;43:514–516.

2. Noone FG, Leigh MW, Sannuti A, Minnick SL, Carson JL, Hazuka M, Zariwala MA, Knowles MR. Primary ciliary dyskinesia: diagnostic and phenotypic features. Am J Respir Crit Care Med 2004;169:459–467.

3. Munro NC, Currie DC, Lindsay KS, Ryder TA, Rutman A, Dewar A, Greenstone MA, Hendry WF, Cole PJ. Fertility in men with primary ciliary dyskinesia presenting with respiratory infection. Thorax 1994;49:684–687.

4. McComb P, Langley L, Villalon M, Verdugo P. The oviductal cilia and Kartagener’s syndrome. Fertil Steril 1986;46:412–416.

5. Knowles MR, Ostrowski LE, Leigh MW, Sears PR, Davis SD, Wolf WE, Hazuca MJ, Carson JL, Olivier KN, Sagel SD, et al. Mutations in RSPH1 cause primary ciliary dyskinesia with a unique clinical and ciliary phenotype. Am J Respir Crit Care Med 2014;189:707–717.

6. Olin JT, Burns K, Carson JL, Metjjan H, Atkinson JJ, Davis SD, Dell SD, Ferkol TW, Mills CE, Olivier KN, et al. Diagnostic yield of nasal scrape biopsies in primary ciliary dyskinesia: a multicenter experience. Pediatr Pulmonol 2011;46:483–485.

7. de Iongh RU, Rutland J. Ciliary defects in healthy subjects, bronchiectasis, and primary ciliary dyskinesia. Am J Respir Crit Care Med 1995;151:1559–1567.

8. Escudier E, Couprie M, Duriez B, Roudot-Thoraval F, Millepied MC, Prulliere-Escabasse V, Labatte L, Coste A. Computer-assisted analysis helps detect inner dynein arm abnormalities. Am J Respir Crit Care Med 2002;166:1257–1262.

9. Antony D, Becker-Heck A, Zariwala MA, Schmidts M, Onoufriadis A, Forouhan M, Wilson R, Taylor-Cox T, Dewar A, Jackson C, et al. Mutations in CCDC59 and CCDC40 are the major cause of primary ciliary dyskinesia with axonal disorganization and absent inner dynein arms. Hum Mutat 2013;34:462–472.

10. Castleman VH, Romio L, Chodhari R, Hirst RA, de Castro SC, Parker KA, Ybot-Gonzalez P, Eses RD, Wilson SW, Wallis C, et al. Mutations in radial spoke head protein genes RSPH9 and RSPH4A cause primary ciliary dyskinesia with central-microtubular-pair abnormalities. Am J Hum Genet 2009;84:197–209.

11. Onoufriadis A, Shoemark A, Schmidts M, Patel M, Jimenez G, Liu H, Thomas B, Dixon M, Hirst RA, Rutman A, et al. Targeted NGS gene panel identifies mutations in RSPH1 causing primary ciliary dyskinesia and a common mechanism for ciliary central pair agenesis due to radial spoke defects. Hum Mol Genet 2014;23:3362–3374.

12. Jeanson L, Copin B, Zariwala MA, Bower R, Sale WS, Loges NT, Fennekamp P, Lindberg S, Stenram U, et al. The nexin-dynein regulatory complex subunit DRC1 is essential for motile cilia function in algae and humans. Nat Genet 2013;45:262–268.

13. Wallmeier J, Al-Mutairi DA, Chen CT, Loges NT, Pennekamp P, Menchen T, Ma L, Shamseldin HE, Olbrich H, Dougherty GW, et al. Mutations in CCNO result in congenital mucociliary clearance disorder with reduced generation of multiple motile cilia. Nat Genet 2014;46:646–651.

14. Boon M, Wallmeier J, Ma L, Loges NT, Jaspers M, Olbrich H, Dougherty GW, Raidt J, Werner C, Amirav I, et al. MCIDAS mutations result in a mucociliary clearance disorder with reduced generation of multiple motile cilia. Nat Commun 2014;5:4418.

15. Werner C, Onnebrink JG, Omran H. Diagnosis and management of primary ciliary dyskinesia. Cilia 2015;4:2.

16. Marthin JK, Nielsen KG. Hand-held tidal breathing nasal nitric oxide measurement—a promising targeted case-finding tool for the diagnosis of primary ciliary dyskinesia. PLoS ONE 2013;8:e57262.

17. Harris A, Bhullar E, Gove K, Joslin R, Pelling J, Evans HJ, Walker WT, Lucas JS. Validation of a portable nitric oxide analyzer for screening in primary ciliary dyskinesias. BMC Pulm Med 2014;14:18.

18. Lundberg JO, Weitzberg E, Nordvall SL, Kyulenstierna R, Lundberg JM, Alving K. Primarily nasal origin of exhaled nitric oxide and absence in Kartagener’s syndrome. Eur Respir J 1994;7:1501–1504.

19. Collins SA, Gove K, Walker W, Lucas JS. Nasal nitric oxide screening for primary ciliary dyskinesia: systematic review and meta-analysis. Eur Respir J 2014;44:1589–1599.

20. Pifferi M, Caramella D, Cangiotti AM, Ragazzo V, Macchia P, Boner AL. Nasal nitric oxide in atypical primary ciliary dyskinesia. Chest 2007;131:870–873.

21. Marthin JK, Nielsen KG. Choice of nasal nitric oxide technique as first-line test for primary ciliary dyskinesia. Eur Respir J 2011;37:559–563.

22. Balfour-Lynn IM, Lavery A, Dinwiddie R. Reduced upper airway nitric oxide in cystic fibrosis. Arch Dis Child 1996;75:319–322.

23. Palm J, Lidman C, Graf P, Alving K, Lundberg J. Nasal nitric oxide is reduced in patients with HIV. Acta Otolaryngol 2000;120:420–423.

24. Nakano H, Ide H, Imada M, Osanai S, Takahashi T, Kikuchi K, Iwamoto J. Reduced nasal nitric oxide in diffuse panbronchiolitis. Am J Respir Crit Care Med 2000;162:2218–2220.

25. Arenal JF, Flores P, Rami J, Murriss-Espin M, Bremont F, Pasto IAM, Serrano E, Didier A. Nasal nitric oxide concentration in paranasal sinus inflammatory diseases. Eur Respir J 2011;37:307–312.

26. Stannard WA, Chilvers MA, Rutman AR, Williams CD, O’Callaghan C. Diagnostic testing of patients suspected of primary ciliary dyskinesia. Am J Respir Crit Care Med 2010;181:307–314.

27. Chilvers MA, McKeen M, Rutman A, Myint BS, Silverman M, O’Callaghan C. The effects of coronavirus on human nasal ciliated respiratory epithelium. Eur Respir J 2001;18:965–970.

28. Tilley AE, Walters MS, Shakhiev R, Crystal RG. Cilia dysfunction in lung disease. Annu Rev Physiol 2015;77:379–406.

29. Omran H, Loges NT. Immunofluorescence staining of ciliated respiratory epithelial cells. Methods Cell Biol 2002;101:307–314.

30. Fliegauf M, Olbrich H, Horvath J, Wildhaber JH, Zariwala MA, Kennedy M, Knowles MR, Omran H. Mislocalization of DNAH5 and DNAH9 in respiratory cells from patients with primary ciliary dyskinesia. Am J Respir Crit Care Med 2005;171:1343–1349.

31. Omran H, Kobayashi D, Olbrich H, Tsukahara T, Loges NT, Hagiwara H, Zhang Q, Leblond G, O’Toole E, Hura C, et al. Ktu/
PF13 is required for cytoplasmic pre-assembly of axonal dyneins. Nature 2008;456:611–616.

68. Frommer A, Hjeij R, Loges NT, Edelbusch C, Jahnke C, Raidt J, Werner C, Wallmeier J, Grosse-Onnebrink J, Olbrich H, et al. Immunofluorescence analysis and diagnosis of primary ciliary dyskinesia with radial spoke defects. Am J Respir Cell Mol Biol 2015. [Epub ahead of print].

69. Hjeij R, Onoufriadis A, Watson CM, Slagle CE, Klena NT, Loges NT, Donnelly WP, Baskin G, Peterfy E, Chodhari R, et al. DNAI2 mutations cause primary ciliary dyskinesia with defects in the outer dynein arm. Am J Hum Genet 2008;83:547–558.

70. Tarkar A, Loges NT, Slagle CE, Francis R, Dougherty GW, Tamayo JV, Shook B, Cantino M, Schwartz D, Jahnke C, et al. DYX1C1 is required for axonal dynein assembly and ciliary motility. Nat Genet 2013;45:995–1003.

71. Knowles MR, Ostrowski LE, Loges NT, Hurd T, Leigh MW, Huang L, Wolf WE, Carson JL, Hazucha MJ, Yin W, et al. Mutations in SPAG11 gene cause primary ciliary dyskinesia associated with defective outer and inner dynein arms. Am J Hum Genet 2013;93:711–720.

72. Olbrich H, Horvath J, Fekete A, Loges NT, Storm van’s Gravesande K, Blum A, Hormann K, Omran H. Axonemal localization of the dynein component DNAH5 is not altered in secondary ciliary dyskinesia. Pediatr Res 2006;59:418–422.

73. Horani A, Brody SL, Ferkol TW. Picking up speed: advances in the genetics of primary ciliary dyskinesia. Pediatr Res 2014;75:158–64.

74. Prevention Genetics. 2015 April 1. Primary ciliary dyskinesia (PCD)/immotile cilia syndrome nextgen sequencing (NGS) panel. https://www.preventiongenetics.comclinical-dna-testing/test/primary-ciliary-dyskinesia-pcd/immotile-cilia-syndrome-nextgen-sequencing-panel/1833/. Accessed 2015 April 1.

75. Ambry Genetics. 2015 April 1. Primary ciliary dyskinesia testing. http://www.ambyrgen.comtestsprimary-ciliary-dyskinesia-testing. Accessed 2015 April 1.

76. Invitae Genetics. 2015 April 1. Primary ciliary dyskinesia. https://www.invitae.comenphysiciancondition-detail/CND007224. Accessed 2015 April 1.

77. Partners HealthCare. 2015 April 1. Bronchiectasis panel (17 Genes) test details. http://personalizedmedicine.partners.orgLaboratory-For-Molecular-MedicineTestsPulmonary-DiseaseBronchiectasis-Panel.aspx. Accessed 2015 April 1.

78. Canciani M, Barlocco EG, Mastella G, de Santi MM, Gardi C, Lungarella G. The saccharin method for testing mucociliary function in patients suspected of having primary ciliary dyskinesia. Pediatr Pulmonol 1988;5:210–214.

79. Raidt J, Wallmeier J, Hjeij R, Onnebrink JG, Pennekamp P, Loges NT, Olbrich H, Haffner K, Dougherty GW, Omran H, et al. Primary ciliary dyskinesia by disruption of the outer dynein arm docking complex formation. Am J Hum Genet 2014;95:257–274.

80. Loges NT, Olbrich H, Fenske L, Mussaﬁ H, Horvath J, Fliegauf M, Kuhl H, Baktai G, Peterfy E, Chodhari R, et al. DNAI2 mutations cause primary ciliary dyskinesia with defects in the outer dynein arm. Am J Hum Genet 2008;83:547–558.
117. Gremmo ML, Guenza MC. Positive expiratory pressure
116. Parsons DS, Greene BA. A treatment for primary ciliary
dyskinesia. Laryngoscope 1993;103:1269–1272.
115. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline
irrigations for the symptoms of chronic rhinosinusitis. Cochrane
Database Syst Rev 2007 Jul 18;(3):CD006394.
114. Parsons DS, Greene BA. A treatment for primary ciliary
dyskinesia: efficacy of functional endoscopic sinus surgery. Laryngoscopy
1993;103:1269–1272.
113. Mener DJ, Lin SY, Ishman SL, Boss EF. Treatment and outcomes
of chronic rhinosinusitis in children with primary ciliary
dyskinesia: where is the evidence? A qualitative systematic
review. Int Forum Allergy Rhinol 2013;3:986–991.
112. Rollin M, Seymour K, Hariri M, Harcourt J. Clinical
expressions of immotile cilia syndrome. Pediatrics 1981;67:
805–810.
111. Campbell RG, Birman CS, Morgan L. Management of otitis
media with effusion: a literature review. Int J Pediatr Otorhinolaryngol
2009;73:1630–1638.
110. Pruliere-Escabasse V, Coste A, Chauvin P, Fauroux B, Tamalet A,
Garabedian EN, Escudier E, Roger G. Otologic features in
ciliary dyskinesia. PLoS ONE 2013;8:e71409.
109. Moller W, Haussinger K, Ziegler-Heitbrock L, Heyder J.
Mucociliary and long-term particle clearance in airways of patients with immotile cilia. Respir Res 2006;7:10.
108. Hadfield PJ, Rowe-Jones JM, Bush A, Mackay IS. Surgical treatments for otitis media with effusion: a systematic review. Pediatrics 2014;133:296–311.
107. Moller W, Haussinger K, Ziegler-Heitbrock L, Heyder J.
Mucociliary and long-term particle clearance in airways of patients with immotile cilia. Respir Res 2006;7:10.
106. White L, Mirrani G, Grover M, Rollason J, Malin A,
Suntharalingam J. Outcomes of Pseudomonas eradication
therapy in patients with non-cystic fibrosis bronchiectasis. Respir Med 2012;106:356–360.
105. Bhatt J, Bhandarkar S, Chandra S, Dasgupta N, Sinha A, Bhuyan A, et al. Azithromycin maintenance treatment on infectious exacerbations of chronic bronchitis in patients with cystic fibrosis. Cochrane Database Syst Rev 2011(7):CD009622.
104. Russo K, Donnelly M, Reid AJ. Segregation-the perspectives of young patients and their parents. J Cyst Fibros 2006;5:93–99.
103. Fauroux B, Tamalet A, Clement A. Management of primary
ciliary dyskinesia: the lower airways. Paediatr Respir Rev 2009;10:55–57.
102. Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–338.
101. Bhandarkar S, Dasgupta N, Sinha A, Bhuyan A, et al. Azithromycin maintenance treatment on infectious exacerbations of chronic bronchitis in patients with cystic fibrosis. Cochrane Database Syst Rev 2011(7):CD009622.
100. Chang CC, Singleton RJ, Morris PS, Chang AB. Pneumococcal vaccines for children and adults with bronchiectasis. Cochrane Database Syst Rev 2009 Apr 15;(2):CD006316. doi: 10.1002/14651858.CD006316.pub3
109. Grimaldi E, Schaffner C, Brown K, Shang S, Tamayo MH, Hegyi K,
Garabedian EN, Cusens D, Coulter S, Cooper J, et al. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. J Clin Invest 2011;121:3554–3563.
108. Weller RS, D’Souza A, Jordan B, Gagnon J, Black A, et al. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. Pediatr Pulmonol 2012;47:68–75.
107. Marchant J, Masters JB, Champion A, Petsky H, Chang AB. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax 2012;67:689–693.
106. Turner JA, Corstjens P, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–338.
105. Pasteur MC, Bilton D, Primary care summary of the British Thoracic Society Guideline on the management of non-cystic fibrosis bronchiectasis. Prim Care Respir J 2011;20:135–140.
104. Moller W, Haussinger K, Ziegler-Heitbrock L, Heyder J.
Mucociliary and long-term particle clearance in airways of patients with immotile cilia. Respir Res 2006;7:10.
103. Pruliere-Escabasse V, Coste A, Chauvin P, Fauroux B, Tamalet A,
Garabedian EN, Escudier E, Roger G. Otologic features in
ciliary dyskinesia. PLoS ONE 2013;8:e71409.
102. Baiker H, Carstensen M, Jorissen M, De Boeck K. Lung structure-function correlation in patients with primary ciliary dyskinesia. Thorax 2015;70:339–345.
101. Moller W, Haussinger K, Ziegler-Heitbrock L, Heyder J.
Mucociliary and long-term particle clearance in airways of patients with immotile cilia. Respir Res 2006;7:10.
100. Hadfield PJ, Rowe-Jones JM, Bush A, Mackay IS. Surgical treatments for otitis media with effusion: a literature review. Int J Pediatr Otorhinolaryngol 2009;73:1630–1638.
109. Weller RS, D’Souza A, Jordan B, Gagnon J, Black A, et al. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. Pediatr Pulmonol 2012;47:68–75.
108. Phillips GE, Thomas S, Heather S, Bush A. Airway response of children with primary ciliary dyskinesia to exercise and beta2-agonist challenge. Eur Respir J 1998;11:1389–1391.
107. Marchant J, Masters JB, Champion A, Petsky H, Chang AB. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax 2012;67:689–693.
106. White L, Mirrani G, Grover M, Rollason J, Malin A,
Suntharalingam J. Outcomes of Pseudomonas eradication
therapy in patients with non-cystic fibrosis bronchiectasis. Respir Med 2012;106:356–360.
105. Pasteur MC, Bilton D, Hill AT. British thoracic society bronchiectasis non CF. British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010;65:1–58.
Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 2013;309:1260–1267.

Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, Masters JB, Diaz A, McCallum GB, Mobberley C, et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurrative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med 2013;1:610–620.

Elborn JS, Tunney MM. Macrolides and bronchiectasis: clinical benefit with a resistance price. JAMA 2013;309:1295–1296.

Kido T, Yatera K, Yamasaki K, Nagata S, Choujin Y, Yamaga C, Hara K, Ishimoto H, Hisaoka M, Mukae H. Two cases of primary ciliary dyskinesia with different responses to macrolide treatment. Intern Med 2012;51:1093–1098.

Yoshioka D, Sakamoto N, Ishimatsu Y, Kaguwata T, Ishii H, Mukae H, Kadota J, Kolmo S. Primary ciliary dyskinesia that responded to long-term, low-dose clarithromycin. Intern Med 2010;49:1437–1440.

Itoh M, Kishi K, Nakamura H, Hatao H, Kioi K, Sudou A, Kobayasi K, Tuchida F, Adachi H, Yagyuu H, et al. A case of immotile-dyskinetic cilia syndrome responding to clenbuterol hydrochloride and azithromycin. Nihon Koyuki Gakkai Zasshi 2002;40:617–621.

Nishi K, Mizuguchi M, Tachibana H, Ooka T, Amemiya T, Myou S, Fujimura M, Matsuda T. Effect of clarithromycin on symptoms and mucociliary transport in patients with sino-bronchial syndrome. Nihon Koyuki Gakkai Zasshi 1995;33:1392–1400.

Pines A. Trimethoprim-sulfamethoxazole in the treatment and prevention of purulent exacerbations of chronic bronchitis. J Infect Dis 1975;128:706–709.

Jordan GW, Krajden SF, Hoeprich PD, Wong GA, Peirce TH, Rausch DC. Trimethoprim-sulfamethoxazole in chronic bronchitis. Can Med Assoc J 1975;112:91–95.

Hart A, Sugumar K, Milan SJ, Fowler SJ, Crossingham I. Inhaled hyperosmolar agents for bronchiectasis. Cochrane Database Syst Rev 2014;4:CD002996.

Nicolson CH, Stirling RG, Borg BM, Button BM, Wilson JW, Holland AE. The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012;106:661–667.

Bilton D, Daviskas E, Anderson SD, Kolbe J, King G, Stirling RG, Thompson BR, Milne D, Charlton B, Investigators B. Phase 3 randomized study of the efficacy and safety of inhaled dry powder manitol for the symptomatic treatment of non-cystic-fibrosis bronchiectasis. Chest 2013;144:215–225.

Wilkinson M, Sugumar K, Milan SJ, Hart A, Crockett A, Crossingham I. Mucolitics for bronchiectasis. Cochrane Database Syst Rev 2014;4:CD001289.