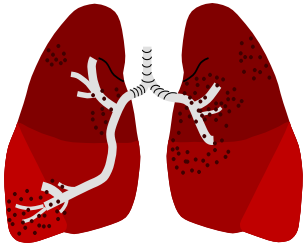
Primer Silyer Diskinezide Son Gelişmeler 2015/6

Prof. Dr. Bülent KARADAĞ

Marmara Üni. Çocuk Göğüs Hast. BD



Primer silyer diskinezi

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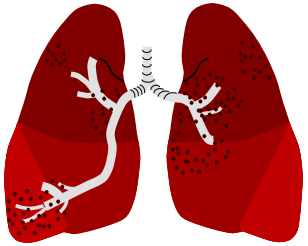
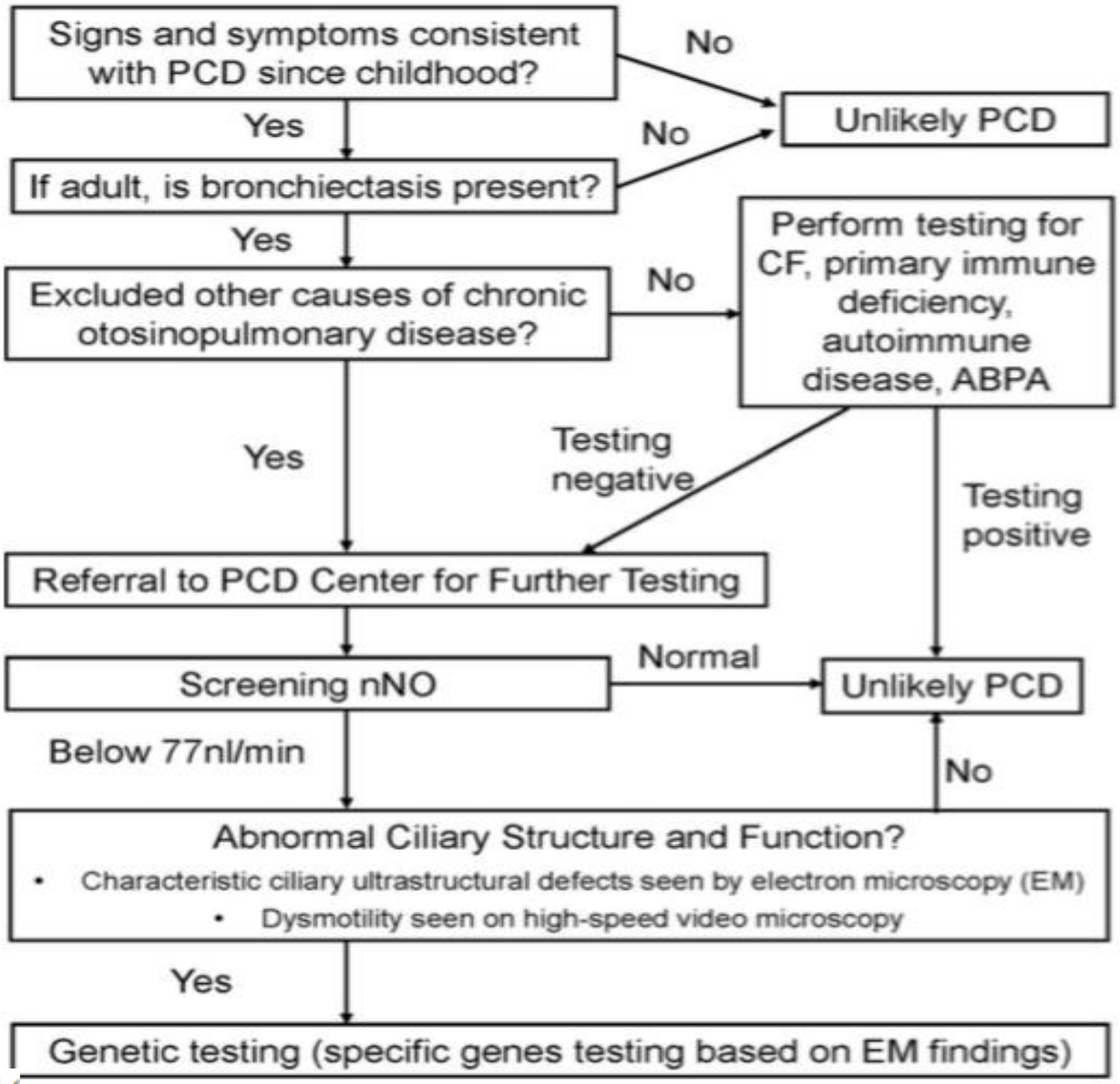


PCD

1. Tanı
2. Klinik
2. Yaşam kalitesi
3. Genetik
4. SFT
5. Tedavi

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

M. Leigh Anne Daniels, MD, MPH and Peadar G. Noone, MD, FCCP, FRCPI



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

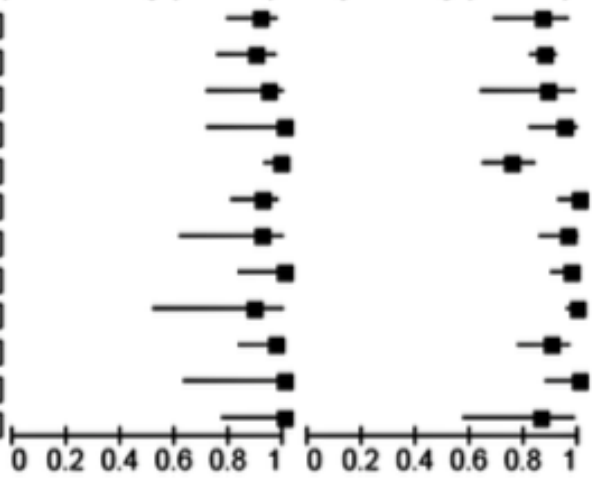
Diagnostic accuracy of nasal nitric oxide for establishing diagnosis of primary ciliary dyskinesia: a meta-analysis

BMC Pulmonary Medicine (2015) 15:153

Panayiotis Kouis[1*], Stefania I. Papatheodorou[1] and Panayiotis K. Yiallouros[1,2]

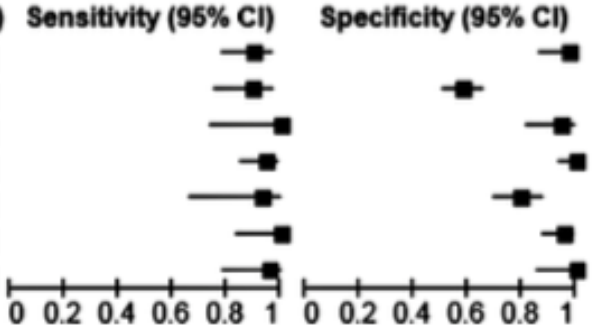
A **VC nNO technique**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Beydon M 2015	41	4	4	25	0.91 [0.79, 0.98]	0.86 [0.68, 0.96]
Boon M 2014	34	24	4	164	0.89 [0.75, 0.97]	0.87 [0.82, 0.92]
Corbelli R 2004	16	2	1	15	0.94 [0.71, 1.00]	0.88 [0.64, 0.99]
Harris A 2014	11	2	0	34	1.00 [0.72, 1.00]	0.94 [0.81, 0.99]
Leigh M 2013	70	21	1	63	0.99 [0.92, 1.00]	0.75 [0.64, 0.84]
Marthin JK 2011 (2)	45	0	4	45	0.92 [0.80, 0.98]	1.00 [0.92, 1.00]
Marthin JK 2011 (3)	11	2	1	44	0.92 [0.62, 1.00]	0.96 [0.85, 0.99]
Mateos Coral D 2011	20	2	0	63	1.00 [0.83, 1.00]	0.97 [0.89, 1.00]
Moreno Galdo A 2010	8	1	1	111	0.89 [0.52, 1.00]	0.99 [0.95, 1.00]
Narang I 2002	30	5	1	43	0.97 [0.83, 1.00]	0.90 [0.77, 0.97]
Piacentini G 2008	8	0	0	27	1.00 [0.63, 1.00]	1.00 [0.87, 1.00]
Santamaria F 2008	14	2	0	12	1.00 [0.77, 1.00]	0.86 [0.57, 0.98]



B **Non-VC nNO technique**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Beydon M 2015	44	1	5	36	0.90 [0.78, 0.97]	0.97 [0.86, 1.00]
Boon M 2014	34	73	4	102	0.89 [0.75, 0.97]	0.58 [0.51, 0.66]
Harris A 2014	12	2	0	34	1.00 [0.74, 1.00]	0.94 [0.81, 0.99]
Marthin JK 2011 (2)	51	0	3	52	0.94 [0.85, 0.99]	1.00 [0.93, 1.00]
Marthin JK 2011 (3)	13	17	1	66	0.93 [0.66, 1.00]	0.80 [0.69, 0.88]
Mateos Coral D 2011	20	3	0	62	1.00 [0.83, 1.00]	0.95 [0.87, 0.99]
Montella S 2011	22	0	1	23	0.96 [0.78, 1.00]	1.00 [0.85, 1.00]



Accuracy of diagnostic testing in primary ciliary dyskinesia

Claire L. Jackson[1,2,7], Laura Behan[1,2,3,4,7], Samuel A. Collins[1,2,3], Patricia M. Goggin[1,5], Elizabeth C. Adam[1,2], Janice L. Coles[1,2], Hazel J. Evans[1,3], Amanda Harris[1,3], Peter Lackie[1,2,5], Samantha Packham[1,3], Anton Page[1,5], James Thompson[1,2], Woolf T. Walker[1,2,3], Claudia Kuehni[6] and Jane S. Lucas[1,2,3]

Eur Respir J 2016; 47: 837–848

TABLE 2 The diagnostic accuracy of nasal nitric oxide (nNO), high-speed video microscopy analysis (HSVMA) and transmission electron microscopy (TEM) analysis to diagnose primary ciliary dyskinesia

	nNO ⩽30 nL·min^{-1}	HSVMA	TEM
Subjects[#]	301 (47)	625 (98)	368 (57)
Positive patients[¶]	34 (45)	60 (80)	71 (95)
Negative patients[+]	267 (47)	565 (100)	297 (52)
True positive	31	60	56
True negative	257	526	297
False positive	10	39	0
False negative	3	0	15
Sensitivity (95% CI)	0.91 (0.76–0.98)	1.00 (0.94–1.00)	0.79 (0.68–0.88)
Specificity (95% CI)	0.96 (0.93–0.98)	0.93 (0.91–0.95)	1.00 (0.99–1.00)
PPV (95% CI)	0.76 (0.60–0.88)	0.61 (0.50–0.70)	1.00 (0.94–1.00)
NPV (95% CI)	0.99 (0.97–1.00)	1.00 (0.99–1.00)	0.95 (0.92–0.97)

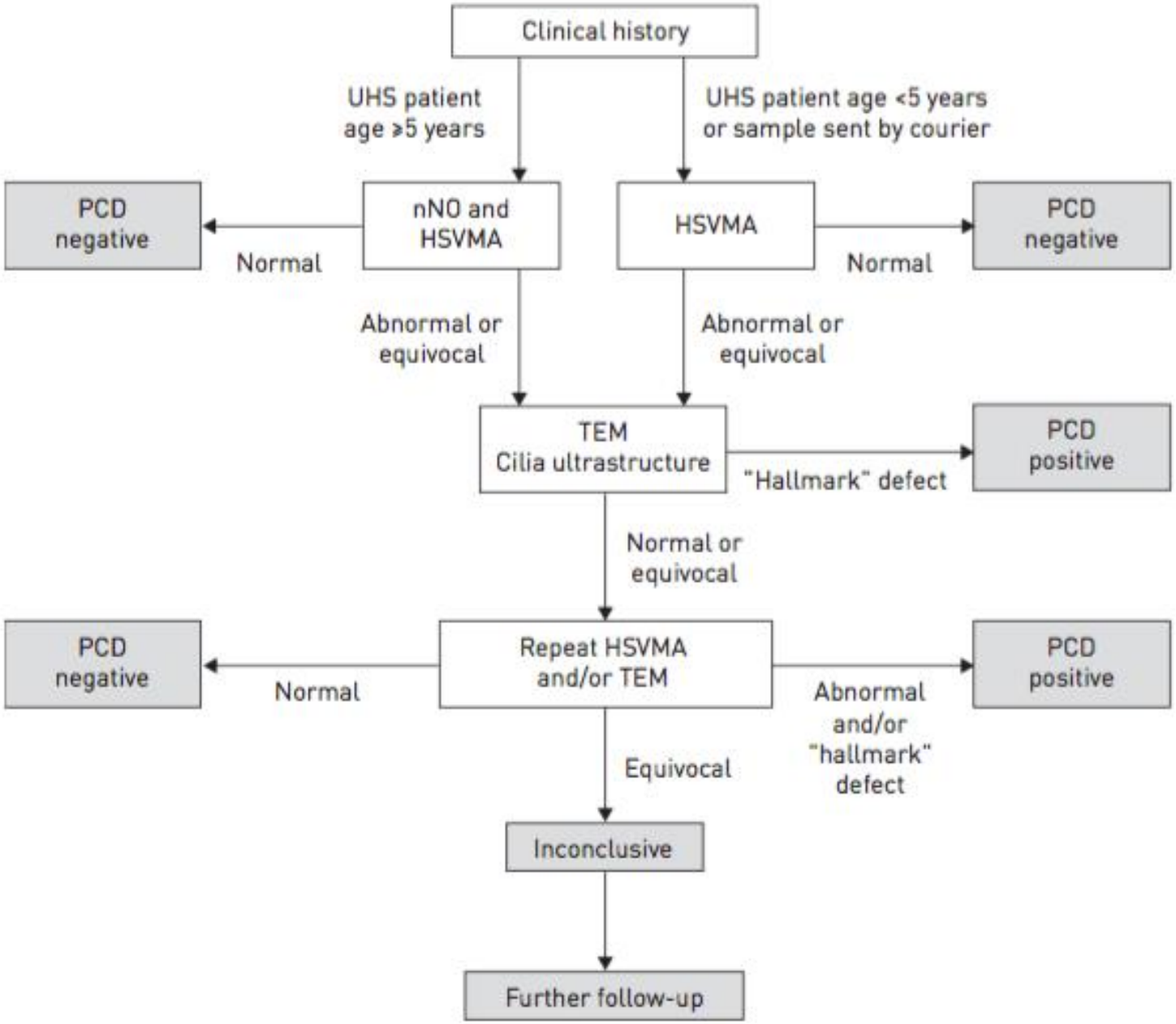


FIGURE 1 Primary ciliary dyskinesia (PCD) diagnostic pathway for patients and samples. Diagnostic tests included nasal nitric oxide (nNO), high-speed video microscopy analysis (HSVMA) and transmission electron microscopy (TEM). Not all patients underwent all tests. UHS: University Hospital Southampton.

Accuracy of diagnostic testing in primary ciliary dyskinesia: are we there yet?

Eric G. Haarman[1] and Miriam Schmidts[2]

Eur Respir J 2016; 47: 699–701 |

In summary, the article by JACKSON *et al.* [5] is an important step towards evidence-based guidelines for PCD diagnostics, including the most commonly used techniques like nasal nitric oxide, HSVM and TEM. But we are not there yet. The work emphasises the importance of HSVM as a technique with relatively high sensitivity and specificity. However, more recently described defects with minor abnormalities in ciliary beat pattern or reduced generation of normal cilia, can easily be missed. Techniques like nasal nitric oxide and TEM are valuable tools for confirming the diagnosis of PCD, but one should be cautious to exclude the diagnosis in the case of normal findings, which contrasts with current practice in many centres. Newer techniques, like genetics and immunofluorescence labelling, hold great promise for the future. As with all clinical dilemma's, the clinician should remain critical in cases of high clinical suspicion and be willing to re-evaluate all diagnostic steps.

PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia

Laura Behan[1,2,3], Borislav D. Dimitrov[4,5], Claudia E. Kuehni[6], Claire Hogg[7], Mary Carroll[1,2], Hazel J. Evans[1], Myrofora Goutaki[6], Amanda Harris[1], Samantha Packham[1], Woolf T. Walker[1,2,4] and Jane S. Lucas[1,2,4]

Eur Respir J 2016; 47: 1103–1112 |

TABLE 2 Clinical symptom characteristics of the derivation group

	Total	PCD-positive	PCD-negative	Odds ratio (95% CI)	p-value
Subjects	641	75	566		
Neonatal symptoms					
Neonatal respiratory support	72 (11.2)	31 (41.3)	41 (7.2)	9.77 (5.53–17.26)	<0.001
Neonatal chest symptoms	153 (23.0)	56 (74.6)	97 (17.1)	13.56 (7.60–24.11)	<0.001
Neonatal rhinitis	57 (8.9)	20 (26.6)	37 (6.5)	5.53 (2.99–10.23)	<0.001
Respiratory symptoms					
Persistent daily wet cough	552 (86.1)	70 (93.3)	482 (85.1)	2.38 (0.93–6.07)	0.069
Recurrent wheeze	254 (39.6)	36 (48.0)	218 (38.5)	1.39 (0.86–2.26)	0.176
Previous pneumonia	227 (35.4)	31 (41.3)	196 (34.6)	1.14 (0.69–1.88)	0.585
Bronchiectasis	202 (31.5)	22 (29.3)	180 (31.8)	0.94 (0.54–1.61)	0.83
Upper airway and ear symptoms					
Perennial persistent rhinitis	386 (60.2)	61 (81.3)	325 (57.4)	3.20 (1.75–5.86)	<0.001
Chronic sinusitis	159 (24.8)	21 (28.0)	138 (24.3)	1.19 (0.69–2.05)	0.52
Hearing loss	127 (19.8)	37 (49.3)	90 (15.9)	5.90 (3.52–9.98)	<0.001
Chronic acute otitis media	165 (25.7)	25 (33.3)	140 (24.7)	1.41 (0.85–2.32)	0.117
Serous otitis media	152 (23.7)	43 (57.3)	109 (19.2)	3.24 (2.11–4.96)	<0.001
Chronic ear perforation	59 (9.2)	9 (12.0)	50 (8.8)	5.9 (3.52–9.98)	0.398
Ear surgery	105 (16.3)	24 (32.0)	81 (14.3)	2.81 (1.64–2.83)	<0.001

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Eur Respir J 2016; 47: 1103–1112 |

TABLE 3 Factors for the prediction of primary ciliary dyskinesia selected by step-wise logistic regression

	Regression coefficient	Odds ratio (95% CI)	p-value	Simplified regression coefficient tool#
Situs inversus	3.54	34.48 (11.6–101.8)	<0.001	4
Gestational age (full term)	2.20	9.06 (2.9–27.4)	<0.001	2
Neonatal chest symptoms	1.91	6.79 (2.7–16.7)	<0.001	2
Neonatal unit	1.90	6.70 (2.7–16.3)	<0.001	2
Congenital cardiac defect	1.57	4.83 (1.1–22.2)	0.043	2
Rhinitis	1.22	3.40 (1.2–8.9)	0.013	1
Ear and hearing symptoms	0.95	2.59 (1.2–5.8)	0.021	1

PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia

PICADAR		
Does the patient have a daily wet cough that started in early childhood?	**Yes** – complete PICADAR **No – STOP**. PICADAR is not designed for patients without a wet cough	
1. Was the patient born pre-term or full term?	Term	2
2. Did the patient experience chest symptoms in the neonatal period (*e.g.* tachypnoea, cough, pneumonia)?	Yes	2
3. Was the patient admitted to a neonatal unit?	Yes	2
4. Does the patient have a situs abnormality (situs inversus or heterotaxy)?	Yes	4
5. Does the patient have a congenital heart defect?	Yes	2
6. Does the patient have persistent perennial rhinitis?	Yes	1
7. Does the patient experience chronic ear or hearing symptoms (*e.g.* glue ear, serous otitis media, hearing loss, ear perforation)?	Yes	1
	Total score =	

FIGURE 2 PICADAR is a predictive score with seven simple questions to predict the likelihood of having primary ciliary dyskinesia (PCD). It can be used in any patients with chronic respiratory symptoms starting in early childhood. The total score is calculated and the individual probability of having PCD diagnosis can be estimated from the probability curve shown in figure 3.

PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia

Laura Behan[1,2,3], Borislav D. Dimitrov[4,5], Claudia E. Kuehni[6], Claire Hogg[7], Mary Carroll[1,2], Hazel J. Evans[1], Myrofora Goutaki[6], Amanda Harris[1], Samantha Packham[1], Woolf T. Walker[1,2,4] and Jane S. Lucas[1,2,4]

TABLE 5 The distribution of scores (≤5, 6–9 and ≥10) in primary ciliary dyskinesia (PCD) positive and PCD-negative participants using PICADAR in the derivation group (n=288) and in the validation group (n=157) (only children <18 years included)

	Derivation group		Validation group	
	PCD-positive	PCD-negative	PCD-positive	PCD-negative
Subjects	50	238	79	78
≤5	3 (6.0)	189 (79.4)	15 (18.7)	59 (75.6)
6–9	29 (58.0)	48 (20.2)	42 (53.3)	16 (20.5)
≥10	18 (36.0)	1 (0.4)	22 (28.0)	3 (3.8)

PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia

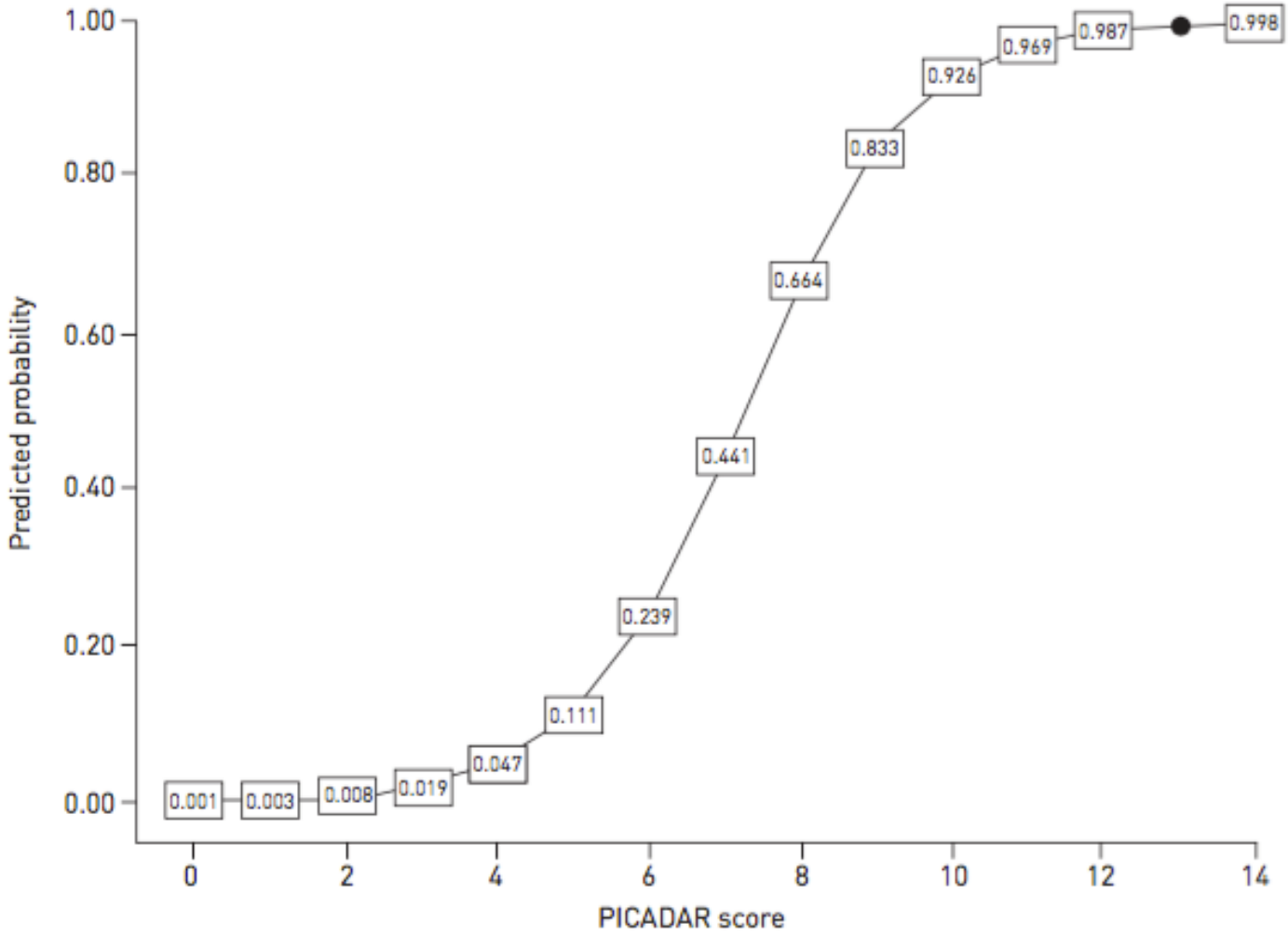

FIGURE 3 PICADAR: probability curve. Once the total PICADAR score is calculated from figure 2, the individual probability of having a primary ciliary dyskinesia diagnosis is estimated from the probability curve.

Clinical Features and Associated Likelihood of Primary Ciliary Dyskinesia in Children and Adolescents

Margaret W. Leigh[1], Thomas W. Ferkol[2], Stephanie D. Davis[3], Hye-Seung Lee[4], Margaret Rosenfeld[5], Sharon D. Dell[6], Scott D. Sagel[7], Carlos Milla[8], Kenneth N. Olivier[9], Kelli M. Sullivan[10], Maimoona A. Zariwala[11], Jessica Pittman[2], Adam J. Shapiro[1*], Johnny L. Carson[1,12], Jeffrey Krischer[4], Milan J. Hazucha[10,12], Michael R. Knowles[10]

ANNALSATS Articles in Press. Published on 12-April-2016 as 10.1513/AnnalsATS.201511-748OC

Table 1. Demographics and nasal nitric oxide values at enrollment for definite PCD and other/undefined groups

	PCD n = 205	Other/Undefined n = 187	*P* value
Female gender	99 (48%)	86 (46%)	0.686
Race – white	171 (83%)	168 (90%)	0.076
Ethnicity - Not Hispanic	179 (87%)	168 (90%)	0.526
Age			
Median; range (years)	8; 0-18	7; 0-18	0.191
Mean ± SD (years)	7.8 ± 5.4	7.0 ± 4.5	0.127
<=5 years	75 (37%)	76 (41%)	0.467
Nasal Nitric Oxide*			
Mean ± SD (nl/min)	20.9 ± 21.8 n = 121	258.3 ± 146.9 n = 102	<0.0001
Below cut-off of 77 nl/min**	117 (97%)	1 (0.9%)	<0.0001

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Criteria-Defined Clinical Features (Definitions in Figure 1)	PCD n = 204*	Other/Undefined n = 185**	Adjusted Odds Ratio (95% Confidence Intervals)***	*P* value
Unexplained neonatal respiratory distress (Feature 1)	116 (57%)	21 (11%)	6.6 (3.5,12.3)	<0.0001
Early onset, year-round wet cough (Feature 2)	128 (62%)	48 (26%)	3.1 (1.7,5.5)	0.0001
Early onset, year-round nasal congestion (Feature 3)	151 (74%)	74 (40%)	3.4 (1.9,6.3)	<0.0001
Laterality defect (Feature 4)	109 (53%)	28 (15%)	7.7 (4.0,14.9)	<0.0001

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Number of Criteria-defined Clinical Features	Sensitivity	Specificity
4	0.21	0.99
3	0.50	0.96
2	0.80	0.72
1	0.96	0.41
0	1.00	0.00

A reach-out system for video microscopy analysis of ciliary motions aiding PCD diagnosis

Israel Amirav[1,7*], Huda Mussaffi[2], Yehudah Roth[3], Miriam Schmidts[4,5], Heymut Omran[6], Claudius Werner[6]
for the Israeli PCD Consortium Investigators

BMC Research Notes (2015) 8:71

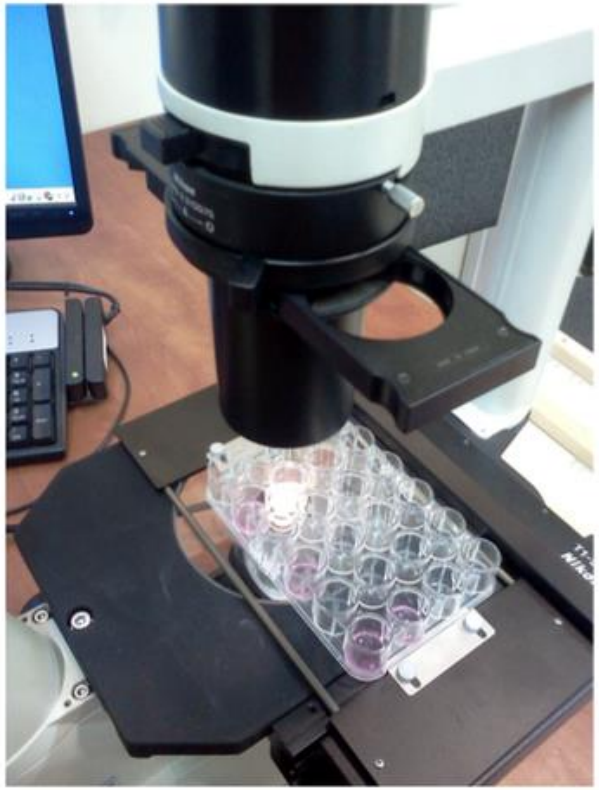
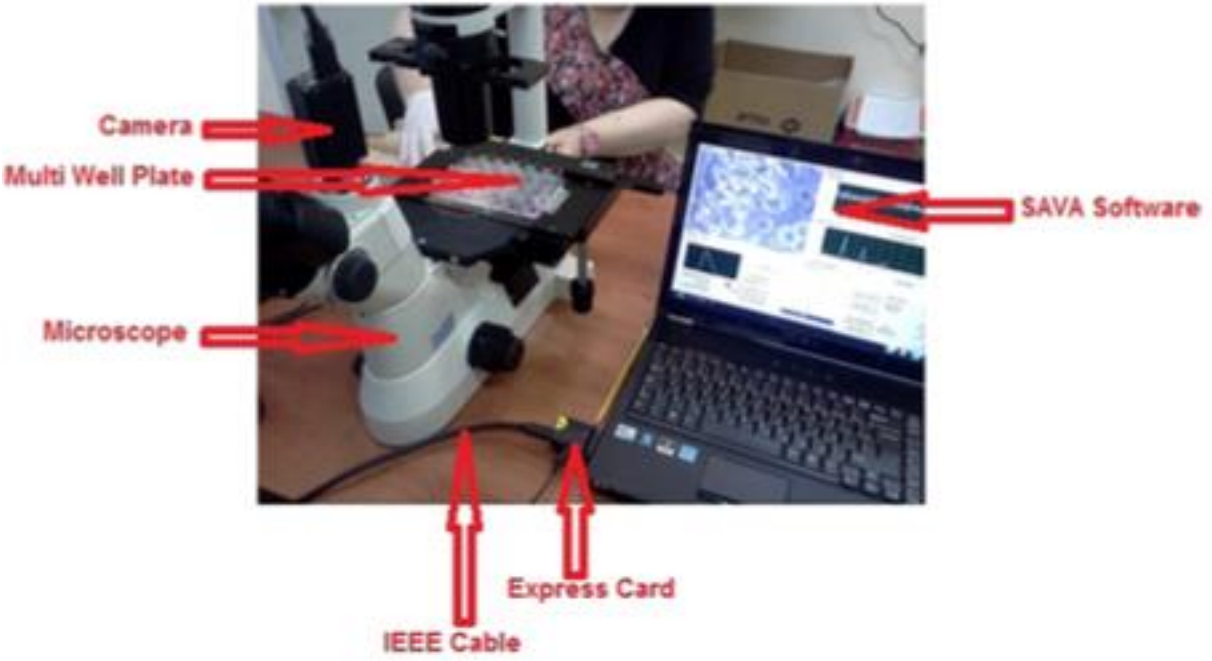


Figure 1 Use of a 24 well plate for microscopy.



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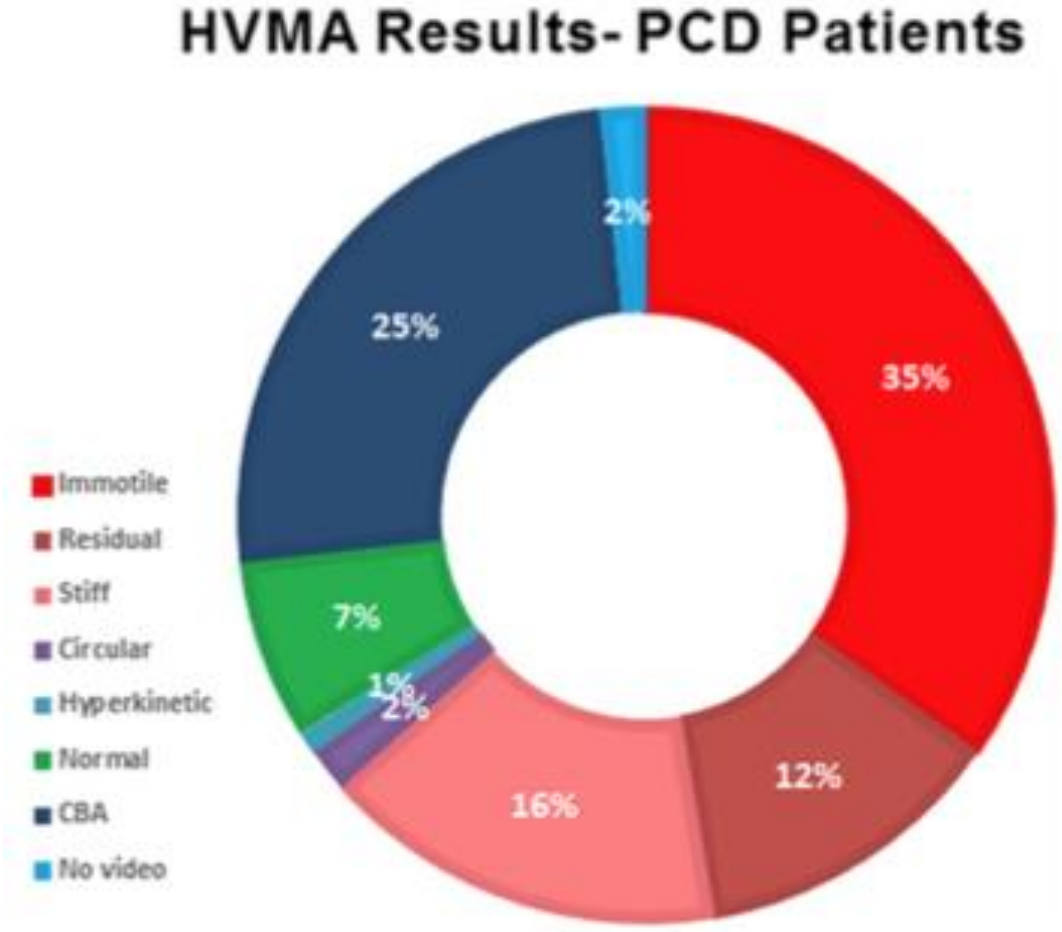
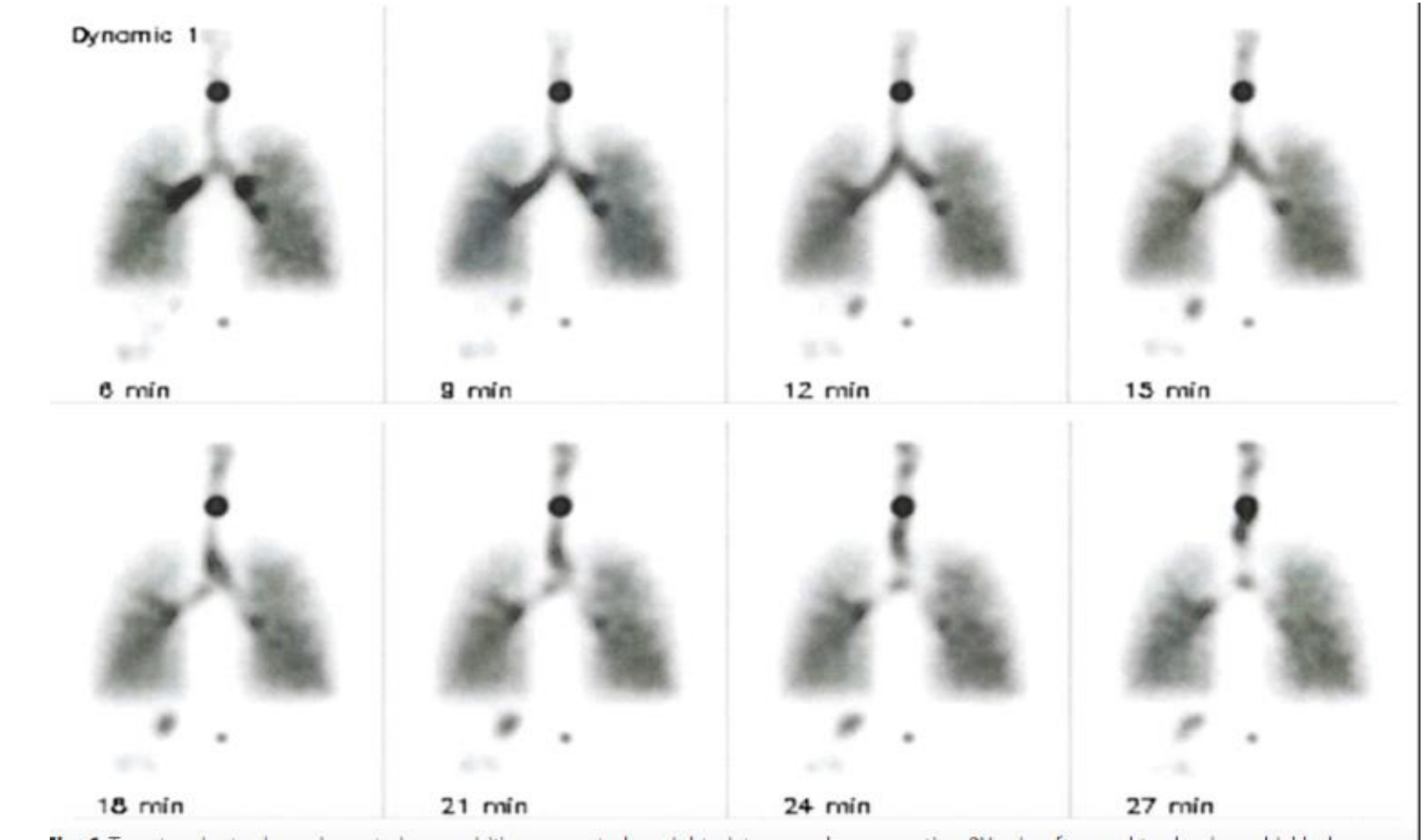


Figure 4 HVMA post-hoc results (percentage of each category) in PCD patients (n = 112).

Clinical value of measurement of pulmonary radioaerosol mucociliary clearance in the work up of primary ciliary dyskinesia

Mathias Munkholm[1], Kim Gjerum Nielsen[2] and Jann Mortensen[1,3*]

EJNMMI Research (2015) 5:39



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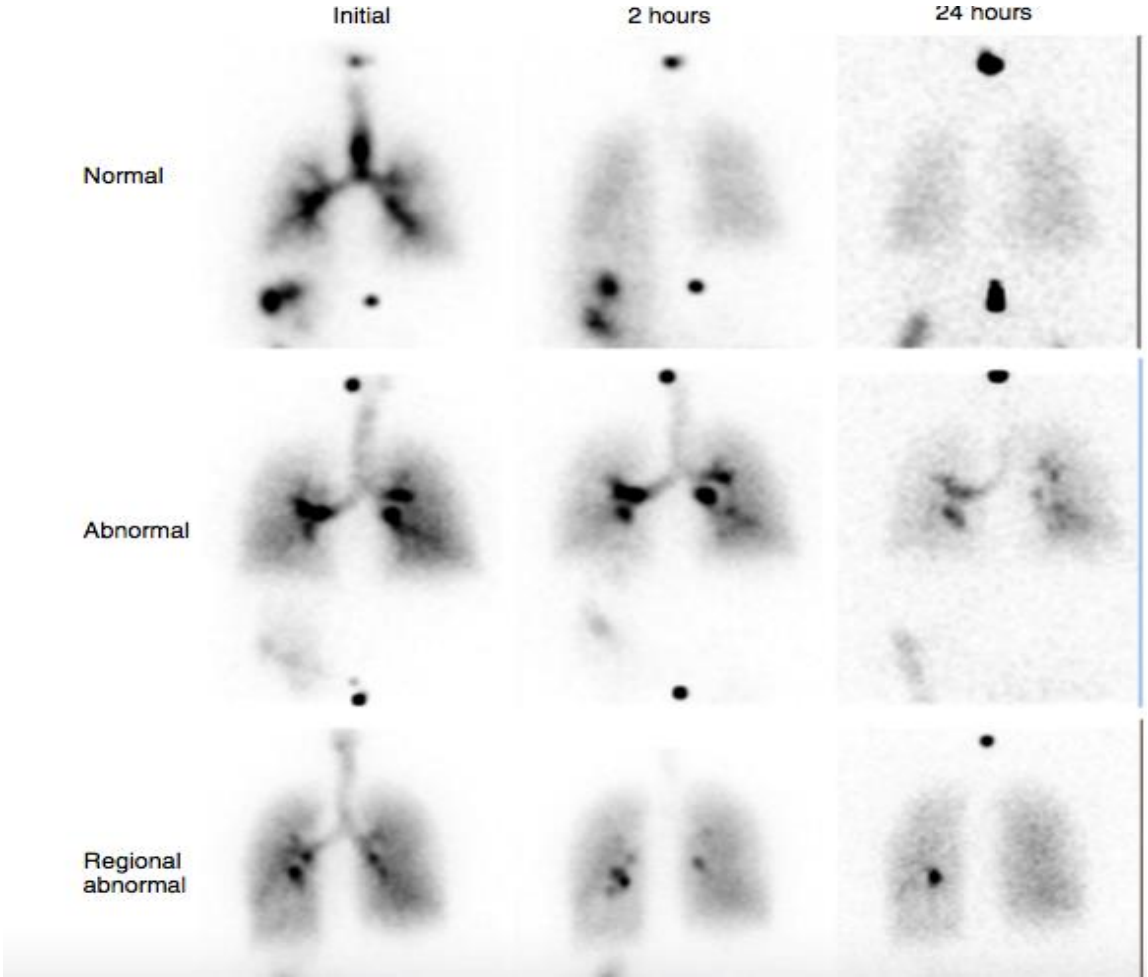

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EJNMMI Research (2015) 5:39

Table 2 PRMC results in relation to final clinical diagnosis

Results from PRMC test	Final clinical diagnosis					
	Verified PCD	Uncertain but probably PCD	Uncertain	Uncertain but probably not PCD	Not PCD	Total
	n = 27 (%)	*n* = 3 (%)	*n* = 32 (%)	*n* = 28 (%)	*n* = 149 (%)	*n* = 239 (%)
PCD/SCD	23 (85.2)	2 (66.6)	7 (21.9)	3 (10.7)	22 (14.8)	57 (23.8)
Inconclusive	4 (14.8)	1 (33.3)	3 (9.4)	1 (3.6)	16 (10.7)	25 (10.5)
Normal or otherwise not consistent with PCD	0 (0)	0 (0)	22 (68.7)	24 (85.7)	111 (74.5)	157 (65.7)

Diagnosis and management of primary ciliary dyskinesia

Claudius Werner*, Jörg Große Onnebrink and Heymut Omran

Cilia (2015) 4:2

Table 2 Methods and limitations used for confirmation of PCD diagnosis

Method	Limitation
Nasal NO level	May be decreased in other disorders, for example, acute sinusitis or cystic fibrosis; rarely normal values may be present in PCD
High frequency video microscopy (HVMA)	Variants with subtle beating abnormality may be interpreted as normal; secondary ciliary dyskinesia due to infection and inflammation is very common - distinction from PCD phenotype may be difficult
Transmission electron microscopy (TEM)	Approximately ~30% of PCD cases have no ultrastructural abnormality; false-positive diagnoses common in some variants (notably inner dynein arm defects)
Immunofluorescence microscopy (IF)	No abnormality in approximately ~20%; technical difficulties if specimen contains a lot of mucus
Genetics	Expensive due to high number of PCD genes; only approximately 60% of cases can be identified by genetic testing at present

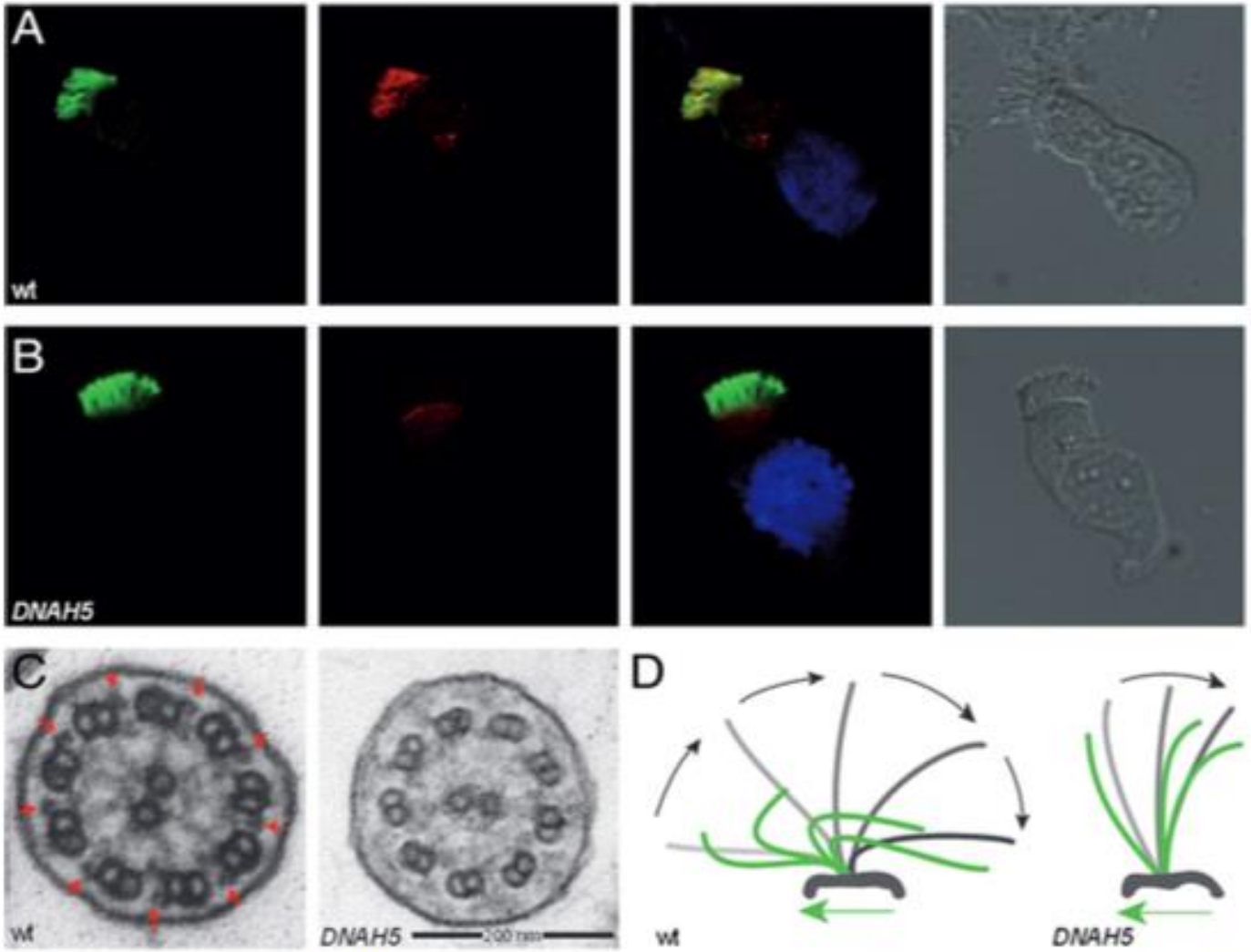

Figure 1 Methods used for PCD diagnosis. (A, B) Immunofluorescence co-staining of human respiratory epithelial cells with DNAH5-specific antibodies (red) and antibodies against acetylated α-tubulin (green). Nuclei were stained with Hoechst 33342 (blue). Overlays and bright-field images are shown on the right. Whereas in healthy human respiratory epithelial cells (wt, A) both DNAH5 and acetylated α-tubulin antibodies co-localize along the entire length of the ciliary axonemes, in an individual with an outer dynein arm defect **(B)**, the ODA heavy chain DNAH5 is absent from the axonemes. **(C)** Transmission electron tomography of healthy respiratory epithelial cells (wt) showing no ultrastructural abnormality. Outer dynein arms (ODAs) are highlighted with red arrows. In an individual with *DNAH5* mutations, ODAs are missing. **(D)** Diagram of ciliary beat patterns as deduced from high-speed videomicroscopy. A normal ciliary beat pattern (wt) is characterized by a strong beating stroke (symbolized in grey) followed by a recovery stroke (symbolized in green). In *DNAH5* mutant cilia, only a minimal residual ciliary activity is present.

Table 3 Genes associated with PCD and corresponding ultrastructure

Gene	Reference	Axonemal/cellular structure or function	Routine TEM		Routine IF	
			Informative[a]	Finding	Informative[a]	Abnormal staining with antibodies against
DNAH5, DNAI1, DNAI2, DNAL1, NME8 (TXNDC3)	[42-46]	ODA subunit	✓	ODA-defect	✓	ODA component
CCDC114, ARMC4, CCDC151	[47-49]	ODA targeting/docking factor	✓	ODA-defect	✓	ODA component
DNAAF1 (LRRC50), DNAAF2 (KTU), DNAAF3, HEATR2, LRRC6, ZMYND10, DYX1C1 (DNAAF4), SPAG1, CCDC103, C21ORF59	[38,50-58]	Cytoplasmic dynein arm assembly or transport factor	✓	IDA + ODA defect	✓	ODA component + IDA component
RSPH1, RSPH4A, RSPH9	[40,59]	RSPH subunit	(✗)	Missing CP or TTD; often normal	✓	RSPH components
CCDC39, CCDC40	[39,60]	NL/DRC factor	✓	microtubular disorganisation + IDA-defect	✓	DRC components + IDA components
CCDC164, CCDC65	[26,58]	NL subunit	✗	NL defect only rarely discernible	✓	NL components
DNAH11	[36]	ODA subunit	✗	Normal	✗	
HYDIN	[27]	CP subunit	✗	Normal (C2b absence only visible in TEM tomography)	✗	
CCNO, MCIDAS	[3,4]	*CCNO*: cytoplasmic centriole assembly and docking factor; MCIDAS: nuclear regulator of *CCNO* and *FOXJ1*	(✗)	Usually misinterpreted as secondary ciliary aplasia; reduced numbers of MMC; basal bodies and rootlets are mislocalized	(✗)	Usually misinterpreted as secondary ciliary aplasia; *MCIDAS:* lack of any axonemal components *CCNO*: Rootletin mislocalization, CCNO deficiency
OFD1, RPGR	[61,62]	Functions related to non-motile cilia; role in motile cilia unknown	✗	Normal/unspecific	✗	

[a]Informative denotes: detectable in routine diagnostics.

CP, central pair tubuli; DRC, dynein regulatory complex; IDA, dynein arm; IF, immunofluorescence microscopy; MMC, multiple motile cilia; NL, nexin link; ODA, outer dynein arm; RSPH, radial spoke head; TEM, transmission electron microscopy; TTD, tubular transposition defect (8 + 1 structure).

Diagnostic Methods in Primary Ciliary Dyskinesia

Jane S. Lucas [1,2,*], Tamara Paff [3,4], Patricia Goggin [1,2], Eric Haarman [3]

Paediatric Respiratory Reviews 18 (2016) 8–17

Çeşitli tanısal testler

Her bir testin avantajı ve kısıtlı olduğu yönler var.

“Altın standart” bir test yok.

İleriderece uzmanlaşmış merkezler örnekleri çalışıp sonucu değerlendirmeli.

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Diagnostic Test	Advantages	Disadvantages	Diagnostic accuracy
Nasal nitric oxide	1. Guidelines exist for conduct of test [33] 2. Meta-analysis demonstrates good sensitivity and specificity[32] 3. Protocols can be standardized for multi-center use[29] 4. Alternatives to 'gold standard' method (velum closure using chemiluminescence analyzer) have acceptable accuracy [35,37]	1. 'Gold standard' method impossible for young children and equipment expensive and non-portable. 2. Standardised approach to use in PCD diagnostics and reporting of results needed 3. Small % of patients have normal NO 4. Normal reference values for younger age groups are lacking	In consecutive patients for PCD diagnostic testing: 1. Cut-off 53 nl/min: sensitivity 0.92, specificity 0.96 [31] 2. Cut-off 77 nl/min: sensitivity 0.98, specificity >0.75 [29]
HVMA	1. Provides assessment of functional defect 2. HSVMA is abnormal in all described cases of PCD. 3. Correlates with TEM [47] and genetic findings [48]	1. Absence of standardized methods of reporting 2. Abnormalities of CBP can be subtle 3. Requires specialist equipment 4. Requires rigorous adherence to quality control 5. Secondary defects are common and experienced scientists are needed with expert knowledge of normal and abnormal findings	Dyskinesia on >90% ciliated edges: ○ sensitivity 0.97 ○ specificity 0.95 to predict a TEM diagnosis [45]

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		knowledge of normal and abnormal findings	
TEM	1. Provides assessment of the ultrastructural defects 2. Correlates to genetics and HVMA 3. Widely used	1. ≈30% of patients have no defect on TEM 2. Potentially altered by secondary dyskinesia 3. Requires specialist equipment and evaluation	Sensitivity: 70-80% Specificity: 100% [46,61] (false positives occur, but can be avoided by evaluating sufficient cilia (>100) and adequate training of staff).
Genetic testing	1. Indisputable and fast diagnosis of PCD in case of biallellic pathogenic mutations in known genes 2. Has relevance to clinical phenotype 3. Provides possibility for carrier testing in isolated populations with high frequency of PCD	1. Cannot rule out PCD (yet) as 20-35% is unknown 2. Commercial testing does not offer complete gene/exon panel 3. Can be difficult to prove pathogenicity/relation to PCD in cases of mutations in novel (candidate) genes or novel mutations in known PCD genes	Sensitivity: 65-80% (estimated) Specificity: 100% [19]
IF	1. Much interest for IF to become more widely available as a diagnostic tool 2. Useful research tool 3. A number of antibodies are commercially available 4. Relatively low cost	1. No evidence for use as a clinical tool yet published 2. The antibodies currently available commercially will not detect all cases 3. Absence of standardized methods or reporting	No published data

Diagnostic Methods in Primary Ciliary Dyskinesia

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Table 2
Who to refer for diagnostic testing.

Patients with early onset of recurrent respiratory tract symptoms and any of the following:

1. Situs inversus (SI) totalis or any heterotaxic syndrome (approximately 50% have normal situs)
2. Neonatal nasal congestion and/or unexplained neonatal distress
3. Positive family history for PCD
4. Males with dysmotile sperm
5. Persistent productive cough/bronchiectasis/severe upper airway after more common causes like allergies, asthma, immune deficiencies and CF have been excluded.
6. Early onset of the combination of both severe upper and lower respiratory tract infections
7. Persistent/frequent intermittent serous otitis media (glue ear) associated with respiratory symptoms

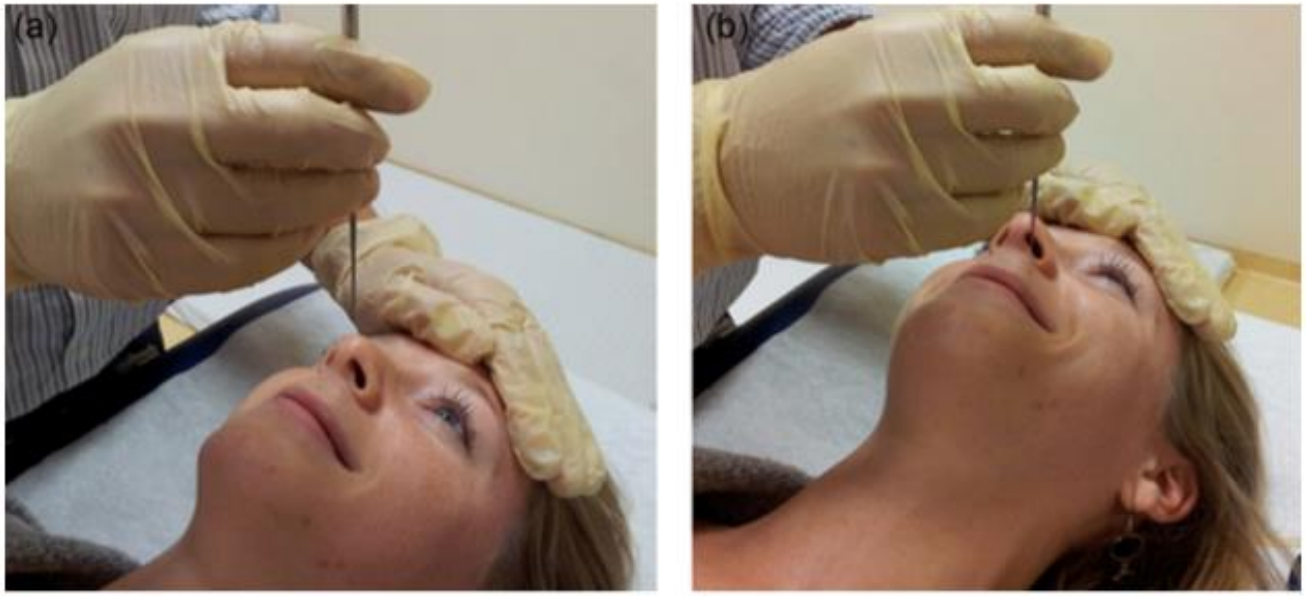

Figure 2. Obtaining an epithelial biopsy using a curette. Only superficial biopsies are required, so minimal force is used. When adequately performed, patient discomfort is minimal.

Ultrastructural defect (by TEM)	Ciliary motion defect (by HVMA)	Clinical phenotype
ODA		
DNAH5	Immotile with occasional stiff moving cilia	Classic
DNAI1	Unknown	Classic
DNAI2	Unknown	Classic
DNAL1	Decreased CBF	Classic
NME8 (TXNDC3)	Mixed populations: normal to immotile	Classic
CCDC103	Complete immotility or lack of coordination with reduced amplitude	Classic
CCDC114	Largely immotile with some twitching cilia	Normal male fertility
ARMC4	Complete immotility or reduced CBF and amplitude	Classic
CCDC151	Complete immotility	Classic
ODA/IDA		
DNAAF1 (LRRC50)	Complete immotility	Classic
DNAAF2 (KTU)	Complete immotility	Classic
DNAAF3	Complete immotility	Classic
HEATR2	Near complete immotility	Classic
LRRC6	Complete immotility	Classic
ZMYND10	Complete immotility or reduced CBF and amplitude	Classic
SPAG1	Near complete immotility	Classic
C21orf59	Complete immotility	Classic
DYX1C1	Largely complete immotility. Some cilia show reduced CBF	Classic
IDA/microtubule disorganisation		
CCDC39	Fast, flickery movement with reduced amplitude	Severe phenotype
CCDC40	Fast, flickery movement with reduced amplitude	Severe phenotype
CCDC65	Stiff, dyskinetic moving cilia	No SI
CCDC164	Increased CBF with reduced amplitude	No SI

CP defects		
RSPH1	Mixed populations: low CBF to immotility and normal CBF with reduced amplitude	No SI. Mild phenotype
RSPH4A	Mixed populations: low CBF to immotility and normal CBF and circular movement	No situs abnormalities
RSPH9	Mixed populations: low CBF to immotility and normal CBF with circular movement	No situs abnormalities
HYDIN	Mixed populations: immotility and reduced amplitude and lack of coordination.	No situs abnormalities
Aplasia/basal body and rootlet mislocalisation		
CCNO	Severe reduction in number of motile cilia. Cilia that are present function normally	No SI. Severe phenotype
MCIDAS	Severe reduction in number of motile cilia. Cilia that are present are immotile	No SI. Severe phenotype
Non specific defects		
OFD1	Mixed populations: normal and chaotic beating pattern	Mental retardation
RPGR	Mixed populations: motile and immotile cilia	Retinitis Pigmentosa
No defect		
DNAH11	Mixed populations: increased CBF with reduced amplitude and low CBF to immotility	Classic

Diagnostic Methods in Primary Ciliary Dyskinesia

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Future Directions

- Establish the evidence base to develop international standards for conduct and reporting of tests.
- Establish the evidence base for international development of a diagnostic algorithm for (i) definite PCD, (ii) probable PCD (iii) PCD excluded.
- Establish the accuracy (sensitivity, specificity, and predictive values of diagnostic tests in well designed 'blinded' studies.

When to suspect primary ciliary dyskinesia in children

Dominic A. Fitzgerald [1,2,*], Adam J. Shapiro [3]

Paediatric Respiratory Reviews 18 (2016) 3–7

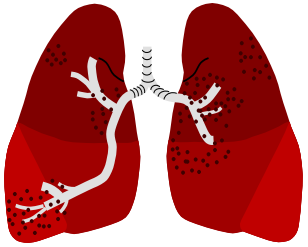
EDUCATIONAL AIMS

The reader will come to suspect the diagnosis of Primary Ciliary Dyskinesia in:

- A term infant with unexplained respiratory distress and migratory collapse on the chest radiograph.
- A toddler with chronic otitis media, purulent otorrhoea and a wet cough.
- A child with laterality defects [situs inversus, dextrocardia, heterotaxy].
- A child with chronic sinusitis and nasal polyposis.
- A child with unexplained bronchiectasis.
- An adult with unexplained bronchiectasis, chronic sinusitis, and infertility.

FUTURE DIRECTIONS FOR RESEARCH

- To ascertain better correlations between phenotype and genotype in PCD which may allow provide insight into differing clinical presentations.
- To expand the utility of nasal nitric oxide testing in younger children as a screening test for PCD



PCD

1. Tanı
2. Klinik
2. Yaşam kalitesi
3. Genetik
4. SFT
5. Tedavi

Presentation of primary ciliary dyskinesia in children: 30 years' experience

Patrick H Hosie,[1] Dominic A Fitzgerald,[2,3] Adam Jaffe,[4,5] Catherine S Birman,[3,6,7] Jonathan Rutland[8,9] and Lucy C Morgan[8,9]

Journal of Paediatrics and Child Health **51** (2015) 722–726

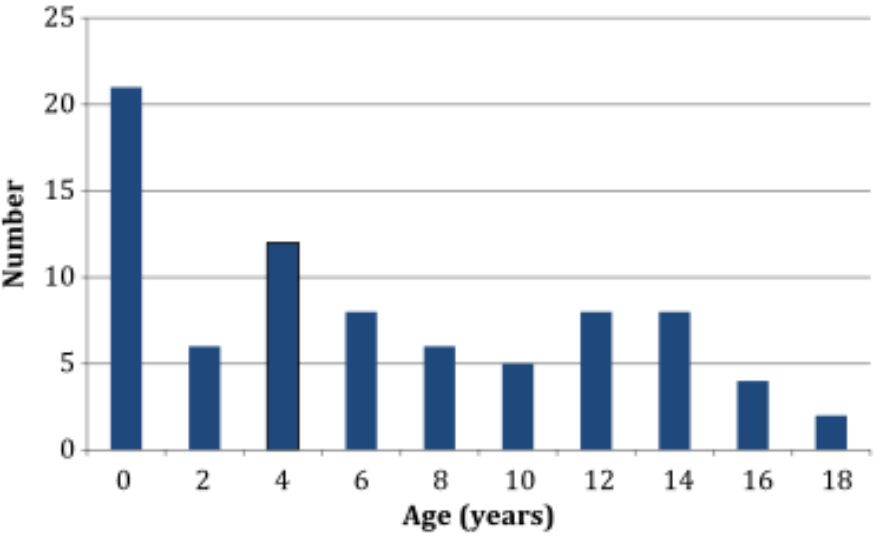


Fig. 1 The age at electron microscopy diagnosis for each child with PCD.

Table 1 Presenting history of children with PCD

Feature	Children (%)	*n* = 84
Situs inversus/situs intermedius	46	39
Neonatal respiratory distress	57	48
Bronchiectasis	32	27
LRTIs	74	62
Rhinosinusitis	71	60
Recurrent cough	81	67
Recurrent otitis media	49	41
Neonatal rhinitis	15 (*n* = 61)	9

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Table 2 Ciliary defects on EM analysis

EM abnormality	Children (%)	$n = 81$
ODA	41	33
ODA + IDA	19	15
ODA + IDA + disorientation	11	9
IDA	7	6
ODA + disorientation	5	4
IDA + microtubular defects	5	4
Disorientation	2	2
Others	9	7
Ciliary aplasia	1	1

Table 3 Ciliary beat pattern on LM

Beat pattern	Children (%)	$n = 80$
Immotile	43	34
Poorly motile	31	25
Abnormal (ineffective, slow, stiff)	21	17
Normal	5	4

Table 4 Signs on presentation

Sign	Children	%	Sample size
Digital clubbing	5	8	$n = 62$
Chest auscultation abnormality	26	53	$n = 49$
Chest wall deformity	5	9	$n = 58$
Dextrocardia	39	46	$n = 84$
Situs inversus	37	44	$n = 84$
Otoscopic abnormality	24	48	$n = 50$
Ear discharge	12	23	$n = 53$
Glue ear	19	45	$n = 42$
Acute sinusitis	14	26	$n = 53$

A longitudinal study of lung bacterial pathogens in patients with primary ciliary dyskinesia

M. C. Alanin[1], K. G. Nielsen[2], C. von Buchwald[1], M. Skov[2], K. Aanaes[1], N. Høiby[3,4] and H. K. Johansen[3,5]

Clin Microbiol Infect 2015; **21**: 1093.e1–1093.e7

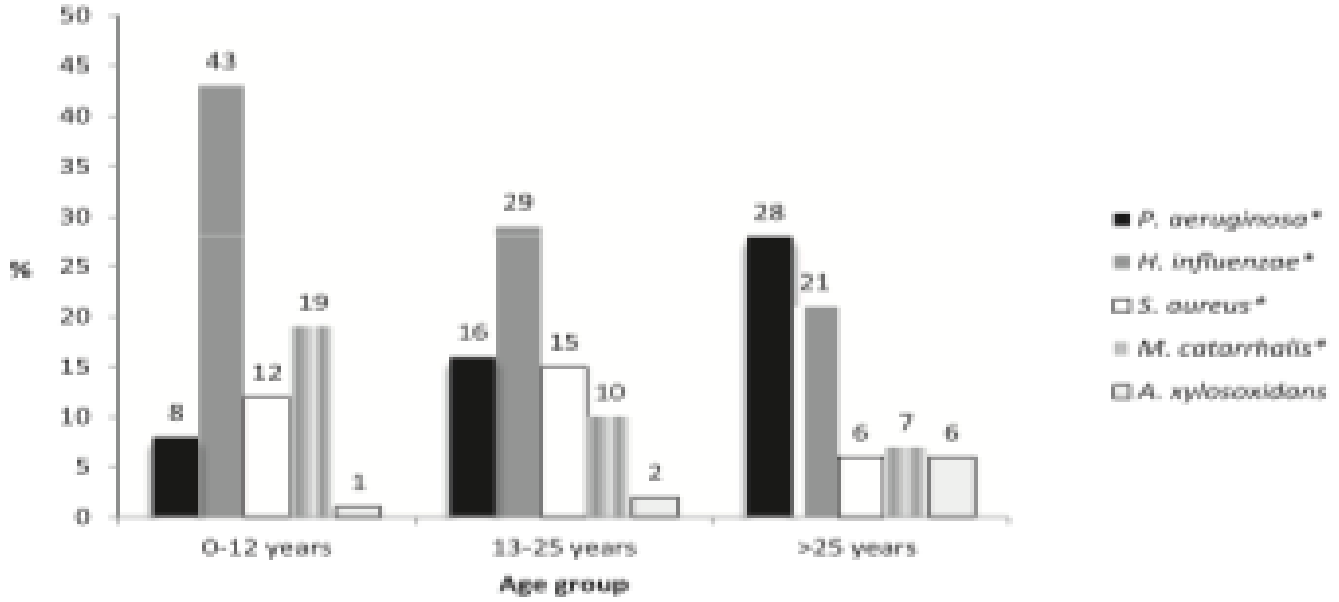

FIG. 1. Percentage of positive samples with *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis* and *Achromobacter xylosoxidans* in patients with primary ciliary dyskinesia according to age group. Patients were followed from 2002 to 2012. Children: 0–12 years, $n = 62$; teenagers and young adults: 13–25 years, $n = 54$; adults >25 years, $n = 38$. A patient can appear in more than one age group. *p <0.05.

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Hastaların %39'u en az bir kez Pseudomonas kolonizasyonu kriterlerini karşıladı.
Daha önce bildirilenden yüksek.

Clinical Features of Childhood Primary Ciliary Dyskinesia by Genotype and Ultrastructural Phenotype

Stephanie D. Davis[1]*, Thomas W. Ferkol[2], Margaret Rosenfeld[3], Hye-Seung Lee[4], Sharon D. Dell[5], Scott D. Sagel[6], Carlos Milla[7], Maimoona A. Zariwala[8], Jessica E. Pittman[2]*, Adam J. Shapiro[9]*, Johnny L. Carson[10,11], Jeffrey P. Krischer[4], Milan J. Hazucha[11,12], Matthew L. Cooper[13], Michael R. Knowles[12], and Margaret W. Leigh[10]

Am J Respir Crit Care Med Vol 191, Iss 3, pp 316–324, Feb 1, 2015

Table 1. Ciliary Ultrastructural Defects and Mutations in 118 Pediatric Subjects with PCD

Ciliary Defect Type	Mutated Gene	<5 yr [*N* (%)] (*n* = 29)	5–18 yr [*N* (%)] (*n* = 89)	All [*N* (%)] (*n* = 118)
ODA only	*DNAH5*	1	27	28
	DNAI1	0	7	7
	DNAI2	0	5	5
	CCDC114	0	2	2
	ARMC4	1	0	1
	No gene identified	3	8	11
Total		5 (17%)	49 (55%)	54 (46%)
ODA + IDA	*LRRC6*	1	2	3
	HEATR2	2	0	2
	SPAG1	0	1	1
	DNAAF2 (KTU)	0	1	1
	DNAAF1 (LRRC50)	0	1	1
	No gene identified	3	7	10
Total		6 (21%)	12 (13%)	18 (15%)
IDA/CA/MTD	*CCDC39*	7	6	13
	CCDC40	8	9	17
	No gene identified	1	9	10
Total		16 (55%)	24 (27%)	40 (34%)
CA or IDA alone	*RSPH4*	1	1	2
	RSPH9	0	1	1
	No gene identified	1	2	3
Total		2 (6%)	4 (4.5%)	6 (5%)

Definition of abbreviations: CA = central apparatus; IDA = inner dynein arm; MTD = microtubular disorganization; ODA = outer dynein arm; PCD = primary ciliary dyskinesia.
71% of patients had identified biallelic gene mutations.

Clinical Features of Childhood Primary Ciliary Dyskinesia by Genotype and Ultrastructural Phenotype

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Table 3. Markers of Disease Severity by PCD Group

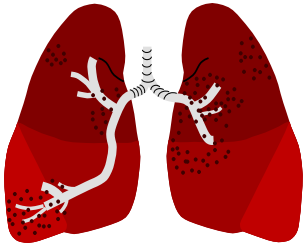
	All (*n* = 118)	ODA Only (*n* = 54)	ODA+IDA (*n* = 18)	IDA/CA/MTD (*n* = 40)	CA or IDA Alone (*n* = 6)	*P* Value*
Height, percentile†	42 (19 to 70) n = 106	42 (20 to 83) n = 51	63 (15 to 77) n = 16	36 (13 to 60) n = 34	44 (24 to 62) n = 5	0.036
Weight, percentile	52 (17 to 80) n = 118	67 (30 to 91) n = 54	76 (34 to 82) n = 18	39 (13 to 52) n = 40	62 (47 to 81) n = 6	<0.0001
BMI, percentile†	63 (32 to 82) n = 106	68 (32 to 92) n = 51	74 (41 to 82) n = 16	46 (26 to 65) n = 34	80 (71 to 84) n = 5	0.003
FEV_1, % pred	89 (67 to 99) n = 86	93 (78 to 101) n = 46	91 (74 to 99) n = 12	72 (58 to 88) n = 24	86 (77 to 93) n = 4	0.003
FEF_{25-75}, % pred	68 (48 to 80) n = 86	73 (57 to 80) n = 46	78 (59 to 94) n = 12	49 (32 to 64) n = 24	75 (53 to 88) n = 4	0.002
Infant $FEV_{0.5}$, *z* score	0.22 (0.12 to 0.31) n = 13	1.00 (0.57 to 1.43) n = 2	0.20 (0.02 to 0.31) n = 3	0.14 (0.01 to 0.22) n = 7	0.38 n = 1	0.144
Infant FEF_{25-75}, *z* score	−0.91 (−1.02 to −0.81) n = 13	0.77 (0.57 to 0.97) n = 2	−0.84 (−0.91 to −0.82) n = 3	−1.02 (−1.25 to −0.91) n = 7	−0.05 n = 1	0.023
Chest CT						
Number of lobes with bronchiectasis	3 (1 to 5) n = 118	3 (1 to 4) n = 54	3 (0 to 5) n = 18	3.5 (1 to 5) n = 40	4.5 (3 to 6) n = 6	0.243
Number of lobes with alveolar consolidation	2 (1 to 3) n = 118	1.5 (1 to 3) n = 54	2 (1 to 3) n = 18	3 (2 to 4) n = 40	2 (1 to 2) n = 6	0.001

Definition of abbreviations: BMI = body mass index; CA = central apparatus; CT = computed tomography; FEF_{25-75} = forced expiratory flow, midexpiratory phase; IDA = inner dynein arm; MTD = microtubular disorganization; ODA = outer dynein arm; PCD = primary ciliary dyskinesia.

Median (first quartile to third quartile).

**P* values for the comparison between the group of IDA/CA/MTD defect and the combined groups of ODA defect only and ODA+IDA defect.

†Subjects <2 years not included.



PCD

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A quality-of-life measure for adults with primary ciliary dyskinesia: QOL–PCD

Jane S. Lucas[1,2,3,7], Laura Behan[1,2,3,4,7], Audrey Dunn Galvin[4], Adrianne Alpern[5], Anjana M. Morris[5], Mary P. Carroll[1,2,3], Michael R. Knowles[6], Margaret W. Leigh[6] and Alexandra L. Quittner[5]

Eur Respir J 2015; 46: 375–383 |

TABLE 2 Participant quotes by topic

Topic	Quote	Country of interviewee/sex/age band in years
Impact of respiratory symptoms	"I had to tell the group not to worry because I start huffing and spluttering as I'm walking."	UK/female/36–50
	"When I listen to myself breathe, I always wheeze."	USA/female/18–35
Impact of sinus symptoms	"I'm always blowing my nose, doesn't matter what weather it is."	UK/female/36–50
	"I always have to blow my nose before I eat if I wanna taste anything."	USA/female/36–50
Impact of ear symptoms/ hearing loss	"You have to ask people to repeat themselves so many times, they're just, like, 'oh don't worry about it'."	UK/male/18–35
	"I can't go white water rafting because I have tubes in my ears and my ears can't get wet."	USA/female/18–35

A quality-of-life measure for adults with primary ciliary dyskinesia: QOL–PCD

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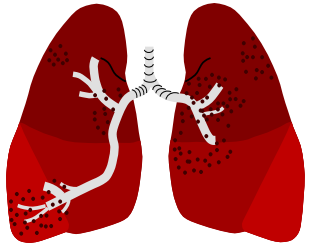
	tubes in my ears and my ears can't get wet.	
Impact of fertility issues	"Finding out that I possibly can't have kids; that's when it started to panic me a little bit."	UK/male/18–35
	"I'm still very uncertain if I ever wanna have children because I don't know how me having this illness will affect them."	USA/female/18–35
Impact of treatment burden	"I don't really want to do it; it's kind of boring and it's not fun and I'd rather do something else. But obviously you have to do it."	UK/female/18–35
	"I think it just requires more planning. I need to wake up earlier or start getting ready for bed earlier, I need to come home from work and do this; it's just more planning."	USA/female/18–35
Emotional functioning	"I'm so frustrated with this illness, I just want it to go away, but, unfortunately, that's how I have to live."	UK/male/18–35
	"...if you go to the doctor [and] you're feeling pretty good and you know your numbers are not good; that can be a big cause of anxiety."	USA/female/18–35
Social functioning	"It has had such a huge impact on my life, and certainly I think it's contributed to the breakup of my first marriage."	UK/female/50–64
	"...there have been times where I've had to cancel things because I've gotten sick. Getting sick can happen overnight; you're fine one day and the next day you feel awful."	USA/female/18–35

TABLE 3 Summary of modifications to QOL–PCD after cognitive testing

	Modifications after cognitive testing
Items added to scales	Respiratory symptoms: Wheezing Chest tightness Sinus symptoms: Post-nasal drip Sinus pain Physical functioning: Carrying heavy things, such as books and shopping bags Health perceptions: I feel healthy Emotional functioning: Felt depressed Felt lonely Social functioning: Stay at home more often than would like Feel comfortable coughing in front of others Feel comfortable blowing nose in front of others Intimacy with a partner (kissing, hugging, sexual activity) Worried about being exposed to others who are sick Comfortable doing treatments (airway clearance, physiotherapy) in front of others Treatment burden Physiotherapy/airway clearance made you feel tired quickly
Items deleted from scales	Health perceptions: I feel in control of my PCD Emotional functioning: Felt angry Felt limited Felt self-conscious Social functioning Self-conscious coughing and blowing my nose in public Treatment burden: Treatments made you feel better Physiotherapy is hard work
Wording modifications	Emotional functioning: "Felt anxious" changed to "felt worried" "Felt frustrated" changed to "felt frustrated about doing your daily



PCD

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Genetics and biology of primary ciliary dyskinesia

Amjad Horani [1,*], Thomas W. Ferkol [1,2], Susan K. Dutcher [3,2], Steven L. Brody [4]

Paediatric Respiratory Reviews 18 (2016) 18–24

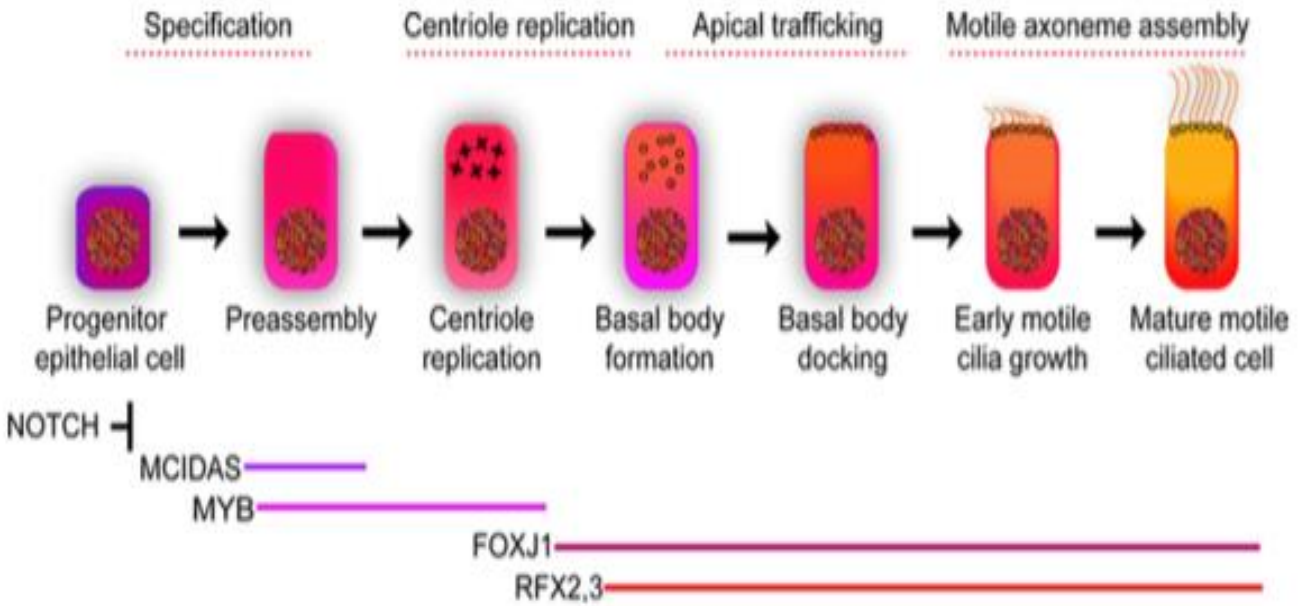

Figure 1. Multiciliated cell differentiation. An airway epithelial progenitor cell, possessing a primary cilium, is directed toward the multiciliated cell type in a low Notch signaling condition. Under the influence of multiple transcription factors, hundreds of centrioles are generated, dock as basal bodies, and nucleate motile cilia in a step-wise process.

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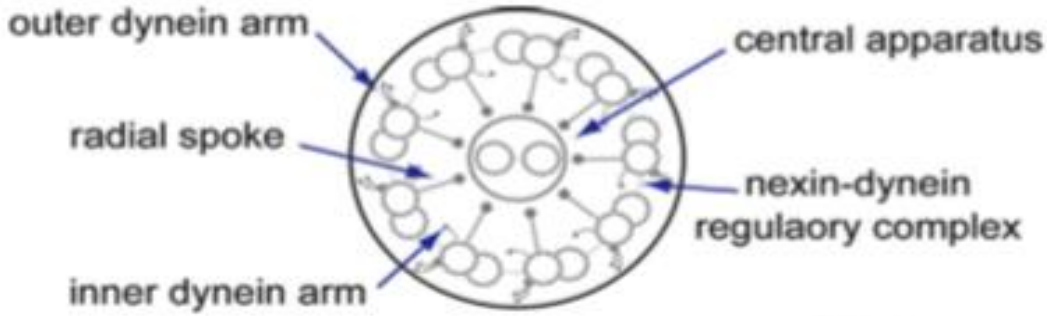
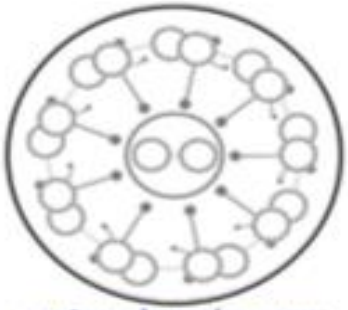
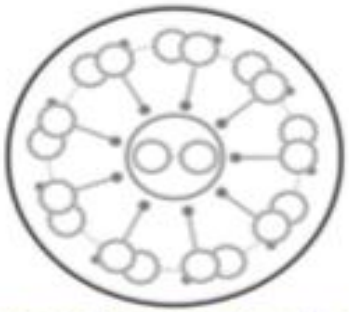
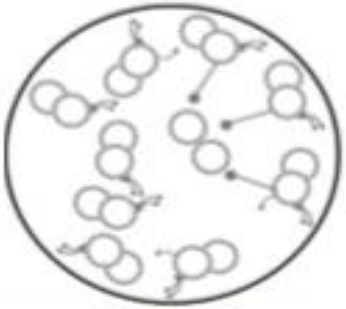




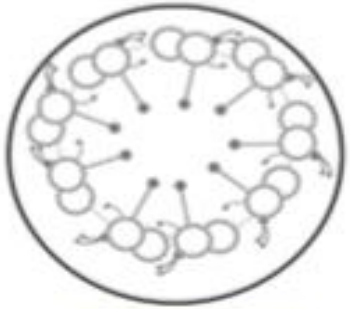
outer dynein arm
DNAH5, DNAI1, DNAI2
TXNDC3, DNAL1, ARMC4,
CCDC114, CCDC151



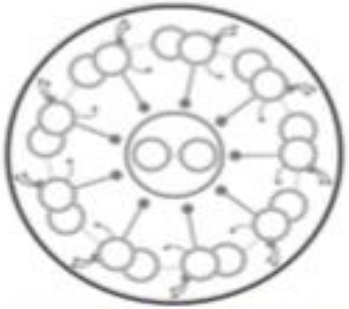
outer and inner dynein arm
LLRC6, DNAAF1, DNAAF2,
DNAAF3, CCDC103, ZMYND10,
HEATR2, DYX1C1, SPAG1, C21orf59



inner dynein arm
and axonemal
dysorganization
CCDC39, CCDC40



central apparatus
HYDIN
with disorganization
RSPH4A, RSPH9



normal ultrastructure
DNAH11, CCDC164,
CCDC65, RSPH1
with rare cilia
CCNO, MCIDAS

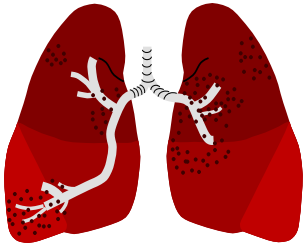
Genetics and biology of primary ciliary dyskinesia

Amjad Horani [1,*], Thomas W. Ferkol [1,2], Susan K. Dutcher [3,2], Steven L. Brody [4]

Paediatric Respiratory Reviews 18 (2016) 18–24

FUTURE DIRECTIONS

- Design and use of DNA microchips for the rapid diagnosis of PCD.
- Genotype-phenotype mapping to understand the heterogeneity of PCD.
- Elucidation of the mechanism of cilia assembly and function to allow for gene specific therapies.



PCD

1. Tanı
2. Klinik
2. Yaşam kalitesi
3. Genetik
4. SFT
5. Tedavi

Lung structure–function correlation in patients with primary ciliary dyskinesia

Mieke Boon,[1] Francois L Vermeulen,[1] Willem Gysemans,[1] Marijke Proesmans,[1] Mark Jorissen,[2] Kris De Boeck[1]

Thorax 2015;**70**:339–345.

Table 2 Spirometry and MBW parameters in HCs and PCD

	HCs (n=70)	PCD (n=38)	PCD with chest CT scan (n=30)	p Value for comparison HCs vs all PCD*	p Value for comparison HCs vs PCD with chest CT*
FEV_1 z-score	0.15 (−0.46 to 0.64)	−1.54 (−2.1 to −0.43)	−1.60 (−2.11 to −0.33)	<0.001	<0.001
FEV_1/FVC z-score	−0.16 (−0.91 to 0.40)	−1.52 (−2.20 to −1.01)	−1.62 (−2.10 to −1.15)	<0.001	<0.001
FEF_{25-75} z-score	−0.39 (−0.91 to 0.42)	−1.99 (−2.68 to −0.61)	−2.18 (−2.68 to −1.28)	<0.001	<0.001
LCI	7.1 (6.7 to 7.5)	9.48 (8.28 to 10.92)	9.48 (8.42 to 11.59)	<0.001	<0.001
LCI z-score	0.17 (−0.54 to 0.67)	3.58 (1.84 to 5.70)	3.58 (2.03 to 6.69)	<0.001	<0.001
$S_{cond} \times V_T$	0.011 (0.006 to 0.018)	0.057 (0.036 to 0.078)	0.060 (0.036 to 0.080)	<0.001	<0.001
$S_{cond} \times V_T$ z-score	−0.21 (−0.74 to 0.55)	4.68 (2.45 to 6.90)	4.93 (2.45 to 7.12)	<0.001	<0.001
$S_{acin} \times V_T$	0.044 (0.034 to 0.063)	0.079 (0.034 to 0.116)	0.079 (0.036 to 0.116)	0.009	0.005
$S_{acin} \times V_T$ z-score	−0.27 (−0.65 to 0.49)	1.17 (−0.64 to 2.58)	1.11 (−0.58 to 2.50)	0.009	0.005

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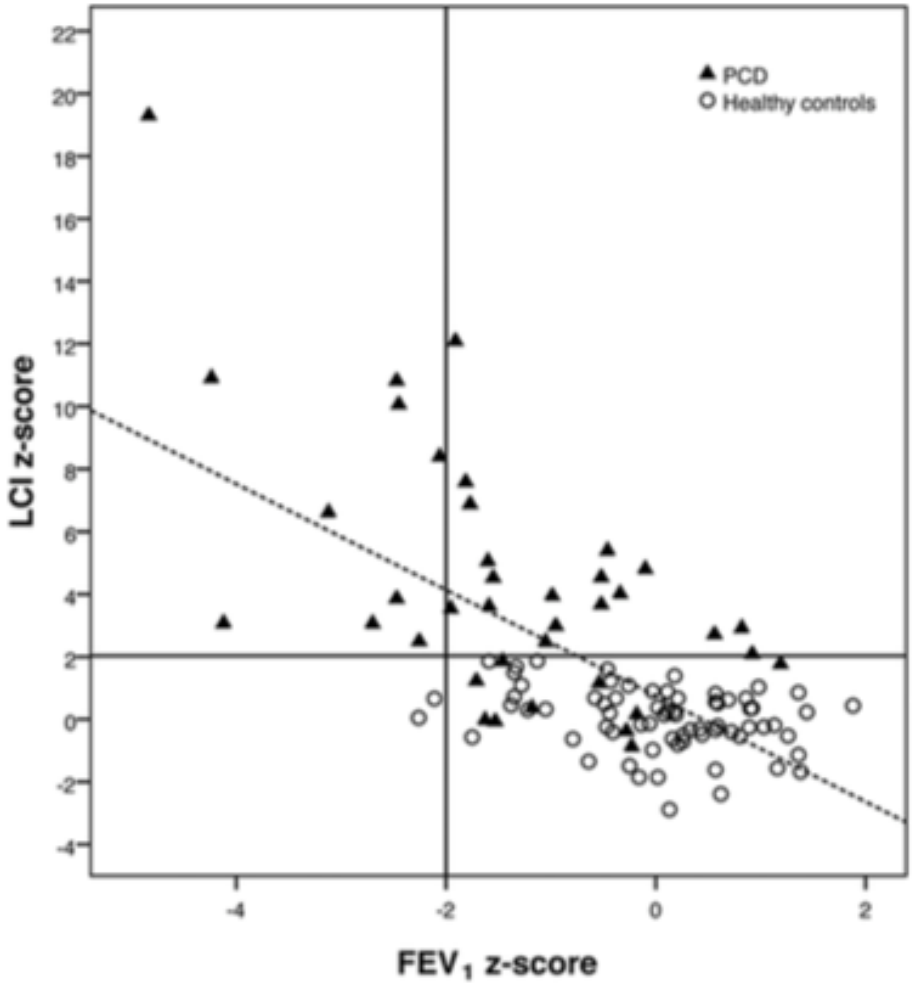

Lung structure–function correlation in patients with primary ciliary dyskinesia

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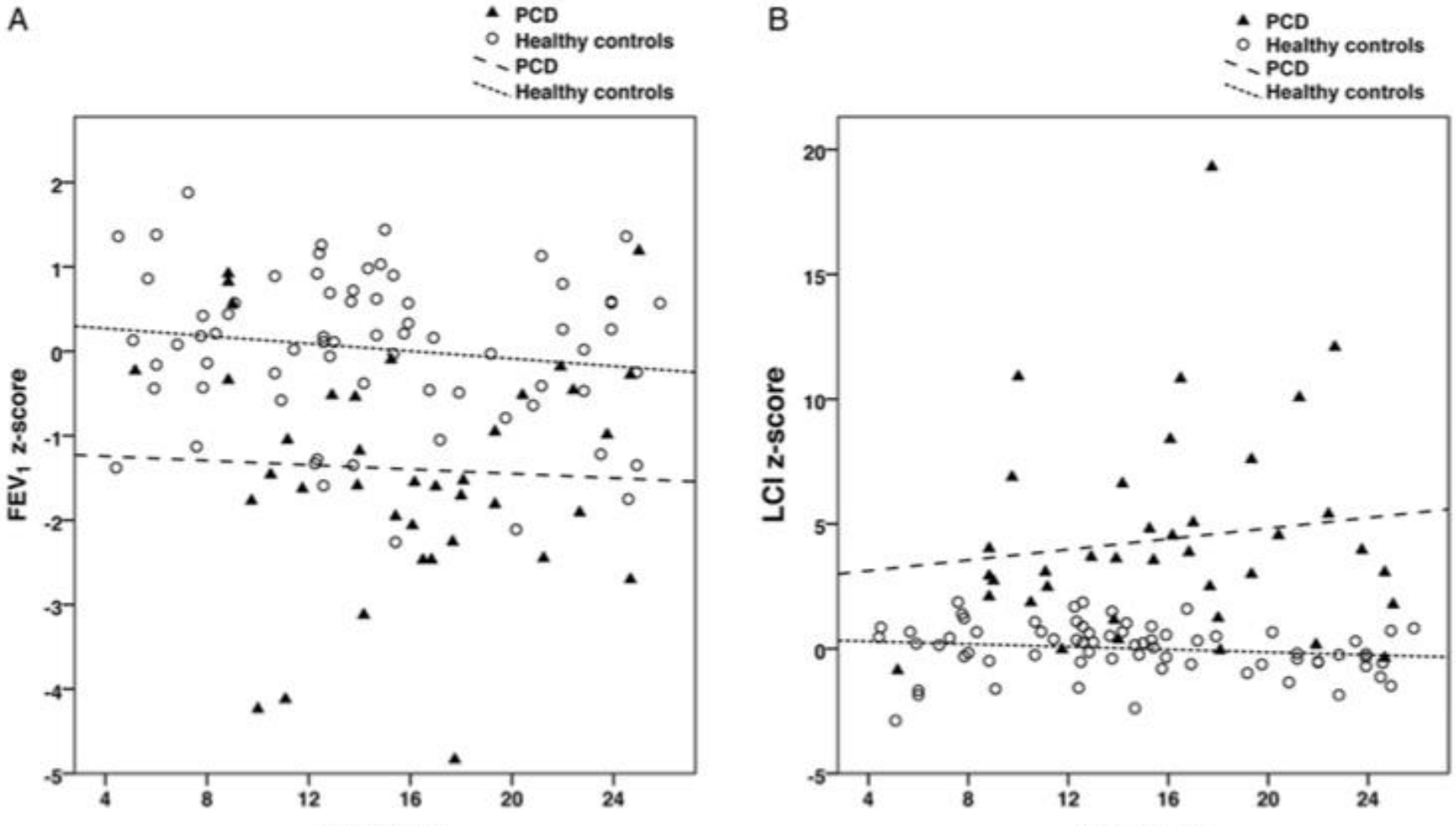

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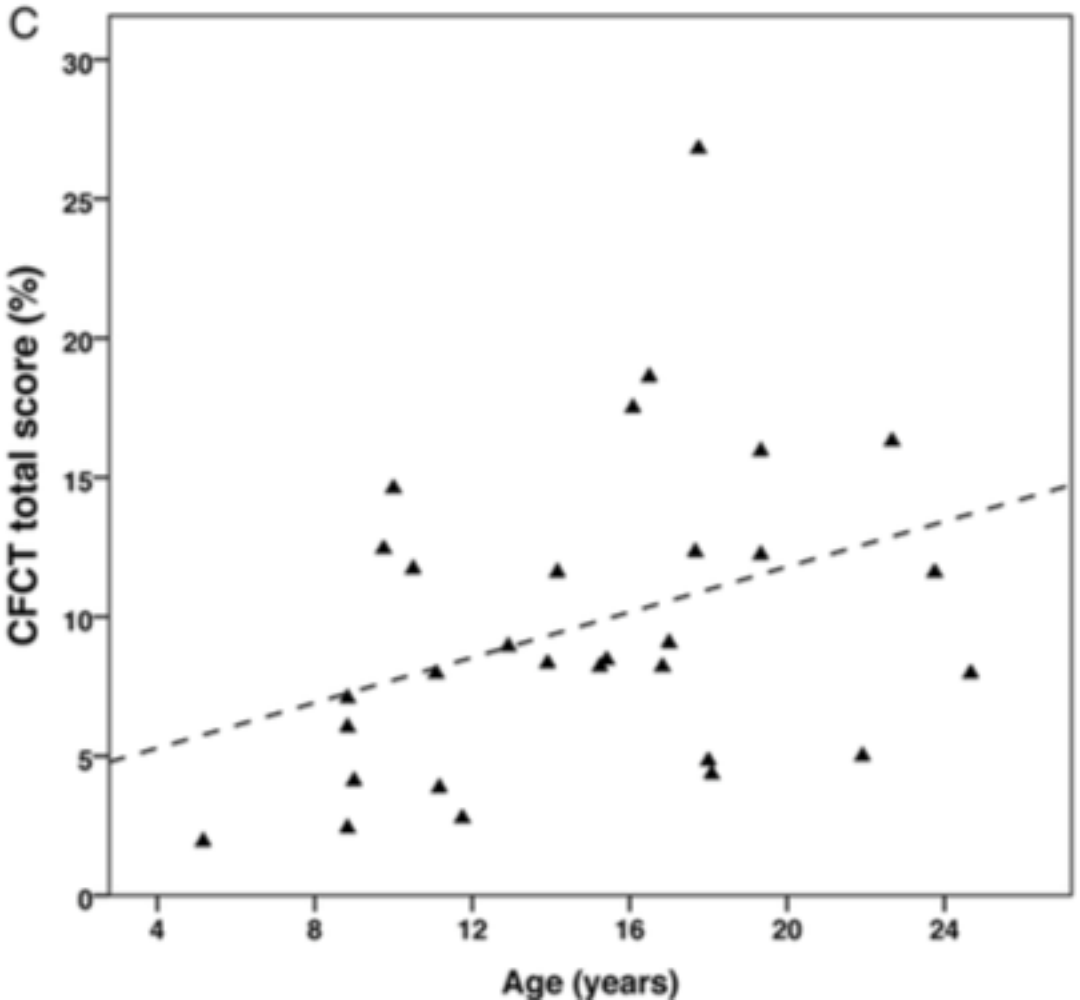

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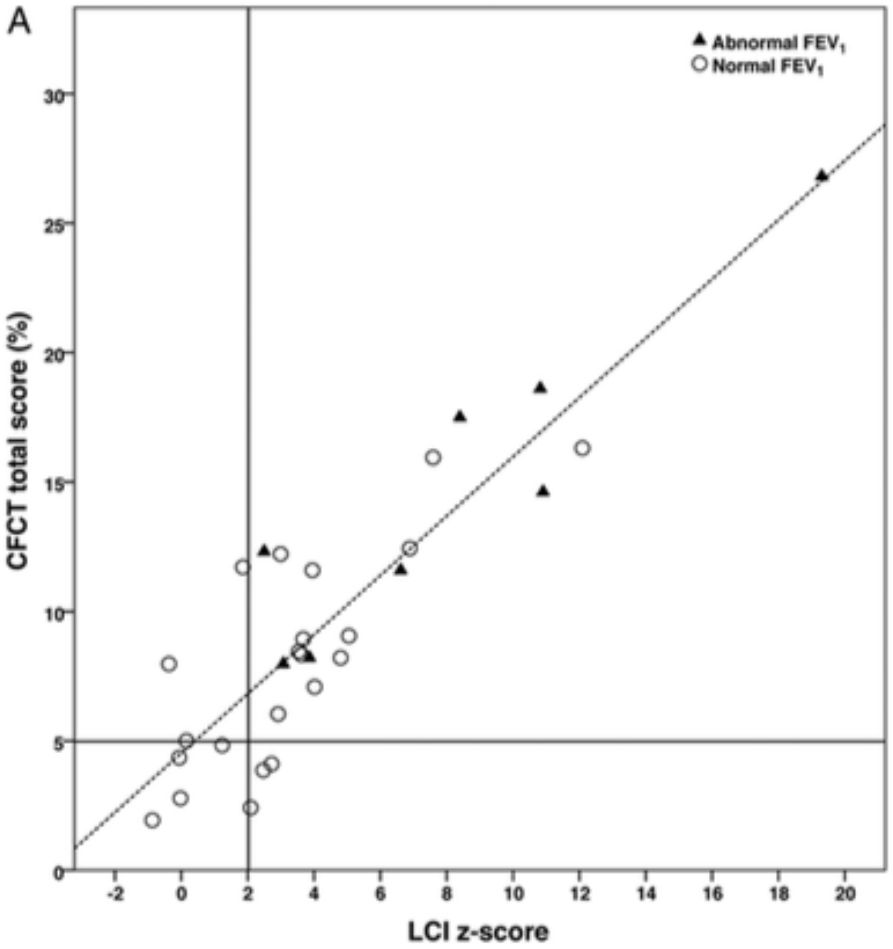

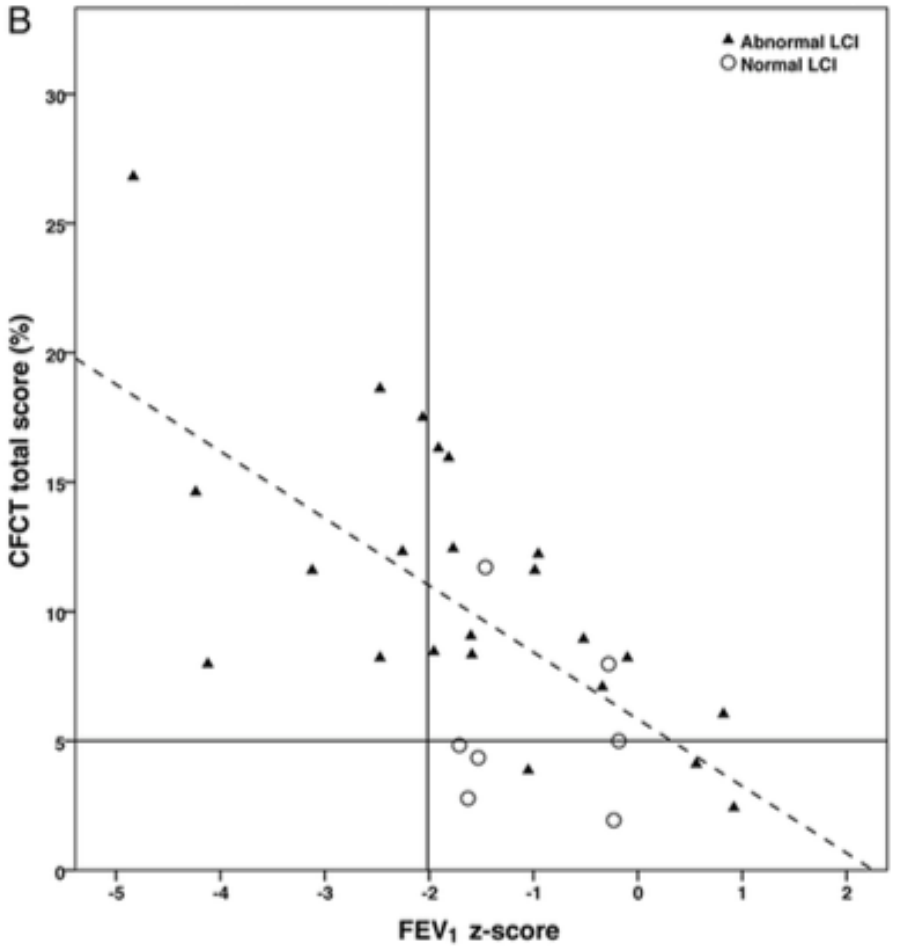

Comparison of Conventional Pulmonary Rehabilitation and High-Frequency Chest Wall Oscillation In Primary Ciliary Dyskinesia

Yasemin Gokdemir, MD,[1]* Evrim Karadag-Saygi, MD,[2] Ela Erdem, MD,[1] Ozun Bayindir, MD,[2] Refika Ersu, MD,[1] Bulent Karadag, MD,[1] Nimet Sekban, Physiotherapist,[2] Gulseren Akyuz, MD,[2] and Fazilet Karakoc, [illegible][1]

Pediatric Pulmonology

2014;49:611–616.

TABLE 3—PFTs of Patients' Before and After Treatment With CPR and HFCWO

PFT	Before CPR, mean ± SD (% predicted)	After CPR, mean ± SD (% predicted)	*P*	Before HFCWO, mean ± SD (% predicted)	After HFCWO, mean ± SD (% predicted)	*P*
FVC	77.0 ± 14.1	81.8 ± 13.0	0.002	75.1 ± 15.3	80.3 ± 13.9	0.002
FEV_1	72.9 ± 14.2	78.7 ± 13.5	0.001	71.4 ± 16.1	77.4 ± 14.6	0.001
PEF	73.8 ± 14.5	82.5 ± 14.5	0.001	70.9 ± 18.0	78.3 ± 17.7	0.002
$FEF_{25–75}$	68.6 ± 27.6	74.9 ± 29.3	0.007	70.5 ± 23.4	76.4 ± 25.6	0.006

Data are presented as mean (SD).
CPR, conventional pulmonary rehabilitation; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec; PEF, peak expiratory flow; $FEF_{25–75\%}$, forced expiratory flow at 25–75% of FVC; HFCWO, high-frequency chest wall oscillation.

Comparison of Conventional Pulmonary Rehabilitation and High-Frequency Chest Wall Oscillation In Primary Ciliary Dyskinesia

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Pediatric Pulmonology 2014;49:611–616.

TABLE 4—Comparison of CPR With HFCWO

	CPR	HFCWO	*P*
△FVC (% change)	7.5	9.0	0.53
△FEV_1 % change)	8.8	9.7	0.80
△PEF (% change)	12.9	12.8	0.98
△$FEF_{25–75}$ (% change)	9.8	9.7	0.81
SpO_2	95.8	96.7	0.89
Comfort (mean)	3.6	4.3	0.04
Effectiveness (mean)	4.5	4.0	0.09

CPR, Conventional Pulmonary rehabilitation; HFCWO, high-frequency chest wall oscillation; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec; PEF, peak expiratory flow; FEF25–75%, forced expiratory flow at 25–75% of FVC; SpO_2, Pulse arterial oxygen saturation.

Treatment recommendations in Primary Ciliary Dyskinesia

Deepika Polineni [1], Stephanie D. Davis [2], Sharon D. Dell [3,*]

Paediatric Respiratory Reviews 18 (2016) 39–45

PCD için kanıta dayalı tedavi YOK.

Önerilerin çoğu CF ve bronşiekteziden uyarlanmış.

PCD tedavisinin temel taşı, günlük solunum fizyoterapisi ile havayolları temizliği ve infeksiyona bağlı alevlenmelerin antibiyotikle ile tedavisi

Rutin takipte mutlaka olması gerekenler: SFT, balgam kültürü, odyometrik testler, rutin aşılamalar (pnömokok ve influenza)

PCD Lung Disease Pathophysiology

Existing Therapeutics

Defective Gene

↓

Defective Protein Product

↓

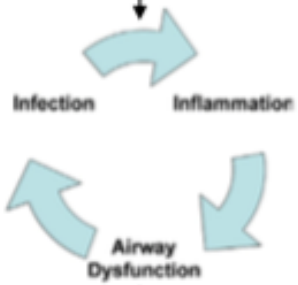
Defective Airway Cilia

↓

Impaired Mucous Clearance

- Hypertonic Saline
- Mannitol
- Dornase Alpha
- Chest Physiotherapy

↓



- Oral or IV Antibiotics
- Inhaled Antibiotics
- Macrolides
- Inhaled corticosteroids
- Systemic corticosteroids

↓

Clinical Symptoms

- E.g., cough, wheeze, dyspnea

End Organ Damage

Treatment	Routinely recommended	Case by case basis	Not recommended routinely
Airway clearance			
chest wall oscillation devices	X		
positive expiratory pressure devices	X		
chest wall percussion	X		
exercise	X		
Antibiotics			
Antibiotic treatment for exacerbation	X		
Inhaled antibiotics		X	
Chronic suppressive antibiotics[*]		X	
Chronic macrolide Antibiotics		X	
Mucolytics			
Dornase alfa			X
N-acetylcysteine			X
Hyperosmolar agents			
Hypertonic saline		X	
Mannitol		X	
Bronchodilators			
Short acting beta –agonists		X	
Long acting beta-agonists (in combination with inhaled steroids)		X	
Corticosteroids			
Inhaled[**]		X	
Systemic[**]		X	
Intravenous immunoglobulin			X
Vaccinations			
Influenza	X		
Pneumococcal	X		
Surgical treatment			
Surgical resection			X
Lung transplantation		X	

Treatment recommendations in Primary Ciliary Dyskinesia

Deepika Polineni [1], Stephanie D. Davis [2], Sharon D. Dell [3,*]

Paediatric Respiratory Reviews 18 (2016) 39–45

FUTURE DIRECTIONS FOR RESEARCH

- Prospective randomized clinical trials of interventions used in patients with PCD
- Correlations of genotype and phenotype in PCD cohorts
- Genotype-based precision based medicine trials
- Determining the underlying mechanisms of disease progression

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

Adam J. Shapiro, MD,[1*] Maimoona A. Zariwala, PhD,[2] Thomas Ferkol, MD,[3] Stephanie D. Davis, MD,[4] Scott D. Sagel, MD, PhD,[5] Sharon D. Dell, MD,[6] Margaret Rosenfeld, MD,[7] Kenneth N. Olivier, MD,[8§] Carlos Milla, MD,[9] Sam J. Daniel, MD,[10] Adam J. Kimple, MD,[11] Michele Manion,[12] Michael R. Knowles, MD,[13] and Margaret W. Leigh, MD,[14] for the Genetic Disorders of Mucociliary Clearance Consortium

Pediatric Pulmonology 51:115–132 (2016)

Major clinical criteria for PCD diagnosis*

1) Unexplained neonatal respiratory distress (at term birth) with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for >24 hr.

2) Any organ laterality defect—situs inversus totalis, situs ambiguous, or heterotaxy.

3) Daily, year-round wet cough starting in first year of life or bronchiectasis on chest CT.

4) Daily, year-round nasal congestion starting in first year of life or pansinusitis on sinus CT.

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

Adam J. Shapiro, MD,[1*] Maimoona A. Zariwala, PhD,[2] Thomas Ferkol, MD,[3] Stephanie D. Davis, MD,[4] Scott D. Sagel, MD, PhD,[5] Sharon D. Dell, MD,[6] Margaret Rosenfeld, MD,[7] Kenneth N. Olivier, MD,[8§] Carlos Milla, MD,[9] Sam J. Daniel, MD,[10] Adam J. Kimple, MD,[11] Michele Manion,[12] Michael R. Knowles, MD,[13] and Margaret W. Leigh, MD,[14] for the Genetic Disorders of Mucociliary Clearance Consortium

Pediatric Pulmonology 51:115–132 (2016)

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

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

Clinical visits
- Pulmonology: 2–4 times/year
- Otolaryngology: 1-2 time/year in children, as needed in adults
- Audiology: at diagnosis and as needed per otolaryngology
- Reproductive medicine: As clinically needed

Long-term surveillance
- Chest radiography: every 2–4 years
- Chest computed tomography: consider at least once after 5–7 years old (when sedation not required and images are of highest quality)[1]
- Airway microbiology cultures: 2–4 times/year
- Non-tuberculosis mycobacterial cultures: every 2 years (and with unexplained clinical decline)
- Pulmonary function testing: 2–4 times/year
- ABPA testing: IgE levels ± evidence of aspergillus specificity at diagnosis, with new onset wheezing, unexplained clinical decline

Preventative therapies
- Airway clearance: daily
- Nasal sinus lavage: daily (when pertinent)
- Standard vaccinations: per local schedule
- Influenza vaccine: annually[2]
- 13-valent pneumococcal vaccine: per ACIP guidelines[3]
- 23-valent pneumococcal vaccine: per ACIP guidelines[4]
- RSV immunoprophylaxis: consider monthly in first winter[5]

An international registry for primary ciliary dyskinesia

Claudius Werner[1], Martin Lablans[2], Maximilian Ataian[2], Johanna Raidt[1], Julia Wallmeier[1], Jörg Große-Onnebrink[1], Claudia E. Kuehni[3], Eric G. Haarman[4], Margaret W. Leigh[5], Alexandra L. Quittner[6], Jane S. Lucas[7], Claire Hogg[8], Michal Witt[9], Kostas N. Priftis[10], Panayiotis Yiallouros[11], Kim G. Nielsen[12], Francesca Santamaria[13], Frank Ückert[2] and Heymut Omran[1]

Eur Respir J 2016; 47: 849–859 |

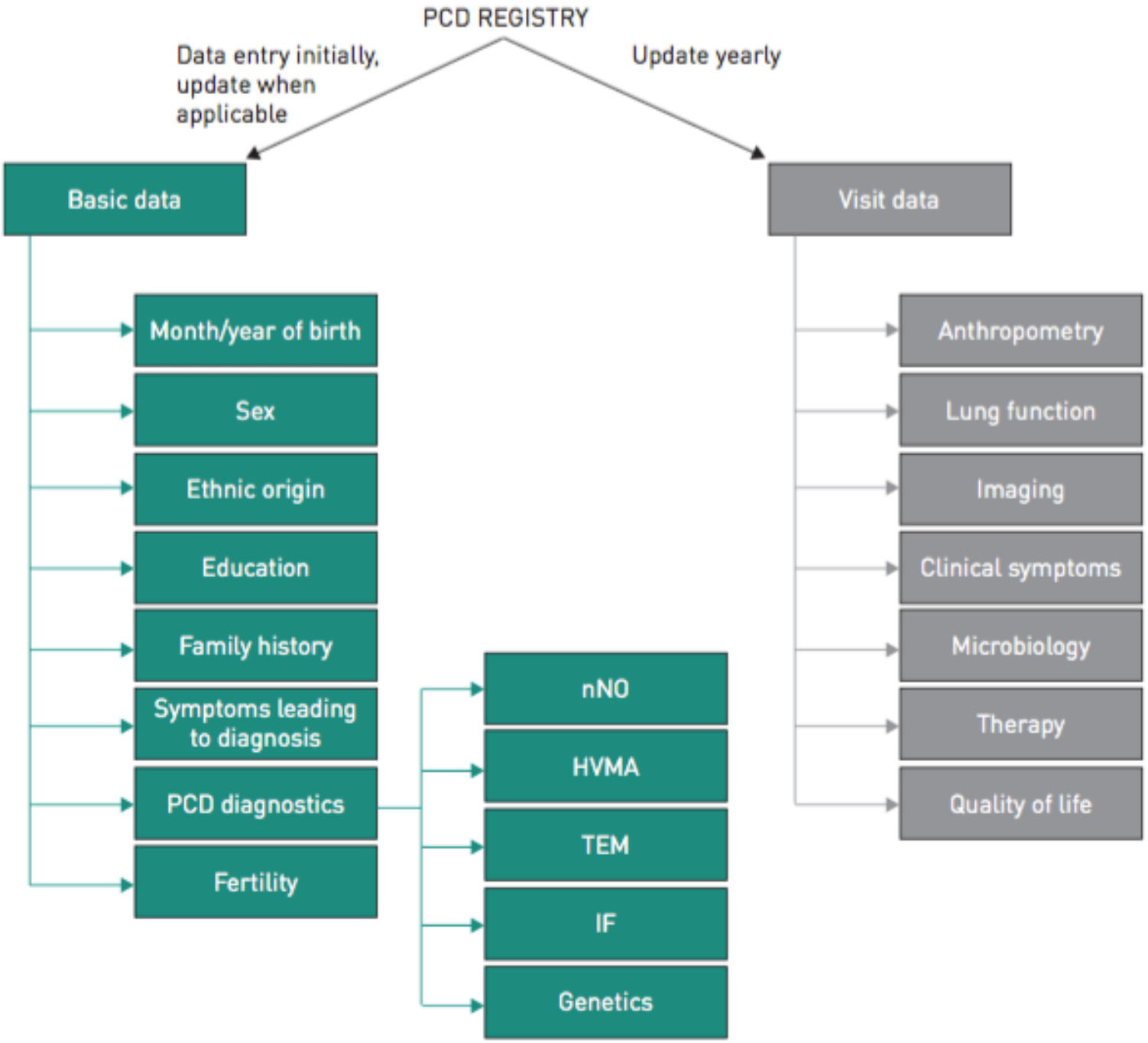
www.pcdregistry.eu

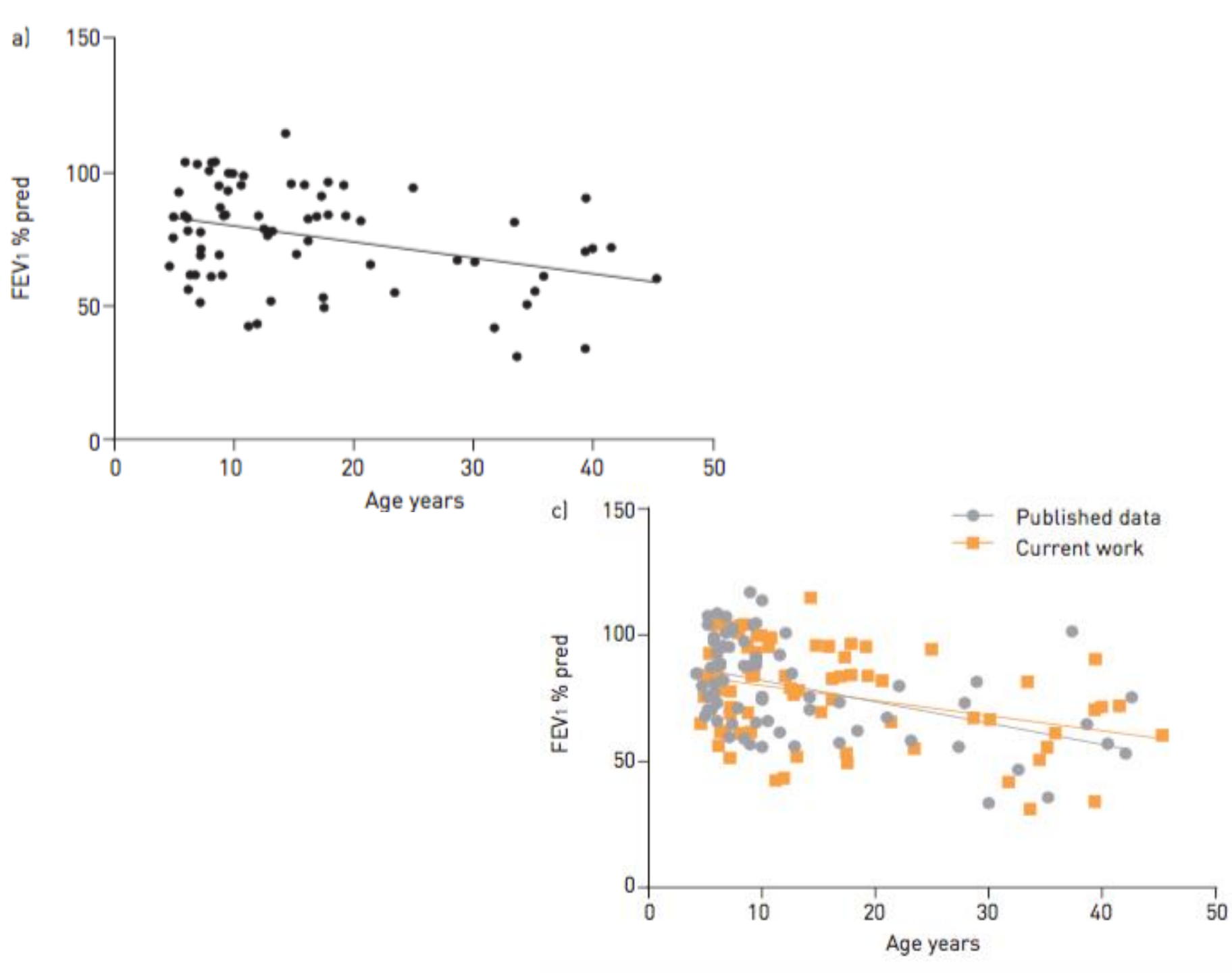
TABLE 1 Basic registry data: items collected at baseline; new information is added when appropriate

Field	Items
Administrative data	Written informed consent
	Patient identification; centre identification
	Birth month, birth year
	Gender
	Ethnic origin
	Socioeconomic background: level of education (parents and patient)
Family history	Parental consanguinity
	Affected siblings
	Other affected family members
Symptoms leading to diagnosis	History of neonatal respiratory distress syndrome
	Situs inversus totalis
	Chronic rhinitis/rhinosinusitis
	Chronic/recurrent otitis media
	Chronic wet cough
	Chronic/recurrent lower airways infection
	Chronic atelectasis
	Heterotaxia
	Congenital heart defect
	Cystic kidney disease
	Hearing loss
	Male infertility
	Hydrocephalus internus
	Retinitis pigmentosa
Male fertility	Number of children, semen analysis, use of assisted reproductive technologies
Female fertility	Number of pregnancies, number of miscarriages, number of ectopic pregnancies, number of children, use of assisted reproductive technologies
Primary ciliary dyskinesia diagnostics	Age, length/height and weight at diagnosis
	Nasal nitric oxide measurement
	High-frequency video microscopy findings
	Transmission electron microscopy analysis
	High-resolution immunofluorescence findings
	Genetic results

TABLE 2 Visit data items collected at least yearly

Field	Items
Anthropometric data	Height/length and weight at visit date
Lung function	Spirometry (FVC, FEV_1, $MEF_{25\%}$, $MEF_{25-75\%}$)
	6MWD
	Multiple-breath washout (LCI, FRC_{mbw})
	Blood gas analysis (pH, carbon dioxide tension, HCO_3^-, base excess, oxygen tension, oxygen saturation)
	Oxygen saturation (pulse oximetry)
Imaging	Chest radiograph
	Chest computed tomography
	Chest magnetic resonance imaging
	Radioaerosol mucociliary clearance analysis
Clinical disease manifestation	Lower airways: haemoptysis (more than traces), infectious exacerbations, pneumothorax
	Upper airways: otitis media, hearing impairment, sinusitis, chronic rhinitis, nasal polyps
	Other conditions: gastro-oesophageal reflux, sinus headache, chest pain
Microbiological findings	Sputum, throat swab, cough swab, laryngeal swab, nasal swab, nasal lavage, bronchoalveolar lavage, ear swab
Therapy	Antibiotics: systemic, inhaled
	Inhalation therapy (not antibiotics): NaCl 0.9%, hypertonic NaCl (at least 3%), bronchodilator, corticosteroids, other
	Other drugs
	Physiotherapy/airways clearance therapy: postural drainage and percussion, autogenic drainage, positive expiratory pressure, active-cycle breathing technique, oscillatory positive expiratory pressure, high-frequency chest compression, exercise training
	Oxygen therapy: intermittent/continuous
	Long-term mechanical ventilation: noninvasive/invasive
	Lung surgery: lobectomy, lung transplantation, other
	Upper-airway surgery: tympanostomy tube insertion, adenotomy, sinus surgery, mastoidectomy, other
	Quality of life: the PCD-specific quality of life questionnaire (QOL-PCD) will be added as soon as validation has been completed


PCD REGISTRY
Data entry initially, update when applicable
Update yearly
Basic data
Visit data
Month/year of birth
Sex
Ethnic origin
Education
Family history
Symptoms leading to diagnosis
PCD diagnostics
Fertility
nNO
HVMA
TEM
IF
Genetics
Anthropometry
Lung function
Imaging
Clinical symptoms
Microbiology
Therapy
Quality of life


a)
150
100
50
0
FEV1 % pred
0
10
20
30
40
50
Age years
c)
Published data
Current work
150
100
50
0
FEV1 % pred
0
10
20
30
40
50
Age years


BOĞAZ