NRS Roadmap BPD/PCD report

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1. Inventory of Dutch research efforts in this field over the past five years (2008-2013) by ISI web of knowledge

Our inventory of Dutch research efforts is based on our personal clinical and basic scientific knowledge of the field, which is a combination of networking and knowledge from literature. Although, bronchopulmonary dysplasia (BPD) and primary ciliary dyskinesia (PCD) are both orphan diseases they further lack any similarity. Therefore, we made a separate survey for both diseases.

The output for BPD is listed below and includes the research subjects from 124 papers from Dutch scientists (average citation per item: 8.26) retrieved from the ISI Web of Knowledge database when searched as: bronchopulmonary dysplasia (Topic) and Netherlands (address) from 2008-2013. Publications initiated by a Dutch research group (first and last author has a Dutch affiliation) are listed in tables 1-3 and in collaboration with others in tables 4-6.

Summary in BPD

Clinical

- Follow up studies of BPD patients: POPS, Neoned study group, MOSAIC cohort, NEUROSIS cohort, LOLLIPOP, individual cohort studies. They focus on pulmonary and neurological outcome. Some smaller studies focus on specific subjects among children with BPD such as retinopathy of prematurity (ROP), growth and body composition, nutritional problems, passive immunisation against RS and gentler respiratory support.
- Comorbidities of BPD: retinopathy of prematurity (ROP), brain damage (cranial bleedings and hypoxia), pediatric pulmonary hypertension and associated cardiac disease (RVH).
- Clinical trials: STOP BPD.
- Case studies on alternative treatment options.
- Non-invasive ventilation after premature birth.
- Invasive, but gentle ventilation after premature birth.
- Surfactant.
- Gender.
- Anti oxidants

Basic / translational.

- New treatment options for experimental BPD in animal models
- Studies on potential prenatal and postnatal causative factors of BPD in animal models, including chorioamnionitis, meconium aspiration (prenatal inflammation) before birth and lung immaturity, resuscitation, aberrant lung

development, RDS, inflammation, congenital diaphragmatic hernia, ventilation and oxidative stress after (premature) birth.

Summary in PCD research

The research efforts that have been done on the topic PCD in the Netherlands have been very limited: only 9 publications could be found (period 2008-2013; overview in table 7).

2. Visibility Dutch research judged by international experts (see also appendix)

Areas with good visibility	Areas with less visibility

3. Research needs

Facts and Figures (2013) [1]
The report "Feiten en Cijfers' on respiratory diseases by the LAN" does not include the orphan diseases BPD and PCD. Therefore the Facts and Figures and the Unmet needs as defined by the LAN rapport cannot be included.

Euro costs[2]
Estimated costs for BPD patients in the first year:
- 40 days of treatment in NICU: 40 x 2500 = 100,000
- 50 days of treatment in regional hospital: 50 x 700 = 35,000
- Treatment for RSV: 6 x 2000 = 12,000
- Number of patients per year: 350

Estimated total costs per year BPD: 350 x 147,000 = 51,450,000 Euro

Estimated costs for PCD patients:
- Approximate number of patients in the Netherlands: 800 (prevalence 1: 15,000-30,000).
- Based on the average costs of CF-patients (approximately 10,000 euro/ year) and taking into consideration the generally less aggressive disease course in PCD patients, we estimate the average costs per year: 800 x 0.5 x 10,000 = 4,000,000 euro.

Estimated costs per year PCD: 4,000,000 Euro

Unmet needs (extracted from: LAN verkenning 2010[3])
BPD
- Patient organizations such as 'de vereniging voor ouders van couveuse kinderen' have been invited to give their opinion.

PCD

- In collaboration with the PCD Belangengroep, research goals have been formulated in the past. There are urgent needs for better and less invasive diagnostic tests and evidence based treatment strategies.
- During recent years, it is becoming increasingly difficult to get reimbursement for non-evidence based treatments (e.g. pulmozyme), though several patients report significant improvement of symptoms.
- In addition, a better general awareness of this orphan disease is needed, as many patients have encountered delayed diagnosis and lack of understanding.

References

[1] Feiten en cijfers 2013 Chronische Longziekten, LAN 2013
[2] Maatschappelijke kosten voor astma, COPD en respiratoire allergie. RIVM Rapport 260544001/2012
[3] Feiten en cijfers chronische Longziekten, LAN 2010

4. Summary of a SWOT analysis of BPD

Results of the web-based SWOT

Strengths	*Weaknesses*
1. Good national clinical collaboration 2. Embedding of research in a clinical setting 3. Basic research, biological mechanisms	1. Small and heterogeneous patient population 2. Multiple treatment protocols in 8 academic hospitals 3. Poor definition lacking pathological characteristics
Opportunities	*Threats*
1. Diagnosis and monitoring 2. Improvement of treatment 3. Improved accessibility to limited patient materials for research	1. Small number of patients 2. Lack of financial support for research 3. Poor drug development

Summary of SWOT analysis PCD

Results of the web-based SWOT

Strengths	*Weaknesses*
1. National collaboration 2. International collaboration (FP-7 project BESTCILIA)	1. Small patient population 2. Scattered patient care 3. Few research groups, limited track-record 4.
Opportunities	*Threats*
1. Central and uniform longitudinal PCD registrations. 2. Improve diagnostics, follow-up and treatment. 3. Raise awareness amongst physicians and public	1. Small number of patients 2. Lack of financial support for research 3. Low awareness of disease and importance of PCD diagnostics.

Relevance of research judged by international experts (order of importance):
See Table *Relevance of research judged by international experts* in appendix

	Mean
Phenotyping and Severity	3.67
Biological mechanisms	4.33
Environment and lifestyle	2.50
Development and ageing	2.33
Prevention	2.67
Diagnosis monitoring	3.50
Therapy medical	3.67
Therapy non-medical	2.00
Biobanking	2.50
Data management clinical studies	2.50
Implementation and care	3.33

BPD

Strength

- Good collaboration between the divisions of neonatology, the departments of Pediatrics of the academic hospitals (Neoned) improves the shared knowledge of this orphan disease in the Netherlands that may result in a better (pharmacological) treatment of BPD and participation of all NICU's in current and future well-designed clinical studies and/or trials (currently STOPBPD trial). Well-designed clinical trials are crucial for future drug development and should be performed in al well- characterized patient population with a uniform treatment protocol and outcome parameters. The new BPD guideline by the "Nederlandse Vereniging voor Kindergeneeskunde (NVK)" will be helpful to achieve these goals.
- Basic research and expertise on biological mechanisms of BPD.

Weaknesses
- BPD is an orphan disease with a limited number of 350 cases per year in a heterogeneous patient population, that is poorly defined and diagnosed.
- This small number of patients is treated in 8 different academic hospitals with different treatment protocols.

Opportunities
- Central and uniform registration of all BPD patients treated in different academic hospitals will improve knowledge. Benchmarking may be valuable and instrumental to gain knowledge and optimize treatment.
- Integration of clinical and experimental data will improve the poor definition of BPD that is currently used.
- COHORT studies and early intervention studies will improve disease understanding and prognosis.
- Prediction models for BPD may be helpful for disease understanding and treatment.
- Advances in neonatal and prenatal clinical care will increase survival of very premature infants and, therefore, will not only lead to an increase in the incidence of BPD, but also to an increased number of patients with severe and multiple handicaps.
- Increased knowledge on BPD and increased accessibility to patients and patient materials will be achieved by strategic collaboration with international pediatric hospitals.

Threats
- The poor diagnosis of BPD in the Netherlands undermines adequate treatment and future research.
- The low number of pediatric patients is not attractive for pharmaceuticals companies to spend significant amounts of money on drug development.
- The low number of pediatric patients is not attractive for governmental and non-governmental organizations to financially support clinical and experimental research, thereby hampering research that is badly needed for better understanding and treatment of the disease.

PCD

Strength
- National collaboration between academic hospitals that have joined forces to share their knowledge: VU University Medical Center, Academic Medical Center Amsterdam and the Radboud University Nijmegen Medical Center. This recently formed collaboration aims to improve shared knowledge and focuses on clarifying the genetic background of Dutch PCD patients and early detection of exacerbations to prevent lung damage. Further, pilot treatment studies are being organized and a National registration is being set up by the Vu University Medical Center.
- International collaboration within Europe (FP-7 project BESTCILIA)

Weaknesses

- PCD is an orphan disease with an unknown number of cases. Many patients are diagnosed later in life or may classified as having non-CF bronchiectasis.
- Patient care is “scattered”: the small number of patients is treated in different academic hospitals, peripheral hospitals and some patients are treated by family physicians, all using different treatment protocols.
- Comparatively few researchers involved in PCD research, limited track-record.

Opportunities
- Central and uniform longitudinal registration of all PCD patients treated in different hospitals will improve knowledge
- Integration of clinical and research data (national and international) will improve the diagnostics, follow-up and treatment of PCD patients
- Raising awareness amongst Dutch physicians and improve communication of results to patients and lay public.

Threats
- The low number of patients is not attractive for pharmaceuticals companies to spend significant amounts of money on drug development.
- The low number of patients and the orphan disease status is not attractive for governmental and non-governmental organizations to financially support clinical and experimental research, thereby hampering research that is badly needed for better understanding and treatment of the disease.
- Low awareness of the disease and the importance of PCD diagnostics and uniform treatment amongst Dutch physicians.

The limited number of responses makes the web-based SWOT analysis inadequate.

5. Description of the interface of your area with those of other Roadmap teams

BPD may be complicated by pulmonary arterial hypertension (PAH)-induced right ventricular hypertrophy BPD may additionally ultimately result in the development of COPD in young adults. Because COPD and persistent PAH cannot be cured at present, lung transplantation is the last “treatment” option for these patients (from 6 years onward). Therefore we anticipate fruitful collaborations with the following roadmap teams: PAH, COPD and lung transplantation.
PCD is characterised by recurrent pulmonary infections and the development of bronchiectasis. As such, there is a clear interface with the following roadmap teams: cystic fibrosis and infectious diseases.

6. Priorities for Dutch research in the area of BPD and PCD for 2014-2019

BPD
- BPD is poorly diagnosed, because the definition of BPD in patients: “the need for supplemental oxygen at the corrected age of 36 weeks postmenstrual age” is incomplete and lacks pathological criteria. A better characterization of the disease and its pre- and postnatal causal factors in patients is badly needed to improve its poor definition.
- Development of prediction models are helpful in selecting patients for treatment and research, including clinical trials.
- Development of drugs to prevent or reduce BPD in ventilated premature infants.

- Development of drugs for treatment of BPD patients to reduce BPD comorbidities, including increased risk for asthma development and early onset COPD and high susceptibility of viral infections.
- Development of standardized non-invasive and gentler invasive ventilation protocols for premature infants.
- Development of standardized follow up protocols for children and adolescents with BPD.

These investments will not only increase the quality of life for BPD patients, who are not only effected in the early neonatal period, but also later in life, but also reduce expensive treatment of comorbidities for which BPD patients are often hospitalized.

PCD
- Therapeutical trials: antibiotics, hypertonic saline, pulmozyme
- Identification PCD gene mutations
- Standardization PCD diagnostics

A general lack of research in these areas, has resulted in sub-optimal diagnostic (both false negative and false positive diagnoses are frequently encountered) and therapeutic patient care. Treatment protocols are now derived from CF-protocols, a disease with a different pathophysiology and, therefore, perhaps a different response to treatment.

7. What is needed to let the research priorities listed be successful?

BPD
- International collaborations will increase the accessibility to BPD patients and patient's materials.
- Financial support by governmental and non-governmental organizations, including industry and charity is badly needed for disease understanding, treatment and prevention.

PCD
- Improved national collaboration between the academic and non-academic centers caring for adult and pediatric PCD patients. This will result in a better characterisation of the disease (national PCD registry), standardization of diagnosis and facilitate multicenter trials
- International collaboration for the same reasons as outlined above.
- Financial support to improve ciliary diagnostics and facilitate multi-center trials

8. What do patients want?

BPD

The Long Fonds interviewed patients and their parents to get an impression of their main questions regarding BPD in 2013. (Project to explore perinatal and postnatal lung disease). The most important questions were:

- What are long-term effects of BPD? Are BPD-patients the future COPD patients?
- What are practical advices/ guidelines concerning nursery, going outside, need for adjustments at home etc.?
- What are the optimal ventilation modalities to prevent BPD?
- How to reduce symptoms?
- Research for an energy-boost-medicine
- Research to evaluate the development of the brain respiratory center and the development of the lungs

PCD

The PCD Belangengroep and the Long Fonds emphasize the importance of general awareness and understanding of this rare disease. Diagnosis and treatment or often delayed. Diagnosis is difficult and rather invasive, especially in children (ciliary biopsies). There is an urgent need for better and less invasive diagnostic tests. Finally, it is becoming increasingly difficult to get reimbursement for several PCD-treatments (all treatments in PCD are non-evidence based due to the rare nature of the disease). This is a major issue for patients and should be resolved.

Table 1. Top 10 most cited clinical BPD research initiated by a Dutch group (first and last author has a Dutch affiliation; reviews are excluded):

Theme	Article	Citations	
		Total	Mean/yr
Motor development	de Kieviet JF, Oosterlaan J. Motor Development in Very Preterm and Very Low-Birth-Weight Children From Birth to Adolescence A Meta-analysis. JAMA 2009; 302:2235-2242.	37	12.3
Chorio - amnionitis	Been JV, Zimmermann LJ. Chorioamnionitis Alters the Response to Surfactant in Preterm Infants. *J* Pediatrics 2010; 156:10-15.	23	11.5
Treatment dexa methasone	Karemaker R, Heijnen CJ. Neonatal dexamethasone treatment for chronic lung disease of prematurity alters the hypothalamus-pituitary-adrenal axis and immune system activity at school age. Pediatrics 2008; 121:E870-E878.	26	6.5
Intervention	Koldewijn K, Nollet F. A Neurobehavioral Intervention and Assessment Program in Very Low Birth Weight Infants: Outcome at 24 Months. *J* Pediatrics 2010; 156: 359-365	21	
Esophageal atresia	Gischler SJ, IJsselstijn H. A prospective comparative evaluation of persistent respiratory morbidity in esophageal atresia and congenital diaphragmatic hernia survivors. J Ped Surg 2009; 44:1683-1690.	18	
Preterm	Groenendaal F, de Vries LS. Complications affecting preterm neonates from 1991 to 2006: what have we gained? Acta Paediatrica 2010; 99:354-358.	16	
Growth factors	Been JV, Zimmermann LJ. Early Alterations of Growth Factor Patterns in Bronchoalveolar Lavage Fluid From Preterm Infants Developing Bronchopulmonary Dysplasia. Ped Res 2010; 67:83-83.	15	
Glutathione synthesis	te Braake, FWJ, van Goudoever JB. Glutathione synthesis rates after amino acid administration directly after birth in preterm infants. Am J Clin Nutr 2008; 88:333-339.	15	
Treatment Ogligo – saccharides	Westerbeek EAM, van Elburg RM. Neutral and acidic oligosaccharides in preterm infants: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr 2010; 91: 679-686.	14	
Treatment Dexa – methasone	Onland W, van Kaam AH. Effects of higher versus lower dexamethasone doses on pulmonary and neuro-developmental sequelae in preterm infants at risk for chronic lung disease: A meta-analysis. Pediatrics 2008; 122: 92-101.	13	

Table 2. Top 10 most cited basic BPD research initiated by a Dutch group (first and last author has a Dutch affiliation; reviews are excluded):

Theme	Article	Citations	
		Total	Mean/yr
Antenatal inflammation	Kramer BW. Antenatal inflammation and lung injury: prenatal origin of neonatal disease. J Perinatol 2008; 28:S21-S27.	34	
Treatment sildenafil	de Visser YP, Wagenaar GTM. Sildenafil attenuates pulmonary inflammation and fibrin deposition, mortality and right ventricular hypertrophy in neonatal hyperoxic lung injury. Respir Res 2009; 10:1-16.	23	
Hypoxia - inducible factors	Rajatapiti P, de Krijger RR. Expression of hypoxia-inducible factors in normal human lung development. Pediatric Dev Pat 2008; 11:193-199.	18	
Ureaplasma parvum	Collins JJP, Kramer BW. Inflammation in fetal sheep from intra-amniotic injection of Ureaplasma parvum. Am J Physiol 2010; 299:L852-L860.	12	
PDE-4	de Visser YP, Wagenaar GTM. Phosphodiesterase-4 inhibition attenuates pulmonary inflammation in neonatal lung injury. Eur Respir J 2008; 31:633-644.	12	
Airway Dimensions	Tiddens HAWM , de Jongste JC. Airway Dimensions in Bronchopulmonary Dysplasia: Implications for Airflow Obstruction. Pediatric Pulmonol 2008; 43:1206-1213.	10	
Treatment dexamethasone	Bal MP, Steendijk P. Long-term cardiovascular effects of neonatal dexamethasone treatment: hemodynamic follow-up by left ventricular pressure-volume loops in rats. J Appl Physiol 2008; 104:446-450.	10	
CC16	Schrama AJJ, Walther FJ. Cord blood Clara cell protein CC16 predicts the development of bronchopulmonary dysplasia. Eur J Pediatrics 2008; 167-1305-1312.	8	
Treatment dexamethasone	de Vries, WB, van Oosterhout MFM. Neonatal Dexamethasone Treatment in the Rat Leads to Kidney Damage in Adulthood. Pediatric Res 2010; 67:72-76.	6	
Epithlial repair	Been JV, van Iwaarden JF. Bronchoalveolar lavage fluid from preterm infants with chorioamnionitis inhibits alveolar epithelial repair. Respir Res 2009; 10: 116.	5	

Table 3. Top 10 most cited reviews in BPD research initiated by a Dutch group (first and last author has a Dutch affiliation):

Theme	Article	Citations	
		Total	Mean/yr
Chorio - amnionitis	Been JV and Zimmermann LJI. Histological chorioamnionitis and respiratory outcome in preterm infants. Arch Dis Fetal Neonatal Ed 2009; 94:F218-F225.	47	
Diaphragmatic hernia	van den Hout L, Tibboel D. Can we improve outcome of congenital diaphragmatic hernia? Pediatric Surg Int 2009; 25:733-743	22	
Treatment dexamethasone	van den Hout L, Reiss L. Actual Outcome in Infants with Congenital Diaphragmatic Hernia: The Role of a Standardized Postnatal Treatment Protocol. Fetal Diagn Ther 2011; 29:55-63.	21	
Treatment hydro - cortisone	Onland, W , Van Kaam AH. Finding the Optimal Postnatal Dexamethasone Regimen for Preterm Infants at Risk of Bronchopulmonary Dysplasia: A Systematic Review of Placebo-Controlled Trials. Pediatrics 2009; 123: 367-377.	17	
Treatment hydrocortisone	Rademaker KJ, van Bell, F. Postnatal hydrocortisone treatment for chronic lung disease in the preterm newborn and long-term neurodevelopmental follow-up. Arch Dis Fetal Neonatal Ed 2008; 93:F58-F63.	14	
Respiratory support	de Winter JP, Zimmermann LJI. Clinical practice - Noninvasive respiratory support in newborns. Eur J Pediatrics 2010; 169:777-782.	9	
Exhaled nitric oxide	Gabriele C, de Jongste JC. Exhaled nitric oxide measurements in the first 2 years of life: methodological issues, clinical and epidemiological applications. It J Pediatrics 2009; 35:21.	5	
Vascular abnormalities	Sluiter I, Rottier, RJ. Vascular abnormalities in human newborns with pulmonary hypertension. Exp Rev Respir Med 2011; 5:245-256.	4	
Gluco - cocorticoids	Onland W, Offringa M. Open-Label Glucocorticoids Modulate Dexamethasone Trial Results in Preterm Infants. Pediatrics 2010; 126:E954-E964.	3	
Sequential design	van der Lee JH, Offringa M. Sequential design with boundaries approach in pediatric intervention research reduces sample size. J Clin Epidemiol 2010; 63:19-27	2	

Table 4. Top 10 most cited collaborative clinical BPD research (reviews are excluded):

Theme	Article	Citations	
		Total	Mean/yr
Short -term outcome	Zeitlin J, Kollee LAA et al. Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: Results from the MOSAIC cohort. Pediatrics 2008; 121:E936-E944.	33	
Conventional ventilation	Cools F, Offringa, M et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. Lancet 2010; 375:2082-2091.	27	
Perinatal management	Deprest JA, Reiss I, Tibboel D. Changing Perspectives on the Perinatal Management of Isolated Congenital Diaphragmatic Hernia in Europe. Clin Perinatol 2009; 36:329.	26	
Restriction on Mortality	Zeitlin J … Kollee L et al. Impact of Fetal Growth Restriction on Mortality and Morbidity in a Very Preterm Birth Cohort. J Peds 2010; 157:733	15	
Clinical features	Berger RMF et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012; 379: 537-546	14	
Obstetric interventions	Kollee LAA et al. Obstetric interventions for babies born before 28 weeks of gestation in Europe: results of the MOSAIC study. Int J Obstet Gynaecol 2009; 116:1481-1491.	12	
RSV	Resch B, Nuijten MJC et al. Cost-effectiveness of palivizumab against respiratory syncytial viral infection in high-risk children in Austria. Clin Therap 2008; 30: 749-760.	12	
MOSAIC cohort	Gortner L, Kollee LAA et al. Rates of Bronchopulmonary Dysplasia in Very Preterm Neonates in Europe: Results from the MOSAIC Cohort. Neonatology 2011; 99:112-117.	11	
Treatment inhaled steroids	Bassler D, van den Anker J et al. The Neonatal European Study of Inhaled Steroids (NEUROSIS): An EU-Funded International Randomised Controlled Trial in Preterm Infants. Neonatology 2010; 97:52-57.	7	
High - frequency ventilation	Cools F, Offringa M. Elective high-frequency oscillatory ventilation in preterm infants with respiratory distress syndrome: an individual patient data meta-analysis. BMC Pediatrics 2009; 9:33.	7	

Table 5. Top 10 most cited collaborative basic BPD research (reviews are excluded):

Theme	Article	Citations	
		total	Mean/yr
Prenatal inflammation	Kramer BW et al. Prenatal inflammation and lung development. Sem Fetal Neonat *Med* 2009; 14:2-7	59	
IL-1	Kallapur SG, Kramer BW et al. IL-1 Mediates Pulmonary and Systemic Inflammatory Responses to Chorioamnionitis Induced by Lipopolysaccharide. Am J Respir Crit Care Med 2009; 179:955-961.	33	
TGF-beta	Alejandre-Alcazar, MA, Reiss I, de Krijger RR, Tibboel D et al. TGF-beta signaling is dynamically regulated during the alveolarization of rodent human lungs. Develop Dyn 2008; 237:259-269.	20	
LPS-induced inflammation	Kallapur SG … Kramer BW et al. IL-8 signaling does not mediate intra-amniotic LPS-induced inflammation and maturation in preterm fetal lamb lung. Am J Physiol 2009: 297:L512-L519.	15	
Phosphodiesterase 4	Woyda, K, Reiss I et al. Inhibition of phosphodiesterase 4 enhances lung alveolarisation in neonatal mice exposed to hyperoxia. Eur Respir J 2009; 33:861-870.	14	
Betamethasone chorioamnionitis	Sweet DG**,** Kloosterboer N, Kramer BW. Maternal betamethasone and chorioamnionitis induce different collagenases during lung maturation in fetal sheep. Neonatology 2008; 94:79-86.	11	
Intra-amniotic LPS	Cheah FC**,** Kramer BW et al. Airway inflammatory cell responses to intra-amniotic lipopolysaccharide in a sheep model of chorioamnionitis. Am J Physiol 2009; 293:L384-L393.	10	
Glucocorticoids	Ladenburger A, Kramer BW et al…Glucocorticoids potentiate IL-6-induced SP-B expression in H441 cells by enhancing the JAK-STAT signaling pathway. *Am J* Physiol 2010; 299:L578-L584.	9	
Lysyl Oxidase	Kumarasamy A, Reiss I, van der Horst I, de Krijger RR, Tibboel D et al. Lysyl Oxidase Activity Is Dysregulated during Impaired Alveolarization of Mouse and Human Lungs. Am J Respir Crit Care Med 2009; 180:1239-1252.	8	

Intra-amniotic	Kuypers E, Kramer BW et al. Intra-amniotic LPS and antenatal betamethasone: inflammation and maturation in preterm lamb lungs. *Am J Physiol* 2012; 302:L380-L389.	7	

Table 6. Top 5 most cited collaborative reviews in BPD research:

Theme	Article	Citations	
		Total	Mean/yr
Resuscitation	Jobe, AH, Kramer BW et al. Injury and inflammation from resuscitation of the preterm infant. Neonatology 2008; 94:190-196.	38	
Medicines	Lenney W, Bont L, Kimpen J et al. Medicines used in respiratory diseases only seen in children. Eur Respir J 2009; 34:531-551.	12	
Paediatric Lung disease	Tibboel D et al. Update in Pediatric Lung Disease 2009; Am J Respir Crit Care Med 2010; 181:661-665.	3	
Paediatrics	Barbato A, Pijnenburg MW et al. Paediatrics in Berlin. Eur Respir J 2009; 34: 436-443	2	
Regenerative therapies	Gortner L, Jellema R, Kramer BW, Reiss I et al. Regenerative Therapies in Neonatology: Clinical Perspectives. Klinische Pediatrie 2012; 224:233-240.	1	

Table 7. List of publication initiated by Dutch research groups (n=6)[1], or in collaboration with Dutch research groups (n=3)[2] in PCD research in the period from 2008-2013.

Theme	Article	Citations	
		Total	Mean/yr
Primary ciliary dyskinesia	Barbato, A, Bush, A. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. 2009; 34:1264-76.[2].	72	
Primary ciliary dyskinesia	Santamaria, F, de Jong, PA Structural and functional lung disease in primary ciliary dyskinesia. Chest 2008; 134: 351-357.[1]	22	
Squence analysis of 21 genes	Geremek M, Witt M. Sequence analysis of 21 genes located in the Kartagener syndrome linkage region on chromosome 15q. Eur J Hum *Genet* 2008; 16:688-95. [1]	8	
Acilia	Wessels MW, Willems PJ. Candidate gene analysis in three families with acilia syndrome. Am J Med	3	

	Genet A 2008;146A:1765-7. [1]		
Gene experssion	Geremek, M, Wijmenga, C. Gene expression studies in cells from primary ciliary dyskinesia patients identify 208 potential ciliary genes. Hum Genet. 2011 Mar;129(3):283-93.[1]	3	
Splice-Site mutations	Onoufriadis A, Mitchison HM. Splice-Site Mutations in the Axonemal Outer Dynein Arm Docking Complex Gene CCDC114 Cause Primary Ciliary Dyskinesia. *Am J Hum Genet.* 2013 Jan 10;92(1):88-98.[2]	2	
Cyanosis	Vermeulen B, Hruda J. Cyanosis when head turned to left in an infant with primary ciliary dyskinesia. Pediatr Pulmonol 2013; 48:88-90. [1]	0	
RPGR mutations	Bukowy-Bieryllo Z, Witt M. RPGR mutations might cause reduced orientation of respiratory cilia. Pediatric pulmonology 2013; 48: 352-363.[2]	0	
Exhaled molecular profiles	Paff T, Haarman EG. Exhaled molecular profiles in the assessment of cystic fibrosis and primary ciliary dyskinesia. J Cyst Fibros 2013; 26: S1569-1993 [Epub ahead of print] .[1]	0	

APPENDIX

Opinions of international key opinion leaders:

Question 1
Which research topics and groups in BPD/PCD research are visible and have impact on pulmonary physicians and researchers outside the Netherland?

Expert 1

Expert 2
I know two groups active on PCD Studies from NL:
1- from Academisch Medisch Centrum/Universiteit van Amsterdam, with the topic on "Neonatal respiratory distress caused by primary ciliary dyskinesia"
2- from Department of Pulmonary Diseases, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, with the topic on "Exhaled molecular profiles in the assessment of cystic fibrosis and primary ciliary dyskinesia".

Expert 3
- Early neonatal lung disease/BPD/Surfactant biology – Kramer, Zimmerman (Maastricht)
- Lung disease and CDH – Tibboel
- Clinical treatment of BPD – Bel, deVries (Utrecht)
- Clinical neonatal reparatory treatment – van Kaan (Amsterdam)
- Individual patient metanalysis – Offringa (now moved I think)
- Neonatal Resuscitation – Te Pas (Leiden though most work in Australia)

Question 2
Which research topics in BPD/PCD research are less visible to physicians and researchers outside the Netherland?

Expert 1

Expert 2
Studies on correlation between Electron Microscopy findings and the different diagnostic tools (nasal NO – Cilia motility – genetics – etc.)

Expert 3
Difficult to say from outside NL but many publications in low impact journals may contribute to low citation rate.

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of **BPD/PCD**

0= no relevant research
5= excellent research international top level

	1	2	3	Mean
Phenotyping and Severity	2	5	4	3.67
Biological mechanisms	4	5	4	4.33
Environment and lifestyle		3	2	2.50
Development and ageing	4	3	0	2.33
Prevention	3	3	2	2.67
Diagnosis monitoring		5	2	3.50
Therapy medical	3	3	5	3.67
Therapy non-medical	1	3	2	2.00
Biobanking		5	0	2.50
Data management clinical studies		5	0	2.50
Implementation and care	3	5	2	3.33