**The International Primary Ciliary Dyskinesia (iPCD) Cohort: methods and first results**

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Words:  **3201/**3000

Tables & Figures: 6/8

Online Supplement: 1 table + agreement template

References: 33/40

**Funding:**

The development of the iPCD Cohort has been funded from the European Union’s Seventh Framework Programme under EG-GA No.35404 BESTCILIA: Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia. PCD research at ISPM Bern is also funded by national funding from the Lung Leagues of Bern, St. Gallen, Vaud, Ticino and Valais and the Milena- Pro Kartagener Foundation. The researchers participate in the network of COST Action BEAT-PCD: Better Evidence to Advance Therapeutic options for PCD (BM 1407).

**Conflict of interest:**

None

**Author Contributions:**

CEK developed the concept and designed the study. CEK, MG and EM identified eligible datasets, drafted agreements and prepared the standardized dataset. MG and FSH cleaned and standardised the data and performed the statistical analyses. All other authors participated in discussions for the development of the study and contributed data. CEK, MG, FSH and JLS drafted the manuscript, all authors contributed to iterations and approved the final version. CEK and MG take final responsibility for the contents.

**Acknowledgements:**

We want to thank all the patients with PCD in the cohort and their families and especially the PCD patient organisations for their close collaboration. We also want to thank all the researchers in the participating centres who were involved in data collection and data entry and worked closely with us through the whole process of participating to the iPCD Cohort. We would like to acknowledge Jingying Wang for her help and technical support in building the REDCap dataset.

Abstract

Data on Primary Ciliary Dyskinesia (PCD) epidemiology is scarce and published studies are characterised by low numbers. In the framework of the EU project “BESTCILIA” we aimed to combine all available datasets in a retrospective international PCD Cohort (iPCD Cohort).

We identified eligible datasets by performing a systematic review of published studies containing clinical information on PCD and by contacting members of past and current European Respiratory Society Task Forces on PCD. We compared the contents of the datasets, clarified definitions and pooled them in a standardised format.

The iPCD Cohort currently includes data on 3013 patients from 18 countries (April 2016). It includes data on diagnostic evaluations, symptoms, lung function, growth, and treatments. Longitudinal data are currently available for 542 patients. The extent of clinical details per patient varies between centers. More than 50% of patients have a definite PCD diagnosis based on recent guidelines. Children 10-19 years old are the largest age group, followed by younger children (≤9 years) and young adults (20-29 years).

This is the largest observationalPCD dataset available to date. It will allow answering pertinent questions on clinical phenotype, disease severity, prognosis and effect of treatments and investigate genotype/phenotype correlations.

**197**/200 Words

**Keywords:** cohort profile, Primary Ciliary Dyskinesia, rare diseases, epidemiology

***Introduction***

Primary ciliary dyskinesia (PCD) is a rare heterogeneous disease; genetic mutations cause functional and/or structural defects of cilia.[1,2] This results in chronic upper and lower respiratory disease, e.g. progressive chronic suppurative lung disease, chronic serous otitis media (glue ear) and chronic rhinosinusitis.[3] Nearly half of PCD patients have situs inversus [4] and some have other heterotaxic syndromes or congenital heart defects.[5,6] PCD affects about 1 in 10’000 people.[2,7] As in most orphan diseases, research has focused on identifying the responsible genes, describing pathophysiological mechanisms, and improving diagnostic tests.[8-11] Clinical characteristics have been described mainly in small case series and literature reviews. A recent meta-analysis found a wide range in reported prevalence of clinical manifestations of PCD. [12] Earlier reports on PCD in children suggested a relatively benign long-term course. This has been questioned by recent publications, which demonstrated that many adult patients develop severe lung disease with chronic Pseudomonas infection, become oxygen-dependent and eventually need lung transplantation.[3,13-16] Although growth and lung function are important predictors of severity and prognosis in many lung diseases,[17] there are little data on PCD, showing contradictory results.[13,15,18-23] There are no age-standardised data on mortality and little is known about factors influencing long-term prognosis. For instance, it is not clear, how mortality and lung function are influenced by different ultrastructural and genetic defects.

Although 7% of the population suffers from one of about 7000 rare diseases,[24] research is scarce for these disorders. Research on PCD and many other rare diseases cannot utilise routine data such as mortality and hospital episode statistics because most rare diseases do not have a dedicated ICD-10 code and can therefore not be identified in routine statistics. The low numbers of patients in each individual centre, call for collaborative research and international studies are essential.

Aware of these issues, clinicians and scientists with a strong interest in PCD formed 10 years ago an international focus group and took a number of initiatives to advance PCD research. The first Task Force on PCD (2006-2009) of the European Respiratory Society (ERS) included 26 countries.[1,7,25] . This European network, under the framework of the EU FP7 project “Better Experimental Screening and Treatment for Primary Ciliary Dyskinesia” (BESTCILIA), joined forces with the North American Genetic Disorders of Mucociliary clearance Consortium. Two work packages of BESTCILIA aimed to improve the availability of international datasets for PCD patients, 1) by setting up a prospective international PCD registry[26], to allow standardised data collection in the future and 2) by identifying and combining available data on PCD in a retrospective international cohort study. This manuscript describes the aims and methods of the international PCD Cohort (iPCD Cohort) and outlines how the data can be accessed for future research.

***Aims of the iPCD Cohort***

The iPCD Cohort assembles available datasets with clinical and diagnostic data from PCD patients worldwide to answer pertinent questions on clinical phenotype, disease severity, prognosis and effect of treatments in patients with this rare multi-organ disease.

This combined international dataset allows investigation of PCD epidemiology in a large international study population, to:

(1) Describe the spectrum of clinical phenotypes and disease severity in PCD patients by age, sex and time period of diagnosis;

(2) Describe short-term and long-term prognosis of PCD, looking at important outcomes such as growth, lung function and respiratory failure, bacterial colonisation, hearing loss, fertility and mortality;

(3) Identify predictors of long-term outcomes, such as age at diagnosis, clinical phenotype, ultrastructural defects, genotype and clinical care.

***Methods***

*Study design*

The iPCD Cohort is a retrospective international Cohort, combining available data on PCD from national or local registries and clinical or diagnostic databases. All participating centres delivered retrospectively collected data; new centres joining the Cohort in the future can also participate with retrospectively collected data.

*Identification of eligible datasets*

1. Systematic literature search

In order to identify published data and eligible datasets we performed a systematic literature search for studies describing clinical manifestations in patients with PCD.[27] We searched the online databases PubMed, Embase and Scopus for studies published since 1980, without restrictions in language or study design, including studies containing information on clinical manifestations of ≥10 PCD patients. We also checked the reference lists of articles to find additional studies. We identified 52 different studies and invited all corresponding authors to participate in the iPCD Cohort.

b) Other sources

Using the database set up in a previous European PCD survey [1,5,7] and personal contacts from the ERS PCD Task Force, we contacted all clinicians who had reported treating PCD patients and asked them to collaborate. This included physicians from Europe, North and South America, the Middle East and Australia.

*Data pooling and standardisation*

Overall, diagnostic definitions have changed over the years. Cut-offs for diagnostic test results depend on laboratory conditions, techniques and equipment used, for example, the reference range for ciliary beat frequency is dependent on the temperature at which analyses are made. Definitions of many clinical manifestations also vary between countries and centres. We observed considerable heterogeneity in content and format between the delivered datasets. For this reason and to obtain comparable data for pooled analyses, we developed a standardised dataset. We discussed the content and format of this dataset with all collaborators, who include experts on PCD diagnostics and clinical care, s and with PCD patient representatives, participating at BESTCILIA meetings. . For diagnostic tests results, in particular, we chose the use of categorical variables in order to achieve standardisation and avoid misclassification at the time of analysis. Content and format of the variables were tailored to the availability of retrospective data, as identified by examination of the received datasets and the prospective international PCD registry[28]. This facilitates the close collaboration between the two datasets for future research.

*Included patients- Diagnostic subgroups*

PCD diagnostics evolved rapidly in recent years[29]. Initially, diagnosis was based on the Kartagener symptoms triad[30] and on transmission electron microscopy findings (EM). Then light microscopy and later high frequency video microscopy (VM) were introduced in the diagnostic algorithm. Currently, recommendations include a combination of EM, VM, nasal nitric oxide (nNO) and genetic testing[11] but availability of tests differs between countries[29]. Therefore, not all PCD patients have been diagnosed according to current recommendations. The iPCD Cohort includes patients diagnosed since 1964, when diagnostic criteria were different. Because of this, we made 3 different diagnostic subgroups based on the results of the available tests. We used the recent guidelines of the ERS PCD Diagnostics Task Force[11] to define “definite PCD” as hallmark EM findings and/or bi-allelic PCD genetic mutations. “Probable PCD” was defined when patients had abnormal VM findings and/or low nNO, using a cut-off of 77nl/min as previously published[31]. All patients who had negative or ambiguous test results or had not been tested so far, were defined as having “clinical PCD diagnosis”. These patients are followed up and treated as PCD at the collaborating centres based on a combination of several of the following features: situs anomalies, persistent cough, persistent rhinitis, chronic or recurrent upper or lower respiratory infections, history of neonatal respiratory symptoms in term infants, based on consensus statements and guidelines available to age[1,11].

*What information is collected*

The iPCD Cohort includes retrospectively collected patient data on the following 11 thematic categories (Table 1): 1) general information; 2) results of diagnostic tests; 3) baseline characteristics; 4) growth and lung function; 5) clinical manifestations; 6) therapy; 7) imaging; 8) microbiology; 9) surgical interventions; 10) neonatal period; and 11) family history. Details on all variables included in the standardised dataset and information on the coding of variables are included in the online supplement (Table S1).

*Infrastructure for data delivery and data rights*

The iPCD Cohort is hosted at the Institute of Social and Preventive Medicine at the University of Bern, Switzerland. Research is performed in close collaboration with all data contributors. We have set-up a safe IT platform (Sharepoint) for uploading already available anonymised datasets. We organized telephone conferences to offer extra support during the initial steps of the data delivery and to discuss questions and comments of the contributing partners. To further facilitate data delivery in the standardised dataset for new partners we created a web-based platform, using the software Research Electronic Data Capture (REDCap) developed at Vanderbilt University, which is widely used in the academic research community[32] and allows data entry and extraction in various formats. Detailed instructions explain how data can be entered. The REDCap environment is completely secure and each contributor has only access to the data of their own centre. We collaborated closely with centres that already had national registries and large retrospective datasets, to help them recode the data into the standardised format and we performed quality controls of the delivered data (e.g. checks for coding errors and plausibility of entered values and dates). Each partner was responsible for ensuring that the delivered data were anonymous and in accordance with the national/local data protection laws. More information on data protection can be found in the online supplement under data protection/ethics. We drafted agreements for data delivery and publication (online supplement), which leave all rights with data contributors.

*Data analysis*

For each planned analysis, all eligible data are validated, cleaned and standardized. We identify outliers and implausible values and if necessary we contact contributors to resolve encountered issues. Based on the research question, we use a one-stage or two-stage random effect individual patient data meta-analysis approach. As PCD diagnostics has evolved quickly in the past and not all patients have diagnostic information that is up to current standards, all analyses will be stratified by level of diagnostic certainty, using the diagnostic subgroups described previously. Whenever is relevant we will perform additional sensitivity analysis including only patients with definite PCD, based on the recent guidelines of the ERS PCD Diagnostics Task Force[11] and will compare these results with the overall analysis results.

*Funding*

The setting-up of the iPCD Cohort (salaries, consumables and equipment) was funded by the EU-FP7 project BESTCILIA (http://bestcilia.eu/) and several Swiss funding bodies, including the Lung Leagues of Bern, St. Gallen, Vaud, Ticino and Valais and the Milena- Pro Kartagener Foundation. Data collection and management at each site was funded according to local arrangements. Most participating researchers and data contributors participate in the COST Action BEAT-PCD: Better Evidence to Advance Therapeutic options for PCD (BM 1407- http://www.beatpcd.org/). Infrastructure is provided for free by the University of Bern, Switzerland where the data are pooled and stored.

*How can data be contributed*

Centres that wish to participate to the project and contribute data can contact the iPCD Cohort to sign a data delivery agreement. They then will receive a password to access the online software REDCap and they will be able to enter their data directly. They can also upload follow-up data or add additional patients at a later time point. In case of large standardised datasets, it is possible to upload them directly. We have developed detailed instructions and offer IT support wherever needed.

*How can data be accessed*

Centres that have entered their data using REDCap will keep constant access to their dataset and can export them directly in various formats for local analyses. We have developed detailed extraction instructions to simplify the procedure.

Researchers wanting to use the iPCD Cohort dataset can propose a topic and a concept sheet describing the planned analyses and publication. All concept sheets have to be approved by all centres contributing data to the proposed analysis under question. After the participating centres agree to contribute their data and sign a publication agreement, we will prepare a partial dataset for the proposed analysis and will work closely with the lead researchers offering methodological input and support. In case additional data is collected to complete the partial dataset for a specific project, this will be added to the iPCD Cohort to enrich it after each project. For further details, contact: pcd@ispm.unibe.ch.

**Results**

*Current dataset*

The iPCD Cohort is an ongoing effort where new centres can still join and participating centres can add data for new patients. By April 2016, data from 21 single centres or Consortia from 18 countries had been contributed. The pooled dataset contained data on 3013 patients (Figure 1). Some countries which have a national reference centre for all paediatric and adult PCD patients (Cyprus, Denmark, France) or a national PCD registry (Italy, Switzerland) contributed their national dataset. Other countries contributed data from their Consortia of several centres (Israel, USA and Canada) or datasets from single centre studies (all remaining centres). The number of patients per centre ranged from 10 to 436 (Table 2). Two paediatric centres contributed datasets only with patients younger than 18 years and 1 with adult patients (≥20 years old). Five paediatric centres included additionally a few young adults. The remaining 13 centres submitted datasets that included both paediatric and adult patients with an age range from 0 to 77 years. The percent of males ranged from 38 to 68% among datasets. General information, results of diagnostic tests, and baseline characteristics (Modules 1-3) are in the basic mandatory dataset, and thus available from all centres and for all 3013 patients or the majority of them (Tables 1 and 3). In addition to these baseline data several centres have also contributed data to the other modules (Table 3). Data on growth are currently available for more than 1500 patients and on lung function for more than 1000 patients. Additional data, such as microbiology, or perinatal history, have been delivered by several groups (Table 1 and Figure 1) and for several hundreds of patients (Table 3). To date, longitudinal data have been contributed for 542 patients from 10 countries (Table 2), with a follow-up period ranging from 2 to 20 years.

*Patient characteristics*

Characteristics of the 3013 patients included in the iPCD Cohort are described in Table 4. Forty-nine percent (1490) were male. Seventy-one percent of patients were followed-up in European centres (39% in Western Europe), 9% in Western Asia, 17% in America and 4% in Australia. More than half of the patients (Table 4) have a definite PCD diagnosis based the recent guidelines of the ERS PCD Diagnostics Task Force[11] Fourteen percent of patients were defined as probable PCD based on their diagnostic test results. In 30% of patients test results were negative or ambiguous or the diagnostic algorithm had not been concluded and the diagnosis was based on clinical grounds based on existing consensus or guidelines. Median current age of patients was 18 years with a range of 1-92 years (Figure 2). Children aged between 10 and 19 years were the largest age group (38%), followed by younger children (0-9 years) and young adults (20-29 years) with 17% and 18% respectively. The percentage of patients in the remaining age groups had a declining trend from 10% for patients aged 30 to 39 years to 4% for patients older than 60 years.

**Discussion**

The iPCD Cohort is the largest PCD dataset available to date. It includes data from 3013 PCD patients from 18 countries; more than half of them have a definite PCD diagnosis using current standards. The main strength of the iPCD Cohort is the large number of patients it includes. This makes it a valuable source for research especially in the field of rare diseases where even large national reference centres may follow a small number of patients. In addition to the basic characteristics and diagnostic test results, which are available from all centres and for more than 3000 patients, the iPCD Cohort includes data on several hundreds of patients on other topics (e.g. growth, lung function, clinical manifestations) from a number of centres; higher numbers than were ever before included in publications on these topics. It is important that for these thematic modules, in case they have contributed data, most centres have included almost complete datasets. Another important is the multinational nature of the Cohort. It offers the possibility, unique for rare diseases, to assess differences in PCD characteristics between countries and ethnic groups. The iPCD Cohort also includes patients of all age groups and although the paediatric population is represented more strongly, this offers the opportunity to study the course of the disease through life. Preliminary analyses on growth, nutritional status and lung function from the iPCD Cohort has already been presented at international conferences, illustrating the quality of the dataset and the feasibility of future studies using the iPCD Cohort. The user-friendly and safe environment of REDCap for the standardised entry of the data is an additional strength of the project. Data contributors can easily type in their data following simple instructions and access it any time with password protected accounts. In addition, they can easily export their dataset in the standardised format easily in a selection or various forms to use for their own analyses.

Some limitations, inherent to the retrospective nature of the iPCD Cohort, have to be kept in mind. For instance, there remains some heterogeneity in definitions among centres. This is not an issue for standardised measurements such as height, weight, spirometry and microbiology/radiology test results but is more relevant for clinical signs. Reference ranges of diagnostic test results vary and depend highly on the expertise, the conditions and equipment and the protocol used at each centre. For standardisation with comparable values, we used categorical coding for numerical values (e.g. frequency of ciliary beating has been coded as……normal/ fast/ slow?). All the items collected in the cohort and their coding were extensively discussed and agreed among collaborators during the development period, taking into account existing national registries and the prospective international PCD registry. This ensures that all important data resources could be pooled and analysed together in future collaborative studies. Another issue is the heterogeneity of the PCD patient population concerning the diagnostic evaluation; diagnostic results can be normal or very subtle in some patients who almost certainly have PCD. Therefore, we have grouped the patients into 3 diagnostic subgroups based on the recent diagnostics guidelines from the ERS Task Force[11] and are planning to take the level of diagnostic certainty into account in all analyses. Participating centres will be encouraged to follow these guidelines for new patients and to re-evaluate the diagnosis of patients in cases where not all testing has been concluded. Although the iPCD Cohort is an important data source for statistically meaningful research, it is not truly representative of the PCD patient population. Countries that have not developed diagnostic facilities yet are underrepresented. There is little evidence on mortality, but life expectancy in PCD is generally described as normal. PCD is underdiagnosed in adults and most centres follow mainly children and younger adults. Thus, adult patients especially of older age are underrepresented in the Cohort.

Most published studies on PCD include a small number of patients. The largest published study on PCD was in the framework of the previous ERS PCD Task Force which included 1192 patients, from 26 countries.[7] In that study the researchers collected basic data from questionnaires addressed to the clinical centres of participating countries. They found a slightly higher proportion of male patients and 85% of the patients were younger than 20 years. Recently, data on 201 patients from the international PCD registry have been described.[26] The authors observed 55% males and almost 50% patients younger than 18 years. Twenty-two percent of the included patients have only clinical diagnosis compared to 35% in the iPCD Cohort. As these two datasets were both built in the framework of BESTCILIA there is an overlap in the patients they include. The international Registry aims to collect prospective data of PCD patients in a standardised way to use for future studies while the iPCD Cohort combines available retrospective datasets of PCD patients in pooled analyses to answer important questions on PCD in a large study population. Although well-designed prospective studies have obvious strengths, it is of great importance to use all available data resources for research in rare diseases such as PCD, where there is still little evidence and management of patients is primarily based on experience derived from other diseases such as cystic fibrosis.

The iPCD Cohort is a valuable resource for epidemiological studies in PCD and it can be further enriched and used in the framework of the BEAT-PCD EU COST Action. BEAT-PCD aims to set up a global, Europe-led multidisciplinary network of PCD clinicians and researchers and the aims of the epidemiological work group include using this dataset for projects on PCD epidemiology. More centres have expressed an interest in contributing data to the Cohort. Some groups had originally contributed a basic cross-sectional dataset and are now adding retrospectively collected repeated measurements (longitudinal data) or they are adding new patients to their datasets or to patients that have already been included. Besides ongoing analyses on growth and lung function, studies are planned on diagnostic tests, clinical manifestations, neonatal symptoms and the role of lobectomy in PCD, using the iPCD Cohort dataset. The iPCD Cohort also contains data on other therapeutic interventions, imaging and microbiology from several centres, which can be used for future studies and can also be used to identify patients for nested studies on PCD.

This dataset is now available to be further exploited and offers a unique opportunity to study PCD in a large international patient-based cohort with sufficient statistical power and use the results of these analyses to improve survival, care and quality of life of PCD patients.

For further details, contact: pcd@ispm.unibe.ch

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