

## **The BEAT-PCD (Better Experimental Approaches to Treat Primary Ciliary Dyskinesia) Clinical Research Collaboration**

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## **Introduction**

The need for collaborative research networks as an effective way forward to improve diagnosis and care of rare inherited diseases is constantly highlighted and primary ciliary dyskinesia (PCD) is no exception. PCD affects 1 in 10,000 people and is genetically and clinically heterogeneous. Dysfunction of motile cilia, caused by defects in one of more than 50 genes, leads to poor mucociliary clearance and progressive upper and lower respiratory disease. Clinical symptoms include neonatal respiratory distress, chronic lung disease with bronchiectasis, rhinosinusitis and hearing impairment, but also infertility and laterality defects. 50% of patients have situs inversus and 6-12% have other defects such as congenital cardiac disease (1, 2)

Through sequential European initiatives including two European Respiratory Society (ERS) Task Forces (2006-2009/ ERS-TF-2014-04 2014-2016)(3), an FP7 funded project (305404 BESTCILIA 2012-2015), and the EU COST Action BEAT-PCD (BM 107; 2015-2019) and more recently the European Reference Network ERN-LUNG (PCD core) we have improved awareness, diagnosis and clinical care for patients with PCD(3-9). Through these collaborations we have built a network of >500 individuals from >30 countries with an interest in PCD (Figure 1). Our members are from a range of different professional backgrounds and specialties; including nurses, physicians, basic scientists, physiologists, physiotherapists, psychologists, researchers, patients and their families.

As a community of researchers over the past few years, we have successfully developed disease registries and cohorts and the first evidence based diagnostic guidelines for PCD (10-12). We have also developed, validated and tested a PCD-specific health related quality of life questionnaire, a standardised PCD-specific form for clinical follow-up and research and consensus statements on electron microscopy terminology and on the definition of pulmonary exacerbations (13-18). Furthermore the first successful multicentre randomized clinical trial of azithromycin to treat PCD was completed and published this year (19). However, there is plenty more to do before PCD research is as advanced as many other respiratory diseases and our achievements have served to highlight the huge gaps in our knowledge and evidence base for clinical practice across Europe (20). For example; diagnosis remains complex with inequalities

between countries and the majority of patients remain undiagnosed (21). Most treatment is based on expert opinion and is borrowed from other diseases such as cystic fibrosis and the clinical course of the disease for the most part remains unknown.

The new BEAT-PCD ERS clinical research collaboration (CRC), supported by the ERS Assembly 7, aims to advance clinical and translational research in PCD through building upon the foundations set by the previous collaborative initiatives (22).

BEAT-PCD ERS CRC has five overarching aims: 1) to improve diagnosis and clinical care of people with PCD; 2) to expand available research resources in the field and develop new ones; 3) to set up a framework for clinical trials; 4) to engage PCD patients and their families in research activities and 5) to develop collaborations with other networks and relevant stakeholders. To achieve these aims BEAT-PCD is organized in seven work packages (WP) with specific focus areas, described in more detail below.

### **Network of PCD research databases and collaborations**

While a decade ago clinical data on patients with PCD were available only from small cross-sectional studies of selected patients, we have now a valuable and fast expanding network of data resources for clinical and epidemiological research in PCD (10, 11, 23-26). We aim to facilitate the collaboration and further development of all available data resources for PCD in Europe and to use them to answer pertinent questions on PCD. We also plan to establish connections with existing PCD registries outside of Europe and with other relevant research networks such as the bronchiectasis registry (EMBARC) (27). One of the main aims of this WP is to set up an online open database (CiliaVar) registering gene mutations and specific combinations of disease-causing variants for PCD, where clinicians can look up rare variants to assess their pathogenicity and associations.

### **Patient engagement activities**

We know that research with patient and public involvement leads to better designed studies, improving recruitment and retention. Despite many countries having their own national support group for PCD patients, there is no central place for a newly diagnosed patient or

parent to receive information. We want to bring national patient organizations closer by creating a platform to exchange high quality information and experiences and to produce educational material for patients and caretakers in collaboration with the European Lung Foundation (ELF). One of the main priorities of BEAT-PCD is to ensure that all CRC activities address patient needs and priorities and we encourage direct patient involvement in research. COVID-PCD, a participatory research study on the impact of COVID-19 in people with PCD, is successfully running in the framework of BEAT-PCD (28).

### **Clinical trials**

There is no strong evidence for the effectiveness of different therapies for PCD; thus, current recommendations are based on expert opinion, extrapolations from CF and other diseases and few, mostly observational, studies in PCD (29). To improve the evidence base for treatment of PCD, BEAT-PCD aims to develop a framework encouraging and setting the standards for development and successful completion of clinical trials. This WP aims to develop, in collaboration with the ERN-LUNG (PCD core), a clinical trials network that will promote clinical trials in PCD by identifying reliable clinical outcome measures and biomarkers, improving trial design and recruiting sufficient numbers of patients through prospective national and international registration and follow-up of PCD patients.

### **Improving PCD diagnosis**

Diagnosis is complex as there is not a single stand-alone test to diagnose PCD, therefore it is necessary to apply a multi-test approach (30, 31). It also varies significantly between countries because of inequalities in access to modern diagnostic facilities. A large proportion of patients are treated without confirmed diagnosis, due to lack of available equipment and expertise in many countries, which makes it necessary to rely on clinical assessment, partial diagnostic testing or support from a reference centre in another country. We aim to improve diagnosis of PCD by developing a platform to exchange diagnostic expertise between centres and supporting centres with limited diagnostic resources, in close collaboration with ERN-LUNG (PCD core). We also aim to standardise reporting of diagnostic results for tests where the need remains e.g. high-speed video microscopy, genetics and immunofluorescence. An ERS task

force, supported by BEATPCD, is currently developing a technical standard for the measurement of nasal nitric oxide to assist diagnosis of PCD in children (TF-2020-02).

### **Clinical care and management**

In contrast to many common conditions, care of patients with PCD requires a multidisciplinary approach. Awareness among physicians is poor and although some countries have established designated PCD centres, in many countries care is heterogeneous and decentralized. In addition to promoting clinical trials, BEAT-PCD aims to improve evidence about the phenotypic variability of PCD also taking into account patients' disease perception by collecting patient-reported outcomes. Overall, BEAT-PCD aims to promote standardization of clinical practices in PCD care across Europe and support the development of evidence-based clinical guidelines and educational resources for healthcare professionals involved in PCD care and patients. In this framework, we will promote the piloting and subsequent use of the standardised form FOLLOW-PCD in interested PCD centres for clinical follow-up and research (14).

### **Engagement with the ERS and dissemination of CRC activities and results**

Dissemination of the work of BEAT-PCD to other physicians and researchers, patients, the public and all relevant stakeholders is of utmost importance for our network. This WP will work in collaboration with all other WPs, to ensure successful communication with the ERS and other CRCs and disseminate widely all activities and results, through the BEAT-PCD website newsletters, networking events, educational meetings and other activities.

### **Project management and governance**

BEAT-PCD is governed by a management committee consisting of the two chairs and the WP leads and co-leads. In addition, a BEAT-PCD advisory board, including relevant stakeholders, works closely with the CRC chairs to ensure that all activities of the network are beneficial to all stakeholders and complimentary to the activities of other relevant initiatives such as the ERN-LUNG (PCD core).

### **Conclusion**

For a rare disease such as PCD, international collaboration is essential to improve patient diagnosis and care. With this ERS CRC, as a large multidisciplinary network of researchers and healthcare professionals, we aim to advance clinical and translational research in different areas of PCD through building upon the foundations set by the previous collaborative initiatives.

If you would like to join us, please contact us at [beatpcd@ers.net](mailto:beatpcd@ers.net). You can also follow updates on Twitter ([@beatpcd](https://twitter.com/beatpcd)) or at our website (<https://beat-pcd.squarespace.com/>).

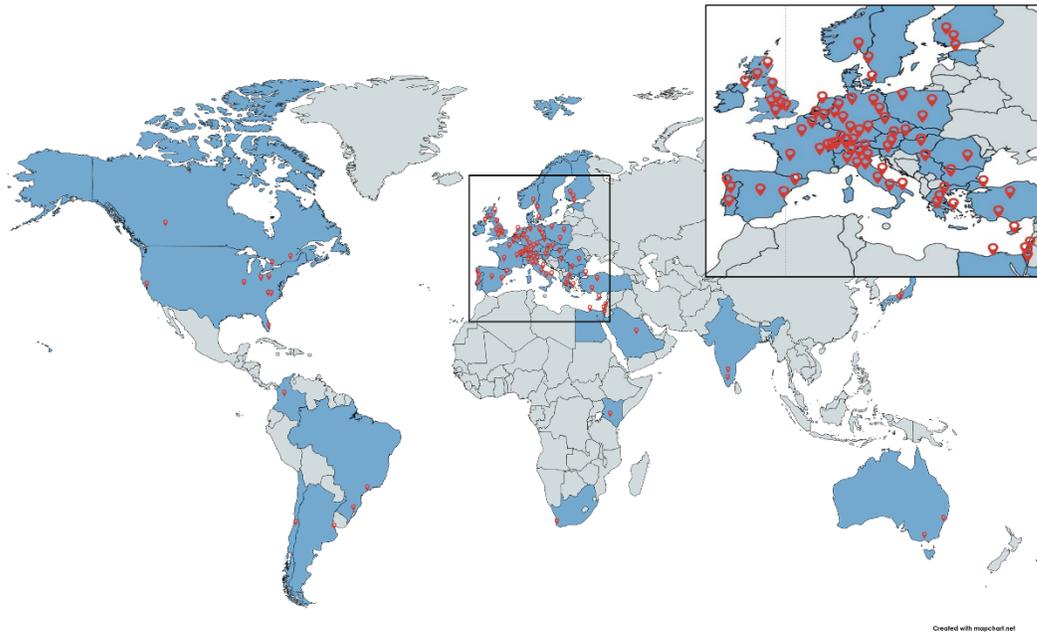
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## Figure 1 legend:

The BEAT-PCD Clinical Research Collaboration Network

Our network includes >500 individuals from >30 countries (countries shaded in blue and cities marked with red pins in the map) with an interest in PCD.



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