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

Myrofora Goutaki[1,2], Suzanne Crowley[3], Eleonora Dehlink[4], René Gaupmann[4], Katie L. Horton[5], Panayiotis Kouis[6], Yin Ting Lam[1], Niki T. Loges[7], Jane S. Lucas[5,8], Jobst F. Roehmel[9] and Amelia Shoemark[10,11] on behalf of the BEAT-PCD Clinical Research Collaboration

Affiliations: [1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [2]Paediatric Respiratory Medicine, Children's University Hospital of Bern, University of Bern, Bern, Switzerland. [3]Paediatric Dept of Allergy and Lung Diseases, Oslo University Hospital, Oslo, Norway. [4]Division of Pediatric Pulmonology, Allergology, and Endocrinology, Dept of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria. [5]School of Clinical and Experimental Sciences, University of Southampton Faculty of Medicine, Southampton, UK. [6]Respiratory Physiology Laboratory, Medical School, University of Cyprus, Nicosia, Cyprus. [7]Dept of General Pediatrics, University Hospital Münster, Münster, Germany. [8]Primary Ciliary Dyskinesia Centre, NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK. [9]Dept of Pediatric Pulmonology, Immunology and Critical Care Medicine, Charité-Universitätsmedizin, Berlin, Germany. [10]Scottish Centre for Respiratory Research, University of Dundee, Dundee, UK. [11]PCD diagnostic centre, Paediatric Dept, Royal Brompton Hospital, London, UK.

Correspondence: Myrofora Goutaki, Institute of Social and Preventive Medicine, University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland. E-mail: myrofora.goutaki@ispm.unibe.ch

@ERSpublications
The BEAT-PCD ERS CRC is a large multidisciplinary network of researchers and healthcare professionals aiming to advance clinical and translational research in different areas of primary ciliary dyskinesia building upon previous collaborative initiatives https://bit.ly/39h3veZ

Cite this article as: Goutaki M, Crowley S, Dehlink E, *et al*. The BEAT-PCD (Better Experimental Approaches to Treat Primary Ciliary Dyskinesia) Clinical Research Collaboration. *Eur Respir J* 2021; 57: 2004601 [https://doi.org/10.1183/13993003.04601-2020].

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, and 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

Received: 22 Dec 2020 | Accepted: 24 Dec 2020

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 [3, 10, 11]. 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 [12–17]. Furthermore, the first successful multicentre randomised clinical trial of azithromycin to treat PCD was completed and published this year [18]. 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 [19]. For example, diagnosis remains complex with inequalities between countries and the majority of patients remain undiagnosed [20]. 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 [21].

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 organised 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, 22–25]. 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) [26]. 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 organisations 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. 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 coronavirus disease 2019 in people with PCD, is successfully running in the framework of BEAT-PCD [27].

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 cystic fibrosis and other diseases, and a few, mostly observational, studies in PCD [28]. To improve the evidence base for treatment of PCD, BEAT-PCD aims to develop a framework promoting 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.

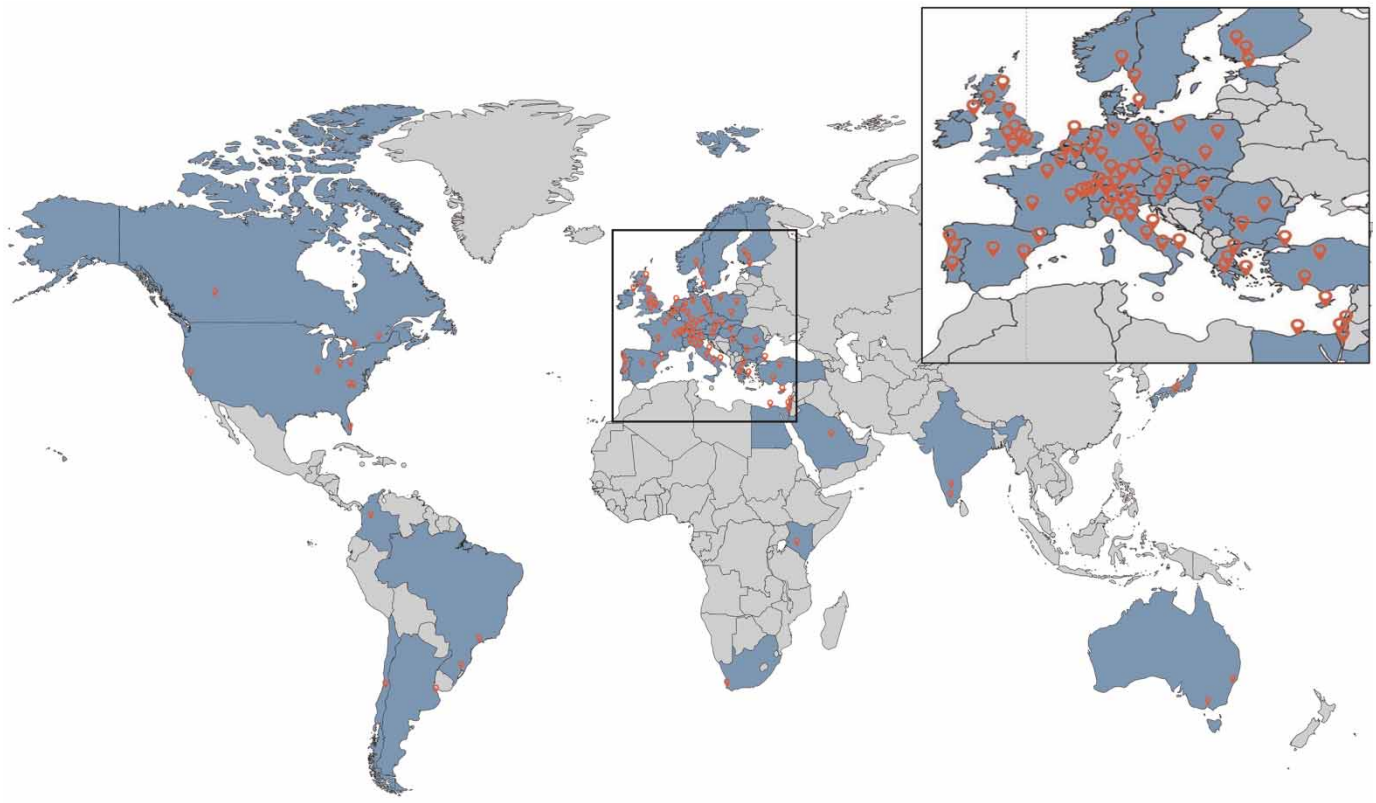

FIGURE 1 The BEAT-PCD Clinical Research Collaboration Network. Our network includes >500 individuals from >30 countries (countries shaded in blue and cities marked with red pins in the map) with an interest in PCD.

Improving PCD diagnosis

Diagnosis is complex as there is not a single stand-alone test to diagnose PCD, so it is necessary to apply a multi-test approach [29, 30]. Diagnosis 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 BEAT-PCD, 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 decentralised. 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 standardisation 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 [13].

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 complementary 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. You can also follow updates on Twitter (@beatpcd) or through our website (https://beat-pcd.squarespace.com/).

Acknowledgements: This article was written on behalf of the BEAT-PCD Clinical Research Collaboration members. Management Committee members: Co-chairs: Amelia Shoemark and Myrofora Goutaki. WP leaders and co-leaders (alphabetical order): Laura Behan, Mieke Boon, Mathieu Bottier, Suzanne Crowley, Eleonora Dehlink, Ernst Eber, Nagehan Emiralioglu, Panayiotis Kouis, Claudia E. Kuehni, Marie Legendre, Niki T. Loges Jane S. Lucas, Bernard Maitre, Kim G. Nielsen, Ana Reula and Jobst Roehmel. Advisory board members: Heymut Omran (head of ERN-LUNG PCD core), Claire Hogg (Lead of BEAT-PCD COST training school), Lucy Dixon (UK PCD support group representative), Jens Brillault (German PCD support group representative), Rene Gaupmann, Katie Horton and Yin Ting Lam (PhD representatives). European Lung Foundation representative: Jeanette Boyd. We would like to thank all members of the BEAT-PCD networks and all patients supporting our activities as well as the ERS office for their support.

Conflict of interest: None declared.

Support statement: This work was supported by the European Respiratory Society (grant: BEAT-PCD CRC funding). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Lucas JS, Davis SD, Omran H, *et al.* Primary ciliary dyskinesia in the genomics age. *Lancet Respir Med* 2020; 8: 202–216.
2 Goutaki M, Meier AB, Halbeisen FS, *et al.* Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. *Eur Respir J* 2016; 48: 1081–1095.
3 Lucas JS, Barbato A, Collins SA, *et al.* European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. *Eur Respir J* 2017; 49: 1601090.
4 Barbato A, Frischer T, Kuehni CE, *et al.* Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. *Eur Respir J* 2009; 34: 1264–1276.
5 Kuehni CE, Frischer T, Strippoli MP, *et al.* Factors influencing age at diagnosis of primary ciliary dyskinesia in European children. *Eur Respir J* 2010; 36: 1248–1258.
6 Farley H, Rubbo B, Bukowy-Bieryllo Z, *et al.* Proceedings of the 3rd BEAT-PCD Conference and 4th PCD Training School. *BMC Proc* 2018; 12: Suppl. 16, 64.
7 Halbeisen F, Hogg C, Alanin MC, *et al.* Proceedings of the 2nd BEAT-PCD conference and 3rd PCD training school: part 1. *BMC Proc* 2018; 12: Suppl. 2, 1.
8 Rubbo B, Behan L, Dehlink E, *et al.* Proceedings of the COST action BM1407 inaugural conference BEAT-PCD: translational research in primary ciliary dyskinesia – bench, bedside, and population perspectives. *BMC Proc* 2016; 10: Suppl. 9, 66.
9 Strippoli MP, Frischer T, Barbato A, *et al.* Management of primary ciliary dyskinesia in European children: recommendations and clinical practice. *Eur Respir J* 2012; 39: 1482–1491.
10 Goutaki M, Maurer E, Halbeisen FS, *et al.* The international primary ciliary dyskinesia cohort (iPCD Cohort): methods and first results. *Eur Respir J* 2017; 49: 1601181.
11 Werner C, Lablans M, Ataian M, *et al.* An international registry for primary ciliary dyskinesia. *Eur Respir J* 2016; 47: 849–859.
12 Behan L, Leigh MW, Dell SD, *et al.* Validation of a health-related quality of life instrument for primary ciliary dyskinesia (QOL-PCD). *Thorax* 2017; 72: 832–839.
13 Goutaki M, Papon JF, Boon M, *et al.* Standardised clinical data from patients with primary ciliary dyskinesia: FOLLOW-PCD. *ERJ Open Res* 2020; 6: 00237-2019.
14 Shoemark A, Boon M, Brochhausen C, *et al.* International consensus guideline for reporting transmission electron microscopy results in the diagnosis of Primary Ciliary Dyskinesia (BEAT PCD TEM Criteria). *Eur Respir J* 2020; 55: 1900725.
15 Lucas JS, Behan L, Dunn Galvin A, *et al.* A quality-of-life measure for adults with primary ciliary dyskinesia: QOL-PCD. *Eur Respir J* 2015; 46: 375–383.
16 Dell SD, Leigh MW, Lucas JS, *et al.* Primary ciliary dyskinesia: first health-related quality-of-life measures for pediatric patients. *Ann Am Thorac Soc* 2016; 13: 1726–1735.

17 Lucas JS, Gahleitner F, Amorim A, *et al.* Pulmonary exacerbations in patients with primary ciliary dyskinesia: an expert consensus definition for use in clinical trials. *ERJ Open Res* 2019; 5: 00147-2018.
18 Kobbernagel HE, Buchvald FF, Haarman EG, *et al.* Efficacy and safety of azithromycin maintenance therapy in primary ciliary dyskinesia (BESTCILIA): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2020; 8: 493–505.
19 Crowley S, Holgersen MG, Nielsen KG. Variation in treatment strategies for the eradication of Pseudomonas aeruginosa in primary ciliary dyskinesia across European centers. *Chron Respir Dis* 2019; 16: 1479972318787919.
20 Rumman N, Jackson C, Collins S, *et al.* Diagnosis of primary ciliary dyskinesia: potential options for resource-limited countries. *Eur Respir Rev* 2017; 26: 160058.
21 Brightling C, Genton C, Bill W, *et al.* ERS Clinical Research Collaborations: underpinning research excellence. *Eur Respir J* 2018; 52: 1801534.
22 Goutaki M, Halbeisen FS, Spycher BD, *et al.* Growth and nutritional status, and their association with lung function: a study from the international Primary Ciliary Dyskinesia Cohort. *Eur Respir J* 2017; 50: 1701659.
23 Ardura-Garcia C, Goutaki M, Carr SB, *et al.* Registries and collaborative studies for primary ciliary dyskinesia in Europe. *ERJ Open Res* 2020; 6: 00005-2020.
24 Halbeisen FS, Goutaki M, Spycher BD, *et al.* Lung function in patients with primary ciliary dyskinesia: an iPCD Cohort study. *Eur Respir J* 2018; 52: 1801040.
25 Halbeisen FS, Shoemark A, Barbato A, *et al.* Time trends in diagnostic testing for primary ciliary dyskinesia in Europe. *Eur Respir J* 2019; 54: 1900528.
26 Aliberti S, Polverino E, Chalmers JD, *et al.* The European multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) ERS clinical research collaboration. *Eur Respir J* 2018; 52: 1802074.
27 Pedersen ES, Collaud EN, Mozun R, *et al.* COVID-PCD – a participatory research study on the impact of COVID-19 in people with primary ciliary dyskinesia. *ERJ Open Res* 2020; in press [https://doi.org/10.1183/23120541.00843-2020].
28 Kuehni C, Goutaki M, Rubbo B, *et al.* Management of primary ciliary dyskinesia: current practice and future perspectives. *In:* Bronchiectasis (ERS Monograph). Chalmers JD, Polverino E, Aliberti S, eds. Sheffield, European Respiratory Society, 2018; pp. 282–299.
29 Shoemark A, Lucas JS. Diagnosis of primary ciliary dyskinesia: Current practice and future perspectives. *In:* Bronchiectasis (ERS Monograph). Chalmers JD, Polverino E, Aliberti S, eds. Sheffield, European Respiratory Society, 2018; pp. 267–281.
30 Shoemark A, Rubbo B, Haarman E, *et al.* The controversies and difficulties of diagnosing primary ciliary dyskinesia. *Am J Respir Crit Care Med* 2020; 201: 120–122.