**Concept sheet for PCD microbiome project**

Microbial diversity in Primary Ciliary Dyskinesia compared to idiopathic bronchiectasis. A BEAT-PCD and EMBARC biobank study.

Writing team (in alphabetical order)

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Possible data providers

All members of BEAT-PCD, EMBARC, - All ERN (European reference network) - Lung members and affiliating or supporting partners

**Background**

Primary ciliary dyskinesia (PCD) is a rare inherited condition where dysfunction of multiple cilia leads to poor mucociliary clearance. Patients suffer from recurrent upper and lower respiratory tract infections which ordinarily lead to bronchiectasis by adulthood.

Patients with PCD tend to be younger, have more severe disease and are more likely to have chronic pseudomonas than patients with idiopathic or post infectious bronchiectasis. Pilot data from 185 patients with bronchiectasis has shown that PCD is a key predictor of reduced microbiome diversity, which in turn is linked to disease severity.

The purpose of this project is to validate these findings in a larger European cohort and describe differences in microbiome and local neutrophilic inflammation among PCD and idiopathic/post infective bronchiectasis

**Aims:**

The aim of this project is:

Compare microbiome composition and diversity along with neutrophil inflammation biomarkers between adult patients with PCD and age gender and FEV1% (above 50% and below 50%) matched patients with idiopathic or post infective bronchiectasis in stable state.

**Methods**

Inclusion criteria:

1. Spontaneous sputum samples held in biobanks with appropriate IRB consent for microbiome studies.
2. Patients with a confirmed diagnosis of PCD (bi-allelic mutations in a gene, or hallmark TEM and with clinical symptoms of the disease) AND for each PCD sputum sample an age, sex and FEV1%predict.<50% or FEV1%predict.>=50% matched patients with idiopathic bronchiectasis who have had PICADAR < 4 and normal nasal NO (>77nl/min).
3. Aetiologies defined as per ERS 2017 bronchiectasis guidelines (1)
4. More than 1 month apart since the last exacerbation/antibiotic course

**Matching parameters for idiopathic or post infective patients with PCD**

* Age (±5)
* Sex
* FEV1%predict.<50% or FEV1%predict>=50%

**Data collection:**

1. **PCD diagnosis** (TEM, Gene, Nasal NO, and high-speed video -where available)

Transmission electron microscopy results should be reported according to international standardised criteria. (2)

Genotype (if available) of patients should include information of the exact mutations by indicating the disease specific gene including both DNA- and protein-level (e.g. DNAH5 (Exon 20: c.3036\_3041delAGCG, p.V1014Lfs\*20 het. + Exon 25: c.C3949T, p.Q1317\* het.)). Results of segregation of autosomal recessive mutations should be provided if available.

Assessment of Nasal NO concentration measured by a NO chemiluminescence analyser in nl/min

1. **PICADAR Score**

Individual components (where available) and total score for the PICADAR should be reported.(3)

1. **Bronchiectasis severity index** (mandatory)

Individual components should be reported. Age (yrs), BMI, FEV1% predicted, number hospital admissions in the past 2 years, exacerbation frequency in last 12 months, MRC dyspnoea score, pseudomonas or other bacteria colonisation status, radiological severity (4)

1. **Additional data**

Sex, inhalation treatments (if available), smoking status and standard microbiology analysis at the time of sample microbiome sample collection (if available).

Sex, smoking status, ongoing inhaled treatments (if available), standard microbiology culture results at the time of sputum microbiome sample (if available) and history of chronic infection

**Sample collection and preparation**

N.2 vials with 0.2 g of sputum each should be aliquoted and sent on dry ice to “Leonardo Terranova, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Pad. Quarto 1 piano, Centro di Ricerca, via pace 9, 20122 Milano, Italy.”

**Ethical Considerations, Data handling and safety**

All participating centres should ensure they have appropriate Ethics Approvals for their institution in accordance with national governing bodies. All data shall only be provided anonymized and following applicable national/local data protection laws.

Material transfer agreements will be put in place between Milan and the sites.

**Anticipated Milestones:**

1. Collaborators agree this concept sheet and confirm sample numbers by 15.12.20
2. Partners set up MTA agreements by 30.1.21
3. Partners ship sputum samples on ice to Milan by 15.2.2021
4. Sample extraction and solubilization, 16s sequencing and inflammatory biomarkers assessment 30.5.2021
5. Data cleaning and analysis 30.06.2021
6. Circulating a first draft of the manuscript by 31.07.2021

**Authorship**

Data providers and departments involved in the study will be offered a co-authorship according to the criteria of the International Committee of Medical Journal Editors, which include all the following: i) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; ii) drafting the work or revising it critically for important intellectual content; iii) final approval of the version to be published; and iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All other partners and collaborators contributing to this trial shall be duly acknowledged in the publication.

References

1. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep;50(3).

2. Shoemark A, Boon M, Brochhausen C, Bukowy-Bieryllo Z, de Santi MM, Goggin P, 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(4).

3. Behan L, Dimitrov BD, Kuehni CE, Hogg C, Carroll M, Evans HJ, et al. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. Eur Respir J. 2016 Apr;47(4):1103–12.

4. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med. 2014 Mar;189(5):576–85.