The time is right for an international primary ciliary dyskinesia disease registry

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Rare diseases present diagnostic and management challenges to patients, healthcare providers and researchers. These diseases are often inherited, typically diagnosed upon presentation during childhood and can have deleterious long-term effects on patient wellbeing [1]. According to the regulatory and policy definition, a rare disease is any condition or disease affecting <200 000 individuals in the USA or in the European Union determined to be of low prevalence (fewer than five affected individuals per 10 000) [2]. With >7000 rare diseases estimated to affect ∼25 million people in North America and 30 million people in Europe [3, 4], even large medical centres are unlikely to have garnered sufficient patient care experience to accurately identify and effectively manage patients with these rare disorders.

Disease-specific registries collect affected patient information that can enrich our current understanding of disease determinants. Registries have been initiated by a diverse set of organisations, including patients and their families, patient advocacy groups, clinicians, national health systems and biopharmaceutical product manufacturers [2]. Ideally, these registries will serve to provide relevant and evidence-based information to patients and families seeking accurate educational materials; clinicians caring for affected patients to learn about the natural history, evolution, risk and outcomes of disease; investigators conducting rare disease research; epidemiologists gathering demographic data; and the drug and device industry exploring new market opportunities [2, 3]. Established in 1955, the Cystic Fibrosis Foundation developed as an effective model for rare disease registries. It continues to track patient health status, treatments and outcomes from >100 medical centres throughout the USA (https://www.cff.org/). As the cystic fibrosis registry has provided invaluable information that has contributed to improved patient care, we anticipate that this model may be similarly successful when applied to other rare diseases such as primary ciliary dyskinesia (PCD).

In this issue of the *European Respiratory Journal*, Goutaki *et al.* [5] report observations from a retrospective international cohort, merging available data on PCD from local and national registries as well as clinical and diagnostic databases including >3000 patients from 21 centres or consortia from 18 countries. As the authors note, this is the largest published data set on PCD, and this collective registry represents an important step toward gathering comprehensive information that will better inform our understanding of PCD.

There are some special challenges to consider when developing a PCD disease registry. First, there is currently no consensus gold standard for diagnosis. This may be due to the nature of PCD, a heterogeneous disease that, as noted by Shapiro *et al.* [6], can result from various defects in ciliary biogenesis, structure,

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function or organisation. Without alignment on definitive diagnostic criteria for PCD, some patients may be diagnosed incorrectly, while others may remain undiagnosed [7]. At present, it is difficult to pinpoint which exact features of history, examination and testing are necessary and sufficient to confirm a diagnosis of PCD. Both the European Respiratory Society (ERS) Task Force guideline for the diagnosis of primary ciliary dyskinesia [8] and PCD Foundation consensus recommendations [6] base the diagnosis of PCD on a combination of clinical features and diagnostic testing. Currently available diagnostic testing includes high-speed video microscopy analysis, nasal nitric oxide, genetic assessment, immunofluorescence and electron microscopy, yet all of these techniques have demonstrable limitations, which have been recently highlighted by the ERS Task Force guideline for the diagnosis of PCD [8].

Previously, ultrastructural ciliary defects visualised by electron microscopy, as described by Afzelius [9] in 1976, constituted the diagnosis of PCD. Of the patients who met the criteria for PCD according to current guidelines, about 70% were found to have electron microscopic abnormalities [10]. By genetic assessment, about 70% of patients with clinical and genetic features of PCD have been found to have biallelic pathogenic variants in one of the 35 genes currently known to be associated with PCD [10], so it has been included to be one of the key diagnostic criteria [6]. In the cohort described by Goutaki *et al.* [5], the numbers of patients with confirmed PCD vary by how the diagnosis of PCD is established. Based on electron microscopic findings (lack of dynein arm, disorganisation of the microtubular doublets or loss of the central microtubular pair) and/or biallelic gene mutation, 56% (n=1718) of 3013 patients in this cohort meet the criteria for definitive PCD diagnosis. Using abnormal light or high-frequency video microscopy findings and/or low ($\leqslant$77 nL·min^{-1}) nasal nitric oxide values [11] as diagnostic criteria, 14% of the patients in this combined dataset had a diagnosis of probable PCD. In 30%, the diagnosis of PCD was made on clinical grounds.

Genetic testing results were only available in 9% of patients in this cohort [5]. The inclusion of genetic testing as the panel of mutations expands will likely increase the number of individuals correctly identified as having PCD.

The data collected for a registry should be standardised across participating sites to ensure consistency of interpretation [2]. Optimally, there should be a consensus on what core data elements to collect [2] and a protocol for how best to integrate and interpret information across data sets and regional areas of care [3]. As the authors of this dataset have noted, consensus was not achieved in the currently described cohort because there was considerable heterogeneity in the content and format of collected data sets [5]. In addition, sites and regions had varying degrees of access to specialised diagnostic testing [12]. Imprecision with testing and variation in interpretation of diagnostic tests introduce further challenges. The recent efforts put forth by the ERS [8] and Shapiro *et al.* [6] to define diagnostic guidelines will certainly contribute to enhancing our ability to consistently and accurately diagnose PCD.

Diagnostic consensus is a crucial first step toward better understanding of PCD. This registry reflects the value of international collaboration, which will serve us well as our knowledge about PCD continues to expand.

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