The flare of care for rare: per aspera ad astra for rare lung diseases!

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Shareable abstract (@ERSpublications)
For rare lung diseases cross border collaborations and joining forces, such as between ERN-LUNG and ERS as well as patient organisations, are crucial to improve diagnosis and management of these diseases. https://bit.ly/3HpqGX1

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Rare lung diseases have been noticed for centuries: studies on a mummy of an Egyptian male from the 12th dynasty (1991–1783 BC) showed the presence of an interstitial lung disease called sand pneumoconiosis [1]. Rare disorders have a great impact on patients and their families, yet they are frequently misdiagnosed and undertreated [2]. This is caused, in part, by general as well as healthcare professionals' lack of knowledge of these disorders. Additionally, because rare disorders are so uncommon, there is frequently a shortage of funding for studies into, and management of, these conditions. The understanding and treatment of rare diseases did not make substantial strides until the end of the 20th century. In 1997, the European Organization for Rare Diseases (EURORDIS) was established to advocate on behalf of patients with rare diseases and their families at the European level [3]. With the adoption of the Orphan Medicinal Products Regulation (following the United States' Orphan Drug Act), a system of incentives for the development of orphan medications was established in the European Union (EU) in 2000. Orphan medication development and approval in Europe have significantly increased since the establishment of these regulations. However, according to the European Medicines Agency, only 8% of the medications with orphan designation finally made it to the market and thereby to the patients. This leaves a major unmet need for better treatments for the more than 30 million people in Europe suffering from a rare disease, including more than 1.5–3 million people afflicted by rare lung disorders [3–5]. So, while on its own a rare disease (per the European definition) occurs in less than one in 2000 people, together they impact many lives [6].

In 2017, the European Reference Networks (ERNs) for rare diseases were established as a component of the EU Horizon 2020 research and innovation programme [7]. The ERNs bring together medical expert centres and specialists from around Europe to improve the diagnosis, management and treatment of rare diseases as well as to stimulate education and research in this field [8]. ERN-LUNG has expanded since 2017 and currently consists of more than 100 centres in 24 European member states. Nine core networks are representing the main groups of rare respiratory diseases (https://ern-lung.eu/mission/), including interstitial lung diseases (ILD), cystic fibrosis, pulmonary hypertension, primary ciliary dyskinesia, non-cystic fibrosis bronchiectasis, α_1-antitrypsin deficiency, mesothelioma, chronic lung allograft dysfunction, and "other rare lung diseases". A tenth group is currently being formed for sarcoidosis. In the past 5 years, ERN-LUNG has sought and increasingly found its role in bringing together patients and care team members to improve the level of care to the best standards found in Europe. Close collaborations with learned societies, most prominently the European Respiratory Society (ERS), have resulted in shared

educational events, publications and guidelines both for patients and healthcare providers. A system of educational scholarships and possibilities for training visits at expert centres has been implemented alongside online courses. Integration with existing clinical research initiatives, such as for bronchiectasis and ILD, has led to better utilisation of resources and additional grants have been won to further strengthen these interactions [9].

In a series of reviews, starting in this issue of the *European Respiratory Review*, four of the nine core networks present an update on current developments in their respective fields. Cullivan *et al.* [10] focus on the recent European guidelines for the diagnosis and treatment of pulmonary hypertension, which were also endorsed by ERN-LUNG [11]. In addition, they highlight new developments including potential novel treatment pathways including the platelet-derived growth factor pathway, serotonin pathway, mTOR (mechanistic target of rapamycin) pathway or activin II receptor and bone morphogenetic protein, as well as novel non-pharmacological interventions. Simonneau *et al.* [12] provide a state of the art review on chronic thromboembolic pulmonary hypertension (CTEPH) based on a summary of the latest international CTEPH conference held in 2021. CTEPH is a rare complication of pulmonary embolism, a highly prevalent situation in every pulmonary practice. Their review provides practical guidance for clinicians to recognise and manage (suspected) CTEPH and includes disease definition, pathophysiology, diagnosis and current treatment strategies.

ILD comprise a wide range of rare and ultra-rare diseases that often pose diagnostic and management challenges. Buschulte *et al.* [13] present a selection of these diseases including pulmonary alveolar proteinosis, pulmonary microlithiasis, pleuroparenchymal fibroelastosis, rare ILDs of genetic origin and finally they discuss different cystic ILDs.

Lung cancer is common and immunotherapy has significantly improved outcomes for a subgroup of patients with nonsmall cell lung cancer in the past decade. Unfortunately, the prognosis for rarer thoracic tumours, such as malignant pleural mesothelioma and thymic epithelial tumours, remains poor for most patients. Dumoulin *et al.* [14] guide us through the current treatment options and new developments for these rare thoracic cancers.

The final collaborative review comes from Nathan *et al.* [15]. Their efforts underline that for diagnosis and management of ultra-rare diseases, such as children's ILD, cross-border collaborations are crucial. Their ERS clinical research collaboration for ILD in children (chILD-EU) is an example of an active and fruitful cross-border collaboration that advances knowledge and management of this young patient group with rare diseases. In their review they provide clues as to when to suspect ILD in children and the subsequent systematic approach for the diagnostic work-up, where there is an increasing role for molecular diagnostics and decreasing role for lung biopsies.

These reviews highlight that in each of these disease areas cross-border collaborations enable small, but important steps forward. Nevertheless, there is still a long road ahead to better diagnosis and management of each of the estimated more than 400 rare lung diseases. Challenges remain to organise and align all different stakeholders to present a strong and unified voice to policymakers to stimulate and facilitate sustainable advances for patients with rare diseases. Initiatives such as the "Rare 2030" foresight study, initiated by the European Parliament and co-funded by the European Commission, and the yet to start European Joint Action "Integration" dealing with better connecting ERNs with the many different national healthcare systems, help to set out policy frameworks to structurally incorporate diagnosis, treatment, care, research, data collection, and European and national infrastructures for rare diseases for the next decade [16]. While the journey to comprehensive support for rare (lung) diseases remains long, joining forces by strong collaborations between ERN-LUNG, ERS and patient organisations, like the European Lung Foundation and patient support groups, as well as other stakeholders in the respiratory field has already set the fire to the "flare of care for rare" and will, in the end, result in optimal care for our patients – per aspera ad astra for rare lung diseases!

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