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Design and rationale of ProSar, the first Danish sarcoidosis registry

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To the Editor,

Incidence and prevalence of sarcoidosis in Scandinavian countries are among the highest in the world (1). Although sarcoidosis is generally considered a benign disease, the overall risk of death in individuals with sarcoidosis is higher compared with the general population (2, 3) and mortality as well as the disease burden related to sarcoidosis is reported to rise (4).

Despite advancements in knowledge of sarcoidosis, there is still limited information regarding epidemiology, health status, treatment, distinct phenotypes and genotypes as well as course of disease.

Systematic data registration is warranted to phenotype patients with sarcoidosis and enhance understanding of the disease variability, which differs among ethnic groups.

Within the field of interstitial lung diseases (ILDs), considerable efforts have been made to develop idiopathic pulmonary fibrosis (IPF) registries, which have facilitated the conduct of large randomized controlled trials and evidence based treatment. Prospectively collected data have provided important information for retrospective analysis (5). Several registries for ILDs including sarcoidosis exist (6,7). In the US a web-based sarcoidosis registry for patient-entered data has been conducted (8). Within European registries, sarcoidosis together with IPF is the most prevalent disease (7). In Denmark, however, a previous cohort study of ILD and a prospective national registry for ILD did not include patients with sarcoidosis (9,10).

The objective of this study is to describe the design and rationale of the Danish sarcoidosis registry ProSar. The registry will collect data on demography, symptoms, organ involvement, biomarkers, diagnostic procedures, comorbidities and treatment in Danish patients with sarcoidosis in a real world clinical practice setting.

The ProSar registry was constructed as a single center registry for collecting prospective non-interventional observational data on Danish patients with sarcoidosis. The registry was designed by respiratory physicians with interest in sarcoidosis in collaboration with specialist representatives for extrapulmonary organ involvement from cardiology, ophthalmology, dermatology, hepato-gastroenterology, neurology, nephrology, rheumatology, otolaryngology, radiology, pathology and nuclear medicine (Figure 1).

Key parameters within the different specialties were proposed by the authors and subsequently reviewed and modified by relevant specialists.

The register reflects the broad variability in symptoms and organ involvement characterizing sarcoidosis. Besides specific organ involvement and damage, sarcoidosis can cause a broad spectrum of non-organ related symptoms such as fatigue, pain and small fiber

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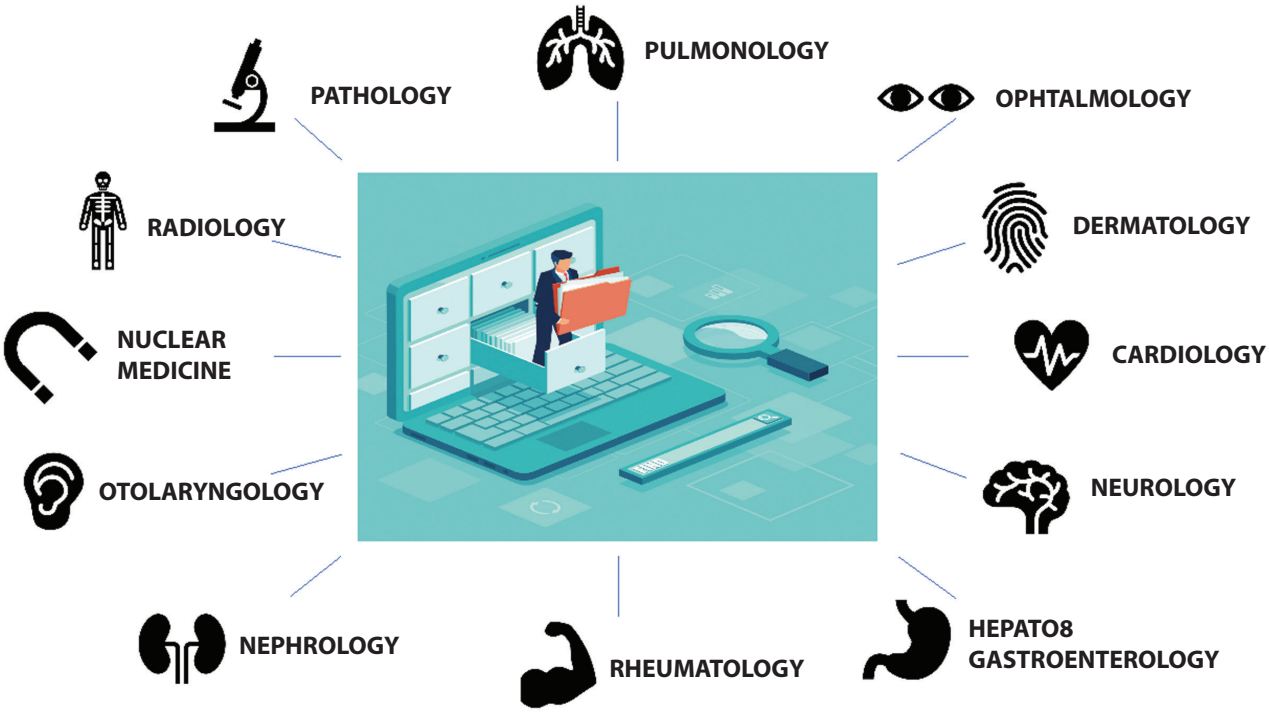

Figure 1. The ProSar registry combines data from different specialties. (FGC /Shutterstock.com)

neuropathy often not captured in the standard clinical diagnostic and monitoring set ups.

Patient reported outcome measures (PROMS) including fatigue, small fiber neuropathy, health status and quality of life (QOL) were incorporated by self-administered questionnaires complete by patients on a tablet and data were entered directly into the register at outpatient visits.

The workflow methodology and software solution of research electronic data capture (REDCap Vanderbilt University, Nashville, TN, USA) was found to be the most appropriate platform for the register. This was based on user friendliness in combination with REDCap being an inexpensive and secure data collection tool storing data in an encrypted web-based database.

In the start-up phase, 150 patients are planned to be enrolled in the registry but eventually all patients with sarcoidosis will be included. Patients will be recruited from the outpatient clinic at the Center for Rare Lung Diseases, Department of Respiratory Diseases and Allergy, Aarhus University Hospital in Denmark. The center treats 400 patients with sarcoidosis and receives approximately 100 new referrals annually.

The eligibility criteria are:

- Age of 18 years or above
- Diagnosis of sarcoidosis
- Able to read and understand Danish and to complete questionnaires in Danish
- Written informed consent.

The registry includes individual data on patient demographics, family history, referral patterns, symptoms, extra-pulmonary organ involvement, comorbidities, treatment and diagnostic investigations (physiological tests, blood tests, radiology and histopathology) as well as PROMS (Table 1).

Data are collected at baseline and at follow up visits 6, 12 and 24 month after enrolment, with the possibility to continue data collection until patient follow-up is terminated.

We present the study design and rationale for ProSar, the first Danish Sarcoidosis registry, which already includes patient data. The registry will hold epidemiological data including clinical characteristics, referral patterns, disease trajectories and treatment

Table 1. Main variables in the registry

	Baseline	Follow up
Eligibility criteria	x	
Patient demographics Gender, age, ethnicity, family history of sarcoidosis, type of referring physician* Smoking status, Occupational status	x x x	 x x
Comorbidities Pulmonary, cardiac, endocrinological, neurological, gastrointestinal, mental, malignant, other	x	x
Disease related data Onset of first symptoms, date of diagnosis Symptoms, height, weight, BMI	 x x	 x
Ekstrapulmonary sarcoid manifestations Löfgren syndrome, Heerfordt syndrome, skin, eye, ENT, CNS PNS, kidney, bone, liver, gastrointestinal disease, joint	x	x
Blood tests CRP, leucocytes, lymphocytes, calcium, angiotensin-converting enzyme, interleukin 2 receptor, immunoglobulins, Blood samples for biobank	x x	x x
Pulmonary function test FVC, FEV1, FEV1/FVC, DLCO, TLC, RV	x	x
Imaging Scadding stage by chest x-ray, HRCT features, PET, MR bone density scan	x	x
Bronchoscopy / BAL /EBUS / TBB / TBCB BAL cytology differential count, CD4/CD8	x	
Histopathology from involved organs Granulomas in biopsy	x x	
Systemic treatment Prednisolone, methotrexate, azathioprine, mycophenolate mofetil, leflunomide, infliximab, adalimumab, oxygen, other	x	x
Local treatment Inhalation medication, (ICS, LABA, LAMA, SABA, SAMA), topical steroid (skin and eyes)		
PROMS KSQ, FAS, SFNSL, MRC, SF12	x	x

*: General practitioner, private practicing specialist, other specialists; ENT: Ear-nose and throat; CNS: central nervous system; PNS: peripheral nervous system. BMI: body mass index. FEV1: forced expiratory volume. FVC: forced vital capacity. DLCO: diffusion capacity of the lung for carbon monoxide. TLC: total lung capacity. RV: residual volume. HRCT: high-resolution computed tomography; PET: positron emission tomography. MR: magnetic resonance. BAL: bronchoalveolar lavage. EBUS: endobronchial ultrasound. TBB: transbronchial biopsy. TBCB: transbronchial cryo biopsy. ICS: inhaled corticosteroids. LABA: long-acting beta-agonist. LAMA: long-acting muscarinic antagonist. SABA: short-acting beta-agonist. SAMA: short-acting muscarinic antagonist. KSQ: King's sarcoidosis questionnaire, FAS: fatigue assessment scale, SFNSL: small fiber neuropathy screening list, MRC: medical research council dyspnoea scale, SF12: short form survey 12-item.

pathways in Danish patients with sarcoidosis. ProSar is characterized by some inherent limitations based on its non-randomized, observational design. As this is a single center study, national epidemiological data on the incidence and prevalence of sarcoidosis cannot be derived. The variable course of the disease from very mild to patients with severe stage IV disease, varying organ involvement and the clinical decisions of the treating physician may introduce bias and compromise the associations between treatment and outcome.

However, the collection of prospective data will provide valuable information regarding epidemiology and treatment patterns in Denmark in a real-world setting.

The registry is user friendly, flexible and easy to access. It is intended to be implemented at other Danish sarcoidosis centers and clinics and has the potential and flexibility to develop into a national Danish registry. The clinical data within the database can be linked to other personal data in the Danish national patient registry system on e.g., data on socio-economics, prescriptions, and general health care. Furthermore, the registry will facilitate future clinical research in sarcoidosis important to patients and has the potential to improve the medical management of and outcome for patients with sarcoidosis.

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