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Flemish network on rare connective tissue diseases (CTD): patient pathways in systemic sclerosis. First steps taken

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ABSTRACT

Despite the low prevalence of each rare disease, the total burden is high. Patients with rare diseases encounter numerous barriers, including delayed diagnosis and limited access to high-quality treatments. In order to tackle these challenges, the European Commission launched the European Reference Networks (ERNs), cross-border networks of healthcare providers and patients representatives. In parallel, the aims and structure of these ERNs were translated at the federal and regional levels, resulting in the creation of the Flemish Network of Rare Diseases. In line with the mission of the ERNs and to ensure equal access to care, we describe as first patient pathways for systemic sclerosis (SSc), as a pilot model for other rare connective and musculoskeletal diseases. Consensus was reached on following key messages: 1. Patients with SSc should have multidisciplinary clinical and investigational evaluations in a tertiary reference expert centre at baseline, and subsequently every three to 5 years. Intermediately, a yearly clinical evaluation should be provided in the reference centre, whilst SSc technical evaluations are permissionably executed in a centre that follows SSc-specific clinical practice guidelines. In between, monitoring can take place in secondary care units, under the condition that qualitative examinations and care including interactive multidisciplinary consultations can be provided. 2. Patients with early diffuse cutaneous SSc, (progressive) interstitial lung disease and/or pulmonary arterial hypertension should undergo regular evaluations in specialised tertiary care reference institutions. 3. Monitoring of patients with progressive interstitial lung disease and/or pulmonary (arterial) hypertension will be done in agreement with experts of ERN LUNG.

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KEYWORDS

European reference networks; Flemish Network of rare diseases; rare connective tissue diseases; systemic sclerosis; patient pathways

Introduction

Since the publication of the 1999 European Commission 'Programme of community action on rare diseases' chronic or severe diseases affecting 5 or less out of 10 000 people are considered as rare [1]. These pathologies pose multiple threats and challenges. The low prevalence of each illness makes it difficult and intensive to perform and provide high-quality research and patient care, leading to delayed diagnosis and limited access to high quality evidence based treatments. Furthermore, small patient populations make the creation of new therapies less attractive, leading to decreased development. The introduction of orphan drug designation in Europe and the United States however greatly stimulated the research and development of drugs in rare diseases [2,3]. Although the individual prevalence is low, the overall number of patients affected by rare diseases represents a significant burden. It has been estimated that six to eight percent of the global population suffers from a rare disease, resulting in 360,000 to 480,000 patients in Belgium, between 27 and 36 million in Europe [4,5]. The last two decades, a great effort was made to counter and control, among others, the abovementioned challenges at the European as well as at the national and regional levels. In 2017, the European Commission launched the European Reference Networks (ERNs), cross-border networks of health care providers and patient representatives with high expertise in rare diseases across the European Union (Figure 1). ERN ReCONNET (rare and complex connective tissue and musculoskeletal diseases) was one of the first reference networks to be established and aims to improve early diagnosis, patient management, care delivery and virtual discussion of clinical cases within the network, affiliated centres or any health care provider. This network groups rare connective tissue and musculoskeletal diseases into three main thematic areas: 1. rare autoimmune, 2. complex autoimmune and 3. rare hereditary connective tissue and musculoskeletal diseases [6]. In line with the mission of these ERNs, Belgium subsequently created rare diseases networks at the regional level, leading to the establishment of the Flemish Networks of Rare Diseases in 2017 (Vlaams Netwerk Zeldzame Ziekten [VNZZ]) (Figure 2). To date, there is no official counterpart in the French Community (for more information on the Belgian healthcare system, see supplementary files, Figure 1). The subnetwork 'Connective tissue – musculoskeletal' is one of the 17 subnetworks and takes care of the management and organisation of rare and/or complex autoimmune/hereditary connective tissue and musculoskeletal diseases, in analogy with ERN ReCONNET. This subnetwork is open for every dedicated stakeholder (healthcare providers and patients, also from outside of Flanders), interested in the care of patients with rare musculoskeletal diseases. The biannual meetings consist of updates on existing guidelines, organisational aspects, information from patient organisations and multidisciplinary discussion of difficult cases (for detailed description on the evolution and organisation of European and regional networks, see supplementary file). The aims of the ERNs include, among others, the promotion of harmonised strategies and actions to reduce inappropriate practice variations and disparities in healthcare, and to support transparent decision making [6]. In line with ReCONNET, the VNZZ subnetwork 'Connective tissue – musculoskeletal' is striving for equal healthcare and making scientific progress available over the whole region. In this way, it prioritised the development of patient centred care and referral pathways between primary care and secondary and tertiary centres, with the pathway for patients with systemic sclerosis (SSc) as a pilot study (Figure 3). On the other

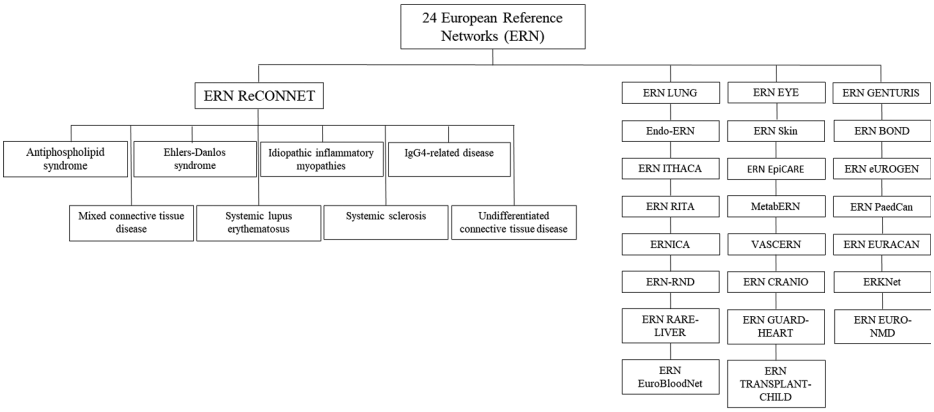

Figure 1. Overview of the different European reference networks. European Reference Networks (ERNs) are virtual cross-border networks that gather patients, doctors and researchers with high expertise in the fields of rare or low-prevalence and complex diseases. Today, there are 24 networks, one for each domain of rare diseases. The rare connective tissue and musculoskeletal diseases are grouped in ERN ReCONNET. ERN BOND: European Reference Network on bone disorders; ERN CRANIO: European Reference Network on craniofacial anomalies and ear, nose, and throat disorders; Endo-ERN: European Reference Network on endocrine conditions; ERN EpiCARE: European Reference Network on epilepsies; ERKNet: European Reference Network on kidney diseases; ERN-RND: European Reference Network on neurological diseases; ERNICA: European Reference Network on inherited and congenital anomalies; ERN LUNG: European Reference Network on respiratory diseases; ERN Skin: European Reference Network on skin disorders; ERN EURACAN: European Reference Network on adult cancers (solid tumours); ERN EuroBloodNet: European Reference Network on haematological diseases; ERN eUROGEN: European Reference Network on urogenital diseases and conditions; ERN EURO-NMD: European Reference Network on neuromuscular diseases; ERN EYE: European Reference Network on eye diseases; ERN GENTURIS: European Reference Network on genetic tumour risk syndromes; ERN GUARD-HEART: European Reference Network on diseases of the heart; ERN ITHACA: European Reference Network on congenital malformations and rare intellectual disability; MetabERN: European Reference Network on hereditary metabolic disorders; ERN PaedCan: European Reference Network on paediatric cancer (haemato-oncology); ERN RARE-LIVER: European Reference Network on hepatological diseases; ERN ReCONNET: European Reference Network on connective tissue and musculoskeletal diseases; ERN RITA: European Reference Network on immunodeficiency, autoinflammatory, and autoimmune diseases; ERN TRANSPLANT-CHILD: European Reference Network on Transplantation in Children; VASCERN: European Reference Network on Rare Multisystemic Vascular Diseases

hand the VNZZ subnetwork 'Connective tissue – musculoskeletal' reference centres (= members of ReCONNET [Ghent University Hospital and Leuven University Hospital]) are continuously responsible for the education of health caregivers in the chain of rare disease patients in the region. Non-exhaustive examples of this continuous education are: integration in the curriculum of rheumatologists of 6 months hands-on training in capillaroscopy, a tool to early detect SSc, a 6 months immersion of caregivers in the chain of treating the SSc patient in the tertiary centre SSc care unit. Additionally, the VNZZ subnetwork 'Connective tissue – musculoskeletal' reference centres shares the scientific results of their research, relevant for the region, through scientific publications to their peers and in lay language to their patients.

SSc is a chronic and debilitating rare connective tissue disease characterised by fibrosis of skin and internal organs, vasculopathy and auto-immunity [7,8]. The disease is classified based on the pattern of skin involvement, as defined by Leroy et al. It comprises limited, limited cutaneous and diffuse cutaneous variants [9]. In 2013, the American College of Rheumatology (ACR) and

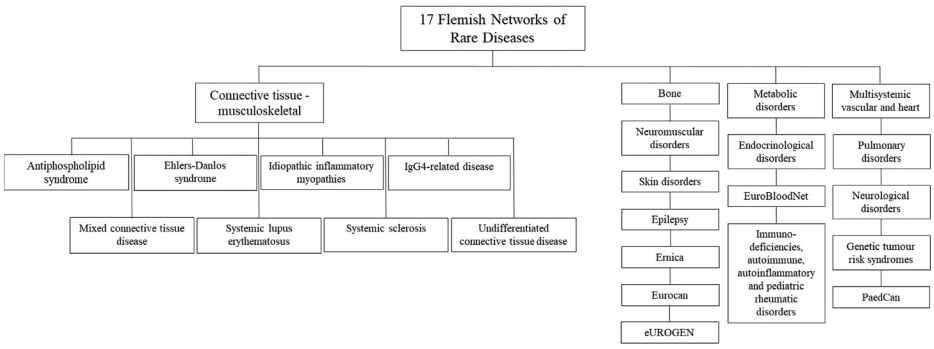

Figure 2. Overview of the different Flemish networks of rare diseases. Similar to the European Reference Networks, the Flemish Networks of Rare Diseases consist of multiple (17) subnetworks, one for each domain of rare diseases. The rare connective tissue and musculoskeletal diseases are grouped in the Connective tissue – musculoskeletal network.

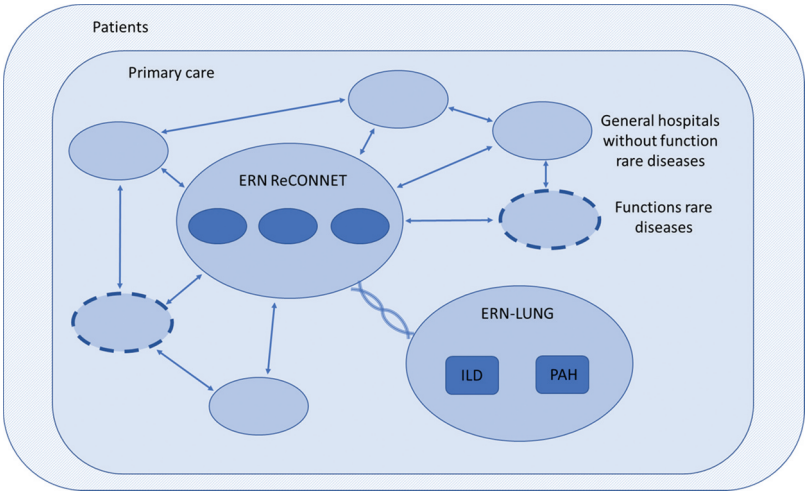

Figure 3. Interactions between the different levels of healthcare. Pictural description of the interactions between the different healthcare levels in the 'Flemish Network of Rare Diseases' subnetwork on connective tissue and musculoskeletal diseases, with patient centricity and participation as overarching principle. ERN: European Reference Network; ReCONNET: Rare and Complex Connective Tissue and Musculoskeletal Diseases: ILD: interstitial lung disease; PAH: pulmonary arterial hypertension

the European Alliance of Associations for Rheumatology (EULAR, formerly the European League against Rheumatism) jointly presented new classification criteria, based on a multicriteria additive point system, with skin thickening of the fingers extending proximal to the metacarpophalangeal joints being sufficient for the patient to be classified as having SSc [10]. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) encompass the most severe complications of SSc, being the leading cause of death [11]. Since early detection and treatment of these complications lead to better survival, thorough screening and multidisciplinary follow-up are paramount [12–14]. In Belgium, SSc patients are comprehensively evaluated yearly (or sooner on indication), as has been stipulated in the Belgian Systemic Sclerosis Cohort (BSSC), an interuniversity rheumatological effort to standardise clinimetrics in SSc since 2006 (main participating centres are Cliniques Universitaires Saint-Luc, Ghent University Hospital, University Hospital Leuven, CHU Brugmann, Hôpital Erasme) [15]. In brief, this annual evaluation comprises standardised clinimetrics, extensive lab works, a six minutes walking test (6MWT), a systematic echocardiography, an electrocardiogram, lung function testing, a High-Resolution Computed Tomography (HRCT) scan of the lungs, a nailfold video capillaroscopy, right heart catherisation (executed in line with clinical practice guideline recommendations) at baseline and finally a consultation with the pneumologist, cardiologist, and rheumatologist [16–18]. In addition, in the Ghent University Hospital SSc Unit (GUSU), members of this team discuss the results of each patient in a weekly multidisciplinary team meeting.

This manuscript aims to report the first steps taken by the network on the development of patient pathways in SSc, as discussed on dedicated network meetings in 2021–2022 (see Figure 4 and supplementary file for the list of participants to the network). A patient representative (KP) presented opportunities and pitfalls in the development of patient care pathways. Subsequently, to achieve consensus on patient care and referral pathways, representatives of secondary and tertiary care facilities and patient organisations discussed three selected questions. These questions, as given below, considered 1. the current operational state of local interdisciplinary meetings, 2. the need for centralised conservation of standardised clinimetrics and finally 3. the point of view concerning follow-up in secondary and tertiary centres anno 2021.

(1) What is the modus operandi of current local multidisciplinary teams?
(2) What is the usefulness of integrating standardised clinimetrics into registries and what is their future when evaluating patient pathways?
(3) Systemic sclerosis is a heterogenic disease. Which patients could be evaluated in secondary centres and which patients should be referred to tertiary centres anno 2021?

Finally, a consent-based proposal on multidisciplinary pathway for SSc patients was reached.

Consensus meeting report

Opportunities and pitfalls when developing patient pathways – a patient's perspective

When developing and designing care paths it is principal to consider the patient's point of view. During this representative discourse, important items concerning patients' perception were addressed. First of all patient centrality is primordial. The generalisation and systematisation of the decision process by means of developing patient pathways should not prevent decision-

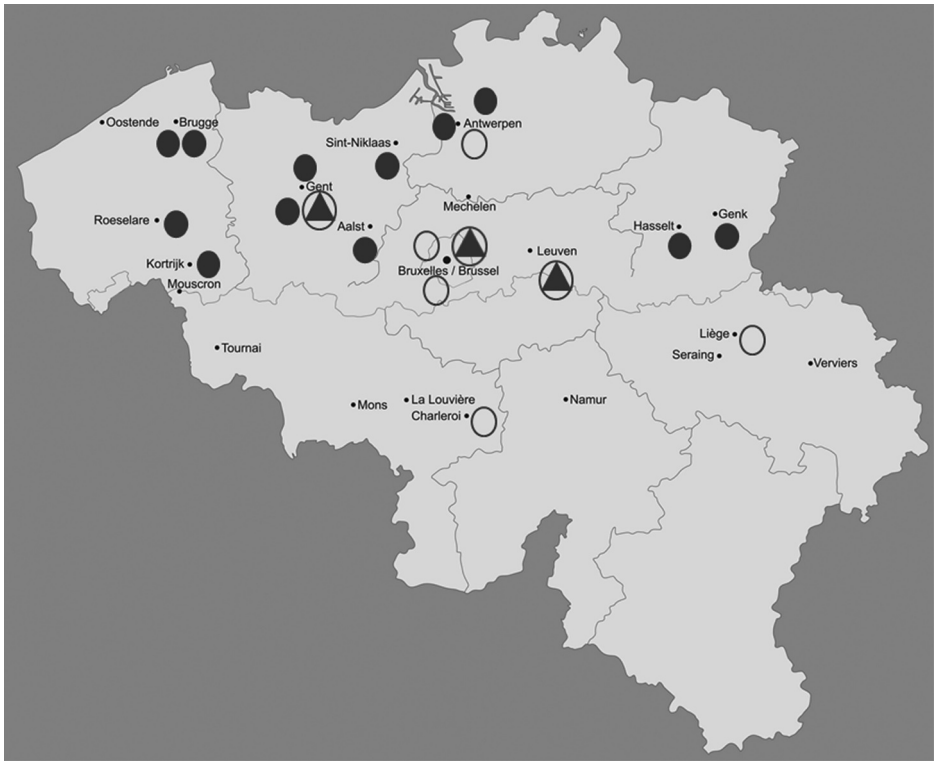

Figure 4. Geographical distribution of centers participating to the 'Flemish Network of rare diseases' subnetwork on connective tissue and musculoskeletal diseases. ▲: ERN ReCONNET member + function rare diseases; ◯: Function rare diseases; ●: Participating General Hospitals without function rare diseases **ERN**: European Reference Network; ReCONNET: Rare and Complex Connective Tissue and Musculoskeletal Diseases; SSc: systemic sclerosis

making to be tailored to the patient's specific situation, wishes and needs. Secondly, every hospital that attends patients with SSc should have sufficient knowledge about the disease, should be able to provide adequate information concerning diagnosis and treatment and should have access to sufficient paramedical personnel to provide the necessary support. In addition, it is important to keep in mind the financial burden of yearly evaluations with many different investigations. For practical and financial reasons, all necessary examinations should ideally be planned on a single day and unnecessary duplication of technical investigations should be avoided. When referring patients from secondary to tertiary care and vice versa, a detailed briefing and medical file should be available in order to ensure smooth information transition. Patients would like fixed and periodical tertiary care evaluations, even when they have a well-controlled disease.

A general overview of the modus operandi of current local multidisciplinary teams

The current operational mechanisms of local multidisciplinary teams regarding systemic sclerosis and rare connective tissue diseases vary and depend on the local hospital. As already discussed above, the GUSU provides a weekly multidisciplinary meeting to discuss difficult cases and test results of the patients who underwent their yearly screening. A similar approach is performed at Cliniques Universitaires Saint-Luc. In other tertiary or large secondary hospitals as UZ Leuven and Ziekenhuis Netwerk Antwerpen (ZNA) there is a similar meeting every week, albeit primarily between rheumatologists. This is also the case in the Jessa Hospital in Hasselt. There is however a well-established cooperation with other disciplines for extensive consultation. Several hospitals such as UZ Brussels, Maria Middelares, Ziekenhuis Oost-Limburg (ZOL), AZ Groeninge, CHU Liège and AZ Sint-Lucas in Bruges, also perform regular multidisciplinary meetings to discuss complex diagnostic cases. In AZ Sint-Jan in Bruges, there is a monthly multidisciplinary meeting and intensive multidisciplinary interaction, in close collaboration with the Ghent University Scleroderma Unit. If there is a large clinical suspicion of SSc or another specific rare connective tissue disease, most second line hospitals refer quickly to a tertiary care facility, as in for example the case in Maria Middelares in Ghent.

The usefulness of registries and their future when evaluating patient care pathways

The usefulness of registries has been proven extensively [15,19–22]. Registries enable pooling of datasets coming from different centres, which is essential to overcome important hurdles when studying rare diseases. Indeed, the small and scattered patient populations challenge traditional research methodologies. Additionally, sharing data facilitates and increases scientific collaboration between experts in the field of rare diseases, across the borders [23,24]. Large international databases generate crucial information on epidemiology, occupational and environmental associations and natural evolution of diseases. Systematic and standardised clinical evaluations and technical investigations familiarises health care providers with the heterogeneity of rare diseases, sharpens gut feelings in unusual disease manifestations and decreases inter-rater variabilities. Therefore, when developing patient care pathways, standardised coordinated way of data sampling is of utmost importance to ensure registry data quality. To minimise variation, preferably the same observer in the same centre should conduct examinations in the same location by the same standardised approach every year. On the patient level, the increasing scientific knowledge results in tangible modifications of treatments and follow-up. For example, a recent multicentric study on the incidence and prevalence of ILD in SSc patients in Flanders (722 patients, up to 12 years follow-up) taught that ILD progresses in both limited and diffuse cutaneous subtypes of SSc with baseline ILD, leading to increased awareness in Belgian caregivers of the need for rigorous and continuous screening for organ involvement in both subgroups [22]. Subsequently, all stakeholders agreed that at baseline all SSc patients, regardless of SSc subtype, should be co-evaluated in a specialised tertiary setting, ideally including the performance of technical investigations. Re-evaluations in the same manner at fixed time intervals (every 3 to 5 years) is paramount. The other years, a clinical evaluation at the same tertiary centre is indicated, followed by multidisciplinary discussion. In between routine follow-up and technical investigations may be performed at the secondary care facilities, as per the decision of peripheral specialists and patients. However, to facilitate the establishment of high-quality registry data and possibility of study generation, examinations should always proceed in a high qualitative and similar systematic manner [16,25].

Which patients could be evaluated in secondary centres and which patients should be referred to tertiary reference centres?

In discussion with engaged representatives of primary care, the need for alert signs and symptoms (red flags) for referral was emphasised. Given the multitude of rare diseases and their heterogeneity, these generic red flags are preferred above disease-specific red flags (such as Raynaud's phenomenon in SSc). When considering the follow-up pathways of SSc patients, several important factors have to be taken into account. First, the severity of the disease has to be examined. The 5 and 10-years survival rates of DcSSc are estimated at 68% and 50%, respectively. This is caused by early (in the disease course) and severe organ involvement [26]. Progressive ILD and PAH are the most common causes of death among patients with SSc [11]. Consequently, the management of patients with early DcSSc, progressive ILD and PAH requires specialised multidisciplinary follow-up.

Secondly, the uniformity and preservation of registry data has to be guaranteed, as discussed above. Subsequently, the local quality and systematic approach of the SSc-specific investigations should be critically reviewed. All involved hospitals should offer regular interactive multidisciplinary meetings and should be able to provide the necessary paramedical supports for the coordinated care. Finally, although the medical indications are critically important by choosing appropriate care, the patient makes the final decision concerning his or her follow-up.

It was uniformly agreed that SSc patients should preferably undergo baseline investigations in tertiary reference centres. For registry purposes and considering viewpoints of patient as stated above, re-evaluations should preferably be offered in the same tertiary centre: annual clinical evaluations and clinical evaluations with technical evaluations every three to 5 years. Additionally, a yearly multidisciplinary discussion should

Table 1. Unmet needs and future actions.

1. Integration of standardised training in early detection of SSc, i.e. capillaroscopy, in the official rheumatology curriculum
2. Integration of training in rare diseases units in the official rheumatology curriculum
3. Adoption of the interaction between tertiary centres, secondary centres and first line caregivers in SSc to other rare connective tissue diseases in Belgium
4. Adoption of international clinical practice guidelines to the Belgian level
5. Further optimisation of the use of the European Commission provided IT platform for clinical consultations between ERN members, the 'Clinical Patient Management System' (CPMS) by extension of its use to any healthcare provider in the chain of rare diseases
6. Financial incentives for multidisciplinary team consultations/discussions integrated in the healthcare system
7. Simplification and defragmentation of Belgian healthcare, to avoid inefficient use of resources and duplication of efforts

ERN: European Reference Network; IT: Information Technology; SSc: systemic sclerosis

take place at the tertiary centre, followed by an extensive written report including treatment recommendations. In case of severe or urgent indications, treatment should be initiated at the tertiary centre. Additional appropriate follow-up is qualified in secondary care units, providing qualitative SSc-specific examinations and support along with multidisciplinary consultations. The coordinated evaluations across care setting and the safe transfer of patient information between health providers should be guaranteed. To optimise care and to enable inclusion in clinical trials and research, patients with early DcSSc and patients with progressive ILD and/or PAH, however, should always be closely monitored in a tertiary reference facility [27].

Management of all patients with SSc should comply with available clinical practice guidelines to ensure optimal up-to-date and evidence-based care [16,28,29].

Conclusions

In the consensus meeting between representatives of primary, secondary and tertiary reference care facilities and SSc patient organisations, the first steps were taken in the development of the first Belgian consensual multidisciplinary standardised patient pathways in SSc. Considering the goals of the ERNs and the 'Belgian Plan for Rare Diseases', this meeting was organised by the Flemish Network of rare connective and musculoskeletal diseases, on behalf of the Flemish government.

From patients' perspective, the importance of transparency, quality of care and patient autonomy were highlighted. Uniform agreement was achieved concerning the broad framework of SSc patients follow-up. In addition, the disease subtypes-based requirements for different level of care and follow-up were identified. Finally, the importance of registries and their quality were emphasised.

Consensus was reached on following key messages:

- Baseline clinical and technical investigations should preferably take place in tertiary reference centres with re-evaluations (clinical + technical investigations) in the same tertiary centre at least every three to 5 years. Additionally, annual clinical evaluations in the tertiary reference centre should be provided for standard clinimetrics with possible SSc-specific investigations in a secondary centre adhering to SSc-specific clinical practice guidelines [28]. Additional monitoring can take place in secondary care units, if these hospitals can provide qualitative SSc-specific examinations and care along with interactive multidisciplinary consultations.
- Patients with early DcSSc, progressive ILD and/or PAH should always undergo thorough evaluations in specialised tertiary reference care institutions. Follow-up will be discussed with the patient and the ERN experts tailored on an individual basis. Monitoring of patients with progressive ILD and/or PAH will be offered in discussion with experts of ERN-LUNG.
- Patients with organ complications that are covered in other ERNs, will be referred to those relevant centres and pathways.

This proposal of interactive multidisciplinary pathways is subsequent to comply with European commission incentives (ERN) to ensure equity of management of rare connective tissue diseases tailored to the Belgian health care provider (Table 1). The value of this collaboration together with collaboration between secondary and tertiary reference centres will be evaluated further.

In conclusion, we propose the first Belgian consensual interactive multidisciplinary pathways for patients with systemic sclerosis, which make a first step to the implementation of the European Commission's directive to offer an access to equal management of rare connective tissue diseases across Europe.

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