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HEALTH SERVICES RESEARCH

ORPHANET BELGIUM DATABASE ACTIVITY REPORT 2021

orphanet

Convention for the support of strategic research on rare diseases in Belgium 2020-2024 (Central Registry of Rare Diseases – Belgian Genetic Tests Database – Orphanet)

CALOMME ANNABELLE • SWINNEN ELFRIEDE

healthy all life long

WHO WE ARE

SCIENSANO can count on more than 700 staff members who commit themselves, day after day, to achieving our motto: Healthy all life long. As our name suggests, science and health are central to our mission. Sciensano's strength and uniqueness lie within the holistic and multidisciplinary approach to health. More particularly we focus on the close and indissoluble interconnection between human and animal health and their environment (the "One health" concept). By combining different research perspectives within this framework, Sciensano contributes in a unique way to everybody's health.
For this, Sciensano builds on the more than 100 years of scientific expertise of the former Veterinary and Agrochemical Research Centre (CODA-CERVA) and the ex-Scientific Institute of Public Health (WIV-ISP).

Sciensano

Epidemiology and Public Health – Health Services Research

Rare Diseases Team

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- The **Orphanet Belgium Management Board** consists of representatives of:

- the Orphanet Belgium team;
- the sponsors of Orphanet Belgium (FPS/SPF/FOD, NIHDI/INAMI/RIZIV);
- ad hoc: experts or representatives of institutes designated for the validation of the data.

- **Sponsors and non-financial partnerships**:

	SPONSORS & NON-FINANCIAL PARTNERSHIPS	
Members of National Board	sciensano	Sciensano's service "Health services research" hosts the Orphanet Belgium team. Sciensano has been a beneficiary in RD-ACTION 677024 (financial support from the European Health Program). At Sciensano, there is internal collaboration with the Infectious Diseases Service to validate data on reference laboratories and screening tests for infectious disease. Since 2020, an internal collaboration has been established with the Belgian Genetic Test Database (BGTD) (Health services research), in order to improve the registration and update of diagnostic tests performed by the 8 officially-recognized genetic centres.
	federal public service HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT	The Federal Public Service Health, Food Chain Safety and Environment has been a beneficiary in RD-ACTION 677024 (financial support from the European Health Program).
	INAMI-RIZIV	The National Institute for Health and Disability Insurance (NIHDI) provides financial support to the Orphanet project. It also provides information on the recognized reference centres working under a revalidation convention.
Ad-hoc experts	RaDiOrg	RaDiOrg, the Belgian umbrella association of patient organisations for rare diseases, plays a role in the validation of data on Belgian patient organizations registered in the Orphanet database.
	COLLEGE GENETICS	The College of Human Genetics in Belgium, which represents the 8 officially-recognized genetic centres, collaborates with the Orphanet team to improve and simplify the process of registration and update of data on genetic testing activities in the Orphanet database.

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ABBREVIATIONS AND ACRONYMS

AZ	Algemeen Ziekenhuis
BE	Belgium
BELAC	Belgian accreditation organisation
BGTD	Belgian Genetic Tests Database
CEGRD	European Commission Expert Group on Rare Diseases
CHU	Centre Hospitalier Universitaire
CRRD	Central Registry of Rare Diseases
CUB	Cliniques universitaires de Bruxelles
EC	European Commission
EQA	External Quality Assessment
ERN	European reference network
EU	European Union
FPS	Federal Public Service (FPS) Health, Food Chain Safety and Environment
GDPR	General Data Protection Regulation
HUDERF	Hôpital Universitaire Des Enfants Reine Fabiola
INAMI	Institut national d'assurance maladie-invalidité
Inserm	The French National Institute of Health and Medical Research / Institut National de Santé et de Recherche Médicale (France)
IS	Information Scientist
MB	Management Board
NMRC	Neuromuscular reference centre
NIHDI	National Institute for Health and Disability Insurance
ORPHAcode	A unique and stable identifier assigned to each rare disease listed in Orphanet. Only ORPHAcodes cover all known rare diseases. ORPHAcodes are aligned with other non-rare disease specific terminologies in use in health systems and in registries, to aid data interoperability
OrphaNetWork	A website assigned to national teams and serving as a collection point for common tools and documents. This website is only accessible to Orphanet collaborators after entering a login and password
QAR	Quality Assurance Review
QC	Quality control
RaDiOrg	Rare Diseases Organisation Belgium
RD	Rare disease
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering
SOPs	Standard Operating Procedures
UZ	Universitair ziekenhuis

INTRODUCTION

In Europe, a disease is defined as rare when it affects less than 1 in 2,000 people[1]. A study[2] published in 2019 by Orphanet in the *European Journal of Human Genetics* estimates the number of people living with a rare disease at 3.5–5.9%, which equates to 263–446 million persons affected worldwide at any point in time. If we report this estimate on the Belgian population, it is equivalent to **about 500,000 people suffering from a rare disease in our country** (not taking into account rare tumours, infectious diseases and poisonings). By definition, each distinct rare disease affects a small group of people. However this study underlines the fact that the issue of rare diseases concerns a large number of the population and represents **an emerging global public health priority.**

72% of rare diseases are of genetic origin. About 70% of rare diseases start in childhood and around 30% of affected children will not reach the age of 5. Few rare diseases are preventable or curable and most often, they are severe, chronic, progressive and significantly affect the quality of life. Almost 6,200 rare diseases[3] have been clinically defined to date and new pathologies are regularly described by researchers. **Rare diseases are numerous but also very heterogeneous**, both in terms of symptoms and prevalence. It appears from the study cited above that the maximum pressure on the population is exerted by only 4.2% of rare diseases. In other words, nearly 80% of all people with a rare disease are affected by the 149 most common rare diseases.

Specific issues are raised in relation to their rarity. In particular, the field of rare diseases suffers from a lack of medical and scientific knowledge. For people affected by rare diseases, it is often difficult to find information on these pathologies, which is scarce and disseminated around the world, or to find qualified professionals to ensure their medical care. Another challenge for these patients is to be able to exchange with other people suffering from the same disease, in order to break the isolation very often felt by people affected by this type of pathologies. Moreover, for physicians and researchers, it is crucial to benefit from means facilitating collaborations on advances in the field.

The **Orphanet portal** (official address of the website: www.orphanet.net) **plays a key role in the research and care spheres.** Over the years, Orphanet has become the leader in collecting, integrating, producing and dissemination of high-quality, manually curated expert-reviewed information and data on rare diseases and orphan drugs. Orphanet is **the only specific resource for rare diseases**: it is **the reference for the nomenclature (ORPHAcodes) and classification of rare diseases**, essential in improving the visibility of rare diseases in health and research information systems.

Orphanet ensures **equal access to knowledge for all stakeholders** and intends to serve the following communities: health care professionals, patients and their relatives, patient organisations, researchers, biotech and pharmaceutical companies, public health and research institutions and public authorities. The information is available in nine languages, including French and Dutch. Every month, more than a million pages of the Orphanet website are consulted from over 200 countries and **Belgium is among the top ten countries of the website's audience**[4].

Orphanet was established in France by the Inserm (French National Institute for Health and Medical Research) **in 1997**. This initiative became a European endeavour from 2000, supported by grants from the European Commission. Orphanet has gradually grown to a **consortium of 42 countries**[5], within Europe and across the globe. Belgium was one of the first countries to join the consortium, in 2001.

In Belgium, participation in Orphanet is supported by the health authorities. Sciensano has been endorsed by the Ministry of Health to host the Orphanet Belgium team. A national board consisting of members from Sciensano, Federal Public Service (FPS) and the National Institute for Health and Disability Insurance (NIHDI) oversees the project. The management of Belgian data registered in Orphanet is a continuous task which is described in the successive agreements "Central Registry of Rare Diseases – Belgian Genetic Tests Database – Orphanet support" concluded between the NIHDI and Sciensano. The convention is monitored by a multi-stakeholder steering committee to determine by consensus the priorities and actions to be undertaken to carry out the project in the most efficient and effective way possible.

The objective of this report is to provide **an overview of the activity and progress performed during the year 2021**. For detailed information on Orphanet missions, services, quality commitment, general data management methodology and a description of the roles of the different members of the Orphanet Belgium team, we refer to the previous activity reports[6-7].

MAIN ACTIVITIES CARRIED OUT IN 2021

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1. Belgian contribution to the Orphanet database [December 2020 – December 2021]

1.1. CONTENT OF THE ORPHANET BELGIUM DATABASE

The management of the Orphanet database is **a continuous and constantly evolving task**. Orphanet data is processed manually by the Belgian team and validated by experts, in accordance with standard operating procedures (SOPs) which include the methodology to be adopted, the workflow to be followed and the inclusion/exclusion criteria for each type of expert resources:

- **The patient-centered services:** patient organisations, federations and alliances; expert centres, networks of expert centres; medical laboratories and diagnostic tests;
- **The research-related activities:** research projects, clinical trials, networks of experts, patient registries, mutation registries and biobanks.

For all types of Belgian expert resources, there has been **a global increase in the amount of data collected over the past year** (Figure 1). However, it should be kept in mind that, for a given resource, there may be little, no variation or even a decrease in the total number of data collected, because an update work has been done during the period concerned by the data analysis. Increasing the quantity of collected data improves indeed the value of a database, but at the same time ensuring the quality of all the data listed, by deleting data that is no longer up to date or by modifying data already registered, is essential to maintain a relevant database. We therefore set up **regular update cycles** in order to check that the information is still sufficiently precise, complete and up to date, as well as to identify all kinds of possible errors such as the presence of duplicates.

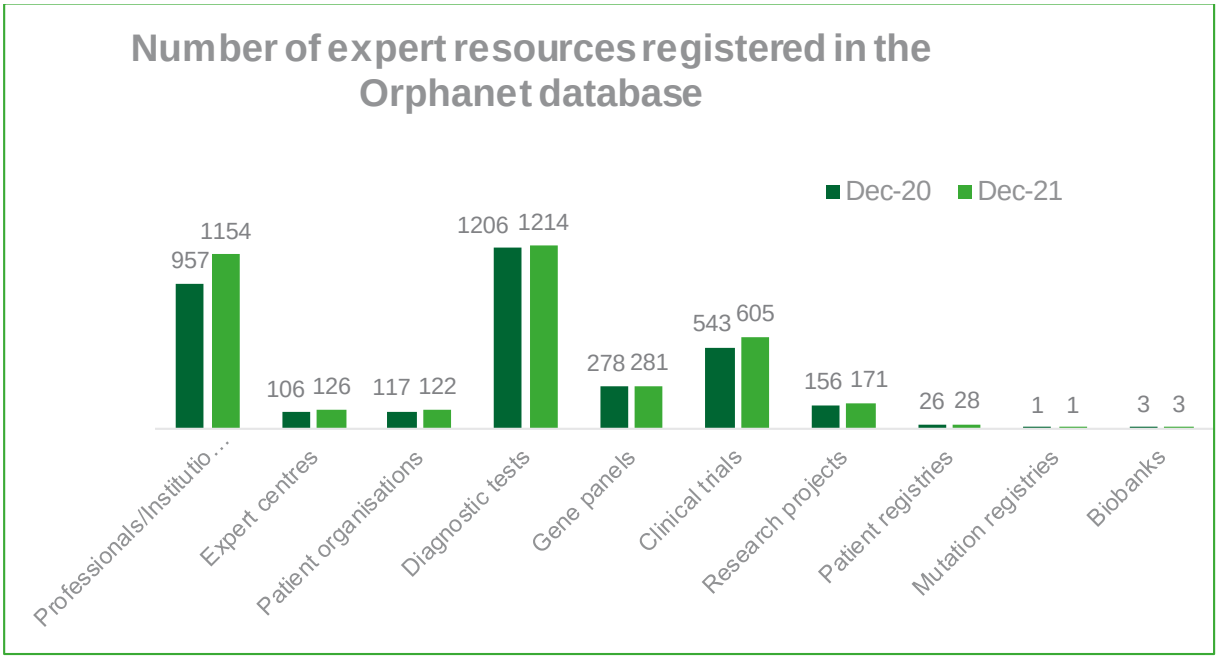

Figure 1. Evolution of the number of Belgian expert resources registered in the Orphanet database between December 2020 and December 2021.

1.2. OVERVIEW OF SOME QUALITY TASKS

1.2.1. IMPROVEMENT OF THE COMPLETENESS AND QUALITY OF THE DATABASE

In 2021, all the quality tasks assigned by the Orphanet coordinating team to the Belgian Information Scientist (IS) were carried out within the given deadlines. To ensure the accuracy of the database, various actions are regularly implemented:

- **Processing of spontaneous requests to create or update the information collected.** This kind of requests can be provided at any time by the professionals, whether by phone, email or via our online registration tool (Collector). Their follow-up is ensured by the national team. With regard to the data passing through Collector, the proper implementation of these requests by the IS is monitored and validated by the Orphanet coordinating team;

- **Proactive searches for information in order to compare it to that of the database.** To this end, official/legitimate sources of information are regularly consulted (scientific publications, the websites of patient organizations or medical laboratories, the BELAC website for accreditations, the EQAs providers websites, the Clinical trials.gov and the European Clinical Trials Database (EudraCT), the database of clinical trials managed by the Federal Agency for Medicines and Health products, the INVENT database, the Belgian official journal, etc.);

- **Carrying out the quality control actions and specific projects included in the "Quality Assurance Reviews (QAR)".** These documents are provided by the Orphanet coordinating team on a regular basis (usually every three months) in order to continually enrich the database and keep it relevant and up-to-date;

- **Carrying out a series of recurrent queries put in place in the frame of the post-release quality control.** Communications about QC tasks can also be made by emails or via OrphaNetWork. Information is sent by the coordinating team to the national ISs describing the aim of the task, the instructions, the deadline and an Excel file with data concerned. In 2021, these tasks concerned for example the diagnostic tests not flagged with the specialty "Molecular genetics" but linked to at least one gene, the research projects, clinical trials, registries and biobanks registered in the database with an online status but whose end date has passed,...;

- **Carrying out a series of recurrent queries according to the evolution of the classification of rare diseases.** The review of the nomenclature and classification of rare diseases is a continuous work. The nomenclature and classification are produced and updated by collaborators of the Orphanet coordinating team with a scientific and/or medical background. They monitor the international scientific literature, consult experts of ERNs,… and perform internal quality control in order to detect and correct inconsistencies in the nomenclature and classifications (such as missing entities identified while gathering information for another request; entities with an incorrect classification level; discrepant representation of a group of disorders between the different classification groups it is included in; inconsistent nomenclature between similar entities, or categories that are empty or no longer in use, among other cases). Decisions proposed by the Orphanet nomenclature managers are discussed and validated during meetings held on a monthly basis with the Orphanet Medical and Scientific Committee, which gathers medical doctors and collaborators of the coordinating team. Those “disease meeting reports” are published on OrphaNetwork and accessible to the national Information Scientists who are in charge of putting in place the necessary corrective information concerning the data of their country. Changes to the database are therefore regularly made to update data related to diseases now classified as obsolete, deprecated or non-rare.

1.2.2. REGISTRATION AND UPDATE OF EXPERT CENTRES

The possibility to register an expert centre on Orphanet depends on the specific situation in the different countries. In Belgium, eligibility criteria are appraised by the Orphanet Belgium management board. The country-specific inclusion criteria taken into account during the selection process are indicated in a document published on the Orphanet Belgium website[8], in order to be transparent on how the data selection is carried out. **Our objective is that 100% of the rare disease centres which meet the criteria established by the Belgian management board are listed in Orphanet.** However, it should be kept in mind that registration in Orphanet is not compulsory for the centres (no legislative framework). The persons in charge of the activity therefore have the possibility of refusing their registration, for lack of time to devote to the validation of their data or for lack of interest.

Two categories of Belgian expert centres are authorized to be registered in Orphanet, as agreed by the Orphanet Belgium Management board. A clear visual distinction between these two categories is well established on the Orphanet website thanks to the use of specific flags (logos):

1) <u>THE OFFICIALLY-DESIGNATED CENTRES</u>

These centres are considered as validated data and are registered in the Orphanet database with the "officially-designated centre of expertise" flag .

These centres include:

- the centres that work under a convention with the National Institute for Health and Disability Insurance (NIHDI) with a specific focus on rare diseases (neuromuscular diseases, cystic fibrosis, hemophilia, hereditary metabolic diseases, pediatric nephrology, refractory epilepsy and spina bifida);
- the genetic centres officially recognized by the regional authorities for their diagnostic and counselling activities;
- the hospitals recognized by the regional health authorities to have a "rare diseases function".

In 2019, a consultation of the NIHDI website was carried out by the Belgian IS, in order to determine which centres working under a convention with the NIHDI were not yet listed on Orphanet. All the missing officially designated reference centres were created on Orphanet. Once the information on expert centres was made accessible on the Orphanet website, the IS informed the involved professionals that the activity had been published and asked them for a final validation. **Regular post-release quality controls of all Belgian expert centres already registered are conducted to ensure data is still up-to-date, accurate and comprehensive.**

2) <u>THE CENTRES PARTICIPATING IN A EUROPEAN REFERENCE NETWORK (ERN)</u>

These centres appear on the Orphanet website with the "member of a ERN" flag but not with the "officially-designated centre of expertise" flag.

Some centres may belong to both categories. In this case, they are represented by the two flags.

ERNs are virtual networks that bring together reference centres from across the European Union. In a given country, individuals suffering from a rare disease may struggle to obtain an accurate diagnosis or appropriate treatment. Indeed, no country alone has the capacity to treat all rare, low-prevalence and complex diseases. ERNs offer patients and clinicians from across Europe access to the best expertise, knowledge and resources, without having to travel to another country. The ERNs receive support from several EU funding programmes. The creation of 24 ERNs covering the major rare disease groups was approved in December 2016 and launched in March 2017 (call 1). Since 2019, the Belgian expert centres participating in an ERN are allowed to be registered on Orphanet.

A list of the ERNs and the Health Care Providers in each participating country can be consulted on the Orphanet international portal[9]. A list of the centres participating in the ERNs in a given country is also available, through a search tool, on the European Commission website[10].

Particular attention was paid to the registration of centres participating in an ERN, in order to offer increased visibility at national and international level to Belgian centres that have acquired recognized expertise in certain rare diseases. Special attention is given to the **links to be established with (groups of) diseases for which the centres have a recognized expertise within the ERN.** A relevant choice of ORPHAcodes must be performed, in order to best reflect the particular area of expertise of the centre while respecting the following Orphanet rules when we link an activity (i.e. an expert centre, a patient organization,…) to a list of diseases: A) the fact that "mother diseases" (group head of several diseases) are linked to "daughter diseases" (sub-types) in the classification; B) if we associate an activity with a "mother disease", the activity will appear as associated with <u>all</u> its "daughter diseases" on the Orphanet website; C) we cannot at the same time establish a link with a group head and a disease under this group head. For ERN-centres, this step requires a thorough consultation of the ERNs websites but unfortunately, for some ERNs, the information currently available on the specific disease coverage of each healthcare provider is not sufficiently detailed (or even absent). Moreover, when present, the data on the ERNs sites rarely provides information on ORPHAcodes covered by the centre but rather on large groups of disorders ("Main Thematic Groups"). When available, the information is carefully analysed in order to assign the centres the ORPHAcodes that most accurately reflect their own recognized area of expertise. The detailed Orphanet classification is sent to the experts in the form of an Excel file in order to determine with them, with as much precision as possible, the rare diseases (ORPHAcodes) for which their participation in the ERNs has been validated.

<u>Remark 1:</u> It should be noted that in some cases, the identification of the specific areas of expertise of the centres (allocation of ORPHAcodes) was based mainly on a self-declaration by the professional due to the lack of detailed information on the ERN websites and that, ***in all cases, the identification of the specific expertise of the national centres belonging to an ERN is not validated by any designation committee in Belgium****.*

*<u>Remark 2:</u> A document with detailed information on the specific expertise of each centre is available on the EC website (*https://ec.europa.eu/health/ern/consultations/2019_call_membership_en *in the following section: "The scope, criteria and thresholds of the diseases covered by each of the 24 ERNs"). However, this Excel file appears to be under construction (missing or incomplete data). A revision of the Belgian ERNs-centres will be considered on the basis of this document, once it is finalized.*

The registration of the Belgian centres, their characteristics and the rare diseases groups for which they participate has started in mid-2019. **<u>97% of Belgian centres that joined an ERN following the first call for membership were registered in Orphanet at the end of 2021</u>** (Table 1). This number has increased sharply since last year (it was 70% at the end of 2020). This is explained by the fact that we have had confirmation that, since Orphanet/Inserm is recognized as an institution of public interest, we don't need to receive the professionals' consent prior to registration. However we must inform them of the registration and explain their rights related to the General Data Protection Regulation (GDPR). We therefore decided to register the missing centres, as long as enough information is available on the ERN sites. The few centres still missing are because we have not yet been able to reach an agreement on the diseases to be associated with these centres and/or because the information concerning the contact persons/data has not been communicated to us.

The development of a document describing the situation of Belgian centres in terms of rare disease management, with analysis of various indicators such as disease coverage, is planned. Its elaboration will depend on the progress of the registration of centres in Orphanet, a sufficient number being of course necessary to have a reliable estimate of the situation. This document will give a general overview of the current management of rare diseases in Belgium and could in particular allow to identify groups of rare diseases for which the offer of care is still insufficient or too fragmented geographically.

NAME OF THE NETWORK	NAME OF THE BELGIAN HOSPITAL (results of the 2016 call for membership) (registered in Orphanet: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE WITHIN THE ERN (source: the ERN websites)	REGISTRATION STATUS IN ORPHANET AT THE END OF 2021
VASCERN: European Reference Network on Rare Multisystemic Vascular Diseases	Cliniques universitaires Saint-Luc: Y	Vascular anomalies	5/5 centres are registered.
	UZ Gent: Y	Hereditable Thoracic Aortic Diseases Medium Sized Arteries	
	AZ Sint-Maarten: Y	Pediatric and Primary Lymphedema	
	UZ Antwerpen: Y	Hereditable Thoracic Aortic Diseases Medium Sized Arteries	
	UZ Leuven: Y	Pediatric and Primary Lymphedema	
ENDO-ERN: European Reference Network on Rare Endocrine Conditions	CUB – Hôpital Erasme-HUDERF: Y (Pediatric and adult units are registered separately in Orphanet)	Adrenal Disorders of Calcium & Phosphate Homeostasis Growth & Genetic Obesity Syndromes Pituitary Sex Development & Maturation Thyroid	6/6 centres are registered.
	Cliniques universitaires Saint-Luc: Y (Pediatric and adult units are registered separately in Orphanet)	Pediatric unit: Genetic Disorders of Glucose & Insulin Homeostasis Growth & Genetic Obesity Syndromes Sex Development & Maturation Adult unit: Adrenal Genetic Endocrine Tumour Syndromes Growth & Genetic Obesity Syndromes Pituitary Sex Development & Maturation Thyroid	
	UZ Brussel: Y (Pediatric and adult units are registered separately in Orphanet)	A modification of the recognized expertise took place during 2021 (from 2 to 8 specialized areas): Pediatric unit: Adrenal Disorders of Calcium & Phosphate Homeostasis Genetic Disorders of Glucose & Insulin Homeostasis Genetic Endocrine Tumour Syndromes Growth & Genetic Obesity Syndromes Sex Development & Maturation Thyroid Adult unit: Adrenal Disorders of Calcium & Phosphate Homeostasis Genetic Disorders of Glucose & Insulin Homeostasis Genetic Endocrine Tumour Syndromes Growth & Genetic Obesity Syndromes Pituitary Thyroid	
	UZ Gent: Y (Thematic centres are registered separately in Orphanet: "Disorders of sex development centre [DSD team]" and "Centre for rare bone, calcium and phosphate disorders")	Disorders of Calcium & Phosphate Homeostasis Genetic Endocrine Tumour Syndromes Sex Development & Maturation	
	UZ Leuven: Y	Genetic Disorders of Glucose & Insulin Homeostasis	
	CHU de Liège: Y	Genetic Endocrine Tumour Syndromes Pituitary	
ERN-LUNG: European Reference Network on respiratory diseases	UZ Antwerpen: Y	Mesothelioma	3/3 centres are registered.
	UZ Leuven: Y (Thematic centres are registered separately in Orphanet: "Centre for cystic fibrosis" and "Centre for pulmonary hypertension ")	Interstitial Lung Diseases Cystic fibrosis Pulmonary Hypertension Primary Ciliary Dyskinesia Non-CF Bronchiectasis Chronic Lung Allograft Dysfunction	
	CUB– Hôpital Erasme: Y	Interstitial Lung Diseases Pulmonary Hypertension Non-CF Bronchiectasis	
EuroBloodNet: European Reference Network on Rare Hematological Diseases	CUB– Hôpital Erasme: Y	Myeloid malignancies Red blood cell defects	5/5 centres are registered.
	Institut Jules Bordet: Y	Lymphoid malignancies	
	UZ Leuven: Y (Pediatric and adult units of the Haemophilia centre are registered separately in Orphanet)	Bleeding - Coagulation disorders	
	CHU de Liège: Y	Myeloid malignancies Red blood cell defects	
	Cliniques universitaires Saint-Luc: Y (Pediatric and adult units of the Haemophilia centre are registered separately in Orphanet)	Bleeding - Coagulation disorders	

NAME OF THE NETWORK	NAME OF THE BELGIAN HOSPITAL (results of the 2016 call for membership) (registered in Orphanet: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE WITHIN THE ERN (source: the ERN websites)	REGISTRATION STATUS IN ORPHANET AT THE END OF 2021
EURO-NMD: European Reference Network for Rare Neuromuscular Diseases	CUB – Hôpital Erasme-HUDERF: Y	Muscle diseases Peripheral Nerve Disease Motor Neuron Disease Neuromuscular Junction Defects Mitochondrial Diseases	5/5 centres are registered.
	UZ Gent: Y (Pediatric and adult units are registered separately in Orphanet)	Muscle diseases Peripheral Nerve Disease Motor Neuron Disease Neuromuscular Junction Defects Mitochondrial Diseases	
	Cliniques universitaires Saint-Luc: Y	Muscle diseases Peripheral Nerve Disease Motor Neuron Disease Neuromuscular Junction Defects Mitochondrial Diseases	
	UZ Leuven: Y (Pediatric and adult units are registered separately in Orphanet)	Muscle diseases Peripheral Nerve Disease Motor Neuron Disease Neuromuscular Junction Defects Mitochondrial Diseases	
	UZ Antwerpen: Y (Pediatric and adult units are registered separately in Orphanet)	The information was made available during the year 2021 : Muscle diseases Peripheral Nerve Disease Motor Neuron Disease Neuromuscular Junction Defects Mitochondrial Diseases	
ITHACA: European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability	UZ Antwerpen: Y	Not available	3/3 centres are registered.
	CUB– Hôpital Erasme: Y	All syndromes exhibiting developmental anomalies and/or intellectual disability	
	UZ Leuven: Y	All syndromes exhibiting developmental anomalies and/or intellectual disability	
ERN-SKIN: European Reference Network on Rare and Undiagnosed Skin Disorders	UZ Gent: Y	Cutis laxa Pseudoxanthoma elasticum Ehlers-Danlos syndrome Buschke-Ollendorf syndrome	3/3 centres are registered.
	CUB– Hôpital Erasme: Y	Hidradenitis suppurativa & related syndromes (PASS, SAPHO, PAPA, PAPASH, PASH)	
	UZ Leuven : Y	Inherited epidermolysis bullosa	
ERN-RND: European Reference Network on Rare Neurological Diseases	CUB– Hôpital Erasme: Y	Cerebellar ataxia and hereditary spastic paraplegias	2/2 centres are registered.
	UZ Leuven: Y (Thematic centres are registered separately in Orphanet: "NMRC adult section, "Huntington clinic", "FrontoTemporal Lobar Degeneration clinic", "Parkinson Plus clinic"")	Cerebellar ataxia and hereditary spastic paraplegias Choreas and Huntington's disease Frontotemporal dementia Atypical parkinsonian syndromes	
EURACAN: European Reference Network on Rare Adult Cancers (solid tumors)	UZ Antwerpen: Y	Thymoma & thymic carcinoma	3/4 centres are registered. **1/4 centre is missing: UZ Leuven.**
	Institut Jules Bordet: Y	Sarcoma Endocrine cancers Rare thoracic cancers	
	UZ Leuven: N	Sarcoma Rare gynecological cancers Rare GU cancers Neurendocrine tumors Rare digestive tract tumors Endocrine cancers Rare thoracic cancers Rare skin cancers and eye melanoma Rare brain cancers	
	CHU de Liège: Y	Rare gynecological cancers	
ERN-PaedCAN: European Reference Network for Paediatric Cancer (haemato-oncology)	UZ Gent: Y	Not available	3/3 centres are registered.
	HUDERF: Y	Not available	
	UZ Leuven: Y	Not available	
ERN BOND: European Reference Network on Rare Bone Disorders	UZ Gent: Y	Not available	2/2 centres are registered.
	UZ Antwerpen: Y	Not available	
MetabERN: European Reference Network for Rare Hereditary Metabolic Disorders	CHU de Liège: Y	Inbors errors of metabolism Amino and organic acids-related disorders Lysosomal storage disorders	6/6 centres are registered.
	Cliniques universitaires Saint-Luc: Y	Inbors errors of metabolism Amino-acids and urea cycle disorders Inbors errors of metabolism with neurological involvement Fatty acid oxydation defects Galactosemia Inborn errors of purines and pyrimidines metabolism	
	UZ Gent: Y	Inbors errors of metabolism (reference to the 183 inborn errors of metabolism listed in the agreement with the Belgian health Insurance) Lysosomal and peroxisomal disorders Amino and organic acid related disorders	
	UZ Antwerpen: Y	Inbors errors of metabolism Lysosomal storage disorders	
	UZ Leuven: Y	Inbors errors of metabolism Congenital disorders of glycosylation	
	UZ Brussel: Y	Inbors errors of metabolism Growth, micronutrients deficiency Phosphocalcium metabolism Amino and organic acid related disorders Mitochondrial diseases Lysosomal disorders	

NAME OF THE NETWORK	NAME OF THE BELGIAN HOSPITAL (results of the 2016 call for membership) (registered in Orphanet: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE WITHIN THE ERN (source: the ERN websites)	REGISTRATION STATUS IN ORPHANET AT THE END OF 2021
GUARD-HEART : Gateway to Uncommon And Rare Diseases of the HEART	UZ Brussel: Y	Rare and complex heart diseases	2/2 centres are registered.
	UZ Leuven: Y	Rare and complex heart diseases (congenital cardiac arrhythmias and cardiomyopathies)	
ERN-EYE: European Reference Network on Rare Eye Diseases	UZ Gent: Y	Retinal rare eye diseases Pediatric ophtalmologic rare diseases	1/1 centre is registered.
eUROGEN: European Reference Network on urogenital diseases and conditions	CHU de Liège: N	Complicated and complex pelvic floor disorders	2/3 centres are registered. **1/3 centre is missing: CHU Liège**
	UZ Gent: Y	Posterior hypospadias Urorectal/anorectal malformations Bladder exstrophy/epispadias Rare urological stone and kidney diseases Non-syndromic urogenital tract malformation Posterior urethral valve Rare and complex urinary stone disease Complicated and complex pelvic floor disorders Rare diseases/conditions affecting the female urethra Rare retroperitoneal diseases/conditions Reconstruction of non syndromical urogenital malformations Urethral reconstruction in rare diseases/conditions Adrenal tumours/Abdominopelvic sarcoma Testicular cancer	
	UZ Leuven: Y	Posterior hypospadias Urorectal/anorectal malformations Bladder exstrophy/epispadias Complex genital reconstructions Rare urological stone and kidney diseases Non-syndromic urogenital tract malformation Posterior urethral valve Complicated and complex pelvic floor disorder Rare diseases/conditions affecting the female urethra Urethral reconstruction in rare diseases/conditions Rare retroperitoneal diseases/conditions Penile cancer Testicular cancer Adrenal tumours/abdominopelvic sarcoma	
ERN GENTURIS: European Reference Network on GENetic TUmour RIsk Syndromes	UZ Gent: Y	Lynch and polyposis Hereditary breast and ovarian cancer Other	3/3 centres are registered.
	UZ Leuven: Y	Neurofibromatosis Lynch and polyposis Hereditary breast and ovarian cancer Other	
	CHU de Liège: Y	Neurofibromatosis Hereditary breast and ovarian cancer	
RARE-LIVER: European Reference Network on Rare Hepatological Diseases	Cliniques universitaires Saint-Luc: Y	The information was made available during the year 2021 : Autoimmune Hepatitis (AIH) Primary Sclerosing Cholangitis (PSC) IgG4 Disease Genetic Cholestatic Disease Alagille Syndrome Dubin-Johnson syndrome Rotor syndrome Progressive familial intrahepatic cholestasis (PFIC) Biliary Atresia Choledochal Cyst Alpha-1-Antitrypsin Deficiency (A1ATD) Wilson Disease Hemochromatosis	3/3 centres are registered.
	UZ Leuven: Y	The information was made available during the year 2021 : Primary Biliary Cholangitis (PBC) Autoimmune Hepatitis (AIH) Primary Sclerosing Cholangitis (PSC) IgG4 Disease Genetic Cholestatic Disease Biliary Atresia Choledochal Cyst Alpha-1-Antitrypsin Deficiency (A1ATD) Wilson Disease (Poly-) Cystic Liver Disease/ congenital fibrosis Vascular Liver Disease Intrahepatic Cholangiocarcinoma (iCCA)	
	UZ Gent: Y	Auto-immune hepatitis / PBC/ PSC/ IgG4-related disease Vascular liver diseases Genetic Cholestatic Disease Biliary Atresia Choledochal Cyst Alpha-1-Antitrypsin Deficiency (A1ATD) Wilson Disease Cystic Liver Disease Intrahepatic Cholangiocarcinoma (iCCA) Liver transplantation (children and adults) Transition clinic for adolescents and young adults with chronic liver disease / post liver transplantation	
ReCONNET: Rare Connective Tissue and Musculoskeletal Diseases Network	Cliniques universitaires Saint-Luc: Y	Not available	2/2 centres are registered.
	UZ Gent: Y	Systemic sclerosis	

NAME OF THE NETWORK	NAME OF THE BELGIAN HOSPITAL (results of the 2016 call for membership) (registered in Orphanet: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE WITHIN THE ERN (source: the ERN websites)	REGISTRATION STATUS IN ORPHANET AT THE END OF 2021
ERKNet: European Rare Kidney Diseases Reference Network	Cliniques universitaire Saint-Luc: Y (pediatric unit and adult unit)	**Pediatric unit: not available** Adult unit: Hereditary glomerulopathies Immune glomerulopathies Tubulopathies Metabolic & stone disorders Thrombotic microangiopathies AD structural kidney disorders Congenital Malformations & Ciliopathies	2/2 centres are registered. **However, the registration of the adult unit of UZ Leuven centre has yet to be finalized.**
	UZ Leuven: **Y for the pediatric unit;** **N for the adult unit**	Pediatric unit: Hereditary glomerulopathies Immune glomerulopathies Tubulopathies Metabolic & stone disorders Thrombotic microangiopathies AD structural kidney disorders Congenital Malformations & Ciliopathies Pediatric CKD & dialysis Pediatric kidney transplantation Adult unit: Hereditary glomerulopathies Immune glomerulopathies Tubulopathies Thrombotic microangiopathies AD structural kidney disorders Congenital Malformations & Ciliopathies	
EpiCARE: European Reference Network on Rare and Complex Epilepsies	UZ Leuven: Y	Not available	1/1 centre is registered.
RITA: Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network	UZ Leuven: Y	Primary Immunodeficiencies Autoinflammatory disorders Autoimmune diseases Paediatric Rheumatic diseases	1/1 centre is registered.
ERNICA: European Reference Network on Rare inherited and congenital anomalies	UZ Leuven: Y	Fetal diagnosis and therapy (including congenital diaphragmatic hernia)	1/1 centre is registered.
ERN TRANSPLANT-CHILD: European Reference Network on Transplantation in Children (incl. HSCT, heart, kidney, liver, intestinal, lung and multiorgan)	Cliniques universitaires Saint-Luc: Y	Pediatric liver transplantation	1/1 centre is registered.
ERN CRANIO: European Reference Network on Rare craniofacial anomalies and ENT disorders	/	/	/
			Total: **65/67 (97,01 %) centres are registered.**

Table 1: Status of registration in the Orphanet database and specific expertise of the Belgian centres participating in one of the 24 existing ERNs for rare or complex diseases (call1, analysis carried out at the end of 2021).

**Note on EURO-NMD and ERN-RND: 1 centre (the NMRC of UZ Leuven) participates in these two ERNs.*

Registration of the new Belgian centres belonging to ERNs (call 2)

Following the first call for applications launched in 2016, the ERNs involved more than 900 highly-specialized healthcare units located in over 300 hospitals in 26 Member States. Over the next 5 years, ERNs have reinforced their capacities to benefit thousands of EU patients suffering from a rare condition. A new call for healthcare providers wanting to join existing ERNs was launched in 2019. On Friday the 26th of November 2021, the European Reference Networks (ERNs) Board of Member States, as given in the Implementing Decision 2014/287/EU Article 10, has approved the application of 620 new members. Among them, **the participation of 28 Belgian centres belonging to 5 university hospitals was approved. These new centres are members of 19 ERNs** (Tables 2 and 3). As a result, Belgium now participates in the 24 existing European reference networks. The registration of these new Belgian centres in Orphanet will take place in the course of 2022, as soon as the necessary information is made available by the ERNs and by the professionals involved.

NAME OF THE ERN	NAME OF THE BELGIAN HOSPITAL (RESULTS OF CALL 2)
CRANIO	Antwerp University Hospital (UZ Antwerpen)
	Ghent University Hospital (UZ Gent)
	Leuven University Hospital (UZ Leuven)
Endo-ERN	Antwerp University Hospital (UZ Antwerpen)
EpiCARE	Brussels Rare and Complex Epilepsies Consortium BRACE (Cliniques Universitaires Saint-Luc and Centre William Lennox, UCLouvain; Hôpital Universitaire Erasme and Hôpital Universitaire des Enfants Reine Fabiola, ULB; Institut de Pathologie et Génétique, Gosselies)
ERKNet	Ghent University Hospital (UZ Gent)
ERN-EYE	Antwerp University Hospital (UZ Antwerpen)
	Leuven University Hospital (UZ Leuven)
ERNICA	Cliniques universitaires Saint-Luc (UCLouvain)
	Ghent University Hospital (UZ Gent)
ERN-LUNG	Cliniques universitaires Saint-Luc (UCLouvain)
	University Hospital Brussels (UZ Brussel)
	Ghent University Hospital (UZ Gent)
ERN-RND	Ghent University Hospital (UZ Gent)
	Antwerp University Hospital (UZ Antwerpen)
EURACAN	Cliniques universitaires Saint-Luc (UCLouvain)
	Ghent University Hospital (UZ Gent)
EuroBloodNet	Antwerp University Hospital (UZ Antwerpen)
eUROGEN	Antwerp University Hospital (UZ Antwerpen)
GENTURIS	University Hospital Brussels (UZ Brussel)
GUARD-HEART	Antwerp University Hospital (UZ Antwerpen)
ITHACA	Cliniques universitaires Saint-Luc (UCLouvain) and IPG
	Ghent University Hospital (UZ Gent)
PaedCan	Cliniques universitaires Saint-Luc (UCLouvain)
RARE-LIVER	Antwerp University Hospital (UZ Antwerpen)
ReCONNET	Leuven University Hospital (UZ Leuven)
RITA	Ghent University Hospital (UZ Gent)
TRANSPLANTCHILD	Ghent University Hospital (UZ Gent, Princess Elisabeth Children's Hospital)

Table 2: New Belgian centres participating in ERNs for rare or complex diseases (results of call 2, by ERN).

NAME OF THE BELGIAN HOSPITAL (RESULTS OF CALL 2)	NAME OF THE ERN
Ghent University Hospital (UZ Gent) (9)	CRANIO
	ERKNet
	ERNICA
	ERN-LUNG
	ERN-RND
	EURACAN
	ITHACA
	RITA
	TRANSPLANTCHILD
Antwerp University Hospital (UZ Antwerpen) (8)	CRANIO
	Endo-ERN
	ERN-EYE
	ERN-RND
	EuroBloodNet
	eUROGEN
	GUARD-HEART
	RARE-LIVER
Leuven University Hospital (UZ Leuven) (3)	CRANIO
	ERN-EYE
	ReCONNET
University Hospital Brussels (UZ Brussel) (2)	ERN-LUNG
	GENTURIS
Cliniques universitaires Saint-Luc (UCLouvain) (6)	EpiCARE
	ERNICA
	ERN-LUNG
	EURACAN
	ITHACA
	PaedCan

Table 3: New Belgian centres participating in ERNs for rare or complex diseases (results of call 2, by hospital).

1.2.3. REGISTRATION AND UPDATE OF DIAGNOSTIC TESTS

For patients affected by a rare disease, obtaining a timely and accurate diagnosis is key in accessing appropriate medical expertise. **Orphanet is the reference database in the framework of the European Commission Expert Group on Rare Diseases (CEGRD) Recommendation on Cross Border Genetic Testing of Rare Diseases in the European Union**[11]. Our database offers, amongst a range of expert resources on rare diseases, a directory of diagnostic tests. Registering the offer of diagnostic tests makes it easy to find the information needed to identify the laboratories involved in performing a specific test. It has also an added-value for the geneticists since this allows to report on the evolution of the techniques. It facilitates cross-border genetic testing, which is particularly interesting in the field of rare diseases. Finally it contributes to the sharing of expertise between professionals and to the possible establishment of collaborations leading to a more efficient use of costly resources.

In 2020, a complete update of the Belgian genetic tests registered in Orphanet was started. This task was accomplished in collaboration with the Belgian Genetic Test Database (BGTD). This database is developed by Sciensano, in close collaboration with the geneticists of the 8 officially-recognized genetic centres. It centralizes comprehensive and relevant information about tests offered in Belgium for the diagnosis of diseases with a genetic basis. There is no obligation to register a genetic testing activity in Orphanet. When a geneticist registers his/her data in the BGTD, he/she is asked to specify whether he/she accepts the publication of the data on Orphanet. If he/she doesn't give his/her agreement, the test can be registered but will not be visible on the Orphanet website intended for the general public. It will only be collected and registered in internal databases for analytical purposes.

By the end of 2021, the data of the 8 genetic centres had been processed and regular data updating activities were continued (new tests to register, deletion of tests no longer carried out, modification of the composition of gene panels, requests for creation of genes not yet registered, change of person in charge of the test,...). When it comes to gene panels, their content changes so often that it is difficult to always be up to date, in order to properly reflect the panels that are in use by laboratories at any given time. We plan to update the centres' panels at regular intervals, at least once a year. However, if a geneticist wishes to modify the data published on Orphanet without having to wait for regular updates, this is of course still possible, by making a request by e-mail to the address 'orphanetbelgium@sciensano.be' or by using our online registration tool[12].

An automated system for transferring information from BGTD to Orphanet following modifications that can be made at any time by the geneticists at the level of BGTD has yet to be set up. The conclusion of agreements and the development of Application Programming Interfaces (APIs) between the BGTD and the Orphanet-Inserm platform should allow regular update transfers of Belgian diagnostic tests to Orphanet in the future. However for the moment, no automatic transfer has been implemented. The communication of information is done manually, on the basis of Excel files updated regularly and shared between the managers of the BGTD and the Orphanet Belgium database.

More than 1,200 tests performed in Belgium laboratories are registered in Orphanet (Table 4).

Specialty	Number of tests registered in Orphanet (dec 2021)
Molecular genetics	894
Biochemical genetics	181
Cytogenetics	54
Bacteriology	30
Immunology	22
Parasitology	12
Virology	11
Other	8
Mycology	1
Pathology	1
	Total: 1214 diagnostic tests

Table 4: Belgian tests registered in the Orphanet database, by specialty (December 2021).

1.2.4. REGISTRATION AND UPDATE OF PATIENT ORGANISATIONS

A revision of the directory of patient associations has been done at the end of 2021. The Orphanet data was crossed with the list of members of RaDiOrg[13] (the Belgian umbrella organization for patients with rare diseases). This work, as well as the consultation of other sources, made it possible to identify 24 associations meeting Orphanet's eligibility criteria. The result of this analysis was sent to RaDiOrg, so that they could carry out similar work. A personalized invitation, with proposed ORPHAcodes to be associated, was sent to each of the missing organizations to offer them registration in Orphanet. The processing of responses began at the end of Q4 2021 and will continue in Q1 2022.

In 2021, **6 Belgian patient organisations were registered in Orphanet**:

- **XLH Belgium** (X-linked hypophosphatemia);
- **Sang pour Sang** (Sickle cell anemia);
- **Overdruksyndroom en Tarlov cysten** (Idiopathic intracranial hypertension; Perineural cyst);
- **Contre Les Affections Inflammatoires Rhumatismales (CLAIR)** (Autosomal systemic lupus erythematosus, Juvenile idiopathic arthritis, Pediatric systemic lupus erythematosus, Rare cutaneous lupus erythematosus, Systemic lupus erythematosus, Scleroderma);
- **Us Too Belgium** (Familial prostate cancer);
- **Cum Cura** (Bone sarcoma, Desmoid tumor, Giant cell tumor of bone, Soft tissue sarcoma, Tenosynovial giant cell tumor).

1 patient organisation was deleted, following its cessation of activity:

- **BOPPI** (« Belgian Organisation for Patients with Primary Immunodeficiences »).

An update of registered patient associations has also been initiated. All associations whose last update dates back more than 2 years (n=94) have been/will be contacted by email (and if necessary, also by phone) to update their data. When possible, the data is always proactively updated on the basis of consultation of the websites, Facebook pages, publications in the Belgian Official Journal and only confirmation of the relevance of published data is requested from the associations. This task will be continued in early 2022.

In order to help patients to use the Orphanet's online registration tool (only available in English) to submit data relating to their associations, **guidelines have been written**, in French and in Dutch.

1.2.5. CONTRIBUTION TO THE ORPHANET NOMENCLATURE AND CLASSIFICATION

In 2021, **one new clinical entity was created in the Orphanet database** thanks to the work of the Orphanet Belgium team: “Acute reversible leukoencephalopathy with increased urinary alpha-ketoglutarate” (also known as ”Acute reversible leukoencephalopathy due to SLC13A3 deficiency”; ORPHA: 615964). It was created in November 2021 in order to properly register the diagnostic test for organic aciduria performed by the UCLouvain laboratory of hereditary metabolic diseases (genetic biochemistry).

For each new disease to be created, the name of the resource at the origin of the request (i.e. the label of the diagnostic test translated in English), the clinical context of the request (clinical diagnostic, pharmacogenetic test, biomarker for the disease, etc.) and a recent scientific publication must be provided by the national IS to the coordinating team.

Requests for the **creation of gene-disease relationships not yet listed** in Orphanet were also submitted. Example: *BRCA1*-Cholangiocarcinoma (ORPHA:70567). This request followed the registration of a Belgian clinical trial in which “a BRCA1 gallbladder cancer” patient was enrolled (NCT03967938). For those new gene-disease associations, a recent scientific publication showing the causal link between the mutated gene and the disease must have been provided by the IS to the coordinating team.

2. Indicators on the Orphanet online registration service activity

Collector is the back-office tool of the online Orphanet registration service[12] (Professor) used by the information scientists, the national validators and the International coordinating team to process the professionals' requests for registering or updating their activities related to rare diseases in Orphanet. This online registration service was launched in the beginning of 2014.

In 2021, 28 forms submitted by Belgian professionals were completely processed. 15 forms concerned new data and 13 were updates to data already registered. This number has fallen sharply compared to the previous year, with Orphanet users seeming to favour communication by emails. This figure needs to be put into perspective. Indeed individual requests usually involve changes in many different related types of data. Moreover, Collector is not the only source available for registration/update requests. As previously said, even if we encourage the use of this registration tool for questions of traceability, many requests are still submitted to the Orphanet Belgium team by emails or phone calls. In this case, the requests are processed but not counted in Collector. However it is always possible to check when the data was updated for the last time following contact with the person responsible for the activity, as shown in the screenshot below (Figure 2). The decrease in the number of forms submitted is probably also explained by the fact that the annual email address verification campaign could not take place in 2021 following the concentration of efforts concerning compliance with the GDPR.

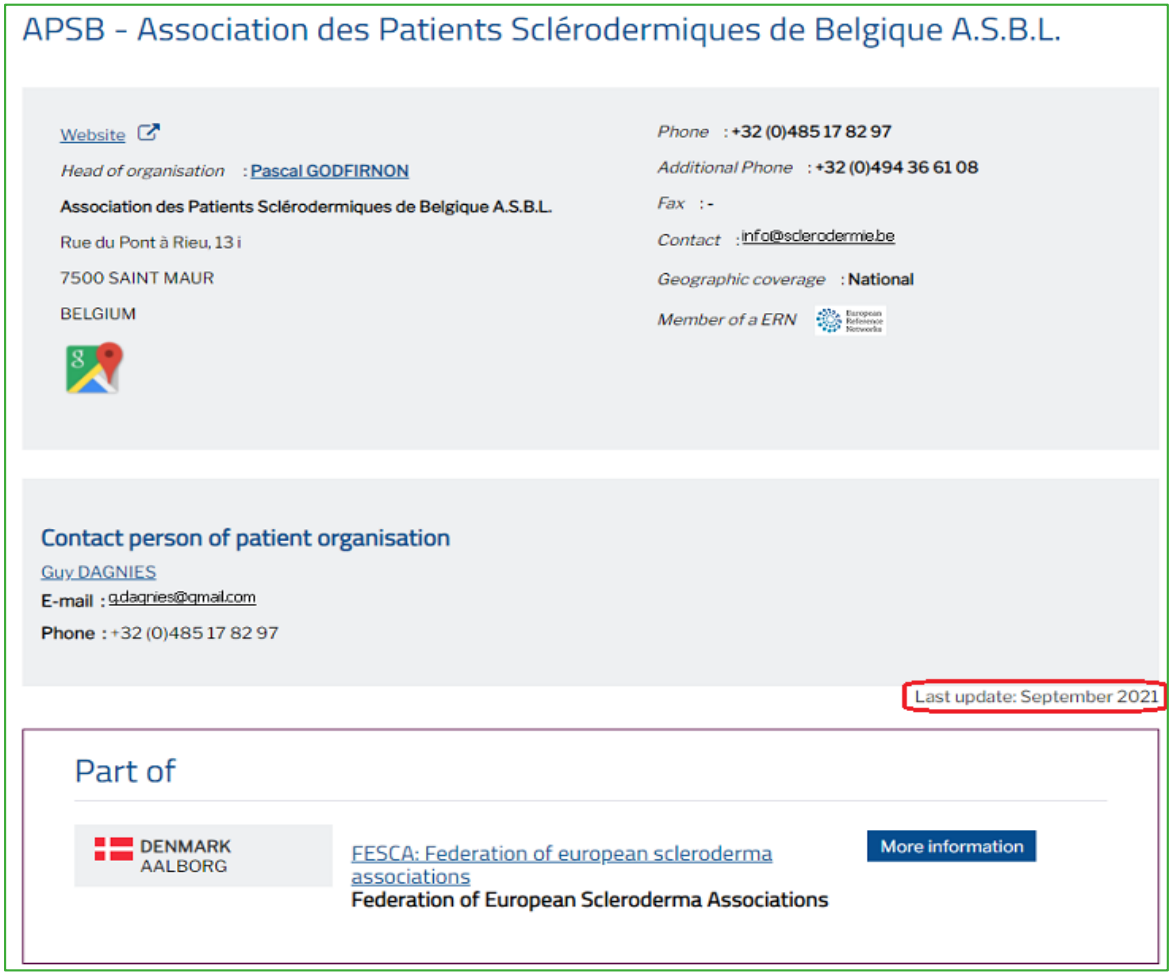

Figure 2 : Screenshot of the Orphanet website: the Orphanet Belgium team updated information about a patient organisation (change of president, additional phone number and flag for participation in an ERN) following email exchanges. The date of the last update is indicated.

3. Other activities

3.1. INFORMATION SCIENTIST TRAINING

As part of the continuous training of Orphanet collaborators, the members of the Orphanet Belgium team participated in various training courses. Following public health measures due to the COVID-19 crisis, the annual training which is usually held in Paris (Orphanet headquarters) could not take place. A distance training course for Information Scientists took place from April to November 2021. 13 sessions of approximatively 2 hours were organized.

The main focus was on:

- **learning how to use the complex Orphanet rare diseases classification**, in order to fully understand how rare disorders are organised into classifications and the consequences of linking resources at different levels of classifications on the way resources are displayed on the website; using **Arbor** tool to explore all the classifications of diseases produced by Orphanet;
- **using the Orphanet tools** (Figure 3) : **Collector** (collection of requests for registration or updates submitted by professionals in **Professor**), **Major** and **Major 2** (international editorial tool to create, update, delete data in the database), **Plator** (allows pre-defined dataset extraction from the database or inject data if rights allow), **Seqtor** (search the links between different entities in the database), **Uploador** (allows to upload a document into the database), **Redminor** (communication tool between the national teams and the coordinating team).

Figure 3 : Orphanet tools overview

Here are some examples of **topics covered by the 2021 IS Orphanet trainings**:

- General presentation of the Orphanet network and portal;
- Nomenclature and classification of rare diseases: What is a rare disease ?; The Orphanet nomenclature and classification: characteristics, purpose and organisation; How to access and use them; How they are updated and maintained; How to search for a disease in the database; How to make a request to the nomenclature team;
- How to link an expert resource to a disease in the database: Understand how expert resources are displayed on the Orphanet website and get familiar with the functional classifications;
- Presentation of the Orphanet tools;
- For each expert resources (expert centres, patient organisations, umbrella organisations/alliances, diagnostic tests, clinical trials, research projects, registries and biobanks): a session specific to each resource on the data collection, data selection, data validation (Pre-release QC), data registration and publication, data post-release quality control, data workflow on each tool;
- For diagnostic tests: an additional session on the registration of gene panels and the registration of external quality assessments and accreditations.

3.2. GDPR TRAINING

In October 2021, the Orphanet coordinating team organised **a training on the regulation in EU law on data protection and privacy** (GDPR). As a European database, Orphanet is required to comply with this regulation. This training focused on two aspects: the legal basis and the tools implemented to keep track of any personal right breach, purge of obsolete personal data and rights exercise.

Moreover, an email was sent in the course of 2021 by the coordinating team to all the professionals registered in the database in order to inform them that they can apply their GPDR rights. According to the GDPR, national teams must respond to each request without undue delay and at the latest within 1 month. **This new legislation requires additional work** since a record of each processing must be kept.

3.3. COMMUNICATION THROUGH EVENTS, MEETINGS AND CONFERENCES

Due to the COVID-19 pandemic, the number of events organized in 2021 to raise awareness about rare diseases and to inform about service activities provided by the Orphanet database and associated tools has been significantly reduced. Most took place in the form of online meetings.

- **PARTICIPATION IN RARE DISEASE DAY 2021**

In Belgium, RaDiOrg[13], the umbrella association for people suffering from a rare disease, is at the origin of the awareness campaign. This year, RaDiOrg organized **a digital media campaign** with two main objectives: raising awareness on rare diseases towards the larger public and stakeholders and raising fund for research in Belgium. The 2021 campaign aimed to make the invisible rare diseases patients visible with the concept of “Not a unicorn”. Contrary to unicorns that everyone knows but that no one has ever seen, 500.000 rare diseases Belgian patients do exist! The campaign was supported by ambassadors and influencers throughout different social media (Facebook, Twitter, LinkedIn, TikTok,…). This campaign was run in February with the highlight on Rare Disease Day. In addition, a national fundraising campaign for research was launched in collaboration with all 8 officially-recognized Belgian medical rare disease centres. The Orphanet Belgium team participated in Rare Disease Day 2021, by disseminating information about the campaign on its national website but also by using promotional material through various channels (use of a logo in their email signature, publication of pictures and messages on the Facebook walls of team members at regular intervals,…).

One of the visuals created for the 2021 campaign highlighting 5 faces of people with rare diseases, each representing different ages and diseases.

The daughter of the Orphanet Belgium database manager supported the 2021 campaign on social media.

- **MEETINGS OF THE ACCOMPANYING COMMITTEE FOR THE FINANCIAL CONTRACT "CONVENTION FOR THE SUPPORT OF STRATEGIC RESEARCH ON RARE DISEASES IN BELGIUM, 2020-2024 (CENTRAL REGISTRY OF RARE DISEASES (CRRD) – BELGIAN GENETIC TESTS DATABASE (BGTD) – ORPHANET BELGIUM"**

The Belgian Orphanet team activities are - together with other rare disease projects - financially supported by the National Institute of Disability and Health Insurance (NIHDI). The financial contract is governed by a multi-stakeholder "Accompanying Committee" in charge of revising the work done and approving new work plans. To this end, **two meetings per year are generally scheduled.**

The first meeting took place on April 28, 2021. Orphanet Belgium team members, as well as other members of the rare disease team at Sciensano, geneticists from officially-designated centres, a representative of patient associations, representatives of the FPS Public Health, Safety of the Food Chain and Environment and representatives of the NIHDI attended. The main objective was to present to our national sponsors the work done in 2020 and to discuss specific topics on which we wanted to obtain the opinion of the Commission. On this occasion, annual activity reports were written concerning the management of the database and the translation activities carried out in 2020. These reports (ENG, FR, NL versions) are accessible on the national website of Orphanet Belgium and on the Sciensano website. A presentation was made concerning the achievements and constraints related to the database managed by Orphanet Belgium. Emphasis was placed on the registration of expert centres belonging to ERNs still missing in the database as well as on the complete revision of the data related to the genetic tests carried out by the genetic centres. The Dutch translation activities were also discussed. The work carried out by our team over the past year has been praised by the Accompanying Committee.

The second meeting was held on October 28, 2021. The main objective was to present and have the 2022 work plan approved. An oral presentation of the planned activities was made on this occasion.

- **PARTICIPATION IN THE EDELWEISS AWARDS CEREMONY**

On November 10, 2021, 170 people gathered at the Palais de l'Afrique in Tervuren for the presentation of the Edelweiss Awards 2021. **Sciensano's rare diseases team, including members of Orphanet Belgium, were among those invited to this important event for people involved in the rare diseases in Belgium.** Edelweiss prizes were awarded to particularly deserving projects and individuals in the field of rare diseases. Public Health Minister Frank Vandenbroucke was present at this ceremony. During this evening, an overview of recent developments and needs relating to the field of rare diseases in Belgium was given. The ceremony was also the opportunity to address the important contributions made within the framework of the rare disease policy in our country.

Eva Schoeters, Director of RaDiOrg-Rare Diseases Belgium and Minister Vandenbroucke

Annabelle Calomme, manager of the Orphanet Belgium database, Katrien Van Der Kelen, manager of the CRRD and Elfriede Swinnen, Orphanet Belgium National Coordinator

3.4. COMMUNICATION THROUGH THE NATIONAL WEBSITE

The Orphanet Belgium team manages a **national website**[14] **available in two languages, French and Dutch**. The Orphanet national website contains information specific to Belgium.

Figure 4: Screenshot of the homepage of the national Orphanet Belgium website.

The following topics are covered:

- **Team/contact:** on this page the contact details of the Orphanet Belgium team can be found;
- **Board:** short description of the Orphanet Belgium board;
- **Partnerships:** the sponsors (FPS Public Health, Sciensano and INAMI/RIZIV) are explicitly mentioned on this page, as well as the cooperation with RaDiOrg;
- **Medicines:** some frequently asked questions about orphan drugs and the specific situation in Belgium are discussed here. There is also an overview of the orphan drugs that are on the market in Belgium. Finally, you can also find the contact details of a hospital pharmacist, M. Marc Dooms (UZ Leuven), who agrees to help people with questions about orphan drugs;
- **Link to the Orphanet online registration tool**, in order to submit a registration form or request an update of activities already registered in the database;
- **National and international news and events:** on the homepage news is shared with the Belgian public. This can include, for example, information about the rare diseases day, call for patients to participate in clinical research, conferences in Belgium and abroad, patient association initiatives etc. **The calendar of events is regularly updated;**
- **General information:** information about Orphanet, rare diseases and orphan drugs (explanations on the activities, organization and financing, latest version of the activity reports, instructional videos on the nomenclature and use of the search tool for a disease or a gene,…) are available on this website, as well as information on the Orphanet quality commitment;
- **Criteria for Belgian Expert Resources:** document mentioning the definitions, sources of information and inclusion/exclusion criteria for expert resources. Documenting inclusion criteria for expert resources in each country is of great relevance for the end-users of Orphanet and professionals to know how data is collected at the country level, as well as the selection criteria used. Therefore a pdf document[8] listing each type of data (expert centres, medical laboratories and diagnostic tests, patient organisations, research projects, clinical trials, registries and biobanks) and our sources of information (i.e. public or private institutions, funding bodies, national umbrella patient organisation, clinical trial databases,...) as well as their inclusion/exclusion criteria can be found in the "Documents" section of our national website. **An updated version of this document was produced in October 2021.**

3.5. ASSISTANCE TO PATIENTS AND PROFESSIONALS

The Orphanet Belgium team regularly receives questions about rare diseases via e-mail ('orphanetbelgium@sciensano.be') **or by phone calls from patients, researchers and healthcare professionals.** The team provides answers to these questions whenever possible, for example by helping to find correct information on a pathology, by referring to an association of patients specific to the pathology (if it exists), by helping in the search for an optimal expertise, or by explaining why a disease cannot be found on the Orphanet portal (definition of the inclusion criteria to be considered a rare disease). When necessary, we refer to the authorized persons (as Orphanet may not answer medical personal queries).

Since RaDiOrg, the umbrella organisation for patient organisations concerning rare diseases in Belgium, acts as "helpline for personal queries", its contact details are available on the Orphanet Belgium website, as well as on the Orphanet portal (Figure 5). RaDiOrg can in particular put in contact people who are suffering of the same pathology, give advice to create a patient association and give visibility to a rare pathology by posting a testimonial on their website.

For a personal query

Orphanet cannot answer personal queries. You should contact a dedicated service.

Country	Organisation	By email	By phone
Australia	The Association of Genetic Support of Australasia: www.agsa-geneticsupport.org.au/	info@agsa-geneticsupport.org.au	+61 2 9211 1462
Austria	Forum Seltene Krankheiten http://www.forum-sk.at/	info@forum-sk.at	+43 (0)512 9003 70532
Belgium	RaDiOrg is the umbrella organisation for patient organisations concerning rare diseases. https://www.radiorg.be/nl/ https://www.radiorg.be/fr/	info@radiorg.be	+32 (0)478 72 77 03 [NL] +32 (0)473 54 18 66 [FR]
Bulgaria	ICRDOD (Information Center for Rare Diseases and Orphan Drugs): www.raredis.org	info@raredis.org	+359 (0)32 57 57 97
Canada	CORD (Canadian Organization for Rare Disorders): www.raredisorders.ca	info@raredisorders.ca	+1-877 302 7273 (English speakers)

Figure 5 : Screenshot of the Orphanet website: RaDiOrg is listed as the Belgian Helpline for personal queries.

When the questions concern **specific information relating to the nomenclature and classification of rare diseases** (for example, request to create a rare disease not yet listed in Orphanet), these are communicated to the members of the coordinating team at Orphanet-Inserm in charge of these aspects. This requires prior scientific research work to support the request (reading and transmission of recent and relevant scientific publications concerning the disease). The main difficulty linked to this objective is the time it takes to obtain a complete answer from Inserm, which is generally quite long (up to several months). This is explained by the fact that this task requires a thorough review of the literature and the consultation of external experts such as those who collaborate with the ERNs.

The frequency of this type of questions coming from external users and the workload it entails is quite difficult to estimate. Indeed, the frequency is very random and some requests require a short time to be resolved while others involve long-term follow-up and multiple stakeholders. A listing of each request is kept in our files.

CONCLUSION AND PERSPECTIVES

Since its creation in 1997, Orphanet has become a well-established and internationally recognized portal dedicated exclusively to rare diseases and orphan drugs. Orphanet is a tool both for healthcare and for research and is the reference for the nomenclature and classification of rare diseases. Its freely-accessible website contributes to help all audiences access high quality expert-reviewed information, to provide the means to identify rare disease patients in health and research information systems with a stable and unique identifier (ORPHAcode), to guide patients and physicians towards relevant services for an efficient patient care pathway and to generate knowledge by producing massive, computable and reusable scientific data.

The Orphanet multi-stakeholder network, developed thanks to sustained European and national efforts, is **a good example of successful cross-European cooperation**. The consortium, which expanded gradually to 42 countries within Europe and beyond, is coordinated by the Inserm in Paris. Each year additional countries ask to become members of the Orphanet community. National teams are located in each participating country of the network. Belgium is part of it for 20 years. The sustainability of the Orphanet national teams in the long-term is essential to meet the challenges arising from a rapidly evolving political, scientific and informatics landscape.

In 2021, the Orphanet Belgium team performed the fundamental database management tasks, which consist in the registration of new data and the regular update of existing data for all types of expert resources listed in Orphanet (expert centres, patient organisations, medical laboratories and diagnostic tests, clinical trials, research projects, registries and biobanks). The day-to-day management of the Orphanet database content is a **continuous task** based on regularly revised standard operating procedures, in order to provide all users with a reliable and up-to-date database on rare diseases.

A particular effort was paid to the registration of expert centres participating in a European Reference Network (ERN). These networks allow the generation and promotion of best practices for rare disease healthcare in Europe, providing data and resources that can contribute to avoid duplicating efforts and making better use of available resources. **97% of the centres that joined an ERN following the first call for membership are now registered**. For centres registered in 2019/2020, an update has sometimes already been necessary in 2021. Following the second call for membership launched in 2019, **Belgium now participates in all 24 existing ERNs**. The participation of 28 new Belgian centres in the ERNs was validated at the end of 2021. At the time of writing this report, the war in Ukraine is raging. In this context, the European Commission must provide information on the location of ERN centres, in order to facilitate access for refugees with rare diseases to the appropriate expertise. It was decided that the centralization of this information will be carried out by Orphanet. This implies that all the national teams will have to **urgently and massively register (or update) the expert centres belonging to an ERN in Orphanet**. This task will therefore be treated as a priority in early 2022, as soon as the minimum dataset will have been identified (healthcare providers, departments in the hospitals, selection of diseases based on the declaration the expert centres made to the EC in order to join the ERNs, coordinator and collaborators in charge of the activity, contact details of the centres,…).

A **complete update of the directory of patient associations is planned for early 2022.** Indeed, following the COVID-19 outbreak, many associations are experiencing difficulties, particularly financial ones, which unfortunately led some of them to cease their activity. Conversely, other organizations have managed to find the time necessary for their creation. This must therefore be implemented at the level of the data registered in Orphanet.

In addition, we will of course **continue to carry out our service tasks**, such as providing assistance to people who contact us regularly via email or phone, as well as the establishment and participation in national awareness-raising and information activities around the Orphanet database and associated tools. The Orphanet Belgium team will, among other things, actively participate in a European project (OD4RD, “Orphanet Data for Rare Diseases”) whose main objective is to **contribute to the generation of data related to rare diseases which are standardized, thanks to the maintenance and implementation of ORPHAcodes at national healthcare providers hosting ERNs or members of an ERN.** This project will notably involve delivering trainings in the two national languages (or in English depending on demand) to people involved in the field of rare diseases in a clinical context (clinicians, coders, people in charge of registries, IT managers,…).

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