ORPHANET BELGIUM DATABASE ACTIVITY REPORT 2020

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

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

March 2021 • Brussels • Belgium

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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 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.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

AZ	Algemeen Ziekenhuis
BE	Belgium
BELAC	Belgian accreditation organisation
BeIMolGen	Belgian Molecular Genetics
BeSHG	Belgian Society for Human Genetics
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
EMRaDi	Euregio Meuse-Rhine Rare Diseases
ERN	European reference network
EU	European Union
EURORDIS	European Organisation for Rare Diseases
FPS	Federal Public Service (FPS) Health, Food Chain Safety and Environment
GDPR	General Data Protection Regulation
HGNC	HUGO Gene Nomenclature Committee, nomenclature committee that approves a unique gene name and symbol for each known human gene
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
OMIM	Online Mendelian Inheritance in Man
ORPHAcode	A unique and stable identifier assigned to each rare disease listed in Orphanet
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 scientific paper recently published by Orphanet in the *European Journal of Human Genetics*[2] confirms that **rare diseases represent a major public health issue**, as the number of people living with a rare disease is estimated at 300 million worldwide. 72% of rare diseases are of genetic origin. About 70% of rare diseases start in childhood and 30% of affected children will not reach the age of 5. Most often, rare diseases are severe, chronic, progressive and significantly affect the quality of life of those affected. Almost 6,200 rare diseases[3] have been clinically defined to date and new pathologies are regularly described by researchers. Specific issues are raised in relation to their rarity. In particular, the field of rare diseases suffers from a deficit of medical and scientific knowledge. For people affected by rare diseases, it is often difficult to find information on these pathologies, which are scarce and disseminated around the world, or to find qualified professionals to ensure their medical care. Moreover, for physicians and researchers, it is essential to benefit from means facilitating collaborations and exchanges 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 in providing high-quality expert-reviewed information on rare diseases and orphan drugs.** 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 eight 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 also maintains the Orphanet rare disease nomenclature (ORPHAcode), essential in improving the visibility of rare diseases in health and research information systems.

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 41 countries**[5], within Europe and across the globe. Belgium was one of the first countries to join the consortium, in 2001.The Orphanet Network's mission is to increase awareness and knowledge on rare disorders and ultimately contribute to improve the diagnosis, care and treatment of patients with rare diseases by making available the Orphanet knowledge base, an organised and dynamic collection of information and data about rare diseases and orphan drugs. 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 report ("Orphanet Belgium activity report 2017-2019"**[6]).

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.

MAIN ACTIVITIES CARRIED OUT IN 2020

1. Belgian contribution to the Orphanet database [September 2019-December 2020]

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 resource (expert centres, patient organisations, medical laboratories and diagnostic tests, clinical trials, research projects, 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 or no variation in the total number of data collected, but 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 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.

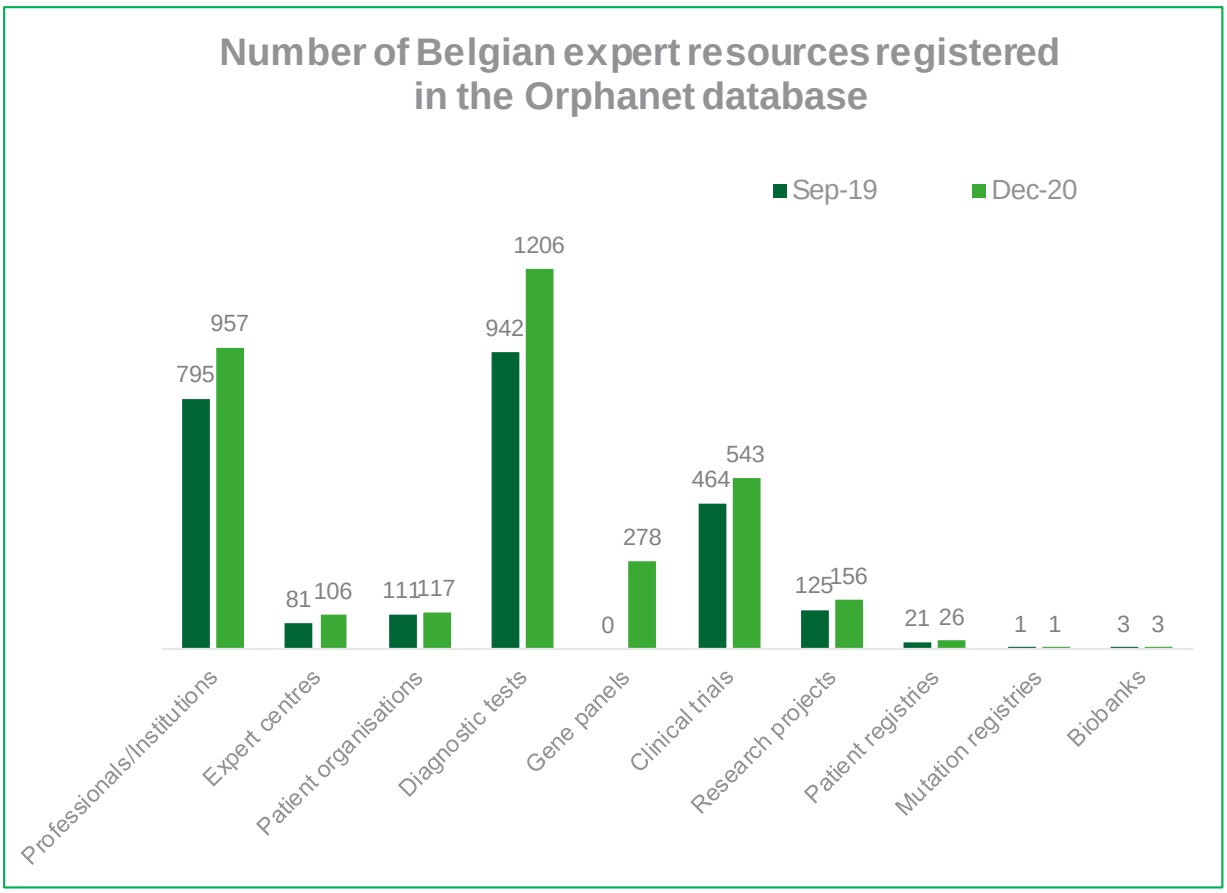


Figure 1. Evolution of the number of Belgian expert resources registered in the Orphanet database between September 2019 and December 2020.

1.2. OVERVIEW OF SOME QUALITY TASKS CONDUCTED BETWEEN OCTOBER 2019 AND DECEMBER 2020

1.2.1. IMPROVEMENT OF THE COMPLETENESS AND QUALITY OF THE ORPHANET DATABASE

In 2020, 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 and unofficial sources of information are regularly consulted by the IS (websites of patient organizations or medical laboratories, BELAC website, Clinical trials.gov, scientific publications, 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 2020, these tasks concerned for example the diagnostic tests not flagged with the specialty "Molecular genetics" but linked to at least one gene, the diagnostic tests linked to at least one gene but not linked to a disease, the research projects registered in the database with an online status but whose end date is exceeded (in this case, they must be tagged as terminated or their end date must be extended according to the reality of each research project),...

- **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 work in progress. The nomenclature and classification are produced and updated by information scientists 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 information scientists 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. There are indeed three main reasons for deleting certain existing entities: 1) Removal by obsolescence: these entities are actually mistakes. They are therefore removed because they should not have been created at the first place, either because they are duplicate of another existing entity, or because they are unclear entities (i.e. not precisely characterized), or because only 1 case is described in the literature (which could be an incidental association of clinical signs). In such a situation, the obsolete ORPHAcode must be referred to an active ORPHAcode; 2) Removal by deprecation: these entities are removed because of evolution of knowledge that results in a representation that is no longer accurate. In other words, the phenotype was initially considered as an independent diagnosis, but is now considered as part of another diagnosis. In such a situation, the deprecated ORPHAcode is moved to the recognized active ORPHAcode; 3) Removal as non-rare in Europe: situation where current epidemiological knowledge is no longer consistent with the European definition of a rare disease. An additional case should be considered: it concerns the case of historical entities. A disease registered in Orphanet is described as "historical" when no new information (clinical, genetic, etc) and/or new cases have been published in the literature in the last 25 years. Those entities are kept in the Orphanet nomenclature and classifications since they are real, clinically well-defined phenotypes (although very old), that can be taken into consideration by clinicians when they need to investigate patients presenting with a seemingly rare, unknown disease sharing similar features. However expert resources cannot be directly linked to a historical entity in the database;

- **Processing of all information provided by professionals following the general annual updates of the resource directory.** Each year, the coordinating team invites by email all professionals registered in the database to update their information published on the Orphanet website. The follow-up of requests is ensured by the national teams. This action also allows to identify any invalid email addresses registered in the Orphanet database that need to be corrected. Indeed, a functional e-mail address is essential to be able to contact the professionals. In 2020, this annual update took place at the end of September. 617 Belgian professionals received an email inviting them to update their data. All requests for modifications received as a result of this action have been taken care of by the Belgian IS. From the graph below (Figure 2), we can notice that the number of invalid email addresses has fallen sharply over the past 3 years, which is a **good indicator of the progress made in terms of Belgian data quality** in Orphanet.

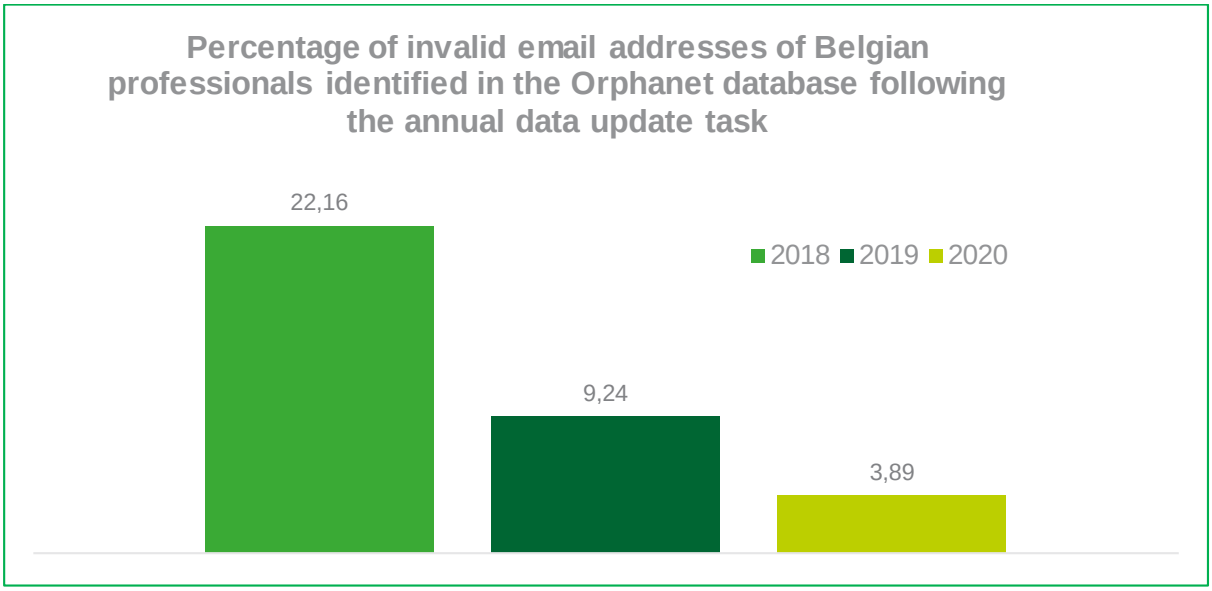


Figure 2. Comparison of the percentage of invalid email addresses of Belgian professionals identified in the Orphanet database following the annual updates performed in 2018, 2019 and 2020.

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.

To assess the quality of the Orphanet database, indicators and objectives are established for each expert resource. A key issue is how to apply the quality indicators to the national level. Indeed the characteristic "coverage" in particular is very country-dependent. **Our objective is that 100% of the rare disease centres which meet the criteria established by the Belgian management board are listed in Orphanet.**

The flowchart below (Figure 3) illustrates the general process for the data collection, registration, validation and quality control of expert centres in Orphanet. Detailed information about the QC process followed for expert centres can be found in published procedures that are available on the Orphanet website[7].

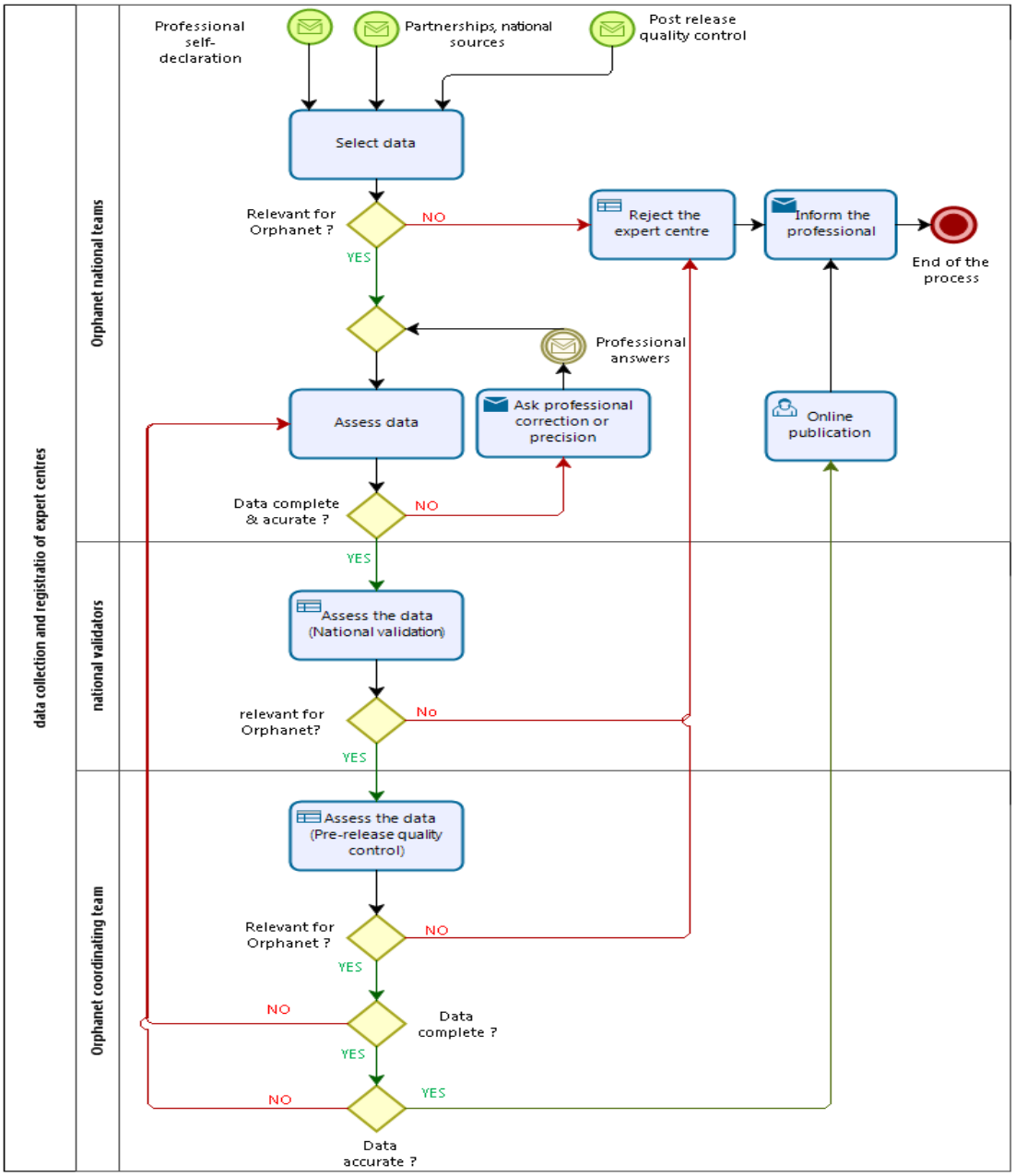


Figure 3: General overview of the Orphanet database workflow for expert centres.

Step 1: Data collection

The process of registration/update of expert centres and networks of expert centres starts with:

- either professionals declaring their activity through the Orphanet online registration service or in any form (e-mail, phone calls, etc.);
- or an exchange of data through a partnership established with a source of data (e.g. in some countries, registration is based on a list of recognized centres which is provided and regularly updated by the national health authorities);
- or a post-release quality control task focused on expert centres or networks of expert centres.

National teams are in charge of identifying the sources of information for expert centres and networks of expert centres in their countries, and are advised to establish partnerships with them to be as exhaustive as possible. **In 2019-2020, invitations to register in Orphanet were sent electronically by the Orphanet Belgium team to all centres that meet the criteria defined by the Belgian management board.**

Step 2: Data selection

The national team starts the data selection by verifying that the expert centre meets the inclusion criteria defined by Orphanet and appraised by the Orphanet Belgium Management Board, according to the national context. The country-specific inclusion criteria taken into account during the selection process are indicated in a document published on the national Orphanet website[8], in order to be transparent on how the data selection is carried out.

An expert centre can offer medical management and/or genetic counselling services. Both options have specific selection criteria in Orphanet.

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:

1) The officially-designated centres

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 are 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.

In 2019-2020, particular attention was paid to the registration of Belgian 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. ERNs are virtual networks that bring together reference centres from across the European Union. They aim to facilitate discussion on rare, low-prevalence and complex diseases that require highly specialized healthcare, with the main objective of sharing the necessary knowledge and resources. The ERNs are co-funded by the European Commission. The creation of 24 ERNs covering the major rare disease groups was launched in March 2017. They involve more than 900 highly-specialized healthcare units from over 300 hospitals in 26 Member States. 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 clinical centres participating in the ERNs in a given country is also available, through a search tool, on the European Commission website[10].

<u>Step 3: Data assessment</u>

If the centre complies with the Orphanet inclusion criteria for expert centres, the national IS analyses the information to check that the mandatory dataset (name of the expert centre in local language and in English; name and address of the institution and of the department/service responsible of the expert centre; name and details (email address and/or phone number) of at least one expert centre coordinator; the disease(s) or group of diseases covered by the expert centre; indication whether the expert centre is officially designated by the national health authorities; indication whether the expert centre is intended for children, adults or both; indication whether the expert centre is a genetic counselling clinic, a medical management clinic or both) is provided and that it is coherent. The website of the expert centre and team members (with a maximum of seven professionals) are registered as an optional dataset. The national IS introduces the necessary corrections before submitting to national and international pre-release quality control. In case of inconsistency or missing information, the IS contacts the professional in order to clarify or obtain the information needed.

Special attention is given to the links to be established with diseases or groups of diseases for which the centres have a recognized expertise in 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 does not provide 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.

Remark 1: It should be noted that in many cases, the identification of the specific areas of expertise of the centres (allocation of ORPHA codes) 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.

Remark 2: In the meantime, a new document related to the 2019 call for membership to the ERNs, with more 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). However, this Excel file appears to be still under construction (missing or incomplete data). A complete revision of the Belgian ERNs-centres will be considered on the basis of this document, once it is finalized.

Step 4: Pre-release national validation

A validation process at the national level is mandatory for expert centres. The Country Coordinator, who is the person responsible for the organization of the Orphanet project at national level, must confirm that the centre selected and assessed by the IS meets the inclusion criteria for registration, paying special attention to the national context and the disease(s) covered by the centre.

Step 5: Pre-release quality control (final validation)

Once the candidate expert centre passed the national validation step, the coordinating team (Inserm) performs a pre-release quality control to assess the relevance and correctness of data collected by the national teams. This quality control is mainly focused on the disease(s) linked and on the coherence of the whole dataset. In case some information is missing or needs correction, the form is sent back to the national teams.

Step 6: Data publication

The information on expert centres is only visible on the Orphanet website once all the quality control steps have been passed and the status of the centre is switched from "stand-by" mode to "online" mode.

The registration of the Belgian centres belonging to ERNs, their characteristics and the rare diseases groups for which they participate has started in mid-2019 and is an ongoing task. 70 % of them were registered in Orphanet at the end of 2020 (see Table 1)**, with the most precise coverage possible for the diseases managed by the centre.**

So far, we have decided not to register centres participating in ERNs that have not responded to our repeated invitations for two main reasons:
1) we need the centres' collaboration to define/validate as precisely as possible the ORPHAcodes that reflect their recognized expertise in the ERN;
2) General Data Protection Regulation (GDPR) issues: we want to obtain the explicit agreement of professionals concerning the publication of their contact data on Orphanet.

In order to increase the registration of centres participating in ERNs in Orphanet, we will put in place additional actions to stimulate the collaboration of the centres in 2021, including sending a new tailored email that will first be submitted to the NIHDI and the FPS (which will be put in copy when sending), in which we will indicate the number of centres belonging to other Belgian hospitals that have already been registered in Orphanet for the ERN concerned.

The European Commission launches calls every 5 years for new members to join the existing ERNs. The last call for membership was made on 30 September 2019. However, due to the COVID-19 outbreak and the consequent public health emergency situations that many healthcare providers face in Europe at the time (including current ERN members who contribute to the evaluation of the applications), a suspension of the examination process has been decided by the Commission for a major part of 2020. As a result, **additional time will be needed to obtain an updated list including the newly approved centres participating in the ERNs following the last call for membership**. As soon as this list is

available, we will establish a schedule in order to plan the registration of the new Belgian members of ERNs in the Orphanet database.

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 in the course of 2021. 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 PARTICIPATING HOSPITAL (REGISTERED IN ORPHANET: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE IN THE ERN (source: the ERN websites)	CONCLUSION
VASCERN: European Reference Network on Rare Multisystemic Vascular Diseases	Cliniques universitaires Saint-Luc: Y	Vascular anomalies	3/5 centres already registered. 2/5 centres still missing.
	UZ Gent: Y	Hereditable Thoracic Aortic Diseases Medium Sized Arteries	
	AZ Sint-Maarten: N	Pediatric and Primary Lymphedema	
	UZ Antwerpen: N	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: N	Adrenal Disorders of Calcium & Phosphate Homeostasis Growth & Genetic Obesity Syndromes Pituitary Sex Development & Maturation Thyroid	5/6 centres already registered. 1/6 centre still missing.
	Cliniques universitaires Saint-Luc: Y	Adrenal Genetic Disorders of Glucose & Insulin Homeostasis Genetic Endocrine Tumour Syndromes Growth & Genetic Obesity Syndromes Pituitary Sex Development & Maturation Thyroid	
	UZ Brussel: Y	Pituitary Sex Development & Maturation	
	UZ Gent: Y	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 already registered. No missing centre.
	UZ Leuven: Y	Interstitial Lung Diseases Cystic fibrosis Pulmonary Hypertension Primary Ciliary Dyskinesia Non-Cystic Fibrosis Bronchiectasis Chronic Lung Allograft Dysfunction	
	CUB– Hôpital Erasme: Y	Interstitial Lung Diseases Pulmonary Hypertension Non-Cystic Fibrosis Bronchiectasis	
EuroBloodNet: European Reference Network on Rare Hematological Diseases	CUB– Hôpital Erasme: Y	Myeloid malignancies Red blood cell defects	3/5 centres already registered. 2/5 centres still missing.
	Institut Jules Bordet: N	Lymphoid malignancies	
	UZ Leuven: Y	Bleeding - Coagulation disorders	
	CHU de Liège: N	Myeloid malignancies Red blood cell defects	
	Cliniques universitaires Saint-Luc: Y	Bleeding - Coagulation disorders	

NAME OF THE NETWORK	NAME OF THE BELGIAN PARTICIPATING HOSPITAL (REGISTERED IN ORPHANET: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE IN THE ERN (source: the ERN websites)	CONCLUSION
EURO-NMD: European Reference Network for Rare Neuromuscular Diseases	CUB– Hôpital Erasme: Y	Muscle diseases Peripheral Nerve Disease Motor Neuron Disease Neuromuscular Junction Defects Mitochondrial Diseases	5/5 centres already registered. No missing centre.
	UZ Gent: Y	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	Muscle diseases Peripheral Nerve Disease Motor Neuron Disease Neuromuscular Junction Defects Mitochondrial Diseases	
	UZ Antwerpen: Y	Not available	
ITHACA: European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability	UZ Antwerpen: Y	Not available	2/3 centres already registered. 1/3 centre still missing.
	CUB– Hôpital Erasme: N	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: N	Cutis laxa Pseudoxanthoma elasticum Ehlers-Danlos syndrome Buschke-Ollendorf syndrome	2/3 centres already registered. 1/3 centre still missing.
	CUB– Hôpital Erasme: Y	Hidradenitis suppurativa & related syndromes	
	UZ Leuven : Y	Inherited epidermolysis bullosa	
ERN-RND: European Reference Network on Rare Neurological Diseases	CUB– Hôpital Erasme: N	Cerebellar ataxia and hereditary spastic paraplegias	1 centre is still missing. For UZ Leuven, 4 centres are registered (FrontoTemporal Lobar Degeneration clinic, Huntington clinic, Parkinson Plus clinic, NMRC*).
	UZ Leuven: Y	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: N	Thymoma & thymic carcinoma	1/4 centre already registered. 3/4 centres still missing.
	Institut Jules Bordet: N	Sarcoma Endocrine cancers Rare thoracic cancers	
	UZ Leuven: N	Sarcoma Rare gynecological cancers Rare genitourinary 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 already registered. No missing centre.
	HUDERF: Y	Not available	
	UZ Leuven: Y	Not available	

NAME OF THE NETWORK	NAME OF THE BELGIAN PARTICIPATING HOSPITAL (REGISTERED IN ORPHANET: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE IN THE ERN (source: the ERN websites)	CONCLUSION
ERN BOND: European Reference Network on Rare Bone Disorders	UZ Gent: Y	Not available	2/2 centres already registered. No missing centre.
	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 already registered. No missing centre.
	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	
GUARD-HEART: Gateway to Uncommon And Rare Diseases of the HEART	UZ Brussel: Y	Rare and complex heart diseases	2/2 centres already registered. No missing centre.
	UZ Leuven: Y	Rare and complex heart diseases (congenital cardiac arrhythmias and cardiomyopathies)	
ERN-EYE: European Reference Network on Rare Eye Diseases	UZ Gent: N	Retinal rare eye diseases Pediatric ophtalmology rare diseases	0/1 centre already registered. 1 centre still missing.

NAME OF THE NETWORK	NAME OF THE BELGIAN PARTICIPATING HOSPITAL (REGISTERED IN ORPHANET: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE IN THE ERN (source: the ERN websites)	CONCLUSION
eUROGEN: European Reference Network on urogenital diseases and conditions	CHU de Liège: N	Complicated and complex pelvic floor disorders	2/3 centres already registered. 1 centre still missing.
	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: N	Lynch and polyposis Hereditary breast and ovarian cancer Other	0/3 centres already registered. 3 centres still missing.
	UZ Leuven: N	Neurofibromatosis Lynch and polyposis Hereditary breast and ovarian cancer Other	
	CHU de Liège: N	Neurofibromatosis Hereditary breast and ovarian cancer	
RARE-LIVER: European Reference Network on Rare Hepatological Diseases	Cliniques universitaires Saint-Luc: Y	Not available	2/3 centres already registered. 1 centre still missing.
	UZ Leuven: Y	Not available	
	UZ Gent: N	Auto-immune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Vascular liver diseases Liver transplantation Chronic liver disease/post liver transplantation in adolescents and young adults	
ReCONNET: Rare Connective Tissue and Musculoskeletal Diseases Network	Cliniques universitaires Saint-Luc: N	Not available	1/2 centre already registered. 1 centre still missing.
	UZ Gent: Y	Systemic sclerosis	

NAME OF THE NETWORK	NAME OF THE BELGIAN PARTICIPATING HOSPITAL (REGISTERED IN ORPHANET: Y(es)/N(o))	PARTICULAR AREA OF EXPERTISE OF THE CENTRE IN THE ERN (source: the ERN websites)	CONCLUSION
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 Autosomal dominant structural kidney disorders Renal malformations Obstructive nephropathies	3/4 centres already registered. 1/4 centre still missing.**
	UZ Leuven: **Y for the pediatric unit;** **N for the adult unit**	**Pediatric unit:** Hereditary glomerulopathies Immune glomerulopathies Tubulopathies Metabolic & stone disorders Thrombotic microangiopathies Autosomal dominant structural kidney disorders Renal malformations Obstructive nephropathies Pediatric chronic kidney disease & dialysis Pediatric kidney transplantation **Adult unit:** Hereditary glomerulopathies Immune glomerulopathies Tubulopathies Thrombotic microangiopathies Autosomal dominant structural kidney disorders Renal malformations Obstructive nephropathies	
EpiCARE: European Reference Network on Rare and Complex Epilepsies	UZ Leuven: Y	Not available	1/1 centre is already registered. No centre is missing.
RITA: Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network	UZ Leuven: N	Primary Immunodeficiencies Autoinflammatory disorders Autoimmune diseases Paediatric Rheumatic diseases	0/1 centre already registered. 1 centre still missing.
ERNICA: European Reference Network on Rare inherited and congenital anomalies	UZ Leuven: N	Fetal therapy (congenital diaphragmatic hernia)	0/1 centre already registered. 1 centre still missing.
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 already registered. No missing centre.
ERN CRANIO: European Reference Network on Rare craniofacial anomalies and ENT disorders	/	/	/
			Total: 50/71 centres already registered. 21 centres still missing.

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 (analysis carried out at the end of 2020).

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

***Note on ERKNet: in Orphanet, we consider 2 centres (a pediatric one and an adult one), even if they are part of the same university hospital, because only the pediatric centres are recognized by the NIHDI. Pediatric and adult rare kidney diseases centres are therefore registered as separate entities flagged differently in the Orphanet database.*

1.2.3. REGISTRATION OF A "RARE DISEASE FUNCTION" FOR 8 BELGIAN HOSPITALS

Since 2014, a "rare disease function" can be attributed to a Belgian hospital. Patients with a rare disease/undiagnosed patients can be referred to such a hospital where expertise for rare diseases is available. This should lead to a diagnosis as soon as possible and the referral of patients towards the care units most able to take charge of their condition. The rare diseases functions are a direct consequence of the Belgian Plan for Rare Diseases[11] (Action 9). The conditions for recognition are defined by a 2014 royal decree[12] and only hospitals with a Centre for Human Genetics can obtain a recognition from regional health authorities for a rare disease function. In Belgium, this function initially concerned 7 university hospitals: "Cliniques universitaires UCL Saint-Luc", "University hospital ULB Erasme", "University hospital CHU Liège", "University hospital UZA", "University hospital UZ Brussel", "University hospital UZ Gent" and "University hospital UZ Leuven".

In 2018, the national board of Orphanet Belgium agreed to publish the 7 Belgian university hospitals on Orphanet, as reference centres for rare diseases. For each of them, a "Multidisciplinary expert team/centre for rare diseases" was created. No specific expert is listed, only the name of the medical coordinator is mandatory. The centres are linked to different large sets of rare diseases representing the head of all the functional classification, so that these centres will appear in the results list of any research of centres for rare diseases carried out on the Orphanet site. Moreover each hospital has been linked to all the ERNs it participates in.

At the end of 2019, the Grand Hôpital de Charleroi (GHdC) and the Institute of Pathology and Genetics (IPG), which have been working together for years, also obtained the "rare disease function" recognition. This eighth rare disease function was registered in Orphanet in the course of 2020.

1.2.4. 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 offers, amongst a range of expert resources on rare diseases, a directory of diagnostic tests to help with this process. Orphanet benefits from a large audience in Europe and around the world, with over 1 million pages viewed each month. Therefore, being published on Orphanet guarantees high visibility for the activities at national and international levels. Registering the offer of diagnostic tests makes it easy to find the information needed to identify the laboratories involved in performing a specific test, for patients and their general practitioner. It has also an added-value for the geneticists themselves since this allows to report on the evolution of the techniques used and in particular to make visible the laboratories that follow the rapid developments of certain techniques such as next generation sequencing (NGS). It also facilitates cross-border genetic testing, which is particularly interesting in the field of rare diseases, due to the differences in national and regional testing offer. 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.

The Belgian diagnostic tests registered in Orphanet had not been updated for many years and most were registered with an incomplete technical procedure, which did not allow to have a good picture of the offer of diagnostic tests in our country. In addition, no gene panel has been recorded to date, which prevented a correct reflection of the rapid evolution of techniques in the field of genetics. This situation was harmful for Orphanet and its users, specially taking into account that Orphanet is mentioned as 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[13].

In 2020, priority was given to the registration and update of diagnostic tests in Orphanet and more working time was allocated to accomplish this task. The timing was indeed opportune since a new database of genetic tests centralizing comprehensive and relevant information about tests offered in Belgium for the diagnosis of diseases with a genetic basis was developed by Sciensano. A collaboration has therefore been established with the Belgian Genetic Test Database (BGTD), in order to prevent geneticists of the 8 officially recognized centres from having to interact both with the manager of the BGTD and with the Orphanet Belgium team, to have their tests created and/or updated on these two platforms. However, it should be understood that this task is not a simple copy and paste of data from one database to another. The tests are analyzed and validated one by one, in order to adapt them to the Orphanet project. The main goal is **to provide standardized and harmonized data to Orphanet users**. This is made possible by ensuring compliance with the procedures established by Orphanet, in which the different rules and inclusion/exclusion criteria are explained. For example, the name of a test in Orphanet must be based on the name of the disease according to the Orphanet classification (and not a synonym or the OMIM name). For each test, we register a name in English and a name in the local language (French or Dutch depending on the laboratory). **Several tools developed by Orphanet-Inserm allowing rigorous data analysis are used**, as for example a tool called Arbor, in order to explore the Orphanet classification of diseases. It helps the IS to make decisions to link an expert resource to the appropriate level in the classifications (i.e. the "granularity", the most precise level with which an expert resource should be linked to a disease in the classification, to be accurately represented). This tool also allows to check the gene-disease relationships and to extract selected classifications in order to submit them to a professional.

The flowchart below (Figure 4) illustrates the general process for the data collection, registration, validation and quality control of diagnostic tests in Orphanet. The information about QC process followed for diagnostic tests can be found in detail in published procedures that are available on the Orphanet website[14]. Diagnostic tests, but also pharmacogenetic tests (i.e. targeted tests for variants associated with pharmaceutical dosage choice or adverse reactions) and tests which provide information on a possible familial predisposition are registered in Orphanet. Tests covering non-rare diseases in the case of the specialty of molecular genetics are also collected, as Orphanet is the reference database for genetic testing in Europe.

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.

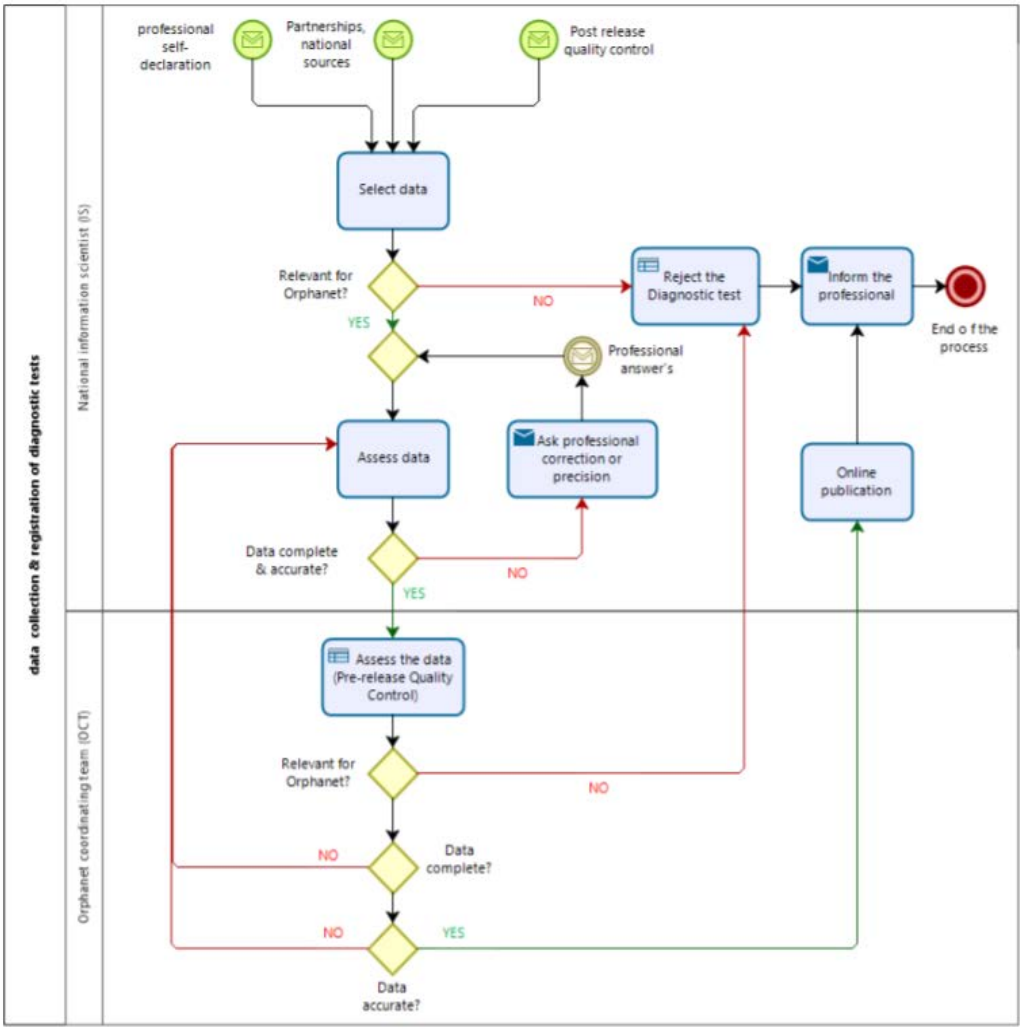


Figure 4: General overview of the Orphanet database workflow for diagnostic tests.

Step 1: Data collection

The process of registering/updating diagnostic tests starts:

- either with data obtained through a partnership. In 2020, the BGTD was used as the main entry point for data thanks to the collaboration established with the geneticists of the eight Belgian Centres of Human Genetics;
- or with professionals declaring their activity through the Orphanet online registration service or in any communication channel established with Orphanet teams (e-mail, phone call, etc.);
- or through a post-release quality control project focused on diagnostic tests.

Step 2: Data selection

The national team must perform a data selection to verify that each diagnostic test meets the inclusion criteria for Orphanet.

Step 3: Data assessment

If the diagnostic test complies with the Orphanet inclusion criteria, the national team analyses the information to check that the mandatory dataset is provided (name of at least one professional responsible for the test, the specific disorder(s) covered by the test, the gene and/or the panel of genes related to the test, the purpose(s) of the test, the technical procedure, etc). If necessary, corrections are made before submitting the data to international pre-publication quality control carried out by Inserm. In case of inconsistency or missing information, the national team will contact the professional in order to clarify or obtain the information needed.

Step 4: Pre-release quality control

Once the candidate diagnostic test passed the national assessment performed by the IS, the coordinating team (Inserm) performs a pre-release quality control to assess the relevance and correctness of data. This quality control is mainly focused on the diseases and genes linked to the test. The coordinating team performs the pre-release quality control as defined in the corresponding procedures. This step aims to ensure that all data are registered homogeneously and with the highest possible quality.

A single file, shared on Google drive by all the national teams, is updated every two weeks and acts as a report for this pre-release quality control step. This preliminary report is submitted to discussion:

- Entries for which no correction is required will be published online by the coordinating team;
- Entries for which corrections are required will be treated and published by the national information scientist once an agreement is found.

Step 5: Data publication

The information on diagnostic tests is only visible on the Orphanet website once all the quality control steps have been passed and the status of the test is switched from “stand-by” mode to “online” mode.

The registration process for diagnostic tests is long and demanding given the number of successive steps and the number of stakeholders involved but it ensures Orphanet users a high-quality of published data. **In 2020, a significant delay has accumulated at Inserm for reasons of limited resources and prioritization of tasks.** Only one person is currently in charge of the final validation of diagnostic tests for the entire Orphanet consortium, which is made up of 41 countries. Accordingly there is a limitation in the number of tests validated by Inserm during each validation cycle: the resources allocated to perform the pre-release QC for diagnostic tests allow the Orphanet coordinating team to assess around 20 tests linked to a panel of genes per week, for all countries of the Orphanet consortium. In Belgium alone, there are currently almost 200 tests awaiting final validation, some of which for several months. It is therefore important to understand that just because a test is not visible on the Orphanet website does not mean that the creation of update work has not started yet.

It is only since 2020 that the Orphanet Belgium team encodes panels of genes using the methods and tools provided by Inserm. By definition, for Orphanet, a panel of genes includes at least 2 genes analyzed together in a single diagnostic test for a particular disease or condition. This means that, in the case of tests where 2 or more genes are analyzed simultaneously, the IS must use a special tool developed for panels in order to register the tests. In Orphanet, we distinguish 2 types of gene panels: commercial or in-house. The main difference between these two types of panels is that the commercial panels can be linked to several tests performed by different laboratories while an in-house panel is linked to one and only one diagnostic test performed by a specific laboratory. Thus, as soon as a commercial panel is customized by modifying certain genes, it will then be considered in-house.

Orphanet-Inserm has developed a special Excel tool with macros to treat the diagnostic tests linked to a panel of genes. This tool is extremely useful because it allows the ISs to:

- define which genes in the panel are registered in the Orphanet database and which are not yet;
- rigorously identify the diseases that should be linked to the diagnostic test, based on the panel content and on the clinical indication of the test provided by the laboratory;
- determine if there are scientifically established gene-disease links that are not yet registered in the Orphanet database. The tool indicates the gene(s) included in the panel that, in Orphanet, do not have an established relationship with at least one of the diseases included in the clinical indication of the test.

Following the registration and update of the tests carried out in the Belgian genetics centres, requests for the creation by the coordinating team of more than 700 genes not yet registered in the Orphanet database were made by the Belgian IS. For each new gene, the approved symbol, the approved name and the HGNC ID must be provided, based on the information available on the "HUGO

Gene Nomenclature Committee at the European Bioinformatics Institute" website, the resource for approved human gene nomenclature[15].

One new rare disease was created in the Orphanet database thanks to the work of the Orphanet Belgium team: "PUM1-associated developmental disability-ataxia-seizure syndrome" (also known as PADDAS syndrome; ORPHA 589515) was created in September 2020 in order to register the diagnostic test for ataxia and spastic paraplegia (gene panel) performed by the UZ Gent genetic centre.

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

Finally, **requests for the creation of 5 gene-disease relationships not yet listed in Orphanet were submitted by the Belgian IS**:

- *VPS13D* - Spinocerebellar ataxia, autosomal recessive 4;
- *RABL3* - Familial pancreatic carcinoma;
- *WTN4* - Mayer-Rokitansky-Küster-Hauser syndrome;
- *CDKN2A* - Pleural mesothelioma;
- *SOLH2* - Primary ovarian failure.

All those requests regarding new gene-disease relationships are still awaiting evaluation from the disease team. In each case, 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.

By the end of 2020, the data from 7 of the 8 genetic centres had already been processed (see Figure 5). At the time of writing this report, 184 genetic tests are still in the pre-publication stage, which means awaiting the final validation by Inserm. Therefore all the updates are not yet published online but most of the work has been done, even if once the green light will be received from the Orphanet coordinating team, time must still be allowed to complete manually the list of genes and diseases related to the tests before the data is put online by the information scientist.

The tests are validated by the coordinating team in chronological order. **At the end of this process, around 1.000 Belgian genetic tests will have been created, updated (for those that were already present in the Orphanet database) and validated before publication in Orphanet. We expect the whole updated dataset to be released by mid-2021 at the latest.** Once all the tests have been published on the Orphanet website, an email will be sent to the professionals of the genetic centre concerned, requesting a final validation of the data. At this time, modifications are of course always possible if the professional deems it necessary (for example, change of the person responsible of the test, modification of the technical procedure, removal of diseases not assessed in this laboratory, test no longer performed etc.).

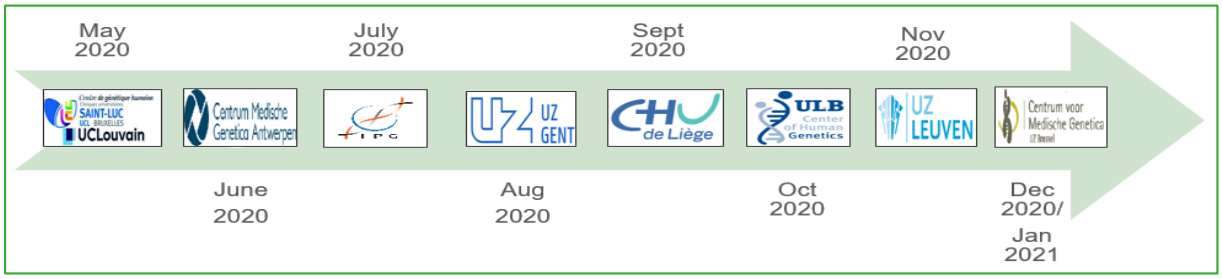


Figure 5: Timeline of the registration in the Orphanet database (Pre-Release QC step) carried out during the year 2020 for the data (diagnostic tests) of the 8 officially designated Belgian genetic centres.

The collaboration established in 2020 between the geneticists, the BGTD and Orphanet has several mutual benefits:

- first, the fact of interacting with a main point of contact, the BGTD which is the preferred entry point for data on genetic testing, saves time for all stakeholders;
- then, the fact that by acting according to a specific workflow described in SOPs, multiple people are involved in the data verification, which ensures high quality of published data;
- the BGTD benefits from analysis tools developed by the Orphanet-Inserm, which provide accurate and up-to-date data on the classification of rare diseases and on the links between the genes of a panel and the diseases assessed by a test;
- finally, the work performed by the Belgian Orphanet team also contributes to enrich the international Orphanet database itself, by identifying genes, diseases and gene-disease relationships that are not yet registered.

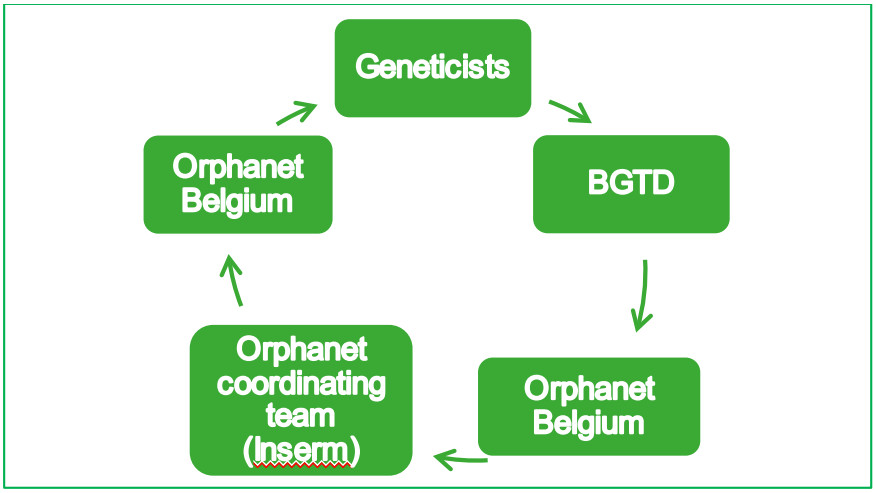


Figure 6: Illustration of the workflow established in 2020 between the different stakeholders for the registration and update of Belgian genetic tests in the Orphanet database.

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 manager of the BGTD and the manager of the Orphanet Belgium database.

When it comes to gene panels, their content changes so often that it is difficult to always be up to date at this level 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, depending on the date of the last update made by the geneticists in BGTD. Each change in the composition of a panel, even of just 1 gene, involves indeed for the IS and for the Orphanet coordinating team hours of analysis (rerun the Excel analysis tool for gene panels and validation work) since a new pre-release QC is required for all updates where the linked disease(s) and/or the panel of genes have been modified. We must therefore define an update rate that is acceptable and reasonable for all stakeholders given the workload that this task represents. However, if a geneticist wishes to modify his/her data published on Orphanet without having to wait for regular updates, this will of course remain possible, by making a request by e-mail to the address 'orphanetbelgium@sciensano.be' or by using our online registration tool[16].

2. Indicators on the Orphanet online registration service activity

Collector is the back-office tool of the online Orphanet registration service (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.

Between January 2020 and end of December 2020, 81 forms submitted by Belgian professionals were completely processed. Of the 81 forms processed, 38 concerned new data and 43 were updates to data already recorded. This number needs to be put into perspective. Indeed individual requests usually involve changes in many different related types of data. It is also important to keep in mind that Collector is not the only source available for registration/update requests. Many requests are submitted to the Orphanet Belgium team by emails or phone calls. In this case, the requests are processed but of course 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 7).

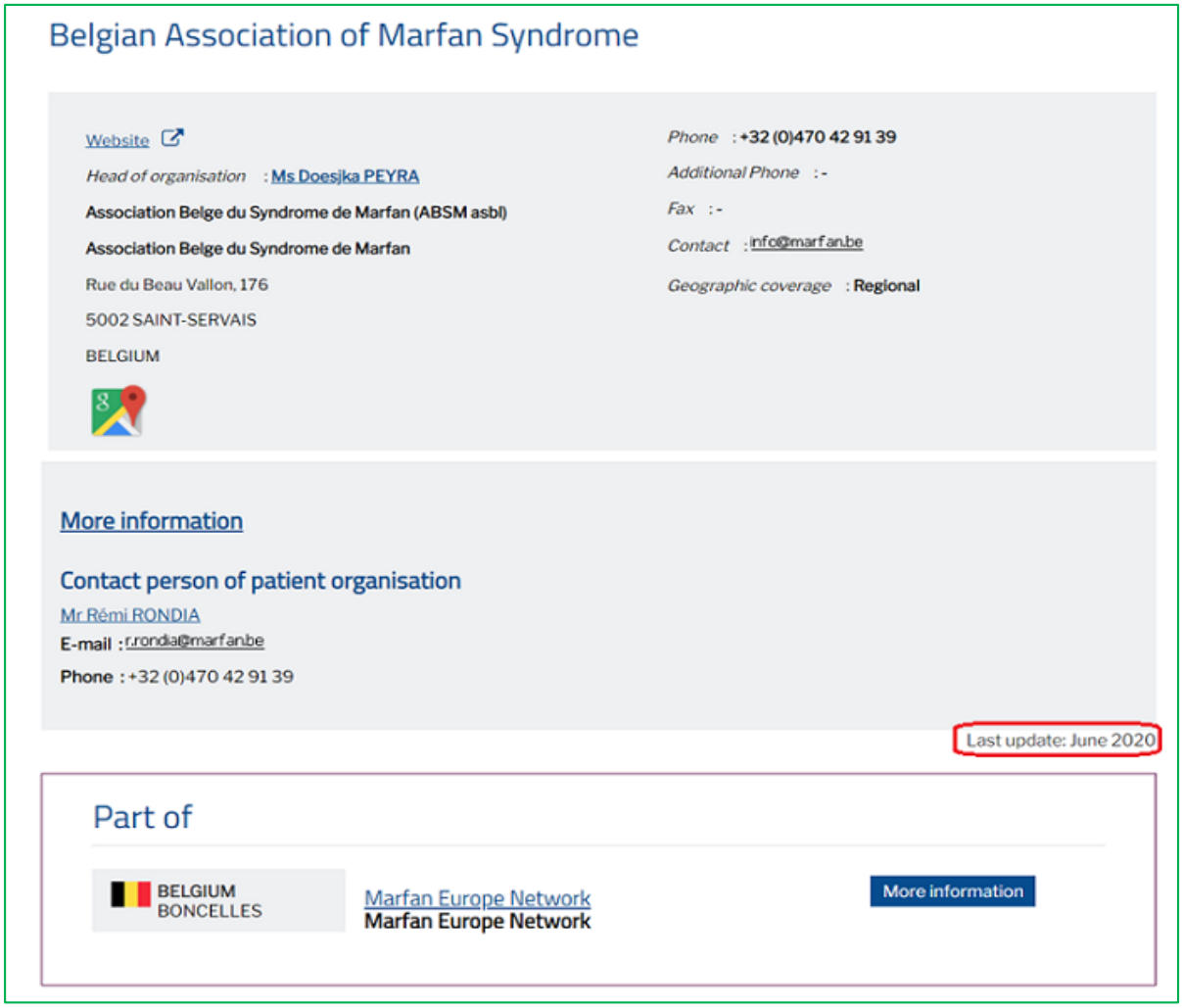


Figure 7 : Screenshot of the Orphanet website: the Orphanet Belgium team updated information about a patient organisation (change of president) in response to a request received through Collector. The date of the last update is indicated.

3. Other activities conducted by the Orphanet Belgium team

3.1. 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 that was scheduled in Paris (Orphanet headquarters) at the end of May 2020 was canceled. In order to ensure the continuity of the training activities, a distance training course for Information Scientists took place from May to November 2020. 12 sessions of approximatively 1h30 were organized, at a rate of about 2 sessions per month.

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 in the website; using the Arbor tool to visualize and navigate through the Orphanet classification;

- **using the Orphanet tools**: Major and Major 2 (input of data), Plator (import and export of large amounts of data), Collector (collection of requests for registration or updates submitted by professionals in Professor), Redminor (internal tracking tool for monitoring issues, suggestions and questions submitted to the coordinating team by the ISs).

As part of the preparation of the annual training, several pre-trainings must be carried out. These **video-trainings** cover general or more specific topics, such as: "What is a rare disease ?", "Orphanet classifications of rare diseases", “How to use Arbor ?”, “How to use Plator ?", “Data collection and registration of Patient organisations”, “Data collection and registration of Expert Centres”, “Data collection and registration of Research Projects”, “Data collection and registration of Clinical Trials” and “Data collection and registration of Diagnostic tests”.

Here are some examples of **topics covered by the 2020 IS Orphanet training**:

- 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 Orphanet database: Understand how expert resources are displayed on the Orphanet website and get familiar with the functional classifications;
- Orphanet tools;
- Expert centres: data collection and selection; data validation (Pre-release QC); data registration and publication; data post-release quality control;
- Patient organisations, umbrella organisations and alliances: data collection and selection; data validation (Pre-release QC); data registration and publication; data post-release quality control;
- Registries and biobanks: data collection and selection; data validation (Pre-release QC); data registration and publication; data post-release quality control;
- Diagnostic tests: data collection and selection; data validation (Pre-release QC); data registration and publication; data post-release quality control; registration of gene panels; registration of external quality assessments and accreditations.

3.2. COMMUNICATION THROUGH EVENTS, MEETINGS AND CONFERENCES

Due to the COVID-19 pandemic, the number of events organized in 2020 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 2020**

The Orphanet Belgium team was strongly involved in the preparation and running of the Rare Disease Day 2020 (see Figures 8-11). In Belgium, RaDiOrg[17], the umbrella association for people suffering from a rare disease, is at the origin of the nationwide awareness campaign. On this occasion, Sciensano (the scientific institute of public health which hosts the Orphanet Belgium team) joined forces with RaDiOrg for the creation of a huge flower carpet made up of around 15,000 origami versions of the edelweiss, a symbol of rarity. The installation adorned the Royal Saint-Hubert Galleries located in the heart of Brussels on February 29, 2020. The flowers symbolically represented the approximately 500,000 people who suffer from a rare disease in Belgium. The rare diseases team of Sciensano was on site all day, alongside other organizations active in the field of rare diseases, to participate in the installation of the carpet and raise awareness among the many passers-by on issues related to rare diseases. The event was the subject of significant media coverage, both written and televised, in our country.

Figure 8: Billboards in French and Dutch containing key statistics on rare diseases, based on the research published in the *European Journal of Human Genetics* (article authored by EURORDIS and Orphanet[2]), were placed among the origami carpets in the Royal Saint-Hubert Galleries in Brussels on 29th February 2020.

Figure 9: Installation of the origami carpet on February 29, 2020 in the Royal Saint-Hubert Galleries, Brussels.

Figure 10: Katrien Van Der Kelen, manager of the Belgian CRRD (left) and Annabelle Calomme, manager of the Orphanet Belgium database (right).

Volunteers from across the country devoted time to fold paper to make those origami flowers. At Sciensano, the members of the rare diseases team organised several workshops and more than 1,400 origami flowers were made by our collaborators.

Figure 11: Sciensano collaborators during an origami workshop organized in February 2020, including Elfriede Swinnen, the Orphanet Belgium National Coordinator and Kris Doggen, head of the service "Health Services Research" hosting the Orphanet Belgium team.

- **EDELWEISS AWARD 2020**

The Rare Diseases team of Sciensano was nominated for the Edelweiss Award 2020, a prize awarded each year by RaDiOrg on the day of rare diseases. It aims to officially recognize the contribution of a personality or an organization in favor of rare diseases in Belgium. On this occasion, a ceremony was organised at the town hall located on the Grand-Place in Brussels late afternoon February 29, 2020. About 200 people attended, including members of patient associations, representatives of the Minister of Health, decision-makers, physicians, researchers and health professionals. During this award ceremony, RaDiOrg highlighted the crucial role played by Orphanet as a reliable information platform for rare diseases. A nomination certificate (Figure 12) was given to the Rare Diseases team of Sciensano, including the members of Orphanet Belgium. A great reward for our work.

Figure 12: Edelweiss awards 2020 nomination certificate received by the Rare Diseases team of Sciensano.

- **PARTICIPATION IN THE PREPARATION OF THE RARE DISEASE DAY 2021**

In order to choose the angle of the next annual awareness campaign, RaDiOrg has assembled a "feedback group" which represents diverse stakeholders and people who have demonstrated involvement in the previous editions of the Rare Disease Day campaign. A brainstorming session took place on September 03, 2020. Orphanet Belgium team was part of this group. Two concepts designed by recognised advertising agencies were assessed. Both have developed an attractive idea aimed at reaching a wider audience and getting the concept of 'rare diseases' imprinted in people's minds.

- **ORPHANET'S ROLE HIGHLIGHTED IN THE FINAL REPORT OF THE EMRaDi PROJECT**

"EMRaDi" is the name of a rare disease project that ran from October 2016 to March 2020. It stands for Euregio Meuse-Rhine Rare Diseases. This project was co-funded by the European Union, the European Regional Development Fund (ERDF) and regional authorities in the three countries of the Euregio Meuse-Rhine (Belgium, Germany and the Netherlands). The EMRaDi project brought together health insurers, university hospitals, patient associations and a university (Maastricht University) in order to improve the quality of life of patients with a rare disease. All the results of the EMRaDi project have been made available since September 1, 2020[18].

As part of this project, Liège University Hospital added the ORPHAcodes in the medical records of patients with rare diseases and created an interdisciplinary page including information on RDs. This procedure facilitates the establishment of statistics on RDs within the hospital and also allows physicians to identify directly when consulting the database if their patients suffer from a RD.

This project proposes a series of specific recommendations for the various target audiences (rare disease patients and their relatives, patient organisations, hospitals and healthcare providers, health insurance funds, policy makers). Among these, many proposals relating to the use of Orphanet have been made: the website of patient associations should systematically provide information on the centres of expertise by means of a link to Orphanet; a presentation of the Orphanet portal should be given as a useful tool to help improve knowledge and diagnosis of rare diseases during the training of health professionals; the websites of university hospitals should make reference to Orphanet in order to better guide patients towards their services (expert centres); the websites of insurance organizations should provide information on RDs with reference to Orphanet as the most reliable European source of information on rare diseases. A brief presentation of Orphanet's activities is included in the EMRaDi information factsheets[19] for rare disease patients and for primary care professionals.

- **MEETING OF THE ACCOMPANYING COMMITTEE FOR THE FINANCIAL CONTRACT " CENTRAL REGISTRY OF RARE DISEASES (CRRD) – BELGIAN GENETIC TESTS DATABASE (BGTD) – SUPPORT ORPHANET BELGIUM"**

The Belgian Orphanet team activities are – together with other rare diseases projects - financially supported by the National Institute of Disability and Health Insurance (NIHDI). The financial contract is governed by a multistakeholder "Accompanying Committee" in charge of revising the work done and approving new work plans on a yearly basis. Besides representatives of the NIHDI and our entire rare diseases team (hosted at the Belgian public health institute Sciensano), the Committee consists of representatives of the FPS Public Health, Safety of the Food Chain and Environment, representatives of genetic centres, the umbrella of rare disease patient organisations (RaDiOrg), the Cancer Registry, the Flemish and Walloon networks for rare diseases, the Belgian Fund for Rare Diseases and Orphan Drugs and others.

An online meeting of the Accompanying Committee for the "Central Registry of Rare Diseases – BGTD - Support Orphanet Belgium" financial contract was held on October 30, 2020. The main purposes were to present the new objectives for the future (mainly 2021). Written project proposals with detailed information on objectives, responsible persons, indicators, risks and timelines were provided. The 2021 work plan with summary slides for each project was presented for approval. The Orphanet Belgium IS gave an overview of the upcoming tasks and new initiatives for the coming year with regards to the management of the Orphanet Belgium database. The translation responsible gave a presentation concerning future activities related to translation to Dutch and validation of the Orphanet website, terminology and scientific abstracts. The achievements, constraints and bottlenecks encountered were discussed. At the end of this meeting, the Accompanying Committee approved the new 2021 workplans.

- **BELMOLGEN WORKGROUP MEETING**

On December 11, 2020, a presentation was made to the members of the Workgroup on Molecular Genetics (BelMolGen) of the Belgian Society for Human Genetics (BeSHG) in order to make the professionals aware of the importance of registering and regularly updating their diagnostic tests on Orphanet. Representatives of the 8 Belgian Centres for Human Genetics attended. Explanations were given on how to submit a request for diagnostic tests registration and update. Special attention was paid to explain the new general way of working established in close collaboration with the BGTD (main data entry point).

3.3. COMMUNICATION THROUGH THE NATIONAL WEBSITE

The Orphanet Belgium team manages a national website[20] available in two languages, French and Dutch. The Orphanet national website contains information specific to Belgium.

Figure 13: Screenshot of the homepage of the national Orphanet Belgium website.

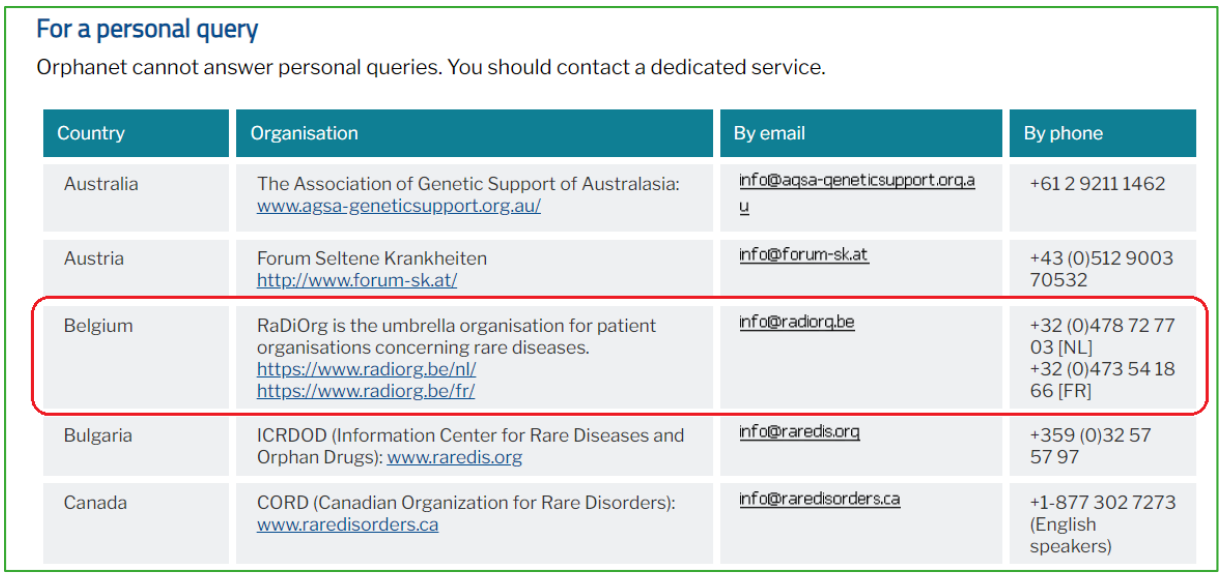
The following topics are covered:

- **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 regularly 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 report; instructional videos on the nomenclature and use of the tool for finding 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, national clinical trial register,…) as well as their inclusion/exclusion criteria can be found in the “Documents” section of our national website.

3.4. ASSISTANCE TO THE PATIENTS

The Orphanet Belgium team regularly receives questions about rare diseases via e-mail ('orphanetbelgium@sciensano.be') or by phone calls. The team provides answers to these questions whenever possible or refers the patients 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 national website, as well as on the Orphanet website (Figure 14). RaDiOrg can in particular help to find correct general information on the pathology, refer to an association of patients specific to the pathology (if it exists), help in the search for an optimal expertise for the pathology, 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[17].



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 14 : 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 by the IS to the members of the Orphanet coordinating team in charge of these aspects, so that they can study the request.

CONCLUSION AND PERSPECTIVES

Over the past 20 years, Orphanet has become a well-established and internationally recognized portal dedicated exclusively to rare diseases and orphan drugs. This website contributes to help all audiences access high quality information amongst the plethora of sometimes unreliable information available online, to provide the means to identify rare disease patients in health and research information systems (ORPHAcodes), 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 network, developed thanks to sustained European and national efforts, is a **good example of successful cross-European cooperation**. The network expanded gradually to 41 countries within Europe and across the globe by 2020. Each year additional countries ask to become members of the Orphanet community. Orphanet national teams are located in each participating country of the Orphanet network. Belgium was one of the first countries to join the Orphanet network, in 2001. The sustainability of the Orphanet national teams in the long-term is essential to meet the new challenges arising from a rapidly evolving political, scientific and informatics landscape.

In 2020, the Orphanet Belgium team performed the basic database management tasks, which consist in the registration of new expert-reviewed 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 an ongoing 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 made at the level of the genetic test repertoire, with the update of nearly a thousand Belgian diagnostic tests in Orphanet. This was made possible thanks to the close collaboration established with the Belgian Genetic Testing Database (BGTD) implemented by Sciensano. This effort should be continued and improved, in particular through the implementation of automated processes to ensure the transfer of information from one database to another (BGTD to Orphanet and vice versa).

Particular attention was also 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 avoiding duplicating efforts and making better use of available resources. Belgium participates in no less than 23 of the 24 existing European Reference Networks. The registration of Belgian ERN-centres in Orphanet is a work in progress and around 70% of these centres have already been referenced. Our objective is that 100% of the Belgian centres belonging to a ERN will be registered in the Orphanet database based on the list of participating centres provided by each ERN and the competent authorities. Our efforts are currently focused on identifying the information necessary for the registration of each of these centres and establish contact with centres that have not yet responded to our invitations in order to register in Orphanet. This task related to the registration of expert centres will therefore be continued in 2021.

During 2021, we plan to dedicate time to recording and updating in Orphanet the data related to specialized non-DNA diagnoses (nationally recognized tests and reference laboratories). For existing and newly registered tests (DNA and non-DNA), we are also considering a **review of all available information regarding EQAs and accreditations** based on information validated by international EQA suppliers or certificates of participation provided by the laboratories.

In addition, we will **continue to perform 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.

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