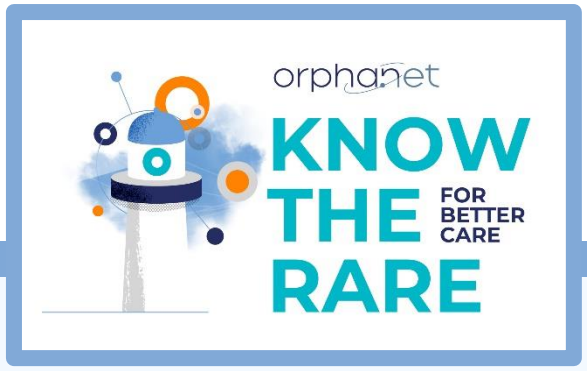

orphanet

2021 Activity Report

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Abbreviation list

BNDMR: French Rare Diseases Data Repository
CHMP : the Committee for Medicinal Products for Human use
CNIL : Commission nationale de l'informatique et des libertés : The French data protection authority
CNSA: French National Solidarity Fund for Autonomy
COMP : the Committee for Orphan Medicinal Products
DG Santé : Directorate General Health and Consumers – European Commission
DIMDI: German Institute of Medical Documentation and Information
ECRIN: European Clinical Research Infrastructure Network
EJHG: European Journal of Human Genetics
EMA: European Medicines Agency
EMBL - EBI: European Bioinformatics Institute
EMQN: European Molecular Genetics Quality Network
EQA: external quality assessment
EUCERD: European Union Committee of Experts on Rare Diseases
FDA: Food and Drugs administration
HGNC : Human Genome Organisation Gene Nomenclature Committee
HPO : Human Phenotype Ontology
ICD: International Classification of Diseases
INSERM: French National Institute of Health and Medical Research
IRDiRC: The International Rare Diseases Research Consortium
ISO : International Organization for Standardization
IUPHAR: The International Union of Basic and Clinical Pharmacology
MA : marketing authorisation
MedRA: Medical Dictionary for Regulatory Activities
MeSH: Medical Subject Headings
NFU: Netherlands Federation of University Medical Centres
OD: orphan drugs
OJRD: Orphanet Journal of Rare Diseases
OMIM: Online Mendelian Inheritance in Man
ORDO: Orphanet Rare Disease ontology
ORS: Orphanet Report Series
RD: Rare diseases
RD-TAG: The Rare Diseases Topic Advisory Group
RNA: Ribonucleic acid
SNOMED-CT: Systematized Nomenclature of Medicine-Clinical Terms
SOPs: Standard Operating Procedures
UMLS: Unified Medical Language System
UniProtKB : Universal Protein Resource Knowledgebase
URL: uniform resource locator
WHO: World Health Organisation
WP: Workpackage

1. Overview

Orphanet is a unique resource, gathering and producing knowledge on rare diseases so as to contribute to improving the diagnosis, care and treatment of patients with rare diseases. Orphanet aims to provide high-quality information on rare diseases, and ensure equal access to knowledge for all stakeholders. 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) at the instigation of the French Ministry of Health in 1997. This initiative became a European endeavour from 2000, supported by grants from the European Commission: Orphanet has gradually grown to a network of 40 countries in 2019, 41 in 2020, and 42 in 2021 within Europe and across the globe.

The final outcomes of the project were presented in a leaflet, available on Orphanet.

1.1. Orphanet's missions

Since its creation in 1997, Orphanet has become the reference source of information on rare diseases. As such, Orphanet is committed to meeting new challenges arising from a rapidly evolving political, scientific, and informatics landscape. In particular, it is crucial to help all audiences access quality information amongst the plethora of information available online, to provide the means to identify rare disease patients, to guide patients and doctors towards relevant services for an efficient patient care pathway, and to contribute to generating knowledge by producing massive, computable, re-usable scientific data.

Orphanet works towards meeting three main goals:

- **Improve the visibility of rare diseases in the fields of healthcare and research by maintaining the Orphanet rare disease nomenclature (ORPHA codes): providing a common language to understand each other across the rare disease field.**

  In a global community, we need to understand each other, although we may not speak the same language. A stable nomenclature, cross-referenced with other international terminologies is therefore essential. In order to improve the visibility of rare diseases in information systems, Orphanet has developed, and maintains, a unique, multi-lingual nomenclature of rare diseases, around which the rest of the data in our relational database is structured. Each disease is assigned a unique ORPHA code: integrating this nomenclature in health and research information systems is essential in ensuring that rare diseases are visible and that different systems can work together. This nomenclature is aligned with other terminologies: OMIM, ICD-10, SNOMED-CT, MedDRA, UMLS, MeSH, GARD. This cross-referencing is a key step towards the interoperability of databases and health information systems.

- **Provide high-quality information on rare diseases and expertise, ensuring equal access to knowledge for all stakeholders: orientating users and actors in the field in the mass of information online.**

  Rare diseases patients are scattered across the globe, as are rare disease experts. Orphanet provides visibility to experts and for patients by providing access to a catalogue of expert services in 37 countries having signed the Network Agreement by disease, such as centres of expertise, laboratories and diagnostic tests, patient organisations, research projects and clinical trials. This data promotes networking, tackles isolation and helps foster appropriate referrals. Orphanet draws on the expertise of professionals from across the world to provide scientific data on rare diseases (gene-disease relationships, epidemiology, phenotypic features, functional consequences of diseases, etc.). In addition, Orphanet produces an encyclopaedia of rare diseases, progressively translated into the 9 languages of the database (Czech, English, French, Spanish, Italian, German, Dutch, Portuguese, Polish) with texts also currently available in Greek, Slovak, Finnish, Hebrew and Russian, freely available online. Orphanet integrates and provides access to high quality information produced around the world, such as clinical practice guidelines and information geared to the general public.

- **Contribute to generating knowledge on rare diseases: piecing together the parts of the puzzle to better understand rare diseases.**

  To develop and curate the scientific data in the Orphanet database, Orphanet works with experts from around the globe, from healthcare professionals and researchers, to patient representatives and professionals from the medical-social sector. The wealth of data in Orphanet and the way this data is structured allows additional knowledge to be generated, helping to piece together data that at times can resemble pieces of an irresolvable puzzle. Integration of this data adds value and renders it interpretable. Orphanet provides standards for rare disease identification, notably via the Orphanet nomenclature, an essential key for interoperability. Orphanet provides integrated, re-usable data essential for research on the www.orphadata.org platform and as structured vocabularies for rare diseases, the Orphanet Ontology of Rare Diseases (ORDO) and the HPO-ORDO ontological module (HOOM). These resources contribute to improving the interoperability of data on rare diseases across the globe and across the fields of health care and research. They are being integrated in several bioinformatics projects and infrastructures around the world in order to improve diagnosis and treatment. Orphanet is committed to networking with partners across the globe in order to help contribute to generating new knowledge on rare diseases.

The integral role played by Orphanet in the research and care spheres has led to its recognition as an IRDiRC Recognised Resource, integration in the French node of ELIXIR, the European Research Infrastructure Consortium uniting Europe's leading life science organisations, and the designation of Orphadata's freely accessible data sets as an ELIXIR Core Data Resource. Orphanet is also a Human Variome Project Recommended System. Orphanet and the ORPHA

nomenclature are also cited as key resources in every European legislative text on rare diseases and as key measures in many national plans/strategies for rare diseases.

1.2. Our services and products

The Orphanet knowledge base is an organised and dynamic collection of information and data on RD and orphan drugs. Added-value data from multiple sources are archived, reviewed, manually annotated and integrated to other data by curators and validated by experts following formalised procedures which are published online in a dedicated section of the website. Furthermore, Orphanet has set up a Quality Management System to ensure the quality of the knowledge base. These unique features make Orphanet an essential tool for different stakeholders, in particular health professionals and researchers, to keep up to date with the constantly evolving knowledge concerning RD.

The data in the database is accessible via a variety of media: the Orphanet website (www.orpha.net), the French Orphanet Guides mobile application, the Orphanet data download platform Orphadata (www.orphadata.org), the Orphanet Rare Disease Ontology (ORDO), the HPO-ORDO Ontological Module (HOOM) and the Orphanet Report Series reports.

- **The Orphanet website provides access to:**
  - A comprehensive inventory of rare diseases classified according to a polyhierarchical classification system. Each disease is mapped with ICD-10, Online Mendelian Inheritance in Man (OMIM), Medical Subject Headings (MeSH), Unified Medical Language System (UMLS), Genetic and Rare Disease Information Center terms (GARD), Medical Dictionary for Regulatory Activities (MedDRA), and associated genes, within its 'identity card' that also includes the relevant prevalence category, age of onset category, and mode of inheritance. Diseases are also annotated with phenotypic features and frequency using HPO, epidemiological data and their functional consequences based on the International classification of functionning (ICF).
  - An encyclopaedia with textual information on rare diseases, presented in the form of a definition, an abstract or an automatically generated text for 8'943 entities in the Orphanet database. For 6'675 clinical entities summary texts are available, written by scientific writers and reviewed by world-renowned experts. Summary texts are produced in English and are then translated into French, German, Italian, Portuguese, Spanish, Dutch, Polish, and Czech. For certain selected diseases, emergency guidelines and disability factsheets are produced in French and then translated.
  - An inventory of high-quality articles published by other journals or learned societies. More than 3700 articles are available via Orphanet, with the permission of the authors and editors, comprising national and international clinical guidelines produced by learned societies that are not published in peer-reviewed journals but available as reports.
  - An inventory of orphan drugs and of drugs intended for rare diseases, at all stages of development, from orphan designation to market authorisation.

- A catalogue of expert services, validated by national experts in the 37 member countries and providing information on: specialised expert centres and centres of expertise, medical laboratories, research projects, clinical trials, patient registries and variant databases, networks, technological platforms and patient organisations.
- Thematic studies and reports on overarching subjects: the "Orphanet Report Series" (ORS), published as PDF documents.
- OrphaNews. The newsletter of the rare disease community, written in English, covering both scientific and political news. This newsletter is also published in French and Italian.

- **Orphanet ressources are available via a mobile app:**
  - **Orphanet Guides:** an app in French giving access to information on French national support mechanisms for patients and their families, information concerning the functional consequences rare diseases and the related standards of care, as well as recommendations for emergency practitioners concerning rare diseases. The app is available for iOS and Android. This app replaced the Orphanet app in 2021.

The Orphadata platform (www.orphadata.org) provides high-quality datasets related to rare diseases and orphan drugs, in a reusable and computable format.

- Freely available datasets: Orphanet Rare Disease Ontology, Orphanet nomenclature and cross-references with other terminologies, classifications, disorders with associated genes, phenotypes associated with rare disorders, linearisation of rare disorders, epidemiological data, data concerning the functional consequences of rare diseases;
- Datasets available via Data Transfer Agreement/Licence: Textual information, catalogues of patient organisations, expert centres, clinical laboratories and diagnostic tests, orphan drugs, and research activities.
- Ontologies (see below)
- Tools and services: A range of tools are available and others, such as APIs, are forthcoming to ease re-use of Orphanet data. For the moment the RD-Code API is available, as well as an ORPHAcodes Dataviz, FAIR Datapoint, ORDO SPARQL Endpoint and HOOM SPARQL Endpoint.

- **The Orphanet Rare Disease Ontology (ORDO),** a structured vocabulary for rare diseases derived from the Orphanet database, capturing relationships between diseases, genes and other relevant features, such as epidemiological figures by geographical region. ORDO provides integrated, re-usable data for computational analysis. In obo and OWL formats

- **HOOM, the HPO-Orphanet Ontological Module.** Orphanet provides phenotypic annotations of the rare diseases in the Orphanet nomenclature using the Human

Phenotype Ontology (HPO). HOOM is a module that qualifies the annotation between a clinical entity and phenotypic abnormalities according to a frequency and by integrating the notion of diagnostic criterion. In ORDO a clinical entity is either a group of rare disorders, a rare disorder or a subtype of disorder. The phenomes branch of ORDO has been refactored as a logical import of HPO, and the HPO-ORDO phenotype disease-annotations have been provided in a series of triples in OBAN format in which associations, frequency and provenance are modeled. HOOM is provided as an OWL (Ontologies Web Languages) file, using OBAN, the Orphanet Rare Disease Ontology (ORDO), and HPO ontological models. HOOM provides extra possibilities for researchers, pharmaceutical companies and others wishing to co-analyse rare and common disease phenotype associations, or re-use the integrated ontologies in genomic variants repositories or match-making tools.

- **The Orphanet Report Series (ORS)** are thematic studies and reports on overarching subject, derived from data in the Orphanet database, published as PDF documents.

1.3. Highlights of 2021

Orphanet international positioning

The Orphanet Network Agreement

At the end of 2021 the Orphanet Network Agreement has now been signed by 38 Institutions from 37 countries (Armenia; Austria; Belgium; Bulgaria; Canada, Croatia; Czech Republic; Hungary; Estonia; Finland; France; Georgia; Germany; Ireland; Israel; Italy; Japan; Kazakhstan; Latvia; Lithuania; Luxembourg; North Macedonia, Malta; Netherlands; Norway; Poland; Portugal; Romania; Russia; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey and United Kingdom). Orphanet contact points are: Argentina, Australia, Cyprus, Tunisia, Morocco.

Orphanet Network Direct Grant

The Orphanet Network Direct Grant was launched in the framework of the 3rd Health Programme in mid-2018 and supported the Orphanet network until the end of 2020, and was extended without extra funding until June 2021. It included 35 participants from 22 countries and had the following objectives:

- To provide the RD community with interoperability tools, in particular around an inventory of RD, to allow for semantic interoperability between countries and between domains (health, research);
- To provide high-quality information on RD, in particular through an encyclopedia in several languages;

- To provide a directory of expert services in order to help patients, physicians and stakeholders find the expertise on a particular disease in Europe and beyond, and to produce data needed to support policy actions;
- To further develop and sustain Orphanet as the reference knowledge base on RD, by establishing and consolidating collaboration within the Orphanet pan-European network and with European Reference Networks (ERNs) for the production, improvement and dissemination of knowledge on rare diseases. It will allow for the creation of a consistent expertise ecosystem for rare diseases in Europe.

The main expected outcome of this project was to consolidate Orphanet as the European database for rare diseases, achieving a position of the international reference for information and data on rare diseases in a steady RD ecosystem as the result of the close cooperation between Orphanet and European Reference Networks.
The final outcomes of the project were presented in a leaflet, available on Orphanet.

Orphanet's sustainability and the EC Steering Group on Promotion and Prevention

To support countries in reaching the international health targets, the European Commission established in 2019 a Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases (the Steering Group on Promotion and Prevention, or SGPP). The Steering Group takes positions on priority actions to be implemented in all areas of health promotion and non-communicable disease prevention, including management of rare diseases. DG Santé is trying to make their major achievements in the rare diseases field sustainable after the current Health Programme; as Orphanet is considered as one the major achievements, having being supported for years and its nomenclature being recognised as a best practice in the field, Orphanet's sustainability has been a focus of discussions at SGPP meetings and the Group's input was sought on plans for a sustainable future for the Orphanet Network.

In 2019, within the scope of the activities aimed at reinforcing Orphanet's European position with a view to attaining a sustainable future, a memo explaining Orphanet's EU added-value activities, in particular in relation to ERNs, was sent to different Directorates, resulting in a meeting with ERN related officers, eHealth Network and DG Connect. Orphanet has also, with the help of EURORDIS, asked National Alliances to help advocate for a sustainable future for Orphanet. In 2019, the Orphanet Operational Committee proposed to the Orphanet Management Board to set up a Sustainability Task Force to follow up on sustainability issues and ensure a more prompt and effective reaction to developments at European level.

Following these activities, at the end of 2019 a SGPP Focus Group dedicated to the question of Orphanet's sustainability was established. The Focus Group was chaired by the representative of the French Ministry of Health and Solidarity at the SGPP. The members of the Focus Group have been designated by their respective Member States following a decision of the SGPP. 12 MS were represented, plus Norway: Austria, Belgium, Czech Republic, France, Ireland, Italy, Lithuania, Latvia, Spain and Sweden. The mandate of the Focus Group was to present a final draft document to the Steering Group in early 2020, for the SGPP's approval. The Orphanet Coordinating team engaged a consultancy firm at the end of 2019 to help

Orphanet work on different scenarios for a sustainable future, as well as a business plan for Orphanet.

The focus group provided a final report to the SGPP in August 2020 recommending that a stepwise approach to sustainability be put into place, which includes a short-term actionable solution with shared contributions to core/transnational activities by network members facilitated through the construction of a non- profit international association under Belgian law, or similar. European Commission support of European added-value activities could also be envisaged through grants/procurement. A long-term sustainability roadmap was also elaborated and recommended to the SGPP.

In 2021 Orphanet continued its endeavours to achieve a sustainability model to ensure its longevity, spearheaded by its Sustainability Task Force, composed of members of the Orphanet Network.
In 2021 the Task Force called on Agent Majeur, a French scientific communications agency in order to craft a number of tools to help Orphanet Network Members make Orphanet better known and advocate at National level for support towards its sustainability goals. These tools include a new slogan reflecting Orphanet's missions and objectives ("Know the rare for better care"), associated visuals, slideshows for different audiences, and a short, animated video presentation to convey Orphanet's missions as regards its end users. The agency also provided a number of coaching sessions to Orphanet Network Members to best prepare them in their meetings with local and regional authorities.

Collaboration with European Reference Networks (ERNs)

In order to improve rare disease knowledge generation and dissemination, Orphanet's collaborates with European Reference Networks (ERNs) for rare diseases. This common endeavour aims to improve rare diseases patients' lives by increasing knowledge and providing equal access to the pool of expertise provided by the ERNs. The coordination of complementary activities was a key action of the EC Direct Grant supporting Orphanet. Work in 2021 focused on the following key areas:

- Improve the Orphanet nomenclature of rare diseases to provide stakeholders with a common, controlled language as a basis to improve the identification of patients and aid access to diagnosis and care, to better structure and optimise rare disease data, and to improve the interoperability between health information systems and research data.
- Several groups of diseases have been revised and finalised so far, including the Orphanet classifications of rare eye diseases (ERN-EYE), primary lymphedema (VASCERN), rare kidney diseases (ERKNet), inherited epidermolysis bullosas (ERNSKIN), as well as anorectal malformations (eUROGEN). Collaborations are also underway with other ERNs, including ERN BOND, ERN CRANIO, MetabERN, EpiCARE, VASCERN, ITHACA, and RITA.

- Revise and enlarge the Orphanet encyclopedia of rare diseases: at the end of 2021 222 texts have been revised in collaboration with ERNs.
- Prove a directory of healthcare, patient support and research activities related to RD: work continued to represent all ERNs' activities.
- Communicate on ERN activities to the RD community: A dedicated section of OrphaNews International provides a showcase, with an edition dedicated to resources provided by ERNs concerning COVID-19 and RD.

RD-CODE: supporting the implementation of ORPHAcodes in health information systems

RD-CODE (www.rd-code.eu/), co-funded by the Third Health Programme, started on January 2019 and ended in December 2021. The objective of this project is to support Member States in improving gathering information on rare diseases by implementation of ORPHA codes.

Starting with countries that had not yet introduced ORPHA codification yet, but that are already actively committed to doing so, this project aimed to demonstrate real-world implementation to guide other countries in the future.

Amongst the resources and tools made available are:

- A **video** explaining the benefits of using ORPHAcodes in Health Information Systems
- A suite of **ORPHA tools**, including the Orphanet nomenclature files for coding purposes, and APIs and tools to aide implementation and coding decision-making (http://www.rd-code.eu/tools/)
- A **virtual helpdesk** with information on the nomenclature and page dedicated to answering questions on nomenclature content and integration in health information systems.
- A new ORPHAcode **to capture remaining undiagnosed patients** after full investigation.

In addition to these tools, **support services, and information resources, guidelines and recommendations** have been developed and refined within the project according to real-world use of ORPHAcodes. A lessons-learned leaflet and public report have also been issued. These are indispensable tools to guarantee the appropriate use of the coding resources allowing comparability across countries and settings.

European Joint Co-fund Programme on Rare Diseases

The European Joint Programme on Rare Diseases (EJP RD; http://www.ejprarediseases.org/) brings over 130 institutions from 35 countries: to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation to improve the impact, reuse and funding of RD research.

The Orphanet Network is a partner, and co-leads activities around coordinated access to data and services within this programme. Orphanet developed a platform of research data based on the continuously updated catalog to help IRDiRC Funders Constitutent Committee devising their strategy, and provides training modules on the Orphanet nomenclature and ORDO. A series of national training sessions were organised and led by Orphanet national teams: in 2021 these took place in Italy, Spain and Norway.

SOLVE-RD: Horizon 2020 project to solve unsolved rare diseases

Led by the University of Tübingen, the Solve-RD consortium (www.solve-rd.eu), allocated €15 million by the European Commission Horizon 2020 programme, has worked from 2018 to improve the diagnosis of rare diseases, hand in hand with the new European Reference Networks (ERN) on rare diseases. The Orphanet coordinating team at INSERM leads the work package in charge of collecting standardised genetic and phenotypic information concerning unsolved rare diseases cases from ERN cohorts and the European Genome Archive, and developing an ontology of unsolved cases that will work alongside the Orphanet Rare Disease Ontology (ORDO) and the HPO-ORDO Ontological Module (HOOM) in order to make new diagnostic hypotheses. The Orphanet team has within this project developed the Rare Disease Case Ontology (RDCO), co-designed similarity algorithms, and organised a series of jamborees with ERNs to discuss results of the application of this methodology to complex diagnostic cases. Feedback mechanisms to improve the process are being implemented in this final year. All deliverables are available on the Solve-RD website.

Rare 2030 foresight study to prepare a future European RD policy

Rare2030 was a new two-year EU Pilot Project launched at the start of 2019, commissioned by the European Parliament, that aimed to guide reflection on rare disease policy in Europe through the next ten years and beyond. Since the adoption of the Council Recommendation on European Action in the field of Rare Diseases in 2009, the European Union has fostered tremendous progress to improve the lives of people living with rare diseases. The project, coordinated by EURORDIS, in which Orphanet- INSERM US14 is a partner, was launched in January 2019. It gathered the input of a large group of patients, practitioners and key opinion leaders to propose policy recommendations that lead us to a better future for people living with a rare disease in Europe. In order to reach these recommendations, an extensive literature review was conducted in 2019 to build a knowledge base, using sources including OrphaNews and the Orphanet database, in order to identify trends and drivers of change that affect the future of rare diseases and inform policy options. Orphanet was one of the lead partners in this work. This knowledge base has informed structured stakeholder dialogue to identify trends and drivers of change of most relevance for policy recommendations. A number of plausible alternative future scenarii concerning the state of health and care for people living with a rare disease in 2030 and beyond were constructed in 2020 on the basis of most relevant trends and drivers. Key stakeholders debated these scenarii and their implications to gather consensus around them. In the last stage of the project (end of 2020), patients, the public and experts at EU and national levels proposed policy options that could pave the way towards preferred future scenarios. Final policy recommendations organised into 8 main recommendations were presented at a major policy event in early 2021. Support to the Orphanet network and database, is a leitmotiv throughout the recommendations. In the recommendation "Optimising data for patient and societal benefit" the importance of the use of the Orphanet nomenclature as an interoperability vector is in particular highlighted and the following is defined as a major goal: *"All data associated with rare diseases is properly coded using the Orphanet nomenclature, including all people with rare diseases that have encountered a centre of expertise having this code as part of their electronic health records".*
Orphanet will remain implicated in the efforts lead by EURORDIS to advocate for a new European action plan on rare diseases, based on the results of the Rare 2030 study. Orphanet will notably participate in the secretariat of the European Stakeholder Network for Rare Diseases launched in 2022 on the European Commission's Virtual Health Policy Platform, that

brings together many of the experts solicited within the Rare 2030 project to work towards the recommendations formulated.

X-eHealth

INSERM, Orphanet's coordinating team is involved in the X-eHealth project, an EU CSA project to support the eHealth expert group in which MS are represented to decide on an eHealth strategy in the EU for EHRs, ePatient summary and ePrescription. The group has adopted an eHealth semantic strategy in which we managed to make sure that RD were included. It also allowed us to include RD use-cases in this project. We participate in the RD implementation use-case. It is extremely important for the RD community to be able to be identified as RD patients when facing unplanned cross-border medical situations.

TEHDaS Joint Action

The TEHDAS Joint Action launched in February 2021 (Towards a "European Health Data Space" (TEHDaS)) involving 25 European countries is the cornerstone of the creation of this European health data space, which aims to facilitate the cross-border sharing of health data for research and innovation (secondary purposes). TEHDaS aims in particular to provide the concepts to be included in the European legislative acts for the future European space. This act was expected to see the light during the French presidency of the Council of the European Union, in the first quarter of 2022. TEHDaS already published its first results which will allow the development of recommendations for the governance and cross-border sharing of health data in Europe. Orphanet is involved in WP5, axed on harmonising national data access procedures, and in WP6, axed on interoperability standards. In particular, ORPHAcodes and ORDO are promoted so as RD are accurately captured in national and European health data spaces.

ERICA

The overarching goal of the project is to is to build on the strength of the individual ERNs and create a platform that integrates all ERNs research and innovation capacity. In this project Orphanet co-leads WP3 which has the general aim of facilitating the Europe-wide implementation of standardised Patient-Centred Outcome Measures (PCOMs) and Patient Reported Outcome Measures (PROMs) for rare diseases while ensuring the involvement of the patient community in their development and validation process. Orphanet contributes to this work with the Disabilities annotations and collaboration with MAPI Research Trust in order to assess what PCOMs and PROMs are already available and what are the gaps, and which could be exploited for more than one disease. Orphanet also contributes to WP6, which is intended for Integration, outreach and dissemination. Orphanet will contribute with the Orphanet database of ERNs' CPGs and clinical trials.

New languages for Orphanet services

2021 saw the launch of the Czech version of the Orphanet website, bringing the number of languages to 9. Orphanet also made available its nomenclature of rare diseases in Turkish and Chinese, bringing the number of languages to 11. These datasets are available on Orphadata.

Collaboration with the World Health Organization

Orphanet contributes to the enrichment of ICD-11 with rare disease terms, as part of the French WHO Collaborating Center since 2021.

Collaboration with SNOMED International

In November 2020 Orphanet (Inserm) and SNOMED International released at SNOMED CT to Orphanet map, with the objective of improving the visibility of rare diseases in terminologies and promoting interoperability among different codification and terminology systems. The SNOMED CT to Orphanet Map Release is the product of a joint project carried out under the renewed 2020 Inserm and SNOMED International collaboration agreement, initiated in 2015. Based on an agreed priority set, new concepts for rare diseases as defined in Orphanet (clinically defined entities occurring in less than 1 in 2,000 inhabitants) have been added to SNOMED CT, and a map created from SNOMED CT to Orphanet.

One of the key use cases for this standardised map is to meet European Union (EU) requirements to implement ORPHA codes in health systems for Rare Diseases epidemiology and research, including use in registries, enabling linkage from SNOMED CT enabled Electronic Health Records (EHRs), and supporting cross-border interoperability with International Classification of Disease (ICD)-based coding systems.

The two organisations plan to publish the SNOMED CT to Orphanet map annually in the October timeframe. The map will be extended over the coming years to include further Rare Diseases included in the Orphanet nomenclature.

Access to the human readable map and accompanying release notes is made available from Orphanet via the Orphadata platform: http://www.orphadata.org/, and the RF2 version from SNOMED International for Members and Affiliates from the organisation's Member Licensing and Distribution Service.

Gene Curation Coalition

In 2021 a **new study** was published in the **Genetics in Medicine** journal on the Gene Curation Coalition (GenCC), composed of several groups and resources providing information on validity of gene-disease relationships of which Orphanet is a founding member. GenCC has created a database bringing together this data: curated gene-disease relationships are submitted by GenCC member organisations, including Orphanet, which is numerically the largest contributor of disease-gene relationships with 5330 submissions. GenCC provides harmonised definitions for different levels of gene–disease validity based on existing resources. The aim of the paper is to show how GenCC enables international collaboration through the standardisation of terminology and the resolution of curation conflicts, thus permitting better consistency in genetic testing and variant interpretation.

Improving quality, transparency and traceability

- In addition to the general SOPs available online and annually updated since 2013, the following procedures were available online in 2021:

General procedures

- Orphanet Standard Operating Procedures
- International Advisory Board rules of procedure
- Orphanet Advisory Board on Genetics Rules of procedures

Procedures concerning the nomenclature

- Orphanet nomenclature, classification and ontology of rare diseases
- ICD-10 coding rules for rare diseases
- Naming rules for the rare disease nomenclature in English
  This document has been translated into Polish (2017) and Spanish (2018) and German (2019) and Japanese (2019)
- Nomenclature production in national language
- Linearization rules for Orphanet classifications

Procedures concerning the collection of information related to rare diseases

1) Scientific information

- Creation and Update of Disease Summary Texts for the Ophanet Encyclopaedia for Professionals
- Orphanet inventory of genes related to rare diseases
- Epidemiological data collection in Orphanet

2) Expert ressources

- Glossary and representation of terms related to diagnostic tests
- Data collection and registration of expert centres in Orphanet
- Data collection and registration of patient organisations in Orphanet
- Data collection and registration of diagnostic tests in Orphanet
- Data collection and registration of research projects in Orphanet

- Data collection and registration of Clinicals trials in Orphanet
- Data collection and registration of patient registries in Orphanet
- Data collection and registration of biobanks in Orphanet

- Orphanet published **a dedicated Orphanet Report Series crediting the experts having contributed to the update of scientific data in Orphanet** in 2021.

- **Application of the General data protection regulation (GDPR) to Orphanet data:** this regulation is applicable since 25 of May 2018 across Europe. Orphanet, having as a legal basis the INSERM's public interest missions, collects personal information of professionals declaring their activities and /or contribute to Orphanet content as experts. A mailing was sent to all the professionals in the database announcing the developments next to come in Orphanet in order to comply with the regulation, as well as allowing them to exerce their modification or suppression rights concerning their personal data in Orphanet if they wish. Orphanet technical SOPs have been updated to take the regulation into account, and a training session was organised for all Orphanet network members including the extra-European ones, for the GDPR applies to them because the data is stored in France. A dedicated mail address is available for any GDPR-related issue: gdpr.orphanet@inserm.fr. Our legal notice on the Orphanet website has been updated. The online data registration and update the Orphanet registration tool was updated in order to make notice of users'

rights more explicit. In 2021 all network members were invited to sign a Confidentiality Agreement, accompanied by updated best-practice documentation for the handling and storage of data.

Orphanet database updates

- **Scientific information:** The Encyclopaedia of RD, the Inventory and classification of RD, the inventory of genes and the inventory of Orphan drugs have all been expanded and updated.
- **The catalogue of expert services:** expert centres, medical laboratories, clinical trials, research projects, networks, registries, infrastructures, mutation databases, biobanks and patient organisations have been expanded and updated.

Orphanet documents update

- **COVID and Rare Diseases Resource:** The COVID-19 pandemic has particularly impacted the rare disease community and expert information is, as ever, of high importance. In order to help professionals and people living with rare diseases find expert recommendations and services concerning COVID-19 and rare diseases, Orphanet published a **list of resources** available in different languages from March 2020. This list includes resources curated by the European Reference Networks and EURORDIS and is updated regularly, most recently integrating recommendations concerning vaccination.
- **The Orphanet Report Series have been updated:** List of Rare Diseases, Prevalence of Rare Diseases, Lists of Orphan Drugs, Registries, List of Research Infrastructures useful to Rare Diseases in Europe, Orphanet Activity Reports, List of experts contributing to the database, and User surveys, as well as the Report *'Vivre avec une maladie rare en France' (Living with a rare disease in France).* The Orphanet Activity report 2020 was translated into French. **A leaflet presenting Orphanet's activities and latest developments has also been produced in English.**

Orphadata

- **The Orphadata catalogue was updated.**

Users satisfaction and key user statistics

- **Users are satisfied with the services provided by Orphanet:** in the 2022 satisfaction survey reflecting the experience of 2021, 97 % of respondents stated that they were very satisfied or satisfied with Orphanet, an decrease of 1% compared to the previous year, but the same result as 2 years ago.
- **5.1 million PDF documents were downloaded in 2021.**
- **Around 20 million visitors came last year from 238 countries.**

Orphanet in numbers

- A network of **42 countries in Europe and beyond**
- A freely accessible website available in **9 languages**
- **41.8 million pages viewed** in 2021
- **5.1 million PDF documents** downloaded in 2021
- Orphanet & ORDO - **IRDiRC Recognized Resources** and **HVP Recommended Systems**
- **Orphadata Science** – An **ELIXIR Core Data Resource**

Database content and website

Diseases

6,197	**rare disorders with unique identifiers : ORPHAcodes**
4,248	**genes linked to 3,821 rare disorders**
4,329	**disorders annotated with HPO terms**
5,810	**disorders annotated with point prevalence data**

Rare disease summaries in 13 languages

6,675	English
4,579	French
6,012	Spanish
5,295	Italian
4,029	German
5,639	Dutch
1,149	Portuguese
1,803	Polish
420	Greek
478	Russian
176	Finnish
113	Japanese
103	Slovak

Directory of expert resources* in the Orphanet network

26,882	Professionals referenced in the database
2,840	Patient organisations and **28** National Alliances for Rare Diseases
8,400	Expert centres
1,633	Medical laboratories dedicated to diagnosis
44,897	Diagnostic tests
9,708	Research projects
8,592	Clinical trials
893	Patient registries
200	Variant databases
168	Biobanks

** Individual resources outside of networks unless otherwise stated*

Data unless stated differently from Orphanet 2021 Activity Report (database content in December 2021-January 2022)

Users

Around **1,65 million visitors per month** from **238 countries**

35 % health professionals
38 % patients, families and support groups
As well as **students, researchers, clinical coders, industry, policy makers.**
Most appreciated products: disease summary texts on diseases, clinical signs associated to a rare disease, classifications of rare diseases, functional consequences of rare diseases (disabilities), epidemiological data*

* Annual Orphanet Users' Survey 2022

Figure 1 Orphanet in numbers (January 2022)

2. Orphanet network

2.1. The Orphanetwork Direct Grant

Orphanet has become a backbone for the rare disease community, with the substantial amount of data developed being not only essential as leverage both for scientific projects as well as policies related to rare diseases in Europe, but also for increasing the awareness and the dissemination of knowledge on RD. Orphanet is mentioned in the European Union's principal documents on RD (e.g. the Commission Communication "Rare diseases: Europe's challenges" of 11 November 2008 and the Recommendation of the Council on an Action in the field of rare diseases of 8 June 2009) as the source of current information on RD in the EU as well as a strategic element of any national plan/strategy on RD, which each Member State was encouraged to develop by the end of 2013. It is also mentioned as a key tool for information on RD in the directive on the application of patients' rights in cross-border healthcare (2011).

The Orphanet Network Direct Grant was launched in the framework of the 3rd Health Programme in mid-2018 and supported the Orphanet network until the end of 2020, and was extended without extra funding until June 2021. It included 35 participants from 22 countries and had the following objectives:

- To provide the RD community with interoperability tools, in particular around an inventory of RD, to allow for semantic interoperability between countries and between domains (health, research);
- To provide high-quality information on RD, in particular through an encyclopedia in several languages;
- To provide a directory of expert services in order to help patients, physicians and stakeholders find the expertise on a particular disease in Europe and beyond, and to produce data needed to support policy actions;
- To further develop and sustain Orphanet as the reference knowledge base on RD, by establishing and consolidating collaboration within the Orphanet pan-European network and with European Reference Networks (ERNs) for the production, improvement and dissemination of knowledge on rare diseases. It will allow for the creation of a consistent expertise ecosystem for rare diseases in Europe.

The main expected outcome of this project was to consolidate Orphanet as the European database for rare diseases, achieving a position of the international reference for information and data on rare diseases in a steady RD ecosystem as the result of the close cooperation between Orphanet and European Reference Networks.

The final outcomes of the project were presented in a leaflet, available on Orphanet.

This initial Direct Grant will be followed by the Orphanet Data for Rare Diseases Direct Grant (OD4RD) a one-year project that started in 2022 co-funded by the European Commision's EU4Health programme that follows up on the work of the previous Direct Grant. OD4RD will continue funding the nomenclature production in English and some scientific content, but will be innovative in terms of national hub development and IT services development. This will help increase the quality of data generated about RD patients by disseminating best practices

for coding with ORPHAcodes, and to provide the means to generate accurate data for exploitation and analysis by ERNs (with whom collaboration will be formalized), hospitals and decision makers, notably to improve their understanding of RD activities.

2.2. Orphanet's Governance

To ensure optimal governance and efficient management of the workflow, Orphanet's governance is organised by three different boards:

- The **Management Board,** composed of country coordinators, is in charge of identifying funding opportunities, approving the global strategy of the project and thus guides the project in its endeavour to provide an optimum service for the end-users, and considering the inclusion of new teams as well as ensuring the continuity of the project.
- The **Orphanet Operating Committee** is an internal consultative Board was installed in 2018 and is in charge of proposing a strategy allowing the consolidation of the Orphanet 'culture' amongst all consortium members, and to determine how to move towards a more effective bilateral communication within the network. This empowers Orphanet as a network, achieving the three strategic axes agreed on by the Management Board in order to confirm Orphanet as the reference European database (consolidate Orphanet's position, make Orphanet sustainable, improve quality, transparency and traceability of data production).

External boards:

- The **International Advisory Board**, composed of international experts, is in charge of advising the Management Board regarding the overall strategy of the project.
- The **Genetic Advisory Board**, composed of geneticists is in charge of advising Orphanet on topics related to the gene database and the database of genetic tests and laboratories.

These boards discuss the evolution of the project in scope and depth; ensuring its coherence and its evolution, in relation to technological developments and to the needs of its end-users, as well as its sustainability.

In 2018, Orphanet member countries signed a new Network Agreement. The initial signatories were 33 Institutions from 32 countries: Armenia; Austria; Belgium; Bulgaria; Canada; Croatia; Czech Republic; Estonia; Finland; France; Germany; Georgia; Hungary; Ireland; Israel; Italy; Latvia; Lithuania; Netherlands; Norway; Poland; Romania; Serbia; Slovenia; Slovakia; Spain; Sweden; Switzerland; United Kingdom; Georgia; Malta and Japan.). In 2019, 3 additional countries joined the Network: Luxembourg, North Macedonia, Turkey. In 2020, Russia and Kazakhstan joined the networks. Five countries complete the network as contact points: Cyprus, Morocco, Tunisia, Argentina, Australia.

The Agreement officialised the existence of the network 'per se' and independently of the European Commission grant agreements, creating, with the recognition of Orphanet's *de facto monopoly* by the European Commission, a clear position for the network.

2.3. Expansion of the network

Since its creation, the quality of data provided by Orphanet has built its reputation and as a result Orphanet has grown as a European consortium, gradually expanding to a Network of 37 countries (in 2020) and 5 contact points. In 2011, Orphanet went further west to include Canada. The network expanded towards Australasia, with Western Australia joining in 2012. In 2014, Georgia and Tunisia joined the consortium followed by Argentina (the first South American country), in 2015. Japan officially joined Orphanet in 2017, with Luxembourg, North Macedonia and Turkey joining in 2019. Russia and Kazakhstan joined in 2020, and collaboration is underway to explore the possibility of creating an Orphanet – China team.

Please refer to the organisational chart at the end of this document for more information about the participating Institutions and team members.

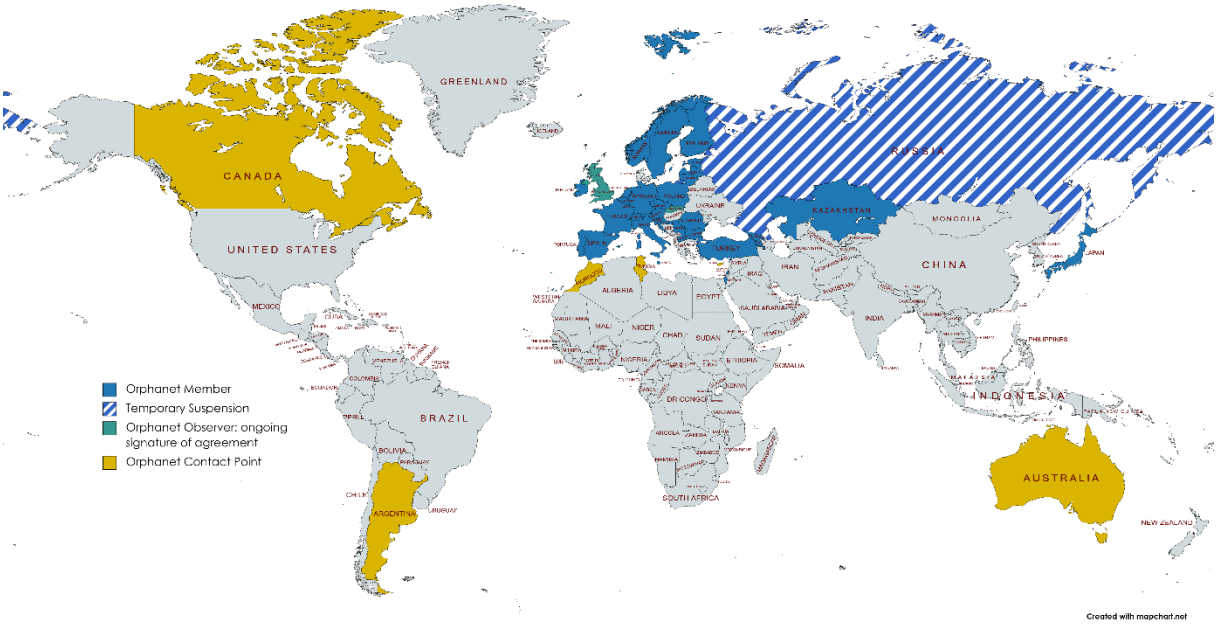


Figure 1 Orphanet Network Members (December 2021)

2.4. Orphanet members and scope of their activity

2.4.1. Coordinating Team

INSERM (the French National Institute of Health and Medical Research), having run Orphanet since 1997, coordinates the Orphanet network. The INSERM team is based at Service Unit 14.

The coordinating team is responsible for the coordination of network activities, the hardware and software aspects of the project, the database of rare diseases (including nomenclature in English, classifications, ontology, gene-disease relationships, scientific annotations), the Quality Management System and the Quality of Data (including the quality control and the coordination of the catalogue of expert resources in the participating countries), the production of the encyclopaedia, technology transfer/business development, partnerships, and the global communication strategy, as well as the training of all members of the network..

The coordinating team is also in charge of updating the database in regards to medicinal products in development, from their designation stage to their marketing authorisation.

2.4.2. Members

The establishment of a catalogue of resources can only be achieved by the consolidation of data collected at the country level. The identification of expert services requires a very good knowledge of the national research and health care institutions and their organisation. All national coordinators are located in high-profile institutions, which provide a suitable work environment for the information scientists, in terms of documentation, secretarial facilities and access to the network.

Members are responsible for collecting, validating and submitting data on expert centres, patient organisations, medical laboratories, research projects, clinical trials, registries, infrastructures, and networks.

Translation of the Orphanet content in the national language is also managed by the national teams, provided that they have a sufficient budget. At the end of 2018 Belgium, France, Germany, Italy, Poland, Spain and Portugal are undertaking the translation of the entire database and website's content into their national language. The Orphanet nomenclature is currently translated into the 9 languages of the website, and also in Turkish and Chinese. The translation of the nomenclature and abstracts in Japanese is ongoing. In 2018 the website was progressively translated into Polish and a Polish version of Orphanet was launched. In 2020 work on a Czech translation of the Orphanet website started with the Czech version launched in 2021.

Management of the national website/entry point to the Orphanet portal is also carried out by every national team in their national language as well as national and international communication and dissemination activities on National team and Network achievements.

Since the beginning of RD-ACTION (the European Joint Action supporting the rare disease field and Orphanet, before the current Direct Grant) National teams can also participate in core database activities if resources are available, and since 2019 the quality control of the database as well. The Orphanet Ireland team has contributed to the IT developments.

2.4.3. ORPHANET CONTACT POINTS

All national contact points are located in high-profile institutions. However, in these countries no dedicated funding is allocated to Orphanet activities, therefore there is no active data collection on expert services. The contact points conduct communication and dissemination activities, notably to raise awareness of rare diseases, and Orphanet, in their country.

3. Orphanet: Products and services

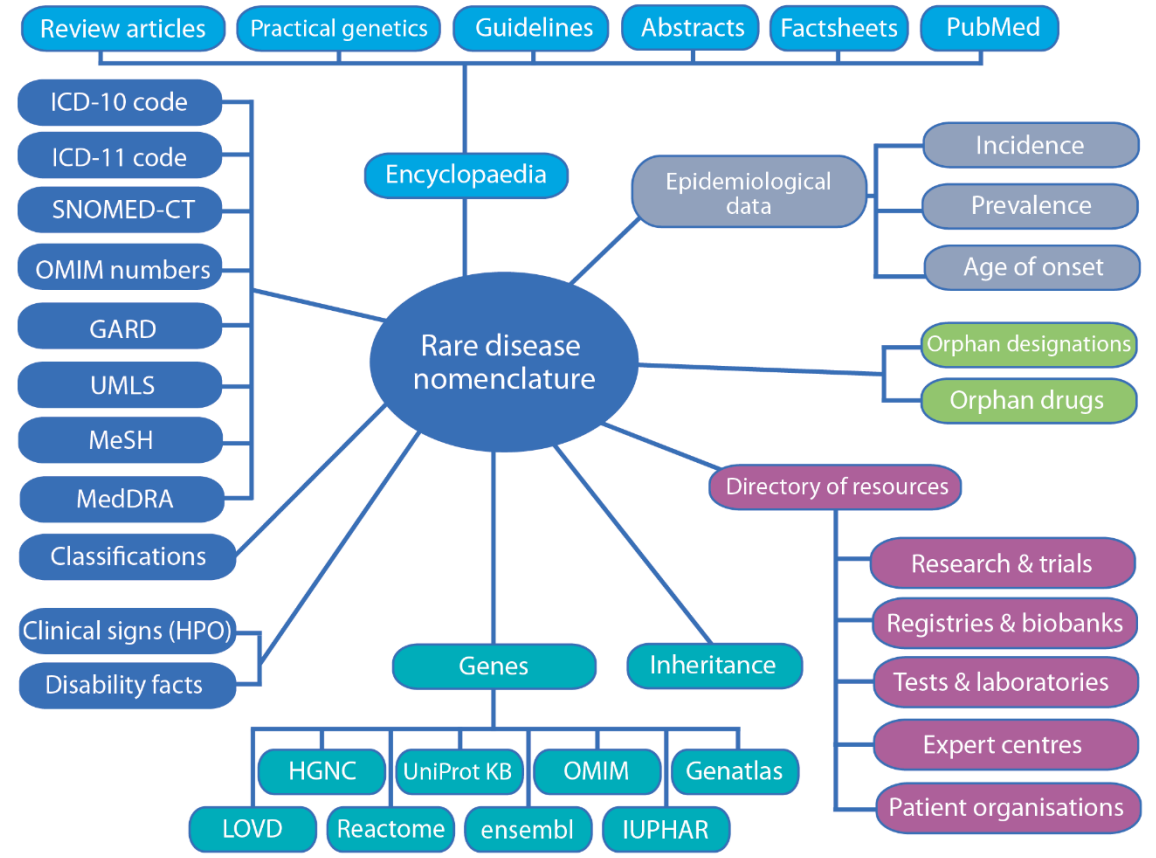


Figure 2 The Orphanet database

The Orphanet knowledgebase is an organised and dynamic collection of information and data about RD and Orphan Drugs. Data from multiple sources are archived, reviewed, manually annotated and integrated to other data by curators and validated by experts following formalised procedures which are published online. A list of expert reviewers having contributed to the scientific content is presented each year as a dedicated Orphanet Report.

Disorders in the Orphanet disease database correspond to rare diseases (defined in Europe as having a prevalence of not more than 1/2,000 persons in the European population), and rare forms of common diseases.

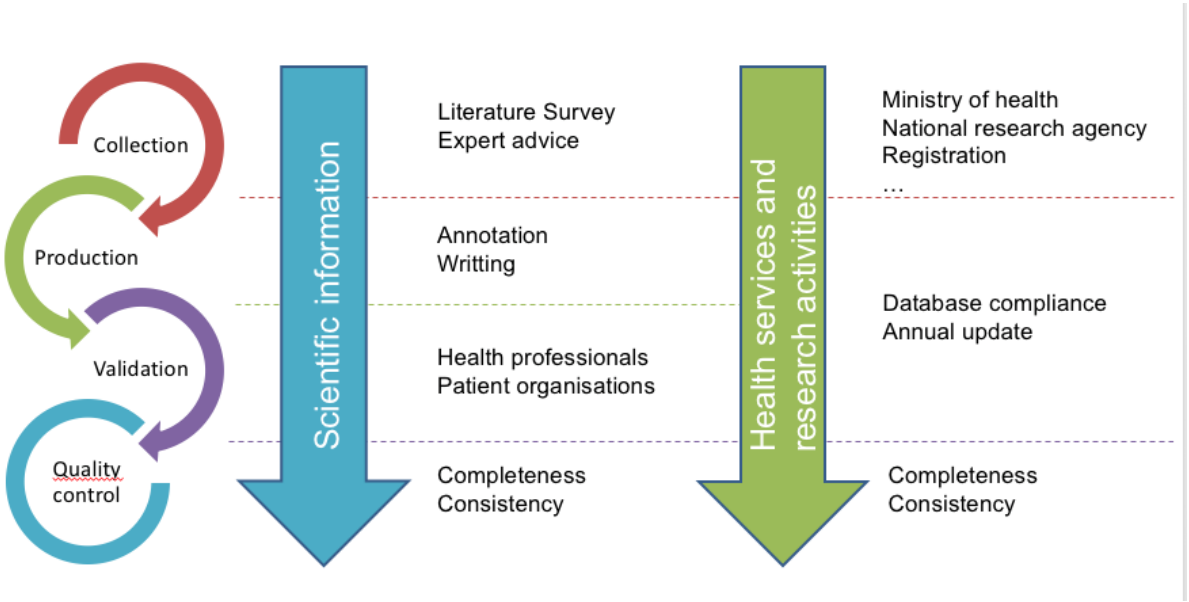


Figure 3 Orphanet data production methodology

The update of the scientific content of the database is performed using a four-step methodology (Figure 3) which consists of a survey of sources, allowing for the collection and production of data by identifying new syndromes, genes or treatments, for the update of classifications of diseases, for the production of various texts (encyclopaedia, guidelines, etc.) and for the update of the update of the catalogue of expert resources in participating countries. All texts and data (annotations on epidemiological data, phenotypes, functional consequences of the disease, genes, etc.) are externally validated (either by internationally recognised experts, learned societies and/or patient organisations, according to the type of text or data). A final step of quality control is carried out to ensure the coherence and completeness of the database.

All the teams that make up the Orphanet network are responsible for the collection, validation and submission of data on expert services in their country. In order to publish data which is relevant and accurate (complete, valid and consistent with other data from the database), validation and quality control is carried out by the coordinating team, and regular updates are performed with other country teams via an intranet.

Also, additional services and new collaborations, notably recently with the European Reference Networks for rare diseases, are developed regularly to resolve the issue of information dispersion and to address specific needs of the different stakeholders.

3.1. Orphanet content: nomenclature of rare diseases

Orphanet provides a comprehensive nomenclature of rare diseases classified according to a polyhierarchical classification system. As new scientific knowledge issues arise, the Orphanet RD inventory and classification system is maintained with regular additions/updates of diseases based on peer-reviewed publications and expert advice (including ERNs). This extensive and evolutionary system consists of classifications organised according to the medical and/or surgical speciality that manages specific aspects of each rare disease within a healthcare system. The diseases have been classified within each speciality according to clinical criteria or aetiological criteria, when diagnostically or therapeutically relevant. The Orphanet classification provides the scope and level of granularity (Figure 5) needed by health professionals with different specialties, including categories (e.g. rare neurological disease), clinical groups (e.g. rare ataxias), disorders (e.g. Machado-Joseph disease) and subtypes (e.g. Machado-Joseph disease type 1).

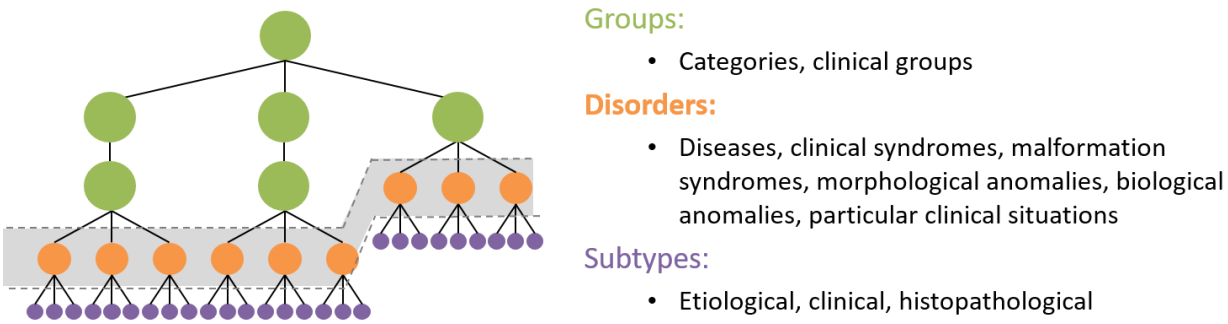


Figure 4 Schema of the Orphanet nomenclature and classifications

Since 2014, each entity in the nomenclature is assigned precisely one of these categories, allowing more accurate information on their typology and exact count. In addition, for diseases now recognised as part of another disease, Orphanet redirects users towards the disease that is now accepted according to recent literature. The disease database contains 9,335 clinical entities[1] and their synonyms (including 6,197 disorders[2]). The nomenclature and classifications can be viewed directly on the www.orpha.net website and/or extracted from Orphadata in XML and JSON formats. An annual version of the nomenclature is released for routine codification in health information systems, as part of a Nomenclature Pack for implementation, developed in the frame of the RD-CODE project. In this pack Orphanet provides a set of files in XML format, including the Orphanet nomenclature file, the Orphanet ICD-10 mapping file, a directory containing the Orphanet classifications, and a PDF describing

[1] Diseases, malformation syndromes, morphological anomalies, biological anomalies, clinical syndromes, particular clinical situation in a disease or syndrome, group of phenomes, etiological subtypes, clinical subtypes, histopathological subtypes, data from December 2021.

[2] Diseases, malformation syndromes, morphological anomalies, biological anomalies, clinical syndromes, particular clinical situation in a disease or syndrome, data from December 2021.

in details all files enclosed in the Orphanet nomenclature pack for coding.

The Orphanet nomenclature is aligned to other terminologies so as to provide a backbone for semantic interoperability between different systems. Rare diseases are aligned with ICD-10 codes (see Table 1). This process follows a set of rules, depending on whether rare diseases are mentioned or not in the tabular list or in the index of ICD-10. Rules for attribution of an ICD-10 code for diseases that are not listed in the ICD are established. More details on the process can be found in Orphanet's ICD-10 coding rules for RD procedure. The ICD-10 alignment is manually curated. Alignments with ICD-11 codes will be released in the near future.

Codes	Aligned ORPHA codes
ICD-10	7,389

Table 1 Number of disorders, groups of disorders or subtypes aligned to ICD-10 codes (December 2021)

Diseases are mapped to one or more OMIM numbers (see Table 2). Exact mappings between the Orpha nomenclature and other terminologies (UMLS, GARD, MeSH and MedDRA) are available online (see Table 2). Mappings to SNOMED-CT are produced in collaboration with SNOMED International and were released as a Beta version in 2020 and a first official release was made available in October 2021 from SNOMED International, with a human readable file made available via Orphadata. Mappings are carried out in a semi-automatic way and are manually curated. Updates follow UMLS releases once a year, however mapping UMLS meta-concepts and related terminologies (MeSH, MedDRA) was not continued in 2020 because a strategic decision was made to include ORPHAcodes in UMLS: the process is ongoing and should be complete in 2022.

All mappings from the Orphanet nomenclature to the target terminology are qualified (exact; narrow-to-broad; broad-to-narrow) and information on the validation status is available. Further annotations are carried out for ICD-10 terms: specific code, inclusion or index term, code attributed by Orphanet, with indication of the validation status.

Terminologies/resources	Mapped disorders, groups of disorders & subtypes
UMLS*	4,726
MeSH*	1,724
SNOMED CT*	5,655
MedDRA	1,140
OMIM**	4,651
GARD	3,742

*Table 2 Number of mapped diseases (groups of disorders, disorders and sub-types) per terminology (December 2021) *Exact mappings only **All mappings*

The Orphanet nomenclature is annotated with phenotypic traits information. From 2015, Orphanet disorders are annotated with the Human Phenotype Ontology, a standard and controlled terminology covering phenotypic abnormalities in human diseases, recognised as the reference in the domain, and a designated IRDIRC Recognized Resource. Each phenotypic term is associated with the frequency of occurrence (obligate, very frequent, frequent, occasional, very rare, excluded), and whether the annotated HPO term is a major diagnostic criterion or a pathognomonic sign of the rare disease. As a result of this work, 4,329[3] disorders or subtypes of disorders are annotated with HPO terms. Further annotations to HPO are being carried out. Based on these annotations, partnerships are being developed to provide an optimised assistance-to-diagnosis tool.

Orphanet provides **epidemiological and natural history information** on each rare disease. Disease inheritance and age of onset categories are provided (Table 3). Point prevalence, annual incidence, prevalence at birth and lifetime prevalence data are now documented in addition to the prevalence intervals available on the website (for Europe, USA and worldwide) (Table 4). Minimum, maximum and mean figures for each item are documented according to geographic zones, when information is available in Orphadata. The number of cases or families reported in the literature is also indicated for very rare diseases. Data sources and validation status are supplied for all data. This new epidemiological data is available for more than 5,800 diseases (groups of diseases, disorders and sub-types) and constitutes a unique and global source of information which we hope is useful to all users concerned, namely policymakers, the research community and the orphan drug industry involved in orphan drug development. The data are made available for download on www.orphadata.org.

Natural history data	Number of groups of disorders, disorders and sub-types
Average age of onset	6,250
Mode of inheritance	5,530

Table 3 Number of disease (groups of diseases, disorders and sub-types) per natural history data *(December 2020)*

Epidemiological data	Number of groups of disorders, disorders and sub-types
Point prevalence	5,810
Prevalence at birth	522
Lifetime prevalence	45
Annual incidence	602

Table 4 Number of diseases (groups of disorders, disorders and sub-types) per epidemiological data (December 2021)

[3] As of December 2021.

Orphanet also provides **information on activity limitation/participation restriction (functional consequences)** described in rare diseases, using the Orphanet Functioning Thesaurus, derived and adapted from the International Classification of Functioning, Disability and Health – Children and Youth (ICF-CY, WHO 2007). The provided information is assessed from the whole patients' population affected by the disease, receiving standard care and management (specific and/or symptomatic management, prevention and prophylaxis, devices and aids, care and support). Functional consequences are organised by their frequency in the patient population. Each functional consequence is recorded with: frequency in the patients' population, temporality, degree of severity, loss of ability when relevant, defined as the progressive and definitive loss of a skill or participation over the course of the disease. There are 715 clinical entities with functional consequences annotated[4].

3.1.1. ADDITIONAL FUNCTIONALITIES IN 2021

The Orphanet team finalised the last stages of the revision of the nomenclature data model to improve and clarify its representation of disease entities in the Orphanet knowledge base and the different products depending on this data on the website and in Orphadata.

As a result of these changes, the classification level (group of disorder, disorder, sub-type of disorder) of an entity is now displayed in each active clinical entity's ID card on the Orphanet website. It is clickable and gives direct access to a visualisation of the entity in the Orphanet classification system. In addition, inactive ORPHAcodes will be hidden to discourage their use, except for deprecated entities, which are available as they represent clinically used diagnoses for which patients and professionals search for information. Automatic texts displayed on the inactive disease pages have been adjusted to clearly emphasise that inactive entities are excluded from the Orphanet nomenclature, and redirect the user towards the active ORPHAcode that needs to be used instead (for obsolete and deprecated entities). It is worth noting that for obsolete entities, the active ORPHAcode indicated as replacement should be viewed as a suggestion, provided to steer the user towards the most appropriate entity using the classification system

To facilitate IT access to nomenclature data and allow flexible implementation across Europe and fields, an API (Application Programming Interface) is now provided. An Orphanet Data visualisation tool has been developed, allowing users to search for the clinical entities (groups of disorders, disorders, sub-types) that are present in the Orphanet nomenclature pack in all the API languages. This work was carried out within the scope of the RD-Code project.

3.2. Orphanet content: Orphanet inventory of genes

Genes involved in rare diseases are entered in the database and updated regularly according to new scientific publications. Genes are associated with one or more diseases, with one or more genetic test, and mutation databases and/or research projects. The data registered

[4] As of December 2021.

includes: annotation with the main name and symbol of the gene (from HGNC) and its synonyms, as well as its HGNC, UniProtKB, Genatlas and OMIM references (in order to cross-reference these websites), in addition to Ensembl (an EMBL-EBI database that maintains automatic annotations for selected eukaryotic genomes), Reactome (an EMBL-EBI open-source, open access, manually curated and peer-reviewed pathway database) and IUPHAR/BPS Guide to Pharmacology databases (see Figure 6 for details). The relationship between a gene and a disease is manually qualified according to the role that the gene plays in the pathogenesis of a disease: causative (both from germline or somatic mutations), modifiers (germline), major susceptibility factors, or playing a role in the phenotype (for chromosomal anomalies). For the disease-causing germline mutations, the information, whether pertaining to a gain or loss of function for the protein, is also provided when available. Information on the typology of the gene (i.e. gene with protein product, non-coding RNA, disorder-associated locus), its chromosomal location and all former symbols and synonyms is also provided. Candidate genes are also included but only when they are tested for in a clinical setting. These annotations represent a unique, added-value service for diagnostic and therapeutic research.

3.3. Orphanet content: Orphanet encyclopaedia

Three distinct encyclopaedias are provided on the Orphanet website: one for health professionals, one for the general public, and one related to disabilities.

3.3.1. Health Professionals Encyclopaedia

- **Summary information**

Textual information on a disease can be presented in the form of a definition, an abstract, or as an automatically generated text (8,943entities in the database had one of these forms of textual information) at the end of 2021.

Orphanet texts (apart from the automatically generated) are unique and written in English by a member of the editorial team and validated by a medical validator. A definition is produced for every rare disorder by a medical writer and submitted for medical validation. Abstracts are reviewed by an invited world-renowned expert. Abstracts are structured in up to 10 sections: Disease definition – Epidemiology – Clinical description – Aetiology – Diagnostic methods – Differential diagnosis – Antenatal diagnosis (if relevant) – Genetic counselling (if relevant) – Management and treatment – Prognosis. Summary information for 6,675 rare diseases, subtypes of RD or groups of RD was available online at the end of 2021.

They are progressively translated into the seven other languages of the website (French, Italian, Spanish, German, Polish, Portuguese, Czech and Dutch). In addition, 175 abstracts are translated in Finnish, 420 in Greek, 478 in Russian, 113 in Japanese and 103 in Slovak: they are available as PDFs (“Summary information”) via the bottom of the corresponding disease page. For an additional 2, 268 clinical entities in the disease inventory, textual information is provided through automatically generated texts (for diseases labelled as a group of diseases,

deprecated entries, subtypes of disorders, particular clinical situations for which there is an orphan designation and conditions for which there is a pharmacogenetic test in the inventory).

- These guidelines are intended for pre-hospital emergency healthcare professionals (a dedicated section is included for their use) and for hospital emergency departments. These practical guidelines are produced in collaboration with French reference centres and patient organisations, and are peer-reviewed by emergency health care physicians from learned societies (*SFMU* in France): as of the end of 2021, 109 emergency guidelines in French were available online. They are being translated into the following six languages: English, German, Italian, Portuguese, Spanish and Polish. 42 emergency guidelines are available in English (including those contributed by BIMDG) 46 in Italian, 24 in German, 46 in Spanish, 17 in Portuguese, and 16 in Polish. Emergency guidelines were downloaded 432'237 times in 2021.

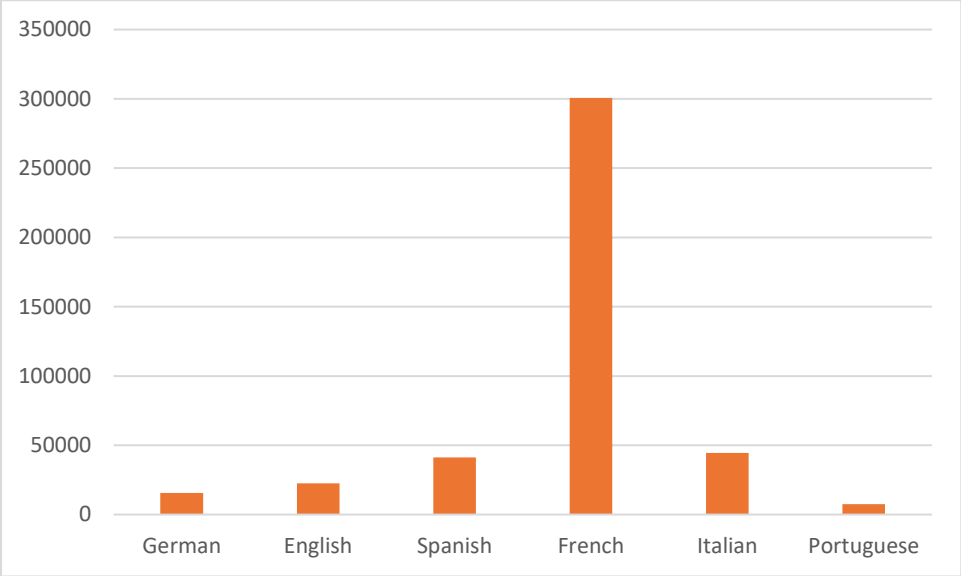


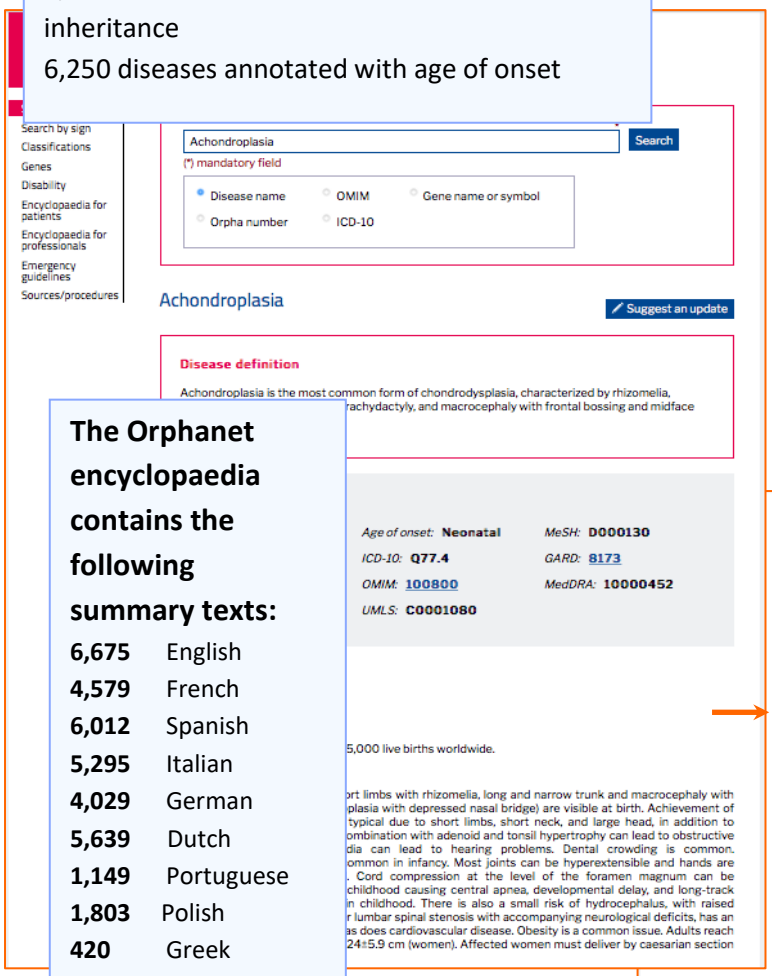
Figure 5 Downloads of Orphanet Emergency Guidelines in 2021 by language

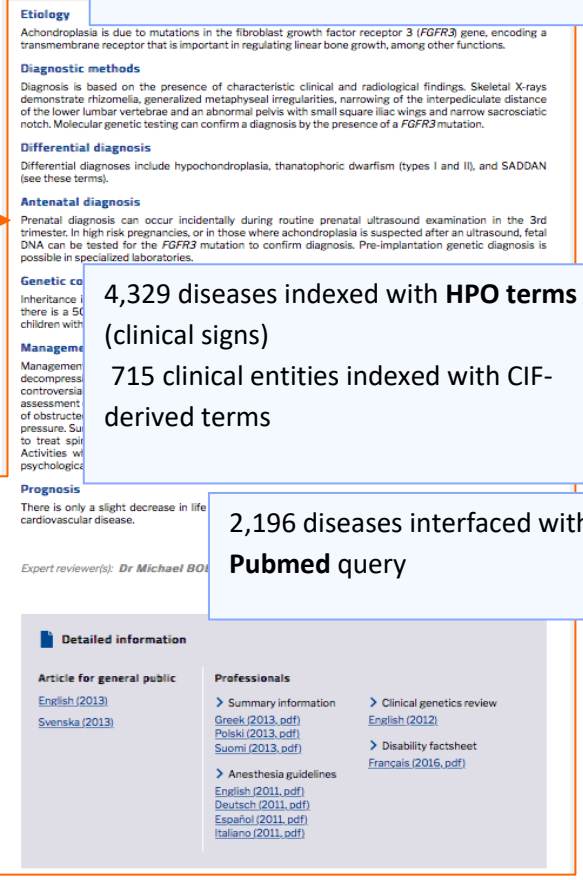
Epidemiology:
5,810 diseases annotated with point prevalence data

Natural history:
5,530 diseases annotated with mode of inheritance
6,250 diseases annotated with age of onset

Mappings:
7,389 diseases mapped to ICD-10
4,651 diseases mapped to OMIM
4,726 diseases mapped to UMLS
1,140 diseases mapped to MedDRA
1,724 diseases mapped to MeSH
3,742 diseases mapped to GARD

Genes:
4,248 genes linked to 3,821 rare diseases
7,100 genes interfaced with HGNC
6,382 genes interfaced with OMIM
4,954 genes interfaced with Genatlas
6,431 genes interfaced with UniProtKB
6,476 genes interfaced with Ensembl
1,538 genes interfaced with IUPHAR-DB
4,425 genes interfaced with Reactome





The Orphanet encyclopaedia contains the following summary texts:

6,675	English
4,579	French
6,012	Spanish
5,295	Italian
4,029	German
5,639	Dutch
1,149	Portuguese
1,803	Polish
420	Greek
478	Russian
176	Finnish
113	Japanese
103	Slovak

4,329 diseases indexed with **HPO terms** (clinical signs)
715 clinical entities indexed with CIF-derived terms

2,196 diseases interfaced with a **Pubmed** query

In-house produced texts: 121 **articles for the general public** in French, **109 emergency guidelines** in French, translated in German, English, Spanish, Italian, Portuguese, and Polish. **81 Disability factsheets** in French

5,575 **external links** for 6,378 diseases

Link to external RD literature*

494	Review articles
746	Clinical genetics reviews
636	Clinical practice guidelines
186	Guidance for genetic testing
1,969	General public articles
200	Anesthesia guidelines

Figure 6 The disease database content as of January 2021 *(*Total of all available languages)*

3.3.2. General Public Encyclopaedia

The general public encyclopaedia was initially a French project supported by the First French National Plan for Rare Diseases in 2005 intended to give complete, reliable, and up-to-date information to patients and their relatives on the diseases that concern them. Since 2011, the general public encyclopaedia texts have been enriched with paragraphs on the functional consequences of rare diseases, including disabilities resulting from the disease, medical and social measures to prevent/limit them and consequences of these disabilities in daily life.

One hundred and twenty-one in-house French texts are available online. Ten have been translated into Spanish. In 2016, because of the lack of dedicated funding, the production of Orphanet's in-house general public encyclopaedia was interrupted. However, Orphanet disseminates high quality texts intended for the general public that are produced by third parties (see sections Links to External Rare Disease Literature).

3.3.3 Disabilities encyclopaedia

As part of the collaboration between CNSA (French National Solidarity Fund for Autonomy) and INSERM, Orphanet provides since 2013 a collection of texts named "disability factsheets" in the Orphanet Encyclopaedia of Disability devoted to the disabilities associated with each rare disease. This collection is addressed to the professionals in the field of disability as well as to the patients and their families. These texts have been elaborated in order to better understand and to assess the needs of people with disabilities associated with a rare disease and to promote guidance and appropriate support in the national health care system as well as in the care and social support system.

Each text contains a description of the disease (adapted from the corresponding summary text from the Orphanet encyclopaedia for professionals) and a focus on disability-related measures and consequences in everyday life (taken from the corresponding text of the Orphanet general public encyclopedia). Since 2016 these texts were produced as stand-alone texts, independent of the General public encyclopaedia. Due to lack of dedicated funding, the production of new Disability Factsheets has been interrupted nowadays.

These texts are available on the Orphanet website via the link "Disability factsheet" at the bottom of the page describing the disease as well as from the "Encyclopaedia for professionals" and "Disability" tabs. Eighty-one of these texts were available at the end of 2021 and they are also available in the Orpha Guides app. They have been downloaded approximately 249'545 times in 2021 (Figure 8). This is relatively stable as compared with the previous year. Translations into Spanish of these texts started in June 2016, with 36 translated at the end of 2021.

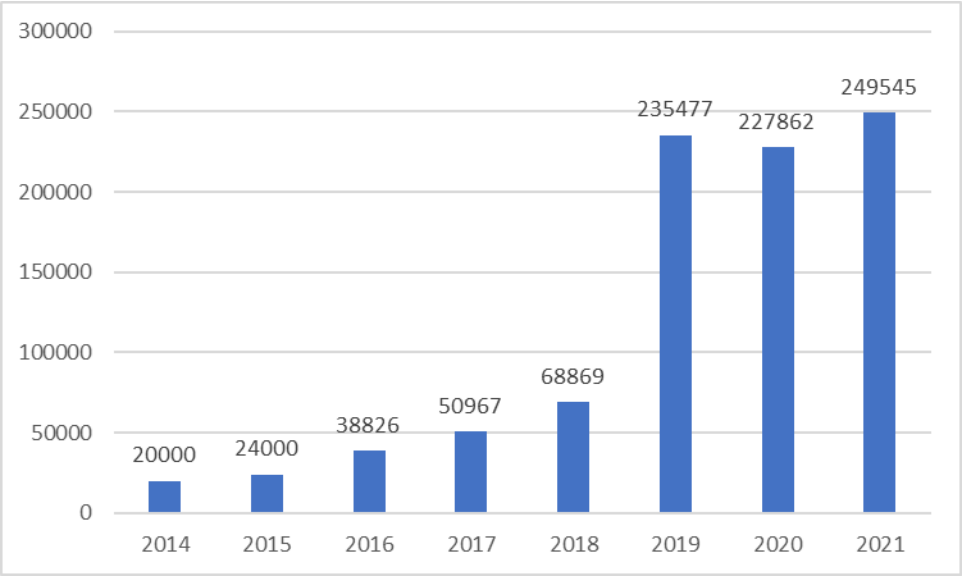


Figure 8 Evolution of number of downloads per year of Disability factsheets since 2014

3.2.4. DIAGNOSTIC CRITERIA

Information on diagnostic criteria is presented in 25 concise documents intended to avoid serial misdiagnosis and to facilitate early therapeutic management. This information, identified as being recognised by experts in the field as a reference in the domain, is extracted from peer-reviewed journals, with a reference to the original paper given at the top of the page.

3.2.5. LINKS TO EXTERNAL RARE DISEASE LITERATURE

With the purpose of disseminating high quality articles through the Orphanet website, Orphanet identifies and assesses articles produced by peer-reviewed journals and learned societies in any of the languages of the Orphanet consortium. Articles are evaluated according to a set of quality criteria. Authorisations from the copyright holder are requested so as to give access to the full text. Numbers of external texts per category are presented in Table 5.

We can distinguish seven distinct externally produced texts accessible from the Orphanet website:

- **Review articles**

494 review articles were online at the end of 2021.

- **Clinical Genetics Review**

These are peer-reviewed disease descriptions focusing on genetic aspects with an implication in the diagnosis, management, and genetic counselling of patients and families with specific

inherited conditions. The clinical genetic review collection comprises 752 articles from GeneReviews (as of December 2021).

- **Clinical practice guidelines**

These guidelines are recommendations for the management of patients, issued by official organisations. There are two kinds of best practice guidelines: anaesthesia guidelines and clinical practice guidelines. They are both produced by learned societies or expert networks and published either in scientific journals or on the learned societies' or health agencies' websites. A methodology of assessment has been developed to review the guidelines based on the AGREEII instrument in order to disseminate only the most accurate ones, after permission of the copyright holder is obtained[5]. The Orphanet website gives access to 636 best practice guidelines at the end of 2021.

- **Guidance for genetic testing**

This collection comprises summary guidance intended to disseminate the best practices in genetic testing. They include Gene Cards (published in the *European Journal of Human Genetics*). 186 guidance documents are available via the website at the start of 2022.

- **Articles for the general public**

Dissemination of general public-intended texts in all languages, externally produced by expert centres or patient organisations (produced in compliance with a reliable methodology), are now selected. 1,969 articles were available on the website at the end of 2021. The breakdown by language is presented in Table 5.

- **Practical genetics articles**

This collection was co-produced by Orphanet and the *European Journal of Human Genetics* (EJHG), the official journal of the *European Society of Human Genetics* up to 2016. 37 freely-accessible articles are published in the *EJHG* (Nature Publishing Group) and are accessible via Orphanet.

- **Emergency guidelines**

Orphanet has established a collaboration with the British Inherited Metabolic Disease Group (BIMDG) to provide links to the emergency guidelines that they produce.

[5] *Clinical Practice Guidelines for Rare Diseases: The Orphanet Database*, Sonia Pavan , Kathrin Rommel, María Elena Mateo Marquina, Sophie Höhn, Valérie Lanneau, Ana Rath, PLOS One, Published: January 18, 2017, https://doi.org/10.1371/journal.pone.0170365

	Article for general public	Review article	Clinical practice guidelines	Guidance for genetic testing	Clinical genetics reviews
Arabic	32	0	1	0	0
Bengali	24	0	0	0	0
Bulgarian	1	0	0	0	0
Chinese	30	0	2	0	0
Croatian	27	0	0	0	0
Czech	28	0	0	0	0
Danish	26	0	0	0	0
Dutch	60	0	2	0	0
English	352	421	217	149	752
Estonian	6	0	0	0	0
Finnish	14	0	0	0	0
French	265	31	232	35	0
Georgian	1	0	0	0	0
German	145	28	158	2	0
Greek	36	0	0	0	0
Hebrew	25	0	0	0	0
Hungarian	26	0	1	0	0
Italian	40	0	1	0	0
Japanese	4	0	0	0	0
Kirghiz	1	0	0	0	0
Korean	1	0	0	0	0
Latvian	26	0	0	0	0
Lithuanian	1	0	0	0	0
Nepali	0	0	2	0	0
Norwegian	26	0	0	0	0
Persian	1	0	0	0	0
Polish	37	0	0	0	0
Portuguese	37	1	2	0	0
Romanian	32	0	0	0	0
Russian	89	0	2	0	0
Serbian	26	0	0	0	0
Slovak	25	0	0	0	0
Slovenian	26	0	0	0	0
Spanish	111	14	30	0	0
Swedish	311	0	0	0	0
Thai	24	0	0	0	0
Turkish	29	0	0	0	0
Ukrainian	26	0	0	0	0
Urdu	2	0	0	0	0
Vietnamese	1	0	0	0	0
TOTAL	**1974**	**495**	**650**	**186**	**752**

***including 241 Orphanet Journal of Rare Diseases reviews*

** not including the in-house produced articles*

Table 5 Total number of Orphanet external content (December 2021): type of text per language

- **Disability factsheets**

A collaboration has allowed Orphanet to link to disability factsheets in Danish, produced by Sjaeldenborger, the Danish Rare Diseases alliance. Two such factsheets were available at the end of 2021.

3.3. Orphanet content: Orphanet catalogue of expert services

Orphanet provides a catalogue of:

- Centres of expertise/genetic counselling clinics and networks of centres of expertise
- Medical laboratories and diagnostic tests
- Patient organisations and umbrella organisations
- Patient registries
- Variant databases
- Biobanks
- Research projects
- Clinical trials
- Platforms and infrastructures

The Orphanet catalogue of expert services is produced by collecting data either from official national sources, or proactively from non-official sources by information scientists in each country of the Orphanet consortium. Data follows a validation process before publication, and is quality controlled. The aim of this multi-step process is to generate high-quality, accurate and robust data: complete, valid, consistent, unique, and uniform with the other data of the database.

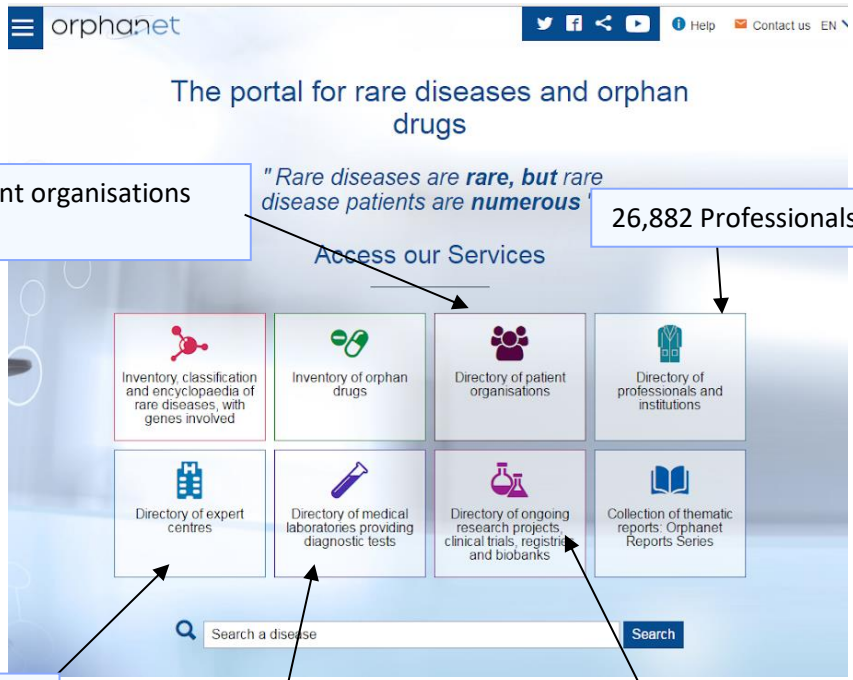
For data from official sources, no pre-release validation is required, but quality control is performed for consistency and added-value annotations are curated (i.e. link to the Orphanet classifications and characterisation of expert services). When issued from non-official sources, data is submitted to a pre-release validation process that is defined by each country following rules established at the national level and eventually with health authorities, to ensure data relevance for the rare disease community. A second round of validation is performed at the Orphanet coordination level to make sure data meets the criteria of relevance for rare diseases, to check coherence across the database and to ensure proper linking with the disease classification system. A third round of quality control is carried out on online published data following a process defined at national level (i.e. annual revision by the Scientific Advisory Board, or by competent authorities). At least once a year, professionals are invited to verify and update the expert services they are involved in.

The 37 countries in which Orphanet members collected data in 2021 are the following:

Armenia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Georgia, Germany, Hungary, Ireland, Israel, Italy, Kazakhstan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, North Macedonia, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom and Japan.

Data collection outside the Orphanet network:
Patient organisations in countries outside the Orphanet network can be registered in the database at their demand if they are an alliance and/or a member of EURORDIS and if they have a legal status or they are registered in an official journal. However, Orphanet does not ensure the regular update of this information. A disclaimer informing the users of this is available on the resource page of the website.
Research related resources (research projects, clinical trials, patient registries, biobanks and variant databases) funded by funding agencies in countries outside of the Orphanet network are collected by the coordinating team if the funding agency is a member of the IRDiRC consortium. Patient registries outside of the Orphanet consortium can also be registered if they fulfil inclusion criteria (Please refer to the technical procedures for an exhaustive list of inclusion criteria).

The catalogue of expert services in the Orphanet network contains the following data:



2,840 Patient organisations

26,882 Professionals referenced in the database

8,400 Expert centres

1,633 Medical laboratories dedicated to diagnosis
44,897 diagnostic tests linked to 5,076 diseases and 3,241 genes and 2,673 panels of genes

9,708 Research projects
8,592 Clinical trials
893 Patient registries
200 Mutation databases
168 Biobanks

Figure 9 Directory of expert services (December 2021)

3.3.4. Data Quality validation of medical laboratories

Medical laboratories listed in Orphanet are those offering tests for the diagnosis of a rare disease or a group of rare diseases, and those performing genetic testing whatever the prevalence of the disease. Information on quality management for medical laboratories and diagnostic tests is provided in Orphanet. Medical laboratories can be accredited and this involves a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out a specific task (ISO 9000: 2000 Quality management systems – fundamentals and vocabulary).
Moreover, medical laboratories can undergo an external quality assessment (EQA) whereby a set of reagents and techniques are assessed by an external source and the results of the testing laboratory are compared with those of an approved reference laboratory (WHO). This allows a laboratory to compare its performance for an individual test or technique against those of other laboratories.

Information on EQA participation is provided annually by Cystic Fibrosis Network, Genomics Quality Assessment (GenQA) and European Molecular Genetics Quality Network (EMQN) with the consent of the concerned laboratories. For other EQA providers, information on participation can be provided by the laboratory itself.

3.3.5. Additional functionalities in 2021

From 2021 it is possible to register any expert resource as a “member of an ERN”. Thus, this
information is visible currently for ERN expert centres in the activity’s ID card, the intermediary list of the activity, and the list of activities linked to the host institution and the professional. Implementation of this display in the rest of the expert resources is foreseen.

3.4. Orphanet content: Orphanet inventory of orphan designations and drugs

The list of orphan designations and drugs includes all those substances that have been granted an orphan designation for a disease considered as rare in Europe, whether they were further developed to become drugs with marketing authorisation (MA) or not. The Orphanet database also includes drugs without an orphan designation as long as they have been granted a marketing authorisation issued by the European Medicines Agency (EMA - centralised procedure) with a specific indication for a rare disease. Some drugs (substance and/or trade name) are also included in the database because they have been tested in a clinical trial performed on a rare disease without such regulatory status.

Drugs with a regulatory status in Europe are collected from reports issued by the two Committees of the EMA: the COMP (Committee for Orphan Medicinal Products) and the CHMP (Committee for Medicinal Products for Human use). Orphanet also collects information on Orphan Drugs from Food and Drug Administration in the USA (FDA).

Orphan drugs are published on the Orphanet website, under the Orphan drugs tab and data is also released within an Orphanet Report Series that is updated every trimester.

The database of orphan drugs and substances contains the following data (as of the end of 2020):

For Europe:

- 1,733 Orphan Designations linked to 1,344 substances and covering 594 diseases
- 412 Marketing Authorizations (of which 142 already had an Orphan Designation and 270 without Orphan Designation), covering 351 diseases.

For the USA:

- 821 Orphan Designations linked to 651 substances and covering 445 diseases
- 453 Marketing Authorizations (of which 444 already had an Orphan Designation and 9 without Orphan Designation), covering 390 diseases.

3.5. Orphanet products: Orphanet Report Series

Orphanet Reports (ORS) are a series of documents providing aggregated data covering topics relevant to all rare diseases. New reports are regularly put online and are periodically updated. These texts are published as PDF documents accessible from the homepage and from every page of Orphanet's website. New versions of these publications are advertised in OrphaNews. Orphanet also provides access to its procedures for data collection and curation in the scope of its Quality Management System.

The ORS and procedures are heavily downloaded: in 2021 they were downloaded at total of 231,810 times for the ORS and 27 814 times for the procedures (Table 6).

	English	French	German	Spanish	Italian	Dutch	Polish	Portuguese	Czech
List of rare diseases in alphabetical order	10348	32922	4556	5944	11813	NA	44304	2212	3348
Prevalence of rare diseases by alphabetical list	20869	2333	8855	1809	1417	3680	NA	510	NA
Prevalence of rare diseases by decreasing prevalence or cases	4497	6626	2698	2763	2154	824	NA	1536	NA
List of Orphan Drugs in Europe	10317	1554	1080	737	764	313	NA	371	NA
Registries for RD in Europe	3094	NA	NA	NA	NA	NA	NA	NA	NA
Vivre avec une maladie rare en France	NA	29255	NA	NA	NA	NA	NA	NA	NA

(N.A. = ORS not available in this language)

Table 6 Number of downloads of selected Orphanet Report Series in 2021 by language

3.6. Orphanet's IT infrastructure

The main IT infrastructure is under the responsibility of Inserm. The production servers are located in one of the largest civil data centres in France, the CINES (Centre Informatique National de l'Enseignement Supérieur). To ensure structural security, the development servers are located in another Inserm building close to the CINES and linked to it by a fibreoptic connection. This allows an excellent connectivity between production servers, development servers and backup environments. The architecture of the servers is represented in Figure 11.

During 2021 the www.orpha.net website was unavailable during May 4th and 5th, July 7th and November 1st. The main issues were network failures, one expected maintenance and a DOS (Denial of Service) due to a massive automated crawl. Still the www.orpha.net

website was available with uptime 98.4%. The audience was 19,876,808 visitors and 41,870,824 view pages in 2021 .OBJ1OBJ:Nevertheless the legacy Inserm Department of Informatics (Inserm DSI), still needs more updates in the coming months. rove data analysis capabilities, using ElasticSearch Cloud solution with Dashboards based on Data visualisation tools Kibana. This component is accessible from the Orphanet's backoffice for Orphanet teams. Our API solutions are all based on the ElasticSearch Cloud solution, plus dedicated web services, hosted and managed by third parties (which ensure availability, even in case of network failures at the Inserm level)

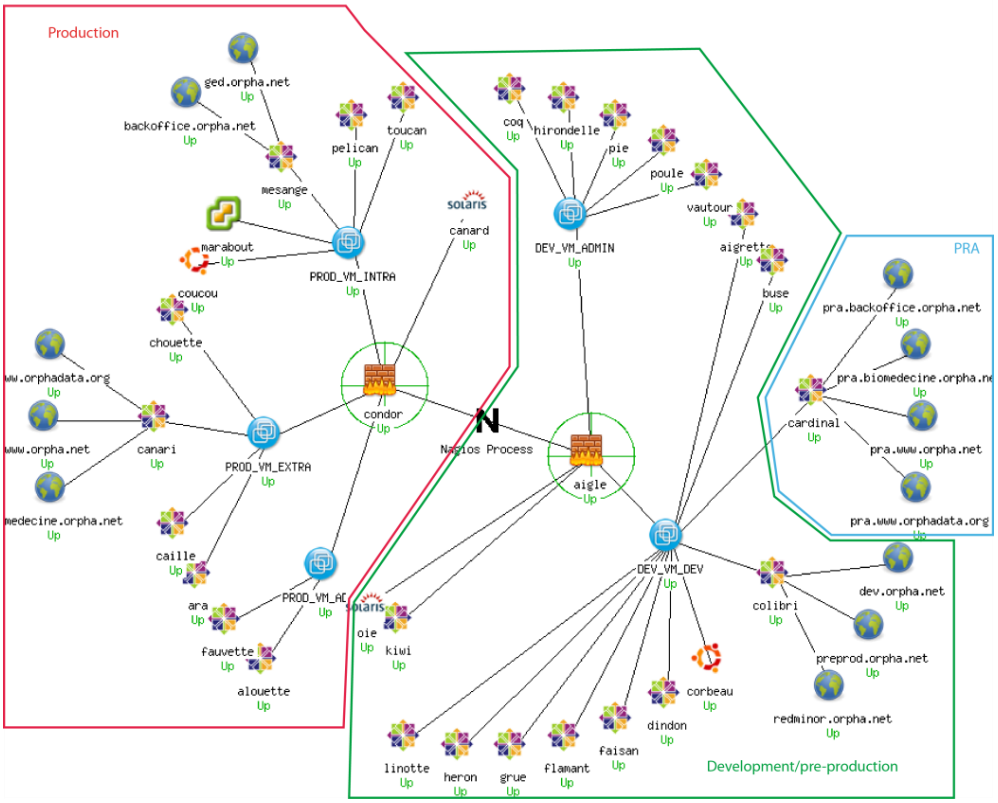


Figure 10 Orphanet's IT architecture in 2020

3.7. Orphanet services: The Orphanet website

The Orphanet website provides a user-friendly homepage with ergonomics that have been designed to provide easier access to the numerous services offered by Orphanet and to enhance usability, with specific emphasis on improving accessibility for visually impaired users (Fig 11). Indeed, the typeface is magnified and information is organised in easy-to-spot blocks with distinctive icons that allow users to more readily navigate the site. The disease search function is in the centre of the homepage.

Figure 11 The Orphanet portal homepage

Professionals and patient organisations can provide updates and add activities to the catalogue of expert resources via a secure account: these registrations are manually processed by the Orphanet local teams and undergo a quality control. Furthermore, the Orphanet website allows users to reach other Orphanet services: Orphadata, OrphaNews, Orphanet Report Series, and to interact with Orphanet, either through the expert registration service, or through the suggest and update functionalities.

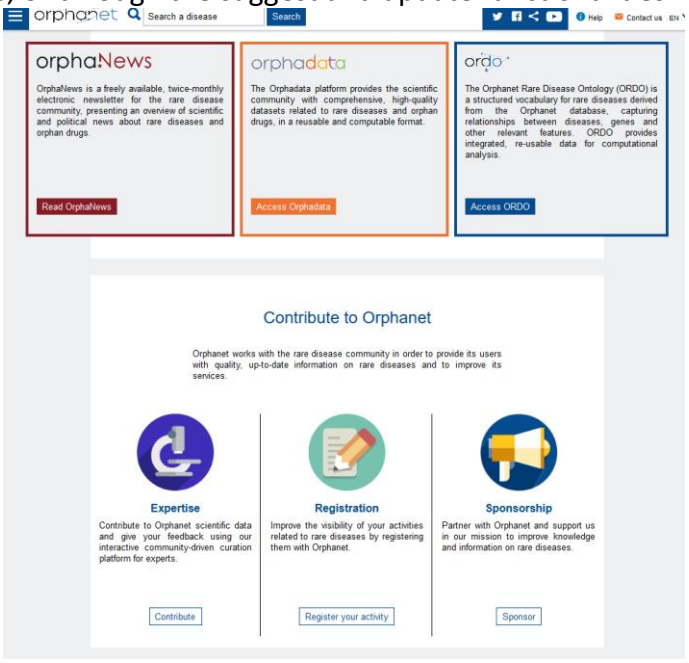


Figure 12 Access to Orphanet services and services for interaction with the curation team

3.7.4. INDEXATION BY SEARCH ENGINES

According to Google, the prominence of the www.orpha.net site can be assessed by the number of results obtained by using the site name as a query, for which there are 2410,000 responses.

Users mainly access the www.orpha.net site through search engines, namely organic searches (92% of sessions according to Google Analytics), and Google alone is the source of 91% of consultations (Figure 13). Organic searches correspond to listings on search engine results pages that appear because of their relevance to the search terms, as

opposed to them being from advertisements. Around 7% of visits come from users directly visiting Orphanet, without passing by a search engine, and the rest come from other sites' referral or social media referrals, for example.

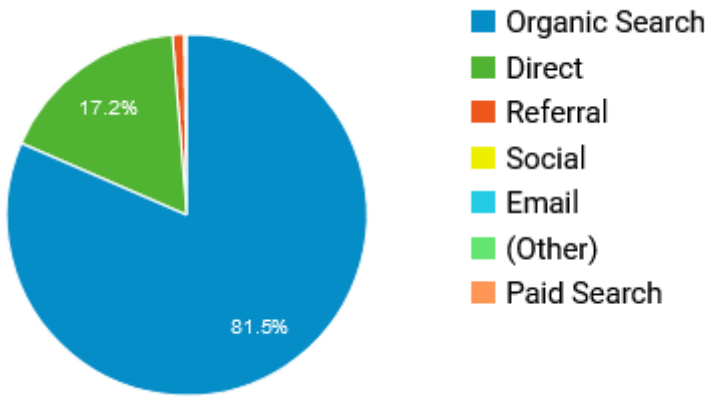


Figure 13 Distribution of the traffic sources
(Source: Google Analytics, 1 January 2021 to 31 December 2021)

The wealth of information available on our site attracts a substantial number of visits due to a sizable corpus of keywords (rather than just certain predominant keywords). The keyword primarily used to access our site is simply "Orphanet". The indexation of our site is of the "long tail" type: more than 55'556 keywords generated traffic to the site in 2021 according to Google Analytics

Google Analytics allows users to trace visits made from mobile devices (Smartphone, tablets): these visits represented 56 % of all visits during 2021, an increase of 6% when compared to 2020, after a marked decrease from 66% in 2019), perhaps a result of the different lockdowns across the world during 2020. The newest version of Orphanet has a responsive design and so provide a much better adaptation to any mobile device.

3.7.5. THE WEBSITE'S AUDIENCE

ORPHANET IN NUMBERS
- 42 million pages viewed
- 5.1 million PDFs downloaded
- Visits from 238 countries

In 2021, around 42 million pages were viewed (around 4 million less than in 2020), thus on average around 115'000 pages were viewed per day (Figure 14).

The Google Analytics tool does not include direct access to PDF documents. However, PDF documents are an important entry point and generate a consistent volume of visits: 5.1 million PDFs were downloaded from the site in 2021.

The users come from 238 countries. The top ten countries are: Italy, United States, France, Germany, Spain, Mexico, Brazil, Netherlands, Colombia, Belgium.

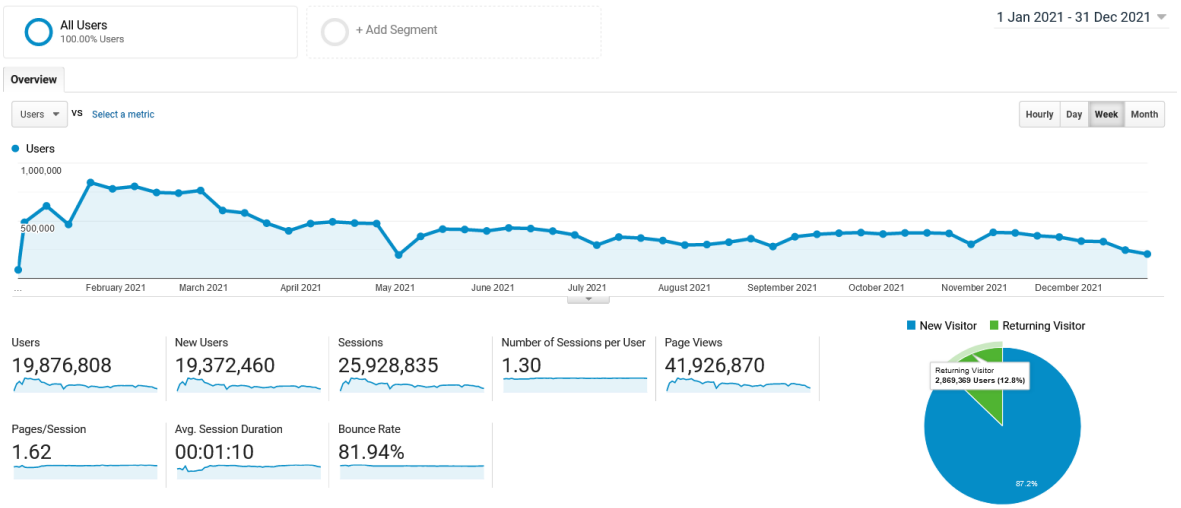


Figure 14 Orphanet website consultations in 2021
(Source: Google Analytics, 1st January 2021 to 31st December 2021)

The tool that is used to track our audience is Google Analytics. It allows 3 parameters to be monitored: sessions, users and page views (this shows a substantial ratio of page views / visitors). It should be noted that the current way in which users and sessions are counted is liable to change. For example, in 2014, the CNIL (*Commission nationale de l'informatique et des libertés* : the French data protection authority) recommended that websites inform users of the measurement tools used on the website, such as Google Analytics. During the summer of 2014 we developed a pop-up that requires users to accept this measurement. In case of refusal or inaction (no change of page for example), the user and the session are not properly recognised by the tool.

The number of sessions remained stable as compared to 2019 at around 26 million (Figure 15), and there was a 2.5% decrease in users as compared to 2020 (19,876,808); the number of pages per session decreased slightly from 1.63 1.62, the average session duration decreased by 6 seconds.

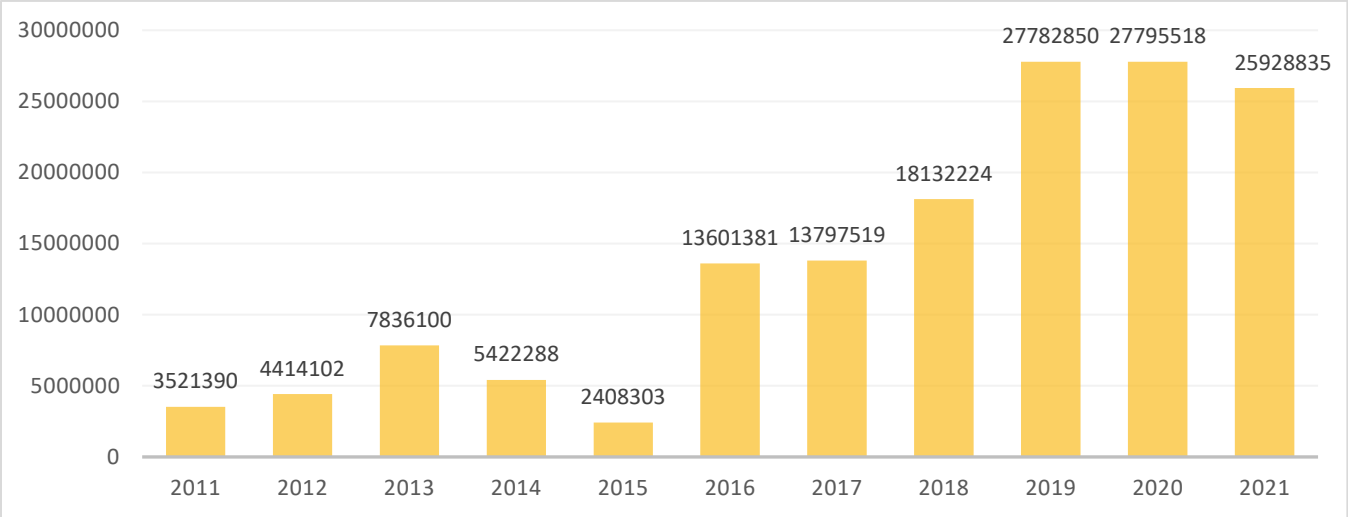


Figure 15 Evolution of number of sessions since 2011 (Source: Google Analytics)

3.7.6. ORPHANET NATIONAL WEBSITES

National websites dedicated to each partner country enable them to have an entry point in their national language(s). The national pages include information on national events, news and access to national policy documents concerning rare diseases and orphan drugs. Beyond the scope of national information, these pages provide access to the international database in seven languages.
As of 31 December 2021, 37 national websites are online. Some of these national websites are published completely in their national language while for other countries, the layout of the national webpage is in English and the mandatory texts (General Information) are in their respective national language.

3.8. Orphanet services: Orphanet Rare Diseases Ontology & HPO-Orphanet Ontological Module

The **Orphanet Rare Disease ontology (ORDO)** is available on three websites Orphadata, Bioportal, and the EBI Ontology Lookup Service.

Initially, ORDO was jointly developed in 2013 by Orphanet and the European Bioinformatics Institute (EMBL-EBI) to provide a structured vocabulary for rare diseases, capturing relationships between diseases, genes and other relevant features which will form a useful resource for the computational analysis of rare diseases. It is derived from the Orphanet database. It integrates nosology (classification of rare diseases), relationships (gene-disease relations, epidemiological data) and connections with other terminologies (MeSH, UMLS, MedDRA, GARD), databases (OMIM, Universal Protein Resource Knowledge

Base (UniProtKB), Human Genome Organisation Gene Nomenclature Committee (HGNC), ensembl, Reactome, IUPHAR, Genatlas) or classifications (ICD-10), complete epidemiological data, mappings and genetic annotations. The ontology is maintained by Orphanet and further populated with new data. Orphanet classifications can be browsed in the EBI's ontology lookup service (OLS). ORDO is updated twice a year and follows the OBO guidelines on deprecation of terms. It constitutes the official ontology of rare diseases. The availability of such relationships between medical terminologies allows RDs to be used as a "pivot" to connect different biological, clinical or genetic ontologies. This interoperability allows for the association of new content and the establishment of new research hypotheses on data that were not initially related to each other. ORDO is generated in English, German, Dutch, Spanish, French, Italian and Polish. This means that ORDO is available in all the Orphanet languages that have an Orphanet nomenclature in national language except Portuguese and Czech.

Orphanet provides phenotypic annotations of the rare diseases in the Orphanet nomenclature using the Human Phenotype Ontology (HPO). **HOOM, the HPO-Orphanet Ontological Module.** launched in 2018, is a module that qualifies the annotation between a clinical entity and phenotypic abnormalities according to a frequency and by integrating the notion of a phenotype being a diagnostic criterion. In ORDO a clinical entity is either a group of rare disorders, a rare disorder or a subtype of disorder. The phenomes branch of ORDO has been refactored as a logical import of HPO, and the HPO-ORDO phenotype disease-annotations (114'918 HPO-Disorder associations and 131,969 HOOM classes of which HPO-Disorder Associations) have been provided in a series of triples in OBAN format in which associations, frequency and provenance are modelled. HOOM is provided as an OWL (Ontologies Web Languages) file, using OBAN, the language used for the Orphanet Rare Disease Ontology (ORDO), and HPO ontological models. HOOM provides extra possibilities for researchers, pharmaceutical companies and others wishing to co-analyse rare and common disease phenotype associations, or re-use the integrated ontologies in genomic variants repositories or match-making tools.

In 2021, ORDO files were downloaded 18'798 times from Orphadata and Bioportal combined.

3.9. Orphanet services: Orphadata

Since Orphanet has become increasingly well known as the reference source for documentation on rare diseases, a growing number of requests for its high-quality data are received. To meet the needs of massive data extraction, Orphadata was created. Orphadata is intended to contribute to accelerating R&D and to facilitate the global

adoption of the Orphanet nomenclature. Orphadata was designated as an ELIXIR Core Data Resource at the start of 2019.

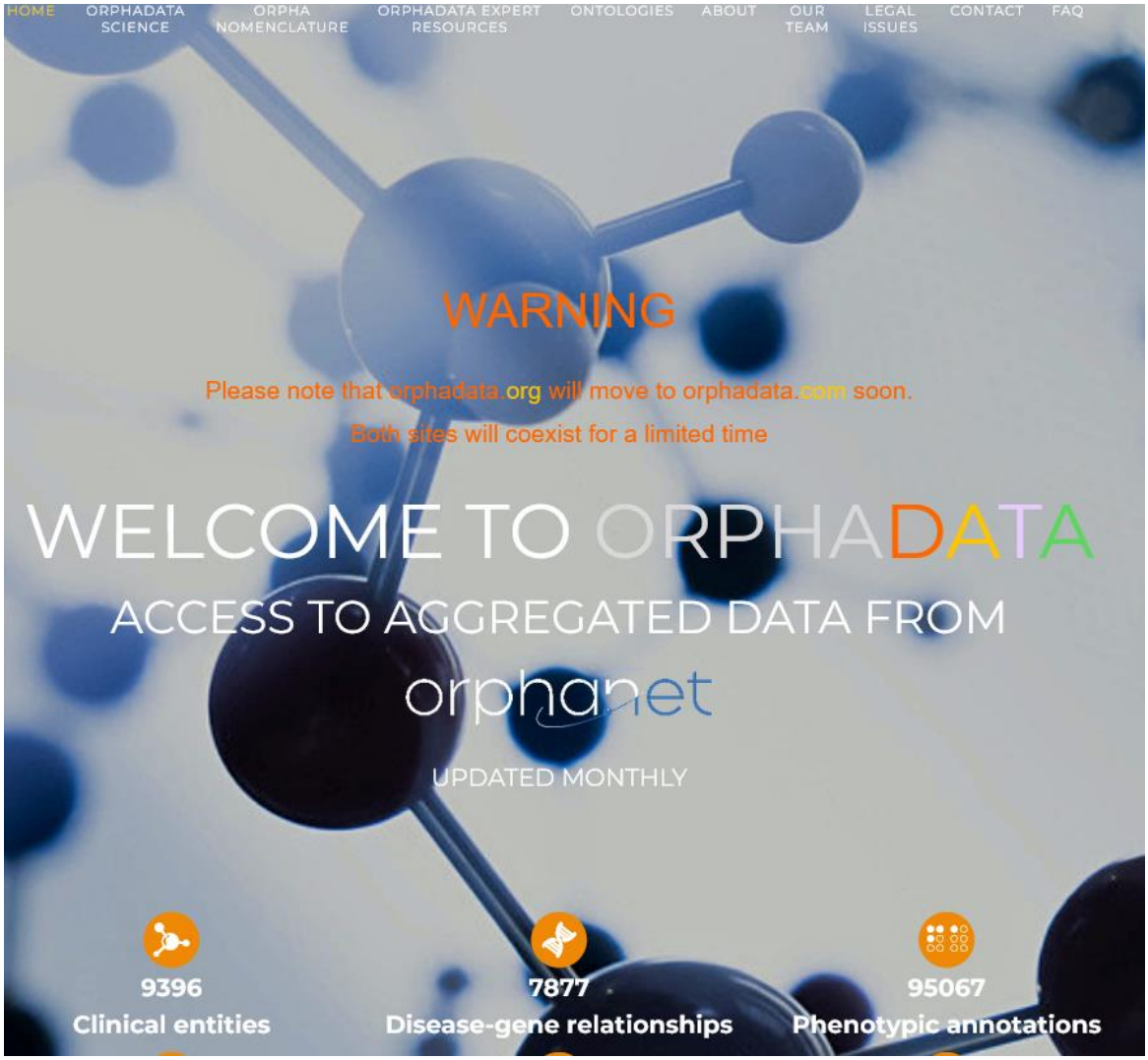


Figure 16 Screenshot of the Orphadata platform

Via this platform Orphanet datasets have been made directly accessible in a reusable format since June 2011. The data sets are available in nine languages: English, French, German, Italian, Portuguese, Spanish, Dutch, Polish and Czech. Part of the datasets are available freely via a Creative Commons licence (CC BY 4.0 from the start of 2019), and some are available via signature of a Data Transfer Agreement for academic research (Table 7) or a licence agreement for for-profit organisations/companies (Table 8).

• **An inventory of rare diseases, cross-referenced with OMIM, ICD-10, MeSH, MedDRA, UMLS, GARD and with genes in HGNC, OMIM, UniProtKB, IUPHAR and Genatlas. Annotations on typology of diseases and genes and of gene-disease relationships. Definitions for RD, XML and JSON format.**
• **A classification of rare diseases established by Orphanet, based on the literature and expert consensus classifications.**
• **Epidemiological data related to rare diseases based on the literature (point prevalence, birth prevalence, lifelong prevalence and incidence, or the number of families reported with respective intervals per geographical area, type of inheritance, interval average age of onset and age of death).**
• **Phenotypes associated with rare disorders (annotations using HPO terms), as well as their frequency.**
• **Linearisation of RD : for analytical purposes, each disorder is attributed to a preferred classification (linearisation) by linking it to the head of classification entity.**
• **Orphanet Rare Diseases Ontology (ORDO)**
• **HPO-ORDO Ontological Module (HOOM)**

Table 7 Products freely accessible on Orphadata (ELIXIR Core Data Resource)

• An inventory of Orphan Drugs at all stages of development, from EMA orphan designation to market authorization, cross-linked with diseases.
• Summary information on each rare disease in eight languages (English, French, German, Italian, Spanish, Portuguese, Dutch, Polish).
• URLs of other websites providing information on specific rare diseases
• A directory of specialised services, providing information on centres of expertise, medical laboratories, diagnostic tests, research projects, clinical trials, patient registries, mutation databases, biobanks and patient organisations in the field of rare diseases, in each of the countries in the Orphanet network.

Table 8 Products accessible on Orphadata after signature of a Data Transfer Agreement/licence agreement. Only non-nominative data are accessible, in accordance with personal data protection laws.
The dataset is updated once a month. The date of the last release is indicated.

Orphadata also gives access since 2019 to the "Nomenclature pack": this data set is specifically for use in coding setting and provides the computable information necessary to achieve the implementation of ORPHAcodes in Health Information Systems. These files are generated and made available once a year, in 9 different languages: Czech, Dutch, English, French, German, Italian, Polish, Portuguese and Spanish.

In the July 2021, following feedback from the RD-Code community, some additional products were included in the pack:

- A Linearisation dataset, that includes all rare diseases present in the Orphanet nomenclature (ORPHAcode and preferred term in English), each with the preferential medical specialty as attributed by Orphanet.
- A "Master file", initially developed in the framework of the EU RD-Action joint action, which contains the minimal information needed for satisfactory data sharing and statistical analysis at the EU level: all active ORPHAcodes present at the Disorder level only (i.e. excluding Groups and Subtypes), with their respective preferred term, synonyms, and aligned ICD-10 codes. This file, which is available in Excel format and in English only, provides a simplified visualisation of the Nomenclature file content, and easier access for users who are not in capacity of exploiting XML files and need a simple tool to help them code rare diseases manually.
- An Orphanet Nomenclature differential file, that enlists all clinical entities that have been created, inactivated (deprecated, obsolete, and non-rare entities), or modified (preferred term, synonyms, definition, aggregation level, etc.) since the previous release.

Orphadata provides a documentation for users that defines and describes the elements of the dataset and gives access to Orphanet procedures relevant to the users of the data, such as the *procedure for producing the nomenclature*, the *methodology of alignment of ICD10 coding rules for rare diseases* , *methodology of linearisation, procedures for the epidemiological data collection in Orphanet*, and *procedures for the inventory of genes related to rare disease*.

The XML models for Orphadata products, and UML schema for ORDO are published on Orphadata. A number of communication documents were also produced in order to explain to users the contents of each of the datasets, as well as ORDO (the Orphanet Rare Disease Ontology) and HOOM (HPO-ORDO Ontological Module), and thus facilitate the use and reuse of the data and tools available via the platform.

In 2021, **Orphadata products (free and on request) were downloaded more than 191,600 times**. This represents a decrease of around 87% compared with 2020 (Figure 17); 2020 was a rather anomalous year as we notice a massive increase in the download of our classifications in 2020, whilst the downloads of the other datasets available was largely stable. The number of downloads in 2021 returned to more classic rates, with a 60% increase compared to 2019.

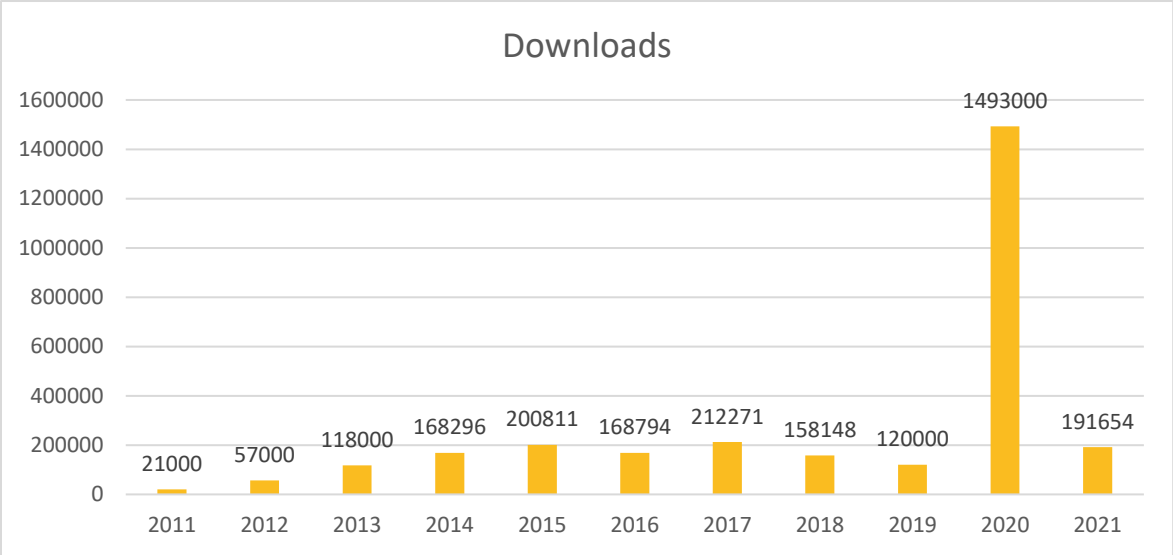


Figure 17 Number of downloads from the Orphadata website since mid-2011. It should be noted that in 2020 there was a massive download of the classifications datasets that constituted an anomaly that has not since been reproduced.

The most requested Orphadata product in 2021 were the classifications of rare diseases (Figure 18 and 19).

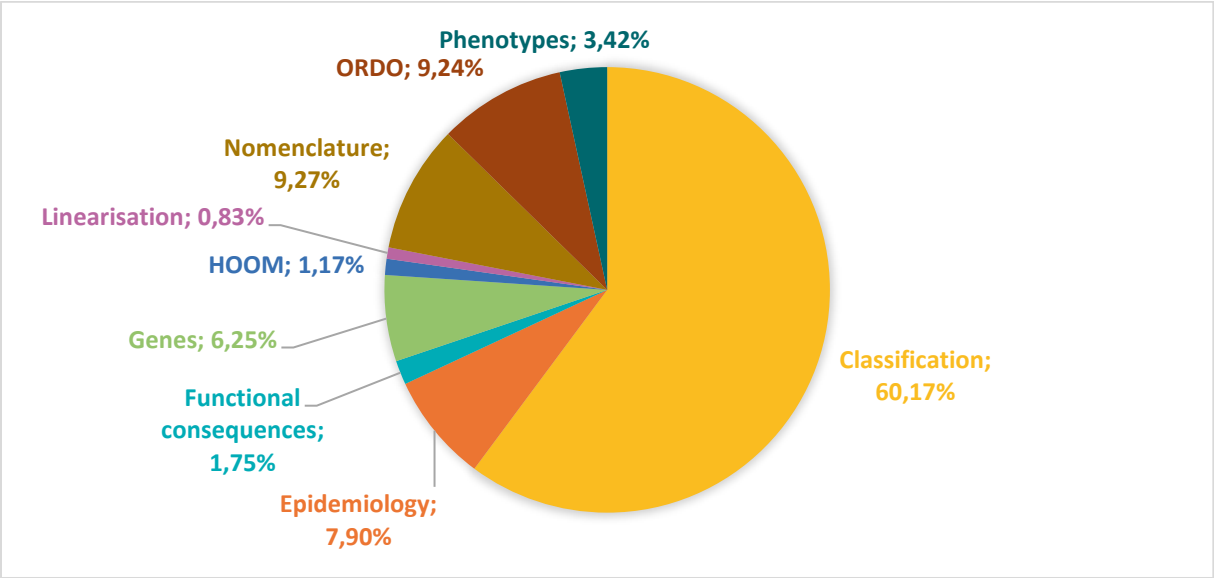


Figure 18 Distribution of the downloads of Orphadata freely available datasets in 2021 [total 177,543 downloads]

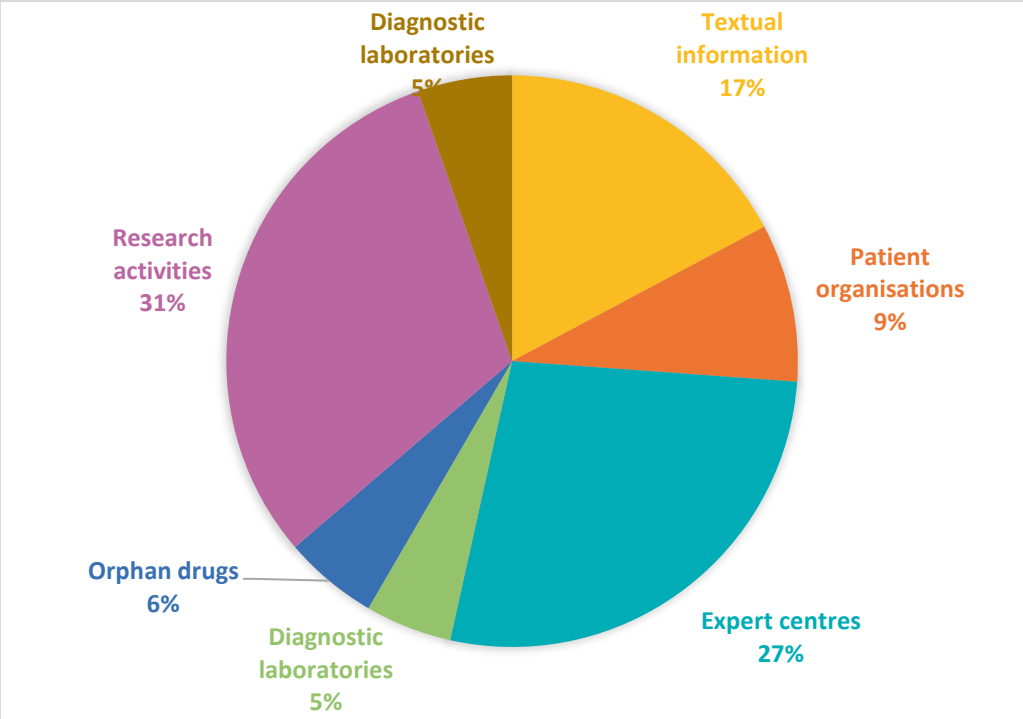


Figure 19 Distribution of the downloads of Orphadata Datasets accessible on demand in 2021 [total of 1,610 downloads]

3.9.4. ADDITIONAL FUNCTIONALITIES IN 2021

The nomenclature of rare diseases was made available in Chinese and Turkish in 2021 on a yearly basis.

An expanded Nomenclature Pack was launched in 2021 with additional files to ease codification of rare diseases (see above).

3.10. Orphanet Services: The OrphaNews Newsletter

OrphaNews is a bimonthly newsletter for the rare disease community, presenting an extensive overview of scientific and political news about rare diseases and orphan drugs. Subscription to this newsletter is free. A literature survey is performed twice a month in order to update the Orphanet database and to collect both scientific and political news to report in OrphaNews. The selection of articles for the newsletter is validated by a multidisciplinary editorial board. News is also submitted from contact points in each of the Orphanet consortium countries.

OrphaNews International was supported by the European Commission's DG SANTE (PP-1-2-2018-Rare 2030) until the start of 2021, and is realised with the support of Fondation IPSEN, under the aegis of Fondation de France, from September 2021. OrphaNews France is supported by the French Muscular Dystrophy Association (AFM-Téléthon), while OrphaNews Italy is supported by Sanofi-Genzyme.

Figure 20 OrphaNews homepage

In 2021 OrphaNews in English had 11, 867 subscribers. OrphaNews in French had 7,041 subscribers and OrphaNews in Italian had 5,464 subscribers.

In order to help professionals and people living with rare diseases find expert recommendations and services concerning COVID-19 and rare diseases, Orphanet published a list of resources available in different languages from March 2020 in a special edition of OrphaNews. This list includes resources curated by the European Reference Networks and EURORDIS and is updated regularly, most recently integrating recommendations concerning vaccination.

3.11. Orphanet Journal of Rare Diseases

Orphanet Journal of Rare Diseases (OJRD) is an open access, online journal that encompasses all aspects of rare diseases and orphan drugs. The journal publishes high quality reviews on specific rare diseases. In addition, the journal may consider articles on clinical trial outcome reports, either positive or negative, and articles on public health issues in the field of rare diseases and orphan drugs. OJRD was indexed in Medline at the end of its first year of existence (2006) and was selected by Thomson Scientific after only two years of being in publication. Its 5-year impact factor is 4.839. Articles have been downloaded over 2,967,555 times as of end 2021. Springer Nature, the publishing house hosting the OJRD, has signed the San Francisco Declaration on Research Assessment (DORA) that intends to halt the practice of correlating the journal impact factor to the merits of a specific scientist's contributions.

Figure 21: Orphanet Journal of Rare Diseases Homepage

4. Users: 2021 satisfaction survey

The 2022 satisfaction survey, assessing satisfaction for the year 2020, was conducted in one phase launched in January 2021 via a popup window appearing on the first page users landed on. The survey was translated into 8 out of the 9 languages of the website (i.e. English, French, Spanish, Italian, Portuguese, Dutch, German and Polish). A total of 9, 389 users gave answers to the questions this year. The results were analysed and presented in a dedicated Orphanet Report, with highlights presented here.

The largest categories of respondents are patients and their entourage including patient organisations (38%) and healthcare professionals (35%). Students also replied the survey (14%), followed by reseachers and users working in education / communication (respectively 4% and 3%).

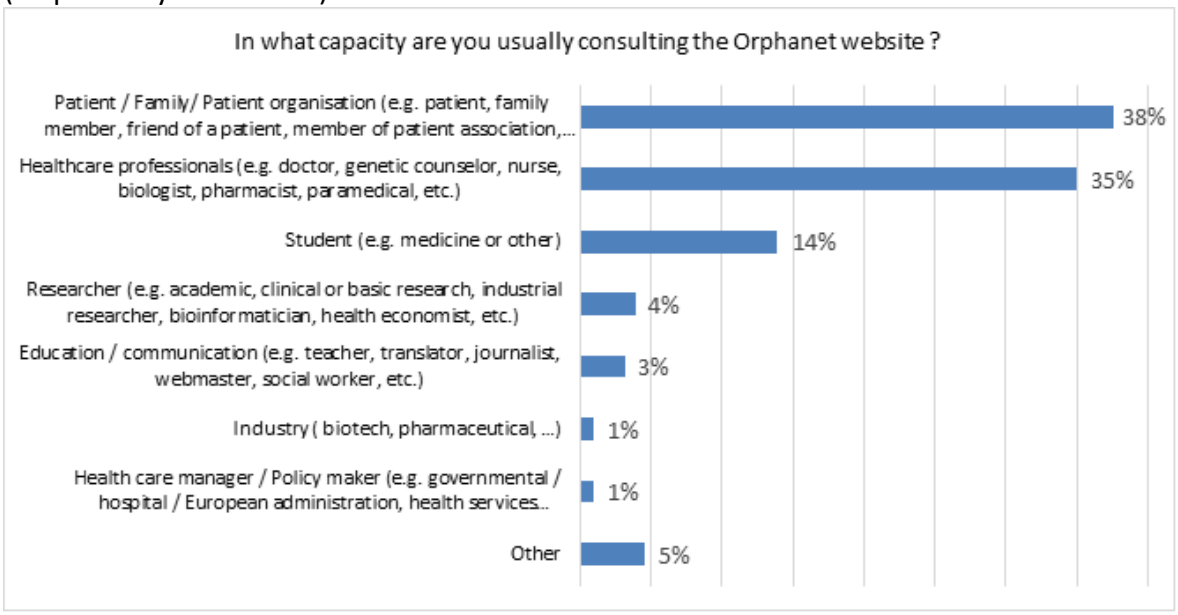


Figure 22: Composition of Orphanet users

The results show that most of the respondents (more than 90%) find that the Orphanet website is user-friendly, that the information is easy to find and that once it is found the information is easy to read and understand.

Services and products giving scientific information on rare diseases (summary texts, clinical signs, epidemiological data, disabilities, etc.~~s,...~~) are the best known. The most useful products for the respondents are the disease summary texts and the clinical signs associated to a rare disease (respectively 90% and 89%) followed by classifications of rare diseases and epidemiological data (84% for both), then functional consequences of rare diseases (81%). This trend is the same as last year with a slight increase in usefulness for disease summary texts (87% last year). The inventory of genes involved in rare diseases is a very useful service for 79% of the respondents, followed by the Orphanet nomenclature of rare diseases / ORPHAcodes and articles produced by other journals and published on the Orphanet website (72% for both).The vast majority of respondents were either very satisfied or satisfied with Orphanet with a total of 97% responding positively.
Thanks to the survey, Orphanet's Net Promoter Score (NPS), which measures the likelihood, on a 1-10 scale, that someone will recommend a company to someone else was calculated. 65% of those responding turned out to be promoters as they responded with a score of 9 or 10, 27% were passive (score of 7 or 8) and 7.5% were detractors (score of 0 to 6). This gives a NPS of 57,7.
To our knowledge, Orphanet is the only service dedicated to providing free information on rare diseases and orphan drugs, that publishes its NPS. Thus, we cannot compare this score to other similar services but is useful in measuring our customer satisfaction when tracked. This score has greatly increased in the last 2 years : 2021 survey, NPS was 54,3 (n=5,299) and 2019 survey , NPS was 47,8 (n=4,199).

Moreover, it is noteworthy that according to these results 65% of the respondents would recommend using Orphanet while only 7.5% would not.

5. Networking: Orphanet's national and international collaborations

Orphanet believes in the effectiveness of sharing data and expertise in order to achieve a deeper understanding of rare diseases and to address the specific needs of different stakeholders.

Thanks to the internally produced, expert-reviewed scientific information that Orphanet offers on rare diseases, Orphanet is often solicited by many different projects to contribute its expertise.
It is for these reasons that new collaborations and partnerships are developed regularly, resulting in the intense scientific collaborative activity described below.

5.1 National plans or strategies for rare diseases

Orphanet teams actively participate in the preparation of National Plans or Strategies for Rare Diseases as they are recognised as experts at the national level. A table resuming the inclusion of Orphanet activities in national plans and strategies for RD is available here.

Orphanet is mentioned either as the reference portal for rare diseases or main source of information on rare diseases in the recommendations and proposed measures of the majority of national plans or strategies adopted to date. The countries below have provided additional information concerning support to Orphanet in national plans and strategies for rare diseases.

Czechia

Orphanet is part of the Third National Plan for Rare Diseases, in particular citing support for the Orphanet nomenclature in Czech to improve coding for rare diseases in health information systems.

Germany

Orphanet Germany is according to the German Action Plan on Rare Diseases, the central information platform in this respect.

The Netherlands

The Minister of Health, Welfare and Sport in the Netherlands appointed the NFU, the Netherlands Federation of University Medical Centers, to coordinate the identification and registration of Dutch centers of expertise for rare diseases together with Orphanet Netherlands and the VSOP (Dutch national patient umbrella organization for rare and genetic disorders). A procedure was developed in which an independent designation committee, advised by medical experts and patient organizations, evaluates potential centers of expertise according to the EUCERD criteria established at the European level. These criteria include the presence of guidelines, protocols, standards and indicators of care, and equally evaluate scientific research, the relationship with patient organization(s) and how the continuity of the center is ensured within the institute. Since this year the application of candidate centers should follow as much as possible the thematic structure of the European Reference Networks (ERNs) to facilitate a smooth collaboration between the centers of expertise and ERNs. Centers from both University Medical Centers and non-university major "top-clinical" hospitals are invited to apply for designation. More information regarding the application and evaluation process is published on the NFU website (in Dutch; https://www.nfu.nl/themas/zorg-op-de-juiste-plek/zeldzame-aandoeningen/vws-erkenning-ecza-jaarlijkse-aanvraagronde). Between the start of the project, in 2015, and 2020, 3 rounds of evaluation took place. From this year on evaluation rounds will take place in a yearly cycle. Currently (results from the evaluation round of 2021 aren't included yet) ~340 medical centers are designated by the Ministry as official Dutch centers of expertise for rare diseases. These centers can be found on the Orphanet website or by using the 'Expertisezoeker' (https://www.expertisezoeker.nl/) developed by the Erfocentrum.

Italy

The **Italian Health Ministry included Orphanet as a reference** in the new version (July 2016) of the Ministerial Decree of December 09, 2015, on Prescription Appropriateness (Italian title of the Decree: "Condizioni di erogabilità e indicazioni di appropriatezza prescrittiva delle prestazioni di assistenza ambulatoriale erogabili nell'ambito del Servizio sanitario nazionale"). The Decree sets up specific conditions for laboratories performing genetic tests in Italy ("Condizioni di erogabilità", as reported in "Allegato 1" of the Decree). In particular, with regard to genetic tests, the document contains the following reference to Orphanet database: "In order to identify single genes, refer to genes reported in the Orphanet database with diagnostic value"). This reference to Orphanet into the Italian legal framework marks an important milestone in its consolidation as a legitimate source of information on rare diseases in Italy. Orphanet was also highly mentioned in the National Plan for Rare Diseases 2013-2016 and the Ministry of Health identified Orphanet as a reference source of information for rare diseases and orphan drugs.

Portugal

The Ministry of Health of Portugal was recommended by the Assembly of the Republic to implement the Integrated Strategy for Rare Diseases, based on an interministerial, intersectoral and interinstitutional cooperation, which makes a complementary use of medical, social, scientific and technological resources.

The Integrated Strategy for Rare Diseases has the mission of developing and improving:

1) Coordination of care;
2) Access to early diagnosis;
3) Access to treatment;
4) Clinical and epidemiological information;
5) Research;
6) Social integration and citizenship.

This Interministerial Commission aims to combat the vulnerability of this population group by reducing the dispersion of information on these diseases, increasing access to diagnostic and therapeutic interventions as well as better referral in the health system. It also aims to improve health literacy of patients, families and caregivers.

Orphanet was recognised as a reference portal and credible source of information on rare diseases, their characteristics, diagnostic and possibilities of treatment, thus being an instrument for improving clinical and epidemiological information on rare diseases.

Under this strategy, a Card of People with Rare Diseases (CPRD) was implemented:

- To ensure access to relevant clinical information, to health care professionals, specially focusing on good practice recommendations in acute care;
- To improve the integrated management of the disease to avoid delay, error and harmful procedures;
- To guarantee the correct referral to Reference Centres;
- To improve continuity of care, between all the levels of care;

This card includes the name and the ORPHAcode of the rare disease, and the name and contact of the Reference Centre. The card is available at the national web-based patient clinical record.

Over the past 5 years, health professionals and facilities have been increasingly interested in requesting CPRD, and up to December 2018, 6112 CPRD were requested. Recognising that coding rare diseases through ORPHA codes is constantly evolving, along with genetic research, the catalogue of rare diseases available at the CPRD was updated during 2018, allowing higher accuracy and updates of the rare disease diagnosis. Additionally, in 2018 a Manual to Support People with Rare Diseases was published which compiles a set of information dispersed in several public institutions, relevant for people with rare diseases.

5.2. Nomenclature and terminologies

ADOPTION OF THE ORPHANET NOMENCLATURE IN HEALTH INFORMATION SYSTEMS

To improve the traceability of rare diseases in health information systems and to increase the recognition of each rare disease in national health and reimbursement systems, Orphanet has developed an evidence-based standardised nomenclature: the ORPHA nomenclature. It is composed of a unique and stable ORPHA number for each entry of the inventory. The ORPHA number can be used for codification purposes.

In 2014, the Commission Expert Group on Rare Diseases adopted a recommendation on ways to improve codification for rare diseases. In this document, Member States are encouraged to consider and explore the feasibility of the use of ORPHA codes at a national level and to include the codification of rare diseases as an area of their national plans/strategies for rare diseases. Support for the large number of Member States who have already expressed their interest in using ORPHA codes (as a complement to existing coding systems) is provided via a dedicated work package (WP5) of the Joint Action for rare diseases RD-ACTION (www.rd-action.eu). This work package has notably produced a survey of current codification situations in the Member States, a review document of existing technical implementations for RD coding, and a Standard procedure and guide for coding with Orphacodes, as well as a beta version of a master coding file, and specifications for the implementation of this file. Specifications for an integrated coding application with Orphacodes have also been produced. Finally, a mapping exercise of the use of ORPHA codes in Europe was carried in 2017.

Following the recognition of the Steering Group on Promotion and Prevention (SGPP) od ORPHAcodes as best practice, RD-CODE (www.rd-code.eu/), co-funded by the Third Health Programme, started on January 2019 and ended in December 2021. The objective of this project is to support Member States in improving gathering information on rare diseases by implementation of ORPHA codes.

Starting with countries that had not yet introduced ORPHA codification yet, but that are already actively committed to doing so, this project aimed to demonstrate real-world implementation to guide other countries in the future.

Amongst the resources and tools made available are:

- A **video** explaining the benefits of using ORPHAcodes in Health Information Systems

- A suite of **ORPHA tools**, including the Orphanet nomenclature files for coding purposes, and APIs and tools to aide implementation and coding decision-making (http://www.rd-code.eu/tools/)
- A **virtual helpdesk** with information on the nomenclature and page dedicated to answering questions on nomenclature content and integration in health information systems.
- A new **ORPHAcode to capture remaining undiagnosed patients** after full investigation.

In addition to these tools, **support services, and information resources, guidelines and recommendations** have been developed and refined within the project according to real-world use of ORPHAcodes. A lessons-learned leaflet and public report have also been issued. These are indispensable tools to guarantee the appropriate use of the coding resources allowing comparability across countries and settings.

In RD-Code 4 countries who had no systematic implementation of ORPHA codification yet participated: Czech Republic, Malta, Romania and Spain. Additional countries countries have already taken some concrete steps in implementing ORPHAcodes in their healthcare systems (Portugal, Germany, France, Belgium, Italy, Norway, Latvia, Czech Republic, Hungary, Cyprus, Switzerland).

Czech Republic

ORPHAcodes are utilised in collaboration with Czech Society of Medical Genetics and Genomics and the General Health Insurance Company for the pilot reimbursement of extra funding for members of the Czech members of the European Reference Networks for Rare Diseases and for reimbursement of next generation sequencing in rare diseases.

France

In 2012, it was decreed that the French hospital system database would use ORPHA codes to code all hospitalised patients. The aim was to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways. Within the French third National Plan for Rare Diseases and also because of the development of electronic health records in France, the French Ministry of Health set up in 2015 an advisory committee for the codification of RD in which Orphanet played a major role. A governmental memo was released in January 2016[6], aimed at centres of reference and centres of competence, making the codification of rare disease patients with ORPHA codes mandatory in the French Rare Diseases Data Repository BNDMR. Orphanet and the BNDMR have developed guidance documents for the codification of rare diseases in the BNDMR. The French Networks of Expertise (Filières de santé maladies rares) are in charge of producing coding guidelines in order to improve quality and consistency of coding in their disease fields. ORPHA codes are being implemented in electronic health records progressively, as the rare diseases minimum dataset is.

[6] http://circulaire.legifrance.gouv.fr/pdf/2016/01/cir_40460.pdf

Germany

After conclusion of the 6 year project on coding of rare diseases which intended to integrate the Orphanet classification of diseases by adding ORPHAcodes and by expanding the inventory of rare diseases within the ICD-10-GM a better alignment of German disease terms within both database systems lead to more congruence between both systems. Now the implementation of the resulting file (Alpha-ID-SE) in Centres of expertise for rare diseases in Germany is ongoing.

The Netherlands

To prepare for the implementation of ORPHAcodes in the Dutch hospital information systems a working group of DHD (Dutch Hospital Data), Nictiz and Orphanet Netherlands checked the alpha mapping file in which SNOMED concepts are linked to specific ORPHAcodes. Several suggestions for modifications and new mappings were sent to both SNOMED International and the coordinating Orphanet team.

Italy

In 2017, ORPHA codes were integrated into the health and research information systems of eight Italian regions. The new national plan regarding the policies on rare diseases (LEGGE 10 novembre 2021, n. 175 Disposizioni per la cura delle malattie rare e per il sostegno della ricerca e della produzione dei farmaci orfani) has been released in November 2021. The article 4 states that the updated list of rare diseases/groups of rare diseases to be covered by the Essential Levels of Care, must refer to the ORPHA codes and to the Orphanet classification system. The ORPHAcode is implemented and currently used by 10 Italian Regions/Regional Registries for rare diseases.

Portugal

The ORPHA nomenclature supports the registration of rare diseases at all NHS levels of care, being the mandatory classification to be used by all rare disease reference centres and by CPRD. The Portuguese Health Information System of the Ministry of Health purchased a licence for the use of SNOMED-CT in the country since January 2014. This licence allows its distribution and use free in Portugal. Access is available to health professionals, the Information and Communication Technologies (ICT), researchers, and all those who are interested in using the terminology.

The Ministry of Health of Portugal was recommended by the Assembly of the Republic to implement a personal card for people with rare disease in order to give them a special status in the health system. In the end of 2013, a card of people with rare diseases was issued. This card is being distributed, since 2014, to patients and it includes relevant information such as, the name and the "ORPHA code" of the disease; the name and contact of the Reference Centre and it has on its back-side specific health recommendations (totally addressed for each patient) to be provided in case of emergency.

5.2.4. COLLABORATION WITH THE WHO

The World Health Organisation (WHO) and Orphanet collaborate on the revision of the International Classification of Diseases (ICD-11).

Orphanet has been entrusted as the operating institution to prepare the proposal for ICD-11 related to rare diseases. The Rare Diseases Topic Advisory Group (RD-TAG) has therefore managed the process of the preparation and peer-review of proposals in order to include rare diseases in every relevant chapter of the electronic version of ICD-11. In 2013, the beta version of ICD-11 was released. To date, 57% of RD in Orphanet are represented in the ICD Joint Linearisation for Mortality and Morbidity Statistics . Expert links to Orphanet are transmitted to maintain up-to-date definitions. A mapping file between ICD11 and ORPHA codes is under production and will be released by Orphanet in 2021. Orphanet contributes to the enrichment of ICD-11 with rare disease terms, as part of the French WHO collaborating center since 2021.

A collaboration is also underway with the WHO's ICTRP (International Clinical Trials Registry Platform) (https://www.who.int/ictrp/en/) and Orphanet. ICTRP aims to offer a complete view of clinical research, which is accessible to all those involved in health care decision-making. It includes therefore rare diseases. The collaboration is aimed at making clinical trials on rare diseases easily identifiable and findable, thus improving knowledge on rare diseases. ICTRP and Orphanet will work to identify and flag all rare disease related clinical trials in the ICTRP database for its users. Rare disease related clinical trials are identified using the Orphanet nomenclature of rare diseases. Clinical trials for rare diseases are exported into the Orphanet database, where additional information is available, in particular the rare disease concerned, the category of clinical trial, and the medicinal product in development, amongst other information. ICTRP users will be able to see all RD-related clinical trials in the Orphanet and IRDiRC countries. This will contribute to raising awareness of rare diseases and facilitating access to the most recent information on clinical trials in the field of rare diseases. This collaboration strengthens Orphanet's position as a reference database in the field of rare diseases by providing an exhaustive clinical trials registry, and will assure that ICTRP users can easily identify clinical trials for rare diseases (http://apps.who.int/trialsearch/).

5.2.5. COLLABORATION WITH SNOMED INTERNATONAL

A collaboration with SNOMED International is ongoing in order to include RD lacking in SNOMED-CT, and to provide alignments between ORPHA codes and SNOMED-CT terms. It will help with the identification of patients with RD in health information systems in countries having adopted SNOMED-CT. The first alignment file was made available in

October 2021, distributed alongside SNOMED CT by SNOMED International to its licensed members in a machine-readable format, and by Orphanet via Orphadata in a human-readable format.

5.2.6. Collaboration with NIH-NCATS' Genetic and Rare Disease Information Center

A partnership was established between Orphanet and the Genetic and Rare Disease Information Center (NIH-NCATS) in 2016. One of the aims of this partnership was to mutualise efforts so as to provide the audiences of both sites with the most complete and up-to-date information on rare diseases. In a first step, the Orphanet and GARD nomenclatures were aligned, so as to allow cross-referencing between the two resources. These alignments can be visualised on the disease identity card on the Orphanet website, and are also included in the nomenclature and cross-references file available on Orphadata.

5.3. Catalogue of services

Portail Romand des Maladies Rares

A collaboration is in place with the Swiss 'Portail Romand des maladies rares' (www.infomaladiesrares.ch) in order to improve the visibility of expert centres on rare diseases registered in Orphanet in Romandy.

5.4. Scientific collaborations and partnerships

5.4.1. Current

Partnership with The International Rare Diseases Research Consortium

IRDiRC was launched in April 2011 to foster international collaborations in rare disease research. IRDiRC united researchers and organisations investing in rare disease research in order to achieve two main objectives, namely to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases by the year 2020. In 2017, such considerable progress was made towards these goals that three new goals were adopted, namely: all patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature, 1000 new therapies for rare diseases will be approved, and methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.

Orphanet collects data on research-related activities funded by IRDiRC members, which are research funding agencies. This requires the expansion of data coverage to new countries such as the United States and South-Korea or South-Africa, amongst others. Thanks to European Commission co-funding (under Support-IRDiRC project and the European Joint co-fund Programme for Rare Diseases, EJP RD), Orphanet has coordinated the development of a rare disease research analysis platform made available to IRDiRC and Orphanet members allowing for easily landscape the research situation and to contribute building a RD research strategy in the IRDiRC realm.

Orphanet also provides regular data analysis for the following indicators on the IRDiRC website on a yearly basis: number of new RD, number of genes linked to RD, and number of medicinal products with an orphan designation and marketing approval for the treatment of RD in the US and/or Europe.

Orphanet hosted the IRDiRC Scientific Secretariat from 2011 to 2018 under the Support-IRDiRC contract. The scientific secretariat was then transferred to another service at the Inserm (ITMO GGB), in the framework of the European Joint Programme on Rare Diseases (EJP RD). In the context of this new organisation, Orphanet remains responsible for the curation of the database of research projects and clinical trials, as well as for the production of indicators.

Collaboration with the European Bioinformatics Institute

Collaboration was established with the **EMBL - EBI** at the end of 2011 to cross-link Orphanet's database with their genomic and their biological pathway data resources (ensembl and Reactome) and is currently ongoing, with cross-references being regularly updated.

Orphanet and EMBL-EBI have jointly developed the **Orphanet Rare Disease Ontology** (ORDO) and in 2014, a new version of this ontology was launched (ORDO 2.0) in collaboration with the EBI; subsequent versions have been produced by Orphanet. The Ontology is updated twice a year.

Collaboration with the French Institute of Bioinformatics – ELIXIR FRANCE

Orphanet is a French Institute of Bioinformatics' contributing platform. The IFB is a national bioinformatics infrastructure bringing together platforms from the main players in research in France: CNRS, INRA, INRIA, CEA and the INSERM, as well as the Curie and Pasteur Institutes and French universities. At the moment, 20 platforms are full members, 7 contributing platforms, and 8 associated teams. The IFB's primary mission is to provide the basic services and resources in the field of bioinformatics for scientists and engineers working in life sciences. Notably, IFB is the French node of the European research infrastructure ELIXIR.

ELIXIR is a distributed infrastructure for life-science information, uniting Europe's leading life science organisations in managing and safeguarding the massive amounts of data being generated every day by publicly funded research. ELIXIR coordinates and develops life science resources across Europe so that researchers can more easily find, analyse and share

data, exchange expertise, and implement best practices. This makes it possible for them to gain greater insights into how living organisms work. As a platform of the IFB, Orphanet is also part of this European research infrastructure, offering data and a bio-ontology of rare diseases to advance research in this field.

After having participated in an ELIXIR pilot use case on rare diseases in the context of the EXCELERATE project and having been included in the ELIXIR Biosharing platformat the start of 2019 the free-access datasets from the Orphanet database provided on Orphadata were designated as an ELIXIR Core Data Resource. The knowledge bases singled out as Core Resources, to which Orphanet now belongs, work as « conceptual authorities » with a clear role in the standardisation of evolving concepts. Orphanet will play this role for rare diseases within the scientific community. The Core Data Resources are also at the core of ELIXIR's long-term sustainability strategy as a European infrastructure for information and life sciences data. ELIXIR aims to ensure that these resources are available long-term and that the life-cycles of these resources are managed such that they support the scientific needs of the life-sciences, including biological research. As a Core Data Resource Orphanet will pursue its work to develop and maintain quality standards for its scientific data and will move forward to adopt FAIR data principles.

Collaboration with NIH-NCATS Genetic and Rare Disease Information Center (GARD)

A partnership between Orphanet and the Genetic and Rare Disease Information Center (NIH-NCATS) was established in 2016. The aim of this partnership is to mutualise efforts so as to provide the audiences of both sites with the most complete and up-to-date information on rare diseases. In a first step, the Orphanet and GARD nomenclatures were aligned, so as to allow cross-referencing between the two resources. In a second step, summary texts from Orphanet (along with a link to the relevant Orphanet disease page and the Orphanet logo) have been included in GARD for the diseases for which GARD does not have a text. This cross-Atlantic partnership, maintained through regular calls, improves the visibility of Orphanet in the United States and is just one of the ongoing efforts to integrate the Orphanet nomenclature, in particular, into the different rare-disease related resources maintained by the NIH (e.g. UMLS, ClinVar, MedGen, GTR).

Collaboration with the World Health Organization

Orphanet contributes to the enrichment of ICD-11 with rare disease terms, as part of the French WHO Collaborating Center in partnership with the French Digital Health Agency since 2021.

Gene Curation Coalition

Orphanet is one of the founding members of the Gene Curation Coalition (GenCC), a coalition composed of several groups and resources providing information on validity of gene-disease relationships. GenCC has created a database bringing together this data: curated gene-disease relationships are submitted by GenCC member organisations, including Orphanet. By providing harmonised definitions for different levels of gene–disease validity based on existing resources, GeneCC aims resolve curation conflicts, thus permitting better consistency in genetic testing and variant interpretation.

MAPI RESEARCH TRUST

Orphanet co-leads WP3 of the European Project ERICA, which has the general aim of facilitating the Europe-wide implementation of standardised Patient-Centred Outcome Measures (PCOMs) and Patient Reported Outcome Measures (PROMs) for rare diseases while ensuring the involvement of the patient community in their development and validation process. Orphanet contributes to this work with the Disabilities annotations and collaboration with MAPI Research Trust in order to assess what PCOMs and PROMs are already available and what are the gaps, and which could be exploited for more than one disease. Outside the scope of this project, Orphanet is working towards linking to MAPI's PROQOLID database in order to provide links from Orphanet to PCOMs and PROMs.

5.4.2. PAST

PARTNERSHIP WITH RARECARENET & JOINT ACTION ON RARE CANCERS (JARC)

From mid-2013, Orphanet has had a partnership with **RareCareNet**, providing them with information on expert centres and rare cancer patient organisations. RareCareNet in return provides Orphanet with information on the epidemiology of rare cancers, and a common effort is currently performed in order to agree on the classification of rare cancers. This work continues in the context of the EU Joint Action on Rare Cancers, which ran from 2016 to 2019 (www.jointactionrarecancers.eu). This Joint Action aimed to integrate and maximise efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers. Orphanet was involved in a number of the work packages, in particular on issues such as the collection of epidemiological data of rare cancers, information on expert centres for rare cancers, clinical practice guidelines, and nomenclature and classifications. Cross-talk with the European Joint Action on Rare Diseases, RD-Action, coordinated by Orphanet, was also been assured. The Joint Action issued ten recommendations for the future of rare cancers in its "Rare Cancer Agenda 2030".

6. Funding

Orphanet's budget was 2.64 million Euros in 2021, originating from 8 different contracts plus Orphanet's valorisation activities for the core activity funding and from various other contracts in some of the participating countries (Figure 23).

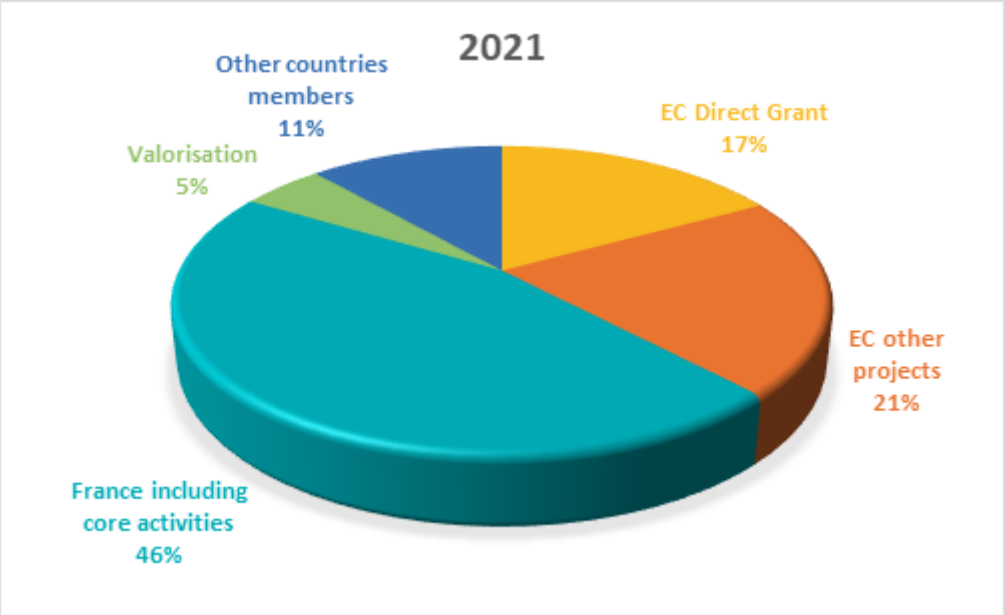


Figure 23 Orphanet's global budget 2021

6.1 Orphanet's core activity funding

Orphanet's core activities include the infrastructure, the coordination activities (management, management tools, quality control, rare disease nomenclature in English, classifications, scientific annotations and production of the encyclopaedia, as well as the Quality Management System -QMS-) and communication, partnerships and valorisation activities. It excludes the collection of data on expert resources in the participating countries as well as translation activities.

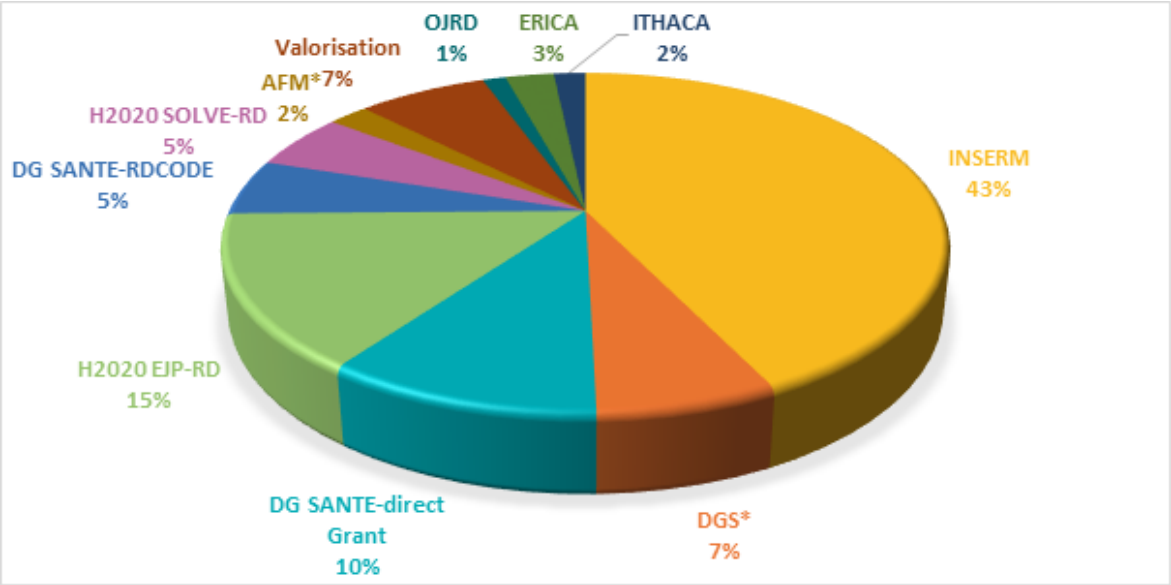


Figure 24 Orphanet core activities funding 2021.

This budget (1.87 million Euros) excludes the costs of infrastructure (office space) which are essentially covered by INSERM (Figure 24).

6.2.4. EUROPEAN FUNDING

The European Commission funds the inventory of rare diseases, the encyclopaedia, and the collection of data on expert resources in European countries (since 2000, DG Health and Consumers Protection grant N°s S12.305098; S12.324970; SPC.2002269-2003220, 2006119, 20091215 and since 2004, DG Research and Innovation grant N°s LSSM-CT-2004-503246; LSHB-CT-2004-512148; LSHB-CT-2006-018933; Health-F2-2008-201230, HEALTH-F2-2009-223355, DG Santé grant 20133305-Operating Grant Orphanet). In 2015, Orphanet participated in the ECRIN Integrating Activity (ECRIN-IA, 284395), funded by the European Union Framework Program 7. From 2012 to 2018 Orphanet coordinated the Support-IRDiRC Contract. From 2015 to 2018 Orphanet coordinated the DG Santé grant RD-ACTION Joint Action 677024. Orphanet coordinated the HIPBI-RD project (ERA-NET Erare Joint calls) [2016-2019]. From 2018, Orphanet participates in the H2020 project Solve-RD (N° 779257) and from 2019, Orphanet participates in the EJP RD (N° 825575) and coordinates RD-CODE (N°26607). Orphanet is part of X-eHealth 951938 since 2020, and from 2021 Orphanet Participates in ERICA (964908), and in the intellectual disability genes project with AP-HP ERN-ITHACA coordination (AP-HP).

The Orphanet network is funded by the Orphanet Direct Grant 831390 (2018-2021).

6.2.5. OTHER CURRENT FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY FUNDING

Instituts thématiques Inserm Institut national de la santé et de la recherche médical	The "Institut National de la Santé et de la Recherche Médicale" finances Orphanet's core activities. *Inserm Transfert* is in charge of supporting Orphanet in providing access to its data to Industry and in providing advice concerning intellectual property.
Liberté • Égalité • Fraternité RÉPUBLIQUE FRANÇAISE MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ	The French Directorate General for Health (DGS) finances Orphanet's core activities.
Co-funded by the Health Programme of the European Union	The European Commission finances the database of diseases and the encyclopaedia in English, as well as the coordination, communication (including OrphaNews International) and IT of the project through the EU Health Programme.
AFMTÉLÉTHON INNOVER POUR GUERIR	The "Association Française contre les Myopathies" finances OrphaNews France and International, the scientific literature survey, as well as data collection on clinical trials.
FONDATION IPSEN	OrphaNews International is realised with the support of Fondation IPSEN, under the aegis of Fondation de France.

Table 9 Other current financial partnerships for core activity funding

6.2.6. CURRENT NON-FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY

Non-financial partners are those that provide services in kind and/or share their expertise for Orphanet core activities.

World Health Organization	Collaboration with the World Health Organisation (WHO) in the process of revising the International Classification of Diseases, and with the International Clinical Trials Registration Platform (ICTRP) in order to improve the visibility of RD clinical trials.
hpo	HPO and Orphanet collaborate on disease-phenotype annotations.
GENATLAS	Cross-referencing with Genatlas which collaborates in updating the data on genes involved in rare diseases.
UniProt	Cross-referencing with UniProt KB which collaborates in updating the data on genes linked to proteins involved in rare diseases.
HGNC HUGO Gene Nomenclature Committee	Cross-referencing with HGNC which collaborates in updating the data on genes involved in rare diseases.

OMIM® Online Mendelian Inheritance in Man®	Cross-referencing with OMIM (The Online Mendelian Inheritance in Man).
REACTOME A CURATED PATHWAY DATABASE	Cross-referencing with Reactome.
e!Ensembl	Cross-referencing with Ensembl.
IUPHAR international union of basic and clinical pharmacology	Cross-referencing with The International Union of Basic and Clinical Pharmacology DataBase (IUPHAR-DB)/ Guide to Pharmacology.
LOVD Leiden Open Variation Database	The LOVD (Leiden Open Variation Database) platform includes links to Orphanet's gene pages, and Orphanet cross-links to LOVD from gene pages.
RD Connect	Orphanet and RD-Connect shared information on biobanks and patient registries in the frame of EJP RD since 2019. Orphanet provides RD-Connect with the nomenclature and ontology of RD for inclusion in RD-Connect's GPAP platform. Both initiatives collaborate in the frame of the Solve-RD project and in EJP RD.
SNOMED International Leading healthcare terminology, worldwide	Collaboration with SNOMED International is ongoing in order to include RD lacking in SNOMED-CT, and to provide alignments between ORPHA codes and SNOMED-CT terms
ifb elixir Core Data Resource	Orphanet is the 30th bioinformatics structure of the French Institute of Bioinfomatics, which is the French node of ELIXIR. Orphadata is an ELIXIR Core Data Resource.
GARD Genetic and Rare Diseases Information Center	Orphanet works with the Genetic and Rare Disease (GARD) Information Center, hosted by NIH-NCATS, in order to align their nomenclatures and improve the provision of textual information on rare diseases.

Table 10 Current non-financial partnerships for core activities

6.2. Financial and non-financial partnerships for national activities

Orphanet's national activities are also supported by national institutions, specific contracts and/or contributions in kind. In European countries, data collection at the national level is also supported by the European Commission. Globally this budget reaches 873 655,49 € in 2021, which is lower than usual due to lack of EC funding in the last 6 months. Please refer to the following section for an overview of funding of national activities.

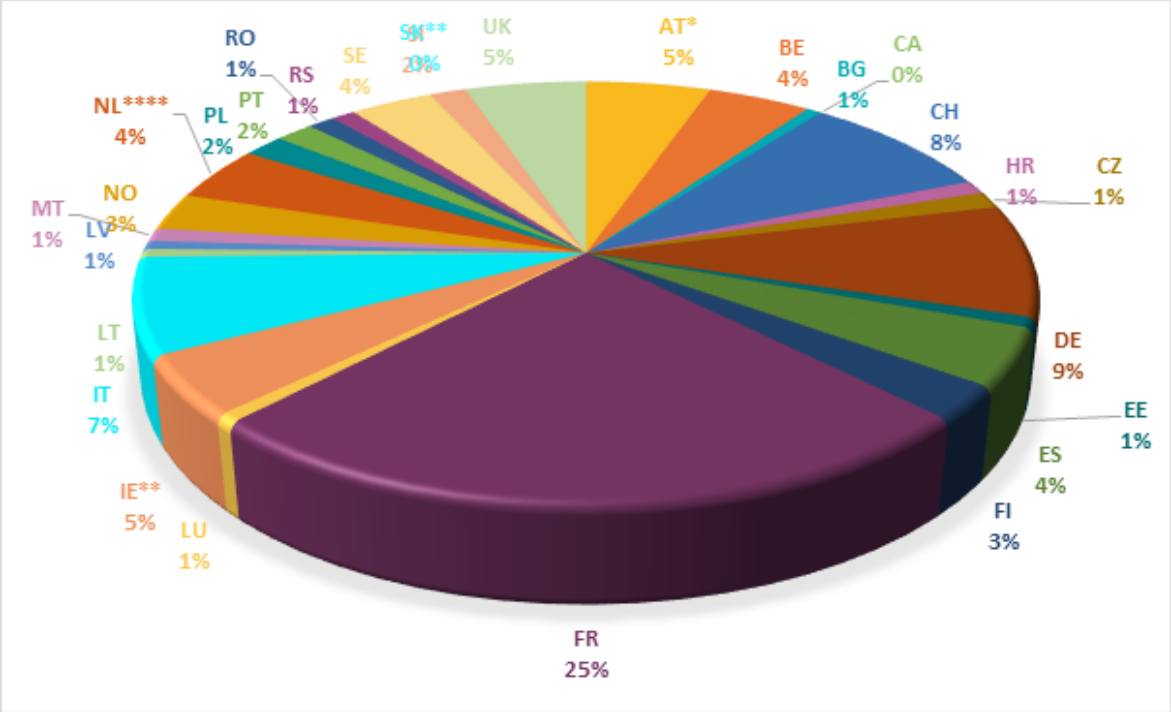


Figure 25 Funding sources for national activities in 2021

6.2.7. PARTNERSHIPS PROVIDING FUNDING FOR NATIONAL ACTIVITIES

Institutional partners host Orphanet's national team activities and contribute to the project by allocating a budget and the time of some of their professionals.

AUSTRIA	
MEDIZINISCHE UNIVERSITÄT WIEN	The Medical University of Vienna is a beneficiary of Orphanet Network 831390 (until 2018: RD-ACTION 677024) and hosts Orphanet Austria since 2004. It further provides part-time funding (in kind) for the work of the country coordinator.
Bundesministerium Arbeit, Soziales, Gesundheit und Konsumentenschutz	The Austrian Ministry of Labour, Social Affairs, Health and Consumer Protection has provided funding to Orphanet Network 831390 from 2018 onwards.
BELGIUM	
sciensano	Sciensano's service "Health Services Research" hosts the Orphanet Belgium team. At Sciensano, there is internal collaboration with Infectious Diseases Service to validate data on reference laboratories and screening tests for infectious disease.
federal public service HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT	The Federal Public Service Health, Food Chain Safety and Environment was a beneficiary in RD-ACTION 677024 (financial support from the European Health Program).
INAMI-RIZIV	The National Institute of Health and Disability Insurance (NIHDI) finances Sciensano to participate in the Orphanet project. The National Institute of Health and Disability Insurance provides information on the recognized reference centers working under a revalidation convention.
BULGARIA	
Bulgarian Association for Promotion of Education and Science BAPES	The Bulgarian Association for Promotion of Education and Science (BAPES) hosts Orphanet Bulgaria's activities.
CROATIA	
Hrvatski savez za rijetke bolesti	Rare Diseases Croatia was a beneficiary in RD-ACTION 677024.

CZECH REPUBLIC	
CHARLES UNIVERSITY	The Charles University Prague - 2nd School of Medicine was a beneficiary in RD-ACTION 677024.
česká asociace pro vzácná onemocnění	The Czech Association of rare diseases finances the activity of the Czech team since April 2012.
SPOLEČNOST LÉKAŘSKÉ GENETIKY ČLS JEP	The Czech Medical Genetics and Genomics Society (www.slg.cz) helps Orphanet CZ in the collection of information on DNA diagnostic laboratories in the country, information on rare diseases clinics - dysmorphology, genetic counseling and information on patient support groups. Genetics professionals work with the overarching Czech rare disease patient association (www.vzacna-onemocneni.cz) which represents more than 30 individual associations. They have a joint partnership for the development of the Czech National Plans for rare diseases following the Czech National Strategy from 2010. The first, second and third Czech National Plans (2012-2014, 2015-2017 and 2018-2020) have been developed under the auspices of the Ministry of Health - Department of Medical Services and in collaboration with the National Coordination Centre for Rare Diseases at UH Motol (www.nkcvo.cz).
ÚZIS ČR	CZ Orphanet team is collaborating together with the Institute of Health Information and Statistics of the Czech Republic on the RD-Code project.
ESTONIA	
TARTU ÜLIKOOL 1632 UNIVERSITAS TARTUENSIS	The University of Tartu was a beneficiary in RD-ACTION 677024.
FINLAND	
RINNEKOTI -Säätiö	Rinnekoti Foundation was a beneficiary in RD-ACTION 677024.
FRANCE	
Liberté • Égalité • Fraternité RÉPUBLIQUE FRANÇAISE MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ	The French Directorate General for Health (DGS) finances the collection of data in France for the expert resources catalogue.
AFMTÉLÉTHON INNOVER POUR GUERIR	The “Association Française contre les Myopathies“ finances OrphaNews France.
FONDATION Groupama vaincre les maladies rares	The “Fondation Groupama pour la santé” contributes to the development of the Orphanet website and the mobile application.

	The "Agence de la biomédecine" finances the monitoring of the list of laboratories, the creation of tools for collecting, managing and monitoring annual activity, as well as funding the compilation of data collected in France.
GERMANY	
	The Medical School of Hanover (MHH) supports data collection.
	Förderverein Orphanet Deutschland e.V., a charity founded by Orphanet Germany to support national activities, provides funding to the team.
	Leadiant GmbH, a pharmaceutical company, provided funding to support national activities 2018.
	Merck Family Foundation, a charitable limited company founded by the Merck Group, is supporting national data collection.
	Pfizer Pharma GmbH, a pharmaceutical company, provided funding to support national activities 2018.
	B.Braun Stiftung, a charity, is supporting the overall knowledge of the database by funding national training sessions for teaching experts on how to use the Orphanet database.
	MVZ Dr. Eberhard & Partner Dortmund (ÜBAG), a private company, provided funding to support national activities 2018.
	Selbsthilfe primäre Hyperoxalurie e.V., a patient association, donated money to support national activities in 2018.
HUNGARY	
	Orszagos tisztifoorvosi hivatal - OTH was a beneficiary in RD-ACTION 677024.
	Semmelweiss Egyetem was a beneficiary in RD-ACTION 677024
ITALY	
	The Italian Health Ministry finances Orphanet-Italy activities through current research funding.

Bambino Gesù OSPEDALE PEDIATRICO	The Bambino Gesù Children's Hospital was a beneficiary in RD-ACTION 677024.
SANOFI GENZYME	Genzyme, a Sanofi Company, finances OrphaNews Italia.
IRELAND	
Feidhmeannacht na Seirbhíse Sláinte Health Service Executive	The Health Service Executive provides co-funding for Orphanet Ireland staff.
JAPAN	
AMED	Japan Agency for Medical Research and Development (AMED) provides funding to the Orphanet Japan's core activities.
Boehringer Ingelheim	Nippon Boehringer Ingelheim Co ., Ltd., a pharmaceutical company, provided funding to support national activities 2021.
LATVIA	
Centre for Disease Prevention and Control of the Republic of Latvia	"Centre for Disease Prevention and Control of Latvia" (Slimību profilakses un kontroles centrs) was a beneficiary in RD-ACTION 677024.
LITHUANIA	
VILNIAUS UNIVERSITETAS 1579 UNIVERSITAS VILNENSIS	The Vilnius University Hospital, "Santariškių Klinikos" Centre for Medical Genetics is a beneficiary in RD-ACTION 677024.
NETHERLANDS	
Ministry of Health, Welfare and Sport	The Dutch Ministry of Health, Welfare and Sport co-funds the work of Dr. Judith Carlier and Prof. Wendy van Zelst-Stams.
Amsterdam UMC Universitair Medische Centra	The Amsterdam UMC contributes to the project by allocating time of Prof. Martina Cornel, chair of the Dutch Orphanet Scientific Advisory Board.
Radboudumc	The Radboudumc contributes to the project by allocating time of Dr. Wendy van Zelst-Stams.

NORWAY	
Helsedirektoratet	The Norwegian Directorate of Health hosts part of Orphanet Norway's activities and contributes to the project by allocating the time of some professionals.
Norwegian National Advisory Unit on RARE DISORDERS	The Norwegian National Advisory Unit for Rare diseases hosts part of Orphanet Norway's activities and contributes to the project by allocating the time of some professionals.
POLAND	
	The "Instytut Pomnik Centrum Zdrowia Dziecka" (Children's Memorial Health Institute) supports Orphanet Poland in all activities inside and outside the institution; e.g. organising conferences for professionals, parents and media; discussions on rare disease with all stakeholders; and improving access to orphan drugs.
Ministerstwo Zdrowia	The Polish Ministry of Health contributes to the translation of the Orphanet encyclopaedia in Polish and contributes to translation of the Orphanet international website.
PORTUGAL	
IBMC INSTITUTO DE BIOLOGIA MOLECULAR E CELULAR INSTITUTE FOR MOLECULAR AND CELL BIOLOGY	IBMC - Institute for Molecular and Cell Biology hosted Orphanet-Portugal from 2009 to June 2015.
U.PORTO INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR UNIVERSIDADE DO PORTO	ICBAS - Instituto de Ciências Biomédicas Abel Salazar, the Biomedical Sciences Institute at the University of Porto, funded Orphanet Portugal activities from 2009 till June 2015.
Direcção-Geral da Saúde www.dgs.pt Ministério da Saúde	DGS - The Directorate-General of Health, at the Portuguese Ministry of Health, was a beneficiary in RD-ACTION 677024 and hosts the Orphanet Portugal team since June 2015.
ROMANIA	
	The "Universitatea de Medicina si Farmacie "Gr.T.Popa" Iasi" was a beneficiary in RD-ACTION 677024.
SLOVAKIA	
	CUMS (UNIVERZITA KOMENSKEHO V BRATISLAVE) was a beneficiary in RD-ACTION 677024.

SLOVENIA	
	The University Medical Centre Ljubljana was a beneficiary in RD-ACTION 677024.
SPAIN	
	The Centre for Biomedical Network Research (CIBER), Area on Rare Diseases (formerly known as CIBERER), has been the partner for Orphanet in Spain since April 2010. CIBER (Institute of Health Carlos III, Ministry of Economy, Industry and Competitiveness) finances the salary of one full-time information scientist and 75% of the salary of a full-time project manager as well as the main activities of the Spanish team. CIBER financed in 2019the different expenses associated to Orphanet Spain activities, such as the production of fliers and attending meetings where the Orphanet team's activities were disseminated.
SWEDEN	
	Karolinska University Hospital, Department of Clinical Genetics, Centre for Rare Disease was a beneficiary in RD-Action 677024.
SWITZERLAND	
	University Hospitals of Geneva is the host institution of Orphanet Switzerland and finances a part-time position for the coordinator and provides some administrative support for the project.
	The National Coordination of Rare Diseases (kosek) signed a cooperation agreement with Orphanet Switzerland in May 2019, allocating a budget for the recruitment of a project manager
TURKEY	
	The Association of Research-Based Pharmaceutical Companies gives non-restricted support for the Turkish translation of the Orphanet webpage and the documents. They supported the creation of the Orphanet-Turkey website and help Orphanet Turkey to prepare and print leaflets for health care professionals and the general public.
UNITED KINGDOM	
	The National Congenital Anomaly and Rare Disease Reg. Service (Public Health England) hosts Orphanet UK activities and contributes to the project by allocating the time of some professionals since August 2014.

Table 11 Partnerships providing funding for national activities

6.2.8. INSTITUTIONAL PARTNERSHIPS PROVIDING SERVICES IN KIND FOR NATIONAL ACTIVITIES

All the Institutions hosting the national Orphanet teams provide their office space, all the necessary supplies to run the team activities and allocate the time of some of their professionals.

ARMENIA	
	The Center of Medical Genetics and Primary Health Care hosts Orphanet-Armenia's activities and contributes to the project by allocating the time of some professionals.
AUSTRALIA	
Government of Western Australia Department of Health	The Office of Population Health Genomics, Department of Health, Western Australia hosts Orphanet Australia's activities and contributes to the project by allocating the time of some professionals.
CROATIA	
	The Zagreb Children's Hospital contributes to the project by allocating the time of the country coordinator
IRELAND	
Mater Hospital Dublin	The Mater Misericordiae University Hospital (MMUH) supports Orphanet Ireland by housing the National Rare Disease Office and Orphanet Ireland. The MMUH provides Clinical Geneticist hours to Orphanet Ireland, and provides Human Resources, Administrative, and IT support.
ISRAEL	
	Sheba Medical Center, Tel Hashomer of Israel hosts Orphanet Israel's activities and contributes to the project by allocating the time of some professionals since June 2014.
JAPAN	
	Foundation for Biomedical Research and Innovation at Kobe (FBRI) hosts the Orphanet Japan's activities and contributes to the project by allocating the time of some professionals.
MOROCCO	

	The National Institute of Hygiene hosts Orphanet Morocco's activities and contributes to the project by allocating the time of some professionals.
SERBIA	
	The Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, hosts Orphanet Serbia's activities and contributes to the project by allocating the time of some professionals.
SPAIN	
	The Príncipe Felipe Research Center (CIPF) hosts Orphanet Spain's activities.
TURKEY	
	The Istanbul University hosts Orphanet Turkey's activities and contributes to the project by allocating the time of some professionals.

Table 12 Institutional partnerships providing services in kind for national activities

6.2.9. NON-FINANCIAL PARTNERSHIPS FOR NATIONAL ACTIVITIES

BELGIUM	
	A partnership exists with RaDiOrg.be, a EURORDIS member, which continued to play a role in the validation of data on Belgian patient organisations in Orphanet.
	The Orphanet team hosted by the Scientific Institute of Public Health collaborates internally with the Service "Infectious Diseases in the general population" to validate data on reference laboratories and tests for infectious diseases.
	The College of Human Genetics in Belgium, which represents the 8 recognized genetic centres, is collaborating with the Orphanet team to improve and simplify the process of registration and update of data on genetic testing activities in the Orphanet database.
	The National Institute of Health and Disability Insurance provides information on the recognized reference centres that work under a convention.
BULGARIA	
	The Association of Medical Students in Plovdiv has been actively promoting Orphanet use in its community. Together, BAPES and AMS-Plovdiv have organised a series of workshops, dedicated to Orphanet.
	The Bulgarian National Alliance of People with Rare Diseases has partnered with BAPES in order to promote Orphanet among rare disease patients in Bulgaria, as well as to list the Bulgarian patient associations on the Orphanet database.

CZECH REPUBLIC	
MINISTERSTVO ZDRAVOTNICTVÍ ČESKÉ REPUBLIKY	The Ministry of Health of the Czech Republic officially supports Orphanet.
CROATIA	
SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET	Rare Diseases Croatia cooperates with its member organisations and with the Medical Faculty of the University of Zagreb.
ESTONIA	
REPUBLIC OF ESTONIA MINISTRY OF SOCIAL AFFAIRS	The Ministry of Social Affairs of Estonia officially supports Orphanet.
FINLAND	
SOSIAALI- JA TERVEYSMINISTERIÖ	The Ministry of Social Affairs and Health of Finland officially supports Orphanet.
DUODECIM TERVEYSPORTTI	Terveysportti (www.terveysportti.fi) is a web service for medical professionals published by Duodecim Medical Publications Ltd, which is owned by the Finnish Medical Society Duodecim. Orphanet was included in Terveysportti's searches concerning the 300 "most common rare diseases". As a result, Orphanet will have a higher profile among the Finnish health care professionals.
FRANCE	
maladies rares	The Ministry of Health and the Ministry of Research officially supports Orphanet in the framework of the French National Plan for Rare Diseases from 2018

AIRFRANCE	"Air France" provides a quota of airline tickets for patients to travel to medical experts or for experts to travel to patients with rare diseases. Orphanet provides expertise on the merits of applications when needed.
MALADIES RARES INFO SERVICES	Orphanet has delegated to "Maladies Rares Info Services", the French helpline for information on rare diseases - 0156538136, the role of replying to unsolicited electronic messages received by Orphanet.
GERMANY	
achse Allianz Chronischer Seltener Erkrankungen	The "Allianz Chronischer Seltener Erkrankungen e.V." (ACHSE) works together with Orphanet Germany on information services for patients.
KINDERNETZWERK WIR HELFEN WEITER	The "Kindernetzwerk e.V. - für Kinder, Jugendliche und (junge) Erwachsene mit chronischen Krankheiten und Behinderungen" provides data on associations in Germany.
gfh	The "Deutsche Gesellschaft für Humangenetik e.V." supports Orphanet by supplying the German team with addresses and information on laboratories and diagnostics.
NAKOS Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen	Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen (NAKOS) officially supports Orphanet.
AWMF	The AWMF (Association of the Scientific Medical Societies in Germany) cooperates with Orphanet DE by supplying the web links of their clinical practice guidelines to the Orphanet encyclopaedia.
DIMDI medizinwissen Deutsches Institut für Medizinische Dokumentation und Information	DIMDI cooperates with Orphanet DE in including the disease terms from the German Orphanet nomenclature into the alpha-code of the ICD-10GM.
HUNGARY	
Emberi Erőforrások Minisztériuma	The State Secretary of Health within the Ministry of Human Resources officially supports Orphanet.
IRELAND	
An Roinn Sláinte DEPARTMENT OF HEALTH	The Department of Health officially supports Orphanet and provides governance of Orphanet Ireland.
NRDO National Rare Diseases Office	The National Rare Disease Office (NRDO) hosts the Orphanet Ireland team. Orphanet is the main source of rare disease resource information for the NRDO Information Line.

	The National Clinical Programme for Rare Diseases (which is a partnership between the Royal College of Physicians Ireland and the HSE provides clinical oversight for Orphanet Ireland through its Clinical Advisory Group.'
	'Rare Diseases Ireland (RDI), the Medical Research Charities Group (MRCG) and the Irish Platform for Patient Organisation, Science and Industry (IPPOSI) together form the Irish National Alliance for Rare Disease. They collaborate in the promotion of Orphanet and rare disease activities in Ireland.
ITALY	
	The "Istituto Superiore di Sanità" officially supports Orphanet.
	Telethon collaborates with Orphanet for the collection of data concerning research projects.
	Uniamo, the Italian Federation of support groups on rare diseases, collaborates with Orphanet in the organisation and promotion of events dedicated to rare diseases, in order to increase public awareness on this particular issue.
	Netgene collaborates with Orphanet for the diffusion of information on rare diseases.
	Farmindustria promotes Orphanet publications.
	Osservatorio Malattie Rare (O.Ma.R.) collaborates with Orphanet in disseminating information rare diseases and the promotion of events.
	The Italian Inter-regional Technical Board for Rare Disorders collaborates with Orphanet in collecting data concerning the Centres of Reference officially recognised in Italy.
LATVIA	
	The Ministry of Health of the Republic of Latvia officially supports Orphanet.
	The Rare Diseases Society in Latvia aims to promote equal rights and opportunities for patients with rare diseases.

PALĪDZĒSIM.LV	Palidzesim.lv is a non-governmental organisation in Latvia which financially supports children and families to confirm a diagnosis of a rare disease by sending patients or medical samples abroad.
LITHUANIA	
MINISTRY OF HEALTH OF THE REPUBLIC OF LITHUANIA	The Ministry of Health of the Republic of Lithuania officially supports Orphanet.
NETHERLANDS	
NFU NEDERLANDSE FEDERATIE VAN UNIVERSITAIR MEDISCHE CENTRA	The NFU (Netherlands Federation of University Medical Centres) coordinates the designation of expert centers for rare diseases. After evaluation of candidate centers according to the EUCERD criteria by external experts the Dutch Ministry of Health is advised on the official designation of individual centers. The Dutch Orphanet team is a partner in this procedure.
erfocentrum	The Erfocentrum provides information to the general public on genetic, mainly rare disorders. A collaboration was established to increase the number of Dutch rare disease summary texts available on both the Orphanet and Erfocentrum websites. In addition, the Erfocentrum displays the list of Dutch designated rare disease expert centers for the general public. .
VSOP	The VSOP (Dutch national patient umbrella organization for rare and genetic disorders) provides information regarding patient organizations dedicated to rare diseases and participates in the designation of Dutch expert centers for rare diseases.
DHD Zorg voor Data	DHD (Dutch Hospital Data), responsible for the Diagnosis thesaurus used in Dutch Hospital information systems collaborates with Orphanet Netherlands to prepare for the implementation of ORPHAcodes in the Diagnosis thesaurus.
Nictiz	Nictiz, the Dutch competence centre for electronic exchange of health and care information, is responsible for the Dutch SNOMED edition and collaborates with DHD and Orphanet Netherlands in the implementation of ORPHAcodes in the Diagnosis thesaurus.
POLAND	
PKU RD	The patient organisation, Ars Vivendi, provides patients and parents with information about Orphanet services and cooperates with Orphanet Poland.
mps	The Polish Association of Patients with Muchopolysaccharidosis and Rare Diseases provides patients and parents with information about Orphanet services and cooperates with Orphanet Poland.

ROMANIA	
Romanian Ministry of Health	The Ministry of Health collaborates with Orphanet Romania in updating data on the Romanian medical system. It officially supports Orphanet.
	Orphanet Romania collaborates with the Romanian Medical Association in updating data on health professionals.
SRGM Societatea Romana de Genetica Medicala	Orphanet Romania collaborates with the Romanian Society of Medical Genetics to set up programs for the development of a national network of diagnosis, investigation and prevention in Centres of Medical Genetics and to promote collaboration with associations of people with genetic/malformative diseases.
ASOCIATIA PRADER WILLI DIN ROMÂNIA	Orphanet Romania collaborates with the Romanian Prader Willi Association in order to bring together the efforts of patients, specialists and families to ensure a better life for all people with genetic diseases.
SLOVAKIA	
	The Ministry of Health of the Slovak Republic officially supports Orphanet.
SLOVENIA	
REPUBLIC OF SLOVENIA MINISTRY OF HEALTH	The Ministry of Health of Slovenia officially supports Orphanet.
SPAIN	
GOBIERNO DE ESPAÑA MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD	The Spanish Ministry of Health, Consumption and Social Welfare- Office for Health Planning and Quality officially supports Orphanet.
Fondo de Investigación en Salud Instituto de Salud Carlos III	The Institute of Health Carlos III (ISCIII) provides Orphanet with data on national research projects funded through the Health Strategic Action Calls.
entidad de utilidad pública feder FEDERACIÓN ESPAÑOLA DE ENFERMEDADES RARAS	The Spanish Federation for Rare Diseases (FEDER collaborates with Orphanet with the updating of Patient Organizations' information, the revision of some texts included in the disability factsheets and articles for the general public, and Orphanet resources dissemination.
SWEDEN	
REGERINGSKANSLIET Ministry of Health and Social Affairs, Sweden	The Ministry of Health and Social Affairs of Sweden officially supports Orphanet.
SWITZERLAND	
HON Health On the Net Foundation	The Health On the Net Foundation owns the domain wwww.orphanet.ch and supports the technical aspect of the Orphanet Switzerland online forms to collect data.

	ProRaris, the Swiss Alliance of patients with rare diseases has established a close collaboration with Orphanet Switzerland in order to identify relevant information services for patients and professionals and in the organisation and promotion of events dedicated to rare diseases, in order to increase public awareness on this particular issue.
TURKEY	
	The Turkish Ministry of Health officially supports Orphanet. It collaborates with Orphanet Turkey for data collection and the dissemination of Orphanet in Turkey.
UNITED KINGDOM	
	The Department of Health officially supports Orphanet.
	Ataxia UK and Orphanet cooperate in the exchange of information, in the validation and online publication of research projects regarding ataxia and in the endorsement and boosting of Orphanet and Ataxia UK activities.
	Orphanet collaborates with Rare Disease UK in the sharing of data and expertise, in the endorsement and promotion of Orphanet and Rare Disease UK activities, and in the development of the UK Strategy for Rare Diseases.Rare disease UK is also a post-validator of information on Orphanet concerning UK PO.
	Orphanet collaborates with Genetic Alliance UK in the sharing of data and expertise, in the endorsement and boosting of Orphanet and Genetic Alliance UK activities, in seeking to raise awareness, improve the quality of services and information available to patients and families and to improve the quality of life for those affected by genetic conditions. Genetic Alliance is also a post-validator of information on Orphanet regarding UK PO.

Table 13 Non-financial partnerships for national activities

7. Communication

7.1. Communication documents

In 2021, A5-size flyers to present Orphanet and Orphanet services were updated when necessary and distributed virtually:

- Orphanet in 4 languages (English, French, Spanish and German)
- Orphadata (English)
- Orphanet application for iPhone and iPad (English)
- ORPHA codes (English)
- Orphanet database structure and main products (English)
- Orphanet rare disease ontology (English)
- Registering your activity as a professional with Orphanet (English)
- Resources for ERNs (English)
- Orphanet tutorials

A short brochure about Orphanet's global positioning and achievements in the previous year was also produced and made available.

7.2. Invitations to give lectures at conferences in 20201

Orphanet representatives, as specialists in the field of rare diseases, were invited to give lectures and to participate with poster presentations in 25 conferences and events worldwide in 2021, with most taking place online due to the COVID pandemic. These lectures were mostly focused on presenting the Orphanet database, the ORPHA nomenclature public health policies, and RD research. In addition to this, Orphanet was also represented in a range of national and international workshops and training sessions in raise awareness of Orphanet data and tools, and to liaise with other rare-disease focused projects.

7.3. Booths at conferences in 2021

The global COVID-19 pandemic meant that many in-person events were cancelled in favour of virtual events. However, virtual Orphanet booths were held in 2 different congresses and events in 2021 as indicated in the list below:

- French Rare Disease Alliance Congress, 11/06/21, Online
- Rare Disease Day Finland, 26/02/21 – 28/02/21, Online

7.4. Articles in peer-reviewed journals

Members of the Orphanet network contributed to the following articles:

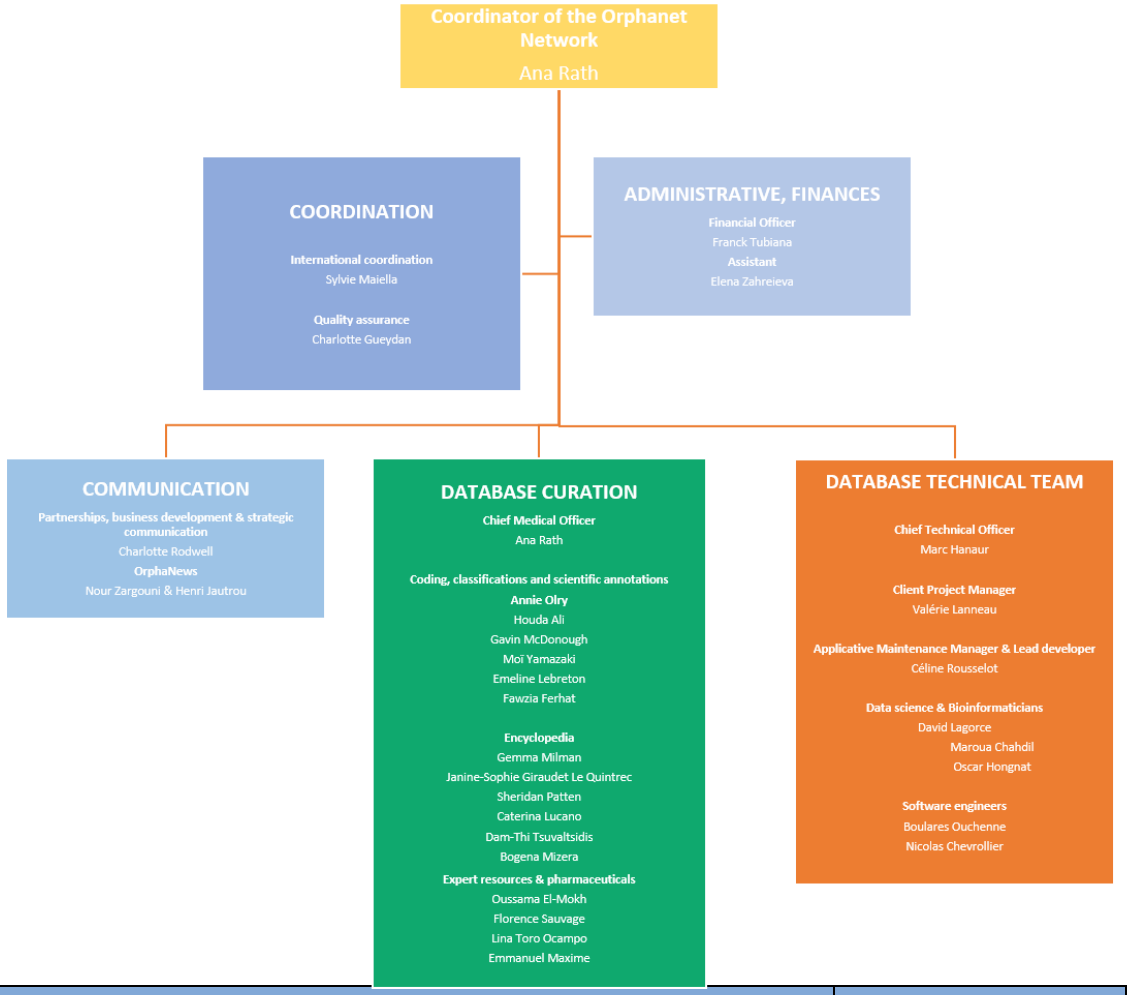
- Zurek, B et al, Solve-RD: systematic pan-European data sharing and collaborative analysis to solve rare diseases, European Journal of Human Genetics, September 2021, https://doi.org/10.1038/s41431-021-00859-0

- The Human Phenotype Ontology in 2021 S Köhler, M Gargano, N Matentzoglu, LC Carmody, D Lewis-Smith, ...Nucleic acids research 49 (D1), D1207-D1217132021
- Launch of the gene curation coalition database. M DiStefano, S Goehringer, J Amberger, CA Tse, M Balzotti, J Berg, ...MOLECULAR GENETICS AND METABOLISM 132, S224-S2252021
- Reply to E. Vicente et al. **A Rath**, DM Lambert, A Olry, C Rodwell, Y Le Cam European Journal of Human Genetics, 1-22020

7.5. Social media

The Orphanet coordinating team maintains a Facebook page (6,103 followers) and a Twitter account (@orphanet : 5,866 followers) as well as the Orphanet Youtube channel. A LinkedIn page was launched in 2022.
The Orphanet Italy team also maintains a Facebook page (17'000 followers) and a YouTube channel. The Orphanet Germany team maintains a Facebook page (405 followers).

8. The Orphanet team in 2021



Network Members and Teams	
Armenia	
Center of Medical Genetics and Primary health care	
Kristine Hovhannesyan	Coordinator
Tamara Sargsyan	Information Scientist
Austria	
Medizinische Universitat Wien	
Till Voigtlander	Coordinator
Ursula Unterberger	Project Manager
Belgium	
Sciensano	
Elfriede Swinnen	Coordinator
Kim Van Roey	Translator
Annabelle Calomme	Information Scientist
Bulgaria	

Bulgarian association for Promotion and Education and Science	
Rumen Stefanov	Coordinator
Eva Popova	Information Scientist
Georgi Iskrov	Assistant Scientist
Canada	
Mc Gill University	
TBA	Coordinator
TBA	Information Scientist
Switzerland	
CMU Institute of Medical Genetics- Geneva university Hospital	
Loredana D'Amato Sizonenko	Coordinator
Martin Arles	Information Scientist
Béatrice Geissbuhler	Information Scientist
Czech Republic	
Charles University Prague	
Milan Macek	Coordinator
Marek Turnovec	Information Scientist
Germany	
BFarm	
Stefanie Weber	Coordinator
Kathrin Rommel	Project Manager
Estonia	
University of Tartu	
Vallo Tillmann	Coordinator
Sille Vahtra	Information Scientist
Spain	
CIBERER	
Francesc Palau	Coordinator
Virginia Corrochano	Project manager
Elisa Checa	Information Scientist
María Elena Mateo	Information Scientist

Finland	
Tkl-THL	
Kääriäinen Helena	Coordinator
Leena Toivanen	Information Scientist
France	
Inserm US14	
Emmanuel Maxime	Information Scientist
Lina Toro Ocampo	Information Scientist
Florence Sauvage	Information Scientist
Oussama El Mokh	Information Scientist
United Kingdom	
Public Health Institute	
Sarah Stevens	Coordinator
Luke Willis	Information Scientist
Dean Ali	Information Scientist
Jeanette Aston	Information Scientist
Georgia	
GeraD	
Tamari Rukhadze	Coordinator
Oleg Kvlividze	Project Manager
Dodo Aglave	Information scientist
Dr Lali Margvelashvili	Advisor
Croatia	
Zagreb university	
Ingeborg Barisic	Coordinator
Mijana Kero	Project Manager
Ireland	
National Centre for Medical genetics	
Eileen Treacy	Coordinator
Debby Lambert	Information Scientist

Rita Marron	Information Scientist
Daniel Murphy	Bioinformatician
Israel	
Chaim Sheba Medical center	
Annick Raas- Rotshild	Coordinator
Vivi Einy	Information Scientist
Italy	
The Bambin Gesù Children's Hospital	
Bruno Dallapiccola	Coordinator
Rita Mingarelli	Project manager
Maria Luisa Dentici	Editorial assos
Clementina Radio	Information Scientist
Michele Nutini	Information Scientist
Serena Ciampa	Information Scientist
Japan	
Translational Research Informatics Center (TRI)	
Dr. Atsuhiko Kawamoto	Coordinator
Keisuke Yuasa	Substitute
Mayuka Sugimoto	Project manager
Lithuania	
Center for Medical genetics-Vilnius University Hospital	
Birute Tumiene	Coordinator
Birute Burnyte	Information Scientist
Luxembourg	
Ministry of Health	
Silvana Masi	Coordinator
Latvia	
Childrens University Hospital	
Ieva Malniece	Coordinator
Inese Ledina	Information Scientist
Madara Kreile	Information Scientist

North Macedonia	
Research Centre for Genetic Engineering and Biothechnology "Georgi D.Efremov"	
Dijana Plaseska- Karanfilska	Coordinator
Predrag Noveski	Information Scientist
Malta	
Ministry of Health	
Neville Calleja	Coordinator
Francis Agius	Coordinator
Netherlands	
NFU/Radboudumc	
Wendy van Zelst- Stam	Coordinator
Judith Carlier De Leeuw Van Weenen	Information Scientist
Norway	
OUF-HS	
Stein Are Aksnes	Coordinator
Lene Martinsen	Project Manager
Maria Emilie Gresslien	Information Scientist
Poland	
Instytut Pomnick Centrum Zdrowia Driecka	
Krystyna Chrzanowska	Coordinator
Agnieszka Madej-Pilarczyk	Information Scientist
Portugal	
DGS - Health General Directorate	
Carla Pereira	Coordinator
Rui Gonçalves	Information Scientist
Cristina Rocha	Project manager
Romania	
Universitatea de Medicina si Farmacie Iasi	
Cristina Rusu	Coordinator
Monica Panzariu	Information Scientist
Russia	
Federal State Budgetary Scientific Institution Research Centre for Medical Genetics	

Sergey Kutsev	Coordinator
Danisa Tashtanbaeva	Project manager
Serbia	
Institute of molecular genetics and genetic engeineering-Belgrade University	
Dragica Radojkovic	Coordinator
Kristel Klaassen	Information Scientist
Maja Stojiljkovic	Project manager
Sweden	
Karolinska Institutet	
Rula Zain	Coordinator
Terese Boderus	Information Scientist
Slovenia	
University Medical Center Ljubljana	
Luca Lovrecic	Coordinator
Nusa Trost	Information Scientist
Slovakia	
Children's Hospital	
Gabriela Hrcková	Coordinator
Turkey	
Institute for Public Health	
Ugur Ozbek	Coordinator
Ilham Satman	Coordinator
Contact points	
Argentina	
Ministry of Health	
Romi Armando	Coordinator
Australia	
Office Population Health genomics	
TBA	Coordinator
Tunisia	
Farhat HACHED University Hospital, Soussa	
Dorra H'MIDA-BEN BRAHIM	Coordinator
Morocco	
Institut National d'Hygiène	

Abdelaziz Sefiani	Coordinator
Imane Cherkaoui- Jaouad	Information Scientist
Information Scientist	
Cyprus	
Cyprus Ministry of Health MMC	
Marios Antoniades	Coordinator

Figure 26 Organisational chart (December 2021)

For any questions or comments, please contact us: contact.orphanet@Inserm.fr

Editor-in-chief: Ana Rath *Managing Editor*: Charlotte Rodwell *Contributing Editor*: Sylvie Maiella
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