2016 Activity Report

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Abbreviation list

BNDMR: French Rare Diseases Data Repository

CEQAS : Cytogenetic European Quality Assessment Service

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

ICD-10GM: German ICD-10

ICHPT: International Consortium of Human Phenotype Terminologies

IHTSDO: International Health Terminology Standards Development Organisation

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 (ORPHA number), 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 Consortium of 40 countries, within Europe and across the globe.

1.1. Orphanet's missions

Over the past 20 years, 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**:

o **Improve the visibility of rare diseases in the fields of healthcare and research by maintaining the Orphanet rare disease nomenclature (ORPHA numbers): 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 number: 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.

o **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 40 countries 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 7 languages of the database (English, French, Spanish, Italian, German, Dutch, Portuguese) with texts also currently available in Polish, Greek, Slovak, Finnish 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.

o **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 health care 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 a structured vocabulary for rare diseases, the Orphanet Ontology of Rare Diseases (ORDO). 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 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, and integration in the French node of ELIXIR, a European Research Infrastructure Consortium uniting Europe's leading life science organisations. 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

Orphanet is currently a comprehensive resource of information and data on RD, notably in terms of referenced documents. It is also the only project that establishes a link between diseases, the existing textual information concerning RD and the appropriate services for patients, researchers, healthcare professionals and decision makers. Moreover, Orphanet's database content is robust and expert validated, updated continuously, and quality controlled. 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 Orphanet mobile application, the Orphanet data download platform "Orphadata" (www.orphadata.org), the Orphanet Rare Disease Ontology (ORDO), 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 indexed 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
  - An encyclopaedia covering more than 6,900 rare diseases or group of diseases, with summary texts 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, Slovak, Greek and Finnish. For certain selected diseases, emergency guidelines and articles for the general public are produced in French and then translated.
  - An inventory of high quality articles published by other journals or learned societies. More than 1800 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 assistance-to-diagnosis tool (Orphamizer), in beta, allowing users to search using HPO (Human Phenotype Ontology) terms.
  - 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 35 member countries and providing information on: specialised expert centres and centres of expertise, medical laboratories, research projects, clinical trials, patient registries and mutation 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 http://france.orphanews.org/archives.htmlFrench and Italian.

- **Orphanet data is available via two mobile apps:**
  - **Orphanet**: an app allowing users to access the list of rare diseases, textual information concerning the disease and associated services, as well as Emergency Guidelines. The app is available via for iOS and Android. This application is available in all languages of the Orphanet website.
  - **Orpha Guides:** an app in French giving access to information on French national support mechanisms for patients and their families, as well as information concerning the functional consequences of over 100 rare diseases. The app is available for iOS and Android.

- **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;
  - Datasets available via Data Transfer Agreement/Licence: Textual information, catalogues of patient organisations, expert centres, clinical laboratories and diagnostic tests, orphan drugs, research activities, and epidemiological data.

- **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. ORDO provides integrated, re-usable data for computational analysis.

- **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 2016

Orphanet international positioning

- A partnership between Orphanet and the **Genetic and Rare Disease Information Center (GARD),** hosted by the National Institutes of Health – National Center for Advancing Translation Sciences(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 are being 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) will be included in GARD for the diseases for which GARD does not have a text. This cross-Atlantic partnership will improve 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).

- From January 2016, Orphanet coordinates the three-year ERare3 ERANET project **HIPBI-RD (Harmonising phenomics information for a better interoperability in the RD field).** Harmonisation of phenomics information including disorders and phenotype traits that are stored in different supports (patient records, databases, registries) in a non-standardised way, is a cornerstone for the production of sound data necessary to foster research. This project builds on three resources largely adopted by the RD community: Orphanet, and its ontology ORDO, HPO and PhenoTips. It is aimed to provide the community with an integrated, RD-specific informatics ecosystem that will harmonise the way phenomics information is stored in databases and in patient files worldwide, and thereby contribute to interoperability. This ecosystem will consist of a suite of tools and ontologies, optimized to work together, and available to clinicians and scientists through commonly used software repositories. Additionally, the ecosystem will improve and streamline the interpretation of variants identified through exome and full genome sequencing by harmonizing the way phenotypic information is collected.

- In November 2016, the **NGO Committee for Rare Diseases** was launched at the United Nations in New York under the patronage of the Conference of NGOs in Consultative Relationship with the United Nations (CoNGO). Orphanet was presented as a global resource for rare diseases at this meeting at which the Orphanet Consortium affirmed their support of the goals of the Committee. Ana Rath, on behalf of the Orphanet Consortium signed the Founding Act on "Rare Diseases and the UN Sustainable Development Goals". Orphanet will soon formally join the committee.

- Orphanet is now member of the **European Joint Action on Rare Cancers** (www.jointactionrarecancers.eu) that aims 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 is 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 diseases, clinical practice guidelines, and nomenclature and classifications. Cross-talk with the European Joint Action on Rare Diseases, RD-Action, coordinated by Orphanet, is also assured.

- From 2016, the **transition to a more distributed model for the production of the encyclopaedia** was launched, with members of the Orphanet Slovakia and Ireland teams assuming responsibility for part of the production of texts in English.

- 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 prescriptionva 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.

Improving transparency and traceability

- **In addition to the general SOPs** available online since 2013, that are updated regularly, the procedures used for the **alignements with ICD-10** and those used to carry out the **linearisation of disorders** are available online since 2014. The following procedures were published online in 2016/early 2017:
  - **Orphanet inventory of rare diseases**
  - **Naming rules for the rare disease nomenclature in English**
  - **Creation and Update of Disease Summary Texts for the Orphanet Encyclopaedia for Professionals**
  - **Orphanet inventory of genes related to rare diseases**
  - **International Advisory Board rules of procedure**
  - **Orphanet Advisory Board on Genetics Rules of procedures**
  - **Glossary and representation of terms related to diagnostic tests**
- From 2016 onwards, Orphanet publishes **a dedicated Orphanet Report Series crediting the experts having contributed to the update of scientific data in Orphanet.**
- The development of the **Orphanet Knowledge Management Platform** (https://curation.orphanet.org/) was carried out in 2016 by partners of the RD-Action consortium in Australia. This platform allows experts in the field of rare diseases to help curate the scientific data in the Orphanet database in a traceable and transparent manner.

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

- **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)*
- **A new Orphanet Report Series, List of Rare Diseases in Polish,** was released for the first time.
- **The Orphanet Activity report 2015 was translated into French, Italian, Spanish and Polish**
- **The Orphadata user guide was updated.**
- **The Orphanet annual user survey was updated** so as to provide information on little-known services to the respondents.

Orphanet website information

- **Orphanet revised its policy concerning the inclusion of non-rare diseases** (according to the EU definition of a prevalence of not more than 1 per 2000 in the EU population). Diseases not meeting this definition have been withdrawn from the website and available datasets. A short

list of borderline diseases were kept in the nomenclature as potentially rare, because evidence is still needed before deciding on their withdrawal. However, some non-rare diseases have been kept in the database (not in the nomenclature, nor searchable on the website) so that we may respect our commitment to representing the genetic testing landscape in Consortium countries, to representing all officially designated expert centres for rare diseases, and all orphan drugs (as some of these can be linked to diseases considered as rare in other countries such as the USA).

- **The date of last update of all activites in Orphanet is now displayed on the website**, in order to give users information on the last time this information was confirmed as being accurate, either by a professional or via an official source.

- **The summary information on each disease now has sub-titles** to improve the readibility of the texts.

- **A new representation of diagnostic tests** went live in 2016, expanding this dataset to give more information to user and allowing them to filter results by speciality/objective, technique, purpose, quality management data (accreditation and participation in EQA schemes), lab and test quality (accredited/participating in EQA), as well as the country in which the laboratory is located.

- **A link to EURORDIS' directory of specialised social services and links to Orphanet sources and procedures were added to the menu of ressources** on each result page of the website, in order to help users find this information.

- **Orphanet now classifies rare diseases with a thesaurus of functional consequences** derived and adapted from the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY, WHO 2007). This data is available via the ['Disability'](#) sub-tab on the Orphanet website.

- **Twitter and Facebook icons were added to the website** in order to ease sharing of Orphanet pages through social networks.

Codification of RD using ORPHA codes

- The implementation of ORPHA codes in national health information systems is ongoing. In addition to the progression of this implementation in **Germany and France**, pilot experiences are being conducted in **Hungary, Latvia and Norway**. ORPHA codes are currently being used in centres of expertise in **the Netherlands and Slovenia**. ORPHA codes are also being implemented in patient registries in **Portugal, UK and Spain**. In **Switzerland**, the Hôpitaux Universitaires de Genève and CHUV implement ORPHA codes in digital patient records since 2015. The use of ORPHA codes as a complement to already existing coding systems is being explored in most EU Member States, as recommended by the European Commission Expert Group on Rare Diseases. A [mapping exercise](#) of the use of ORPHA codes in Europe is underway in the context of RD-Action and will be available in 2017.

Users satisfaction

- **Users are satisfied with the utility of the services provided by Orphanet:** in the 2016 satisfaction survey, on average 79% of respondents stated that the services they knew of and used were very useful or useful to them.

- **12 million PDF documents downloaded in 2016.**

- **1.1 million visitors per month from 232 countries.**

Database content and website

A freely accessible site available in 7 languages
47 million pages viewed in 2016
12 million PDF documents downloaded in 2016
An IRDiRC Recognized Resource

Diseases

6,084   rare diseases with unique identifiers : ORPHA numbers
3,715   genes for 3,566 rare diseases
2,630   diseases indexed with HPO terms
5,299   diseases annotated with prevalence/incidence data

Rare disease summaries in 11 languages

4,089   English
3,314   Italian
3,299   French
3,159   German
3,074   Spanish
1,182   Portuguese
663   Dutch
167   Finnish
647   Polish
424   Greek
103   Slovak

Catalogue of expert resources in 40 countries worldwide

21,791   professionals
7,230   expert centres
2,537   patient organisations
1,676   medical laboratories
42,982   diagnostic tests
1,856   research laboratories
2,475   research projects
2,455   clinical trials
744   patient registries
621   mutation databases
142   biobanks

Figure 1 Orphanet in numbers

2. Orphanet consortium

2.1. The RD-ACTION Joint Action

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).

Because of this assessment, the evolution of the Orphanet database of rare diseases into a more European, sustainable model has been set as one of the main objectives of RD-ACTION (www.rd-action.eu), the new Joint Action on RD co-funded by the 3rd EU Health Programme and launched on 17^{t}September 2015 in Luxembourg. This instrument combines funding from the European Commission and each of the participating Member States, as well as from Switzerland, Canada and Australia, as collaborating stakeholders.

Following the two previous Joint Actions (Orphanet Joint Action and EUCERD Joint Action) RD-ACTION demonstrates the renewed support of the European Commission (EC) in the field of rare diseases, through its Directorate General for Health (DG SANTE). This work will last three years (until June 2018) and follows the logic of coherence and continuity vis-à-vis the previous actions, but aims to go further in terms of concrete implementation and consolidation of policies. This action is coordinated by Orphanet (INSERM, US14), bringing together 63 European and non-European participants.

RD-ACTION has three main objectives:
- contribute to the implementation, by member states, of the recommendations of the EC Panel in relation to policies on these diseases,
- support the development of Orphanet and make it sustainable,
- help Member States to introduce the ORPHA codes in their health care systems to make rare diseases visible.

RD-ACTION was designed in the spirit of integration and coherence so that the data produced by Orphanet can contribute in the necessary analysis of policy recommendations and political action that will then guide the production, operation and dissemination of this data. Participants will ensure effective communication between each of the member states and the EC Panel, in order to concretely support the implementation of their recommendations. Most of the Orphanet country coordinators contribute to the work of RD-ACTION's work packages, therefore participating to the RD codification and policy implementation.

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 guide 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.

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 the framework of the RD-Action Joint Action 2015-2018, most of the Orphanet activities are co-funded by the EC. As a result, the Orphanet Management board also refers to the General Assembly of the RD-Action project (please refer to www.rd-action.eu for additional information).

2.3. Expansion of the consortium

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 Consortium of 35 countries to the East and to the South. In 2011, Orphanet went further west to include Canada. The consortium 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.

Please refer to the organisational chart at the end of this document for more information about the participating Institutions and team members.
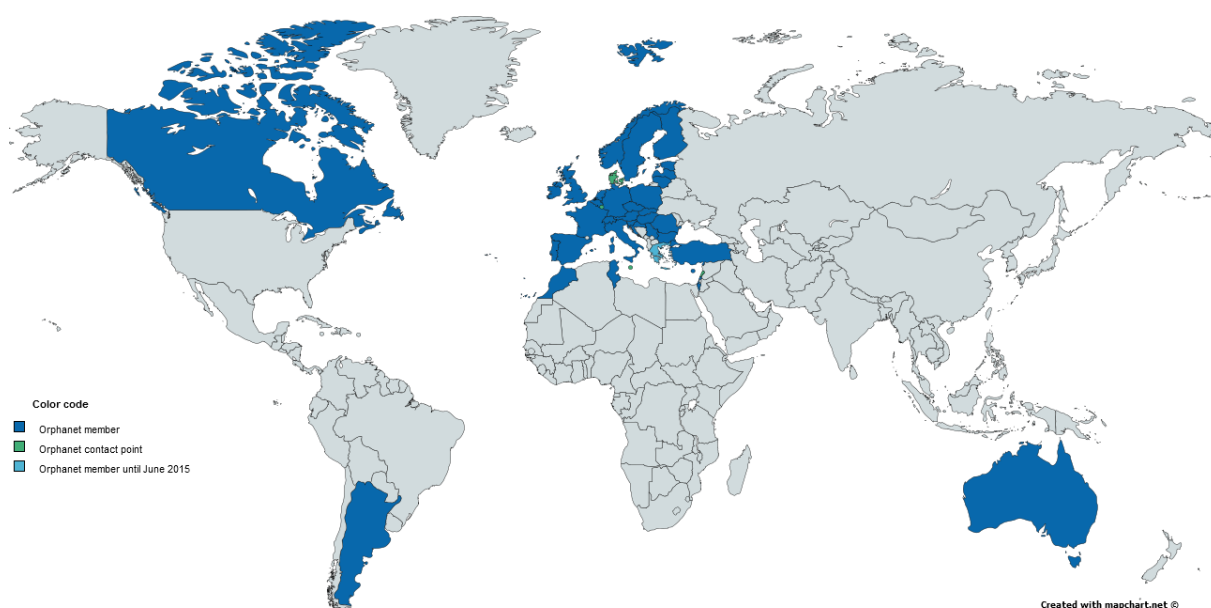
Figure 2 *Orphanet members and contact points*

2.4. Orphanet members and scope of their activity

2.4.1. COORDINATING TEAM

The coordination of the consortium is managed by the coordinating team, located in Service Unit 14 of INSERM (the French National Institute of Health and Medical Research). INSERM has been the coordinator of the Orphanet consortium since 2001.

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

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.

From the start of 2017, a transition in the distribution of activities is underway so as to allow Orphanet consortium members to take on responsibilities in the core activities (starting with the production of the encyclopaedia) in addition to the collection and translation activities described in 2.4.2.

2.4.2. MEMBERS

The establishment of a directory 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 clinical trials, medical laboratories, expert centres, research projects, registries, platforms, networks and patient organisations.

Translations of the Orphanet content in the national language are also managed by the national teams, provided that they have a sufficient budget. Currently Belgium, France, Germany, Italy, Spain and Portugal are undertaking the translation of the entire website's content into their national language, while the Polish, Finnish, Slovak teams are translating the summary texts encyclopaedia. The Orphanet nomenclature is currently translated into the 7 languages of the website, and also into Polish.

From 2016, the transition to a more distributed model for the production of the encyclopaedia was launched, with members of the Orphanet Slovakia and Ireland teams assuming responsibility for part of the production of texts in English.

The development of the Orphanet Knowledge Management Platform, a platform allowing experts in the field of rare diseases to help curate the scientific data in Orphanet, was carried out in 2016 by partners of the RD-Action consortium in Australia.

Management of the national website/entry point to the Orphanet portal is also carried out by every national team in their national language.

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 national contact point is in charge of validating the already available national information and the data submitted by national professionals through the online registration tool.

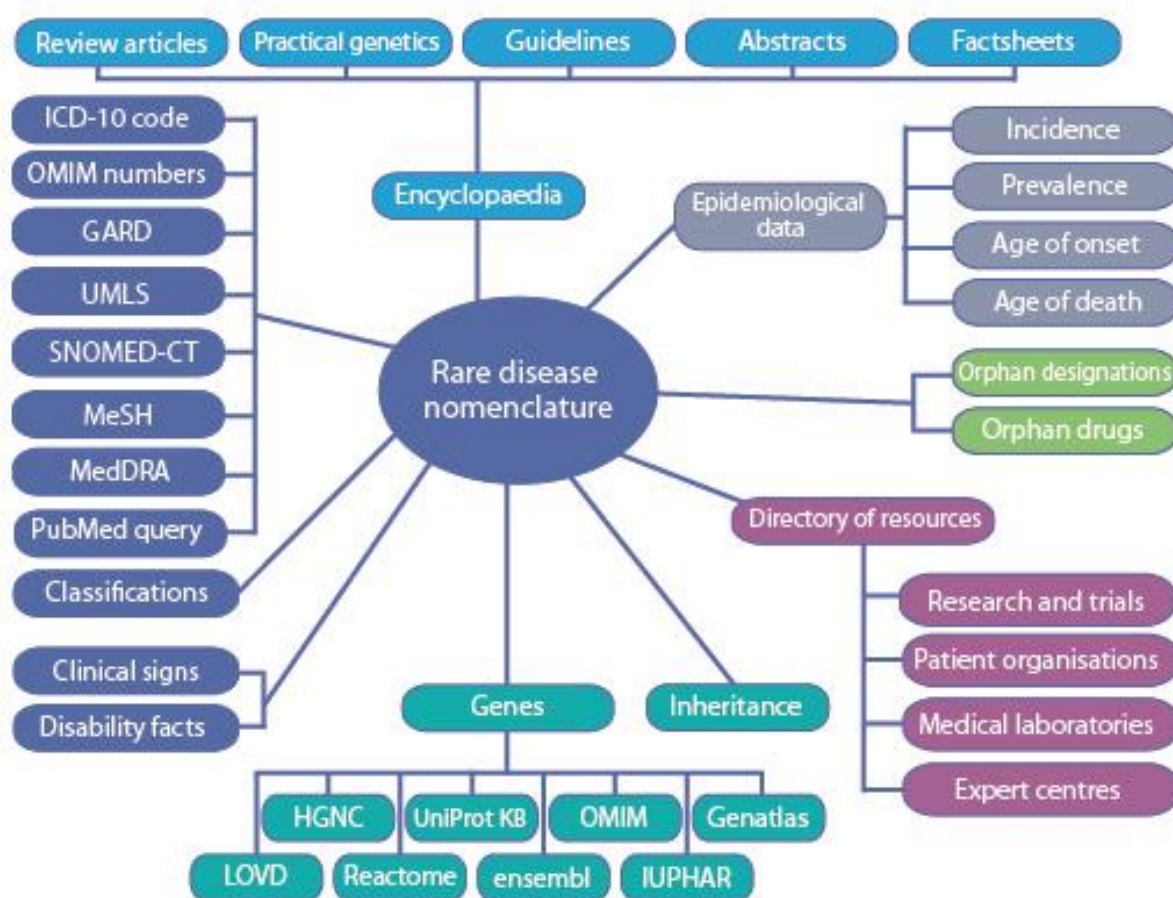# 3. Orphanet: Products and services

Figure 3 The Orphanet database

Orphanet is an evolutive, relational knowledge database with added value, as the scientific content produced in-house is expert-validated (list of expert reviewers having contributed to the scientific content is presented each year as a dedicated Orphanet Report) and integrated with other available resources, as shown in the diagram presented in Figure 3 and described hereafter.

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), rare forms of common diseases, and diseases for which prevalence figures are unknown but are potentially rare. Some diseases that are non-rare in Europe but that are rare in other countries, like the USA, can be considered for inclusion if their addition is necessary in order to represent expert services in these countries.
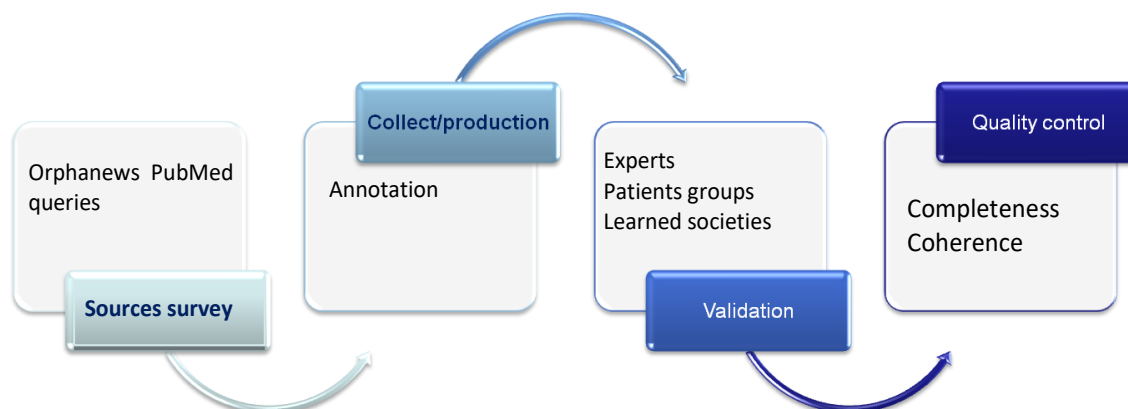
Figure 4 Orphanet data production methodology

The update of the scientific content of the database is performed using a four step methodology (Figure 4) 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, and is the basis for the production of various texts (encyclopaedia, guidelines, etc.). 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.
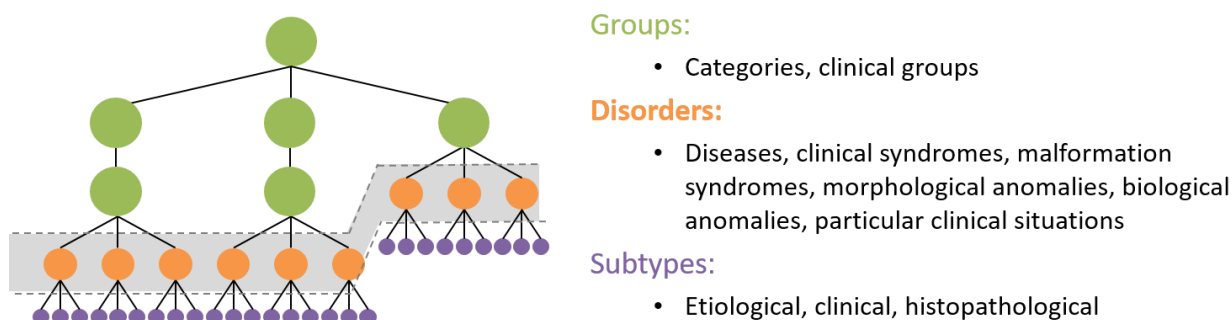
All the teams that make up the Orphanet consortium are responsible for the collection, validation and submission of data on expert services in their country. In order to publish data which is relevant and accurate (complete, valid and consistent with other data from the database), validation and quality 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 are developed regularly to resolve the issue of information dispersion and to address specific needs of the different stakeholders.

3.1. Orphanet content: Inventory of rare diseases

Orphanet provides a comprehensive inventory 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. 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) can be viewed directly on the www.orpha.net website and/or extracted from Orphadata in XML format.

Groups:
- Categories, clinical groups

Disorders:
- Diseases, clinical syndromes, malformation syndromes, morphological anomalies, biological anomalies, particular clinical situations

Subtypes:
- Etiological, clinical, histopathological

Figure 5 Schema of the Orphanet nomenclature and classifications

Since 2014, each clinical entity is assigned precisely one of these categories, allowing more accurate information on their typology and exact number. Other precisions include updates on 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 9,374 clinical entities[1] and their synonyms (including 6,084 disorders[2]).

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.

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[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.

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

Codes	Aligned ORPHA numbers
ICD-10	7,090

Table 1 Number of disorders, groups of disorders or subtypes aligned to ICD-10 codes

Diseases are mapped to one or more OMIM numbers (see Table 2). Exact mappings between the Orpha nomenclature and other terminologies (UMLS, MeSH and MedDRA) are available online (see Table 2). Mappings to SNOMED-CT are produced in collaboration with IHTSDO and are available upon request to IHTSDO. Mappings are carried out in a semi-automatic way and are manually curated. Updates follow every UMLS release.

All mappings 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	2,884
MeSH	1,761
SNOMED CT	5,333
MedDRA	1,168
OMIM	4,390

Table 2 Number of mapped diseases (groups of disorders, disorders and sub-types) per terminology

The Orphanet nomenclature is annotated with phenotypes. 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, 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, 2,630 diseases are annotated with HPO terms. Further annotations to HPO are being carried out. In 2017, the Orphamizer tool (Phenomizer-Orphanet) tool was launched in beta allowing users to retrieve a differential diagnosis using a set of phenotypes from HPO. This tool is developed by Sebastian Köhler from the Charité, Berlin, Germany.

Orphanet provides epidemiological and natural history information on each rare disease. Disease inheritance patterns and age of onset categories have been refined for more accurate information (Table 3). Prevalence, annual incidence, prevalence at birth and lifetime prevalence data are now documented in addition to the prevalence intervals already available (Table 4). Minimum, maximum

and mean figures for each item are documented according to geographic zones, when information is available. 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 5,300 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 via signature of a Data Transfer Agreement (academia) or licence fee (private sector): Europe, USA and worldwide prevalence intervals are provided via the website.

Natural history data	Number of groups of disorders, disorders and sub-types
Average age of onset	5,310
Mode of inheritance	5,248

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

Epidemiological data	Number of groups of disorders, disorders and sub-types
Point prevalence	5,299
Prevalence at birth	488
Lifetime prevalence	46
Annual incidence	435

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

3.1.1. ADDITIONAL FUNCTIONALITIES IN 2016

Orphanet revised its policy concerning the inclusion of non-rare diseases (according to the EU definition of a prevalence of not more than 1 per 2'000 in the EU population). Diseases not meeting this definition have been withdrawn from the website and available datasets. However, some non-rare diseases have been kept so that we may respect our commitment to representing the genetic testing landscape in Consortium countries, to representing all officially designated expert centres for rare diseases, and all orphan drugs (as some of these can be linked to diseases considered as rare in other countries such as the USA). However, these exceptions are not included in the Orphanet nomenclatures and classifications.

Orphanet now classifies rare diseases with a thesaurus of functional consequences derived and adapted from the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY, WHO 2007). This information, aimed at professionals in the medico-social sector, patients and their carers, will be of use in particular in the evaluation, support and holistic care of people living with a disability as a result of a rare disease. The data will also help improve knowledge concerning these disabilities, notably by putting into a place a common language to describe these functional consequences.

This data is available via the 'Disability' sub-tab on the Orphanet website. Users can search by disease and will obtain a structured information on the functional consequences of the disease, as well as a link to a Orphanet Disability Encylopaedia article if available, as well as a link to the Eurordis directory of specialised social services. This tool thus constitutes a complete source of information on the functional consequences associated with rare diseases. For each disease, the functional consequences are organised in decreasing order of frequency and also annotated with their severity (limitation/total restriction, severe, moderate, low) and temporality (permanent, episodic, delayed acquisition, loss of capacity). This tool allows the user to access a rapid and complete overview of the eventual consequences of the disease that should be assessed/anticipated. It also allows professionals to fill in medical certificates using an adapted vocabulary derived from ICF. The tool was developed in English but is now available in the 7 languages of the Orphanet website. This data is now available for 525 diseases.

Figure 6 Screenshot of the new Disability tool on the Orphanet website

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 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 (International Union of Basic and Clinical Pharmacology) databases. 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, modifiers (both from germline or somatic mutations), 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. 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.

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.

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 (6,941 entities in the database have one of these forms of textual information).

Orphanet texts (apart from the automatically generated) are unique and written in English by a member of the editorial team. Definitions and abstracts are then reviewed by an invited world-renowned expert. Abstracts and definitions 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 4,089 rare diseases is available online.

They are translated into the six other languages of the website (French, Italian, Spanish, German, Portuguese and Dutch). In addition, 167 abstracts are now available in Finnish, 647 in Polish, 103 in Slovak and 424 in Greek. For the additional 2'852 entries 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).

- **Practical genetics articles**

These articles are co-produced by Orphanet and the *European Journal of Human Genetics* (EJHG), the official journal of the *European Society of Human genetics*. Freely-accessible articles are published in the *EJHG* (Nature Publishing Group) and are accessible via Orphanet.

- **Orphanet Emergency Guidelines**

These guidelines are intended for pre-hospital emergency health care 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: 75 emergency guidelines in French are available online. They are being translated into the following six languages: English, German, Italian, Portuguese, Spanish and Polish. 20 emergency guidelines are available in English, 42 in Italian, 24 in German, 22 in Spanish, 17 in Portuguese, and 17 in Polish.
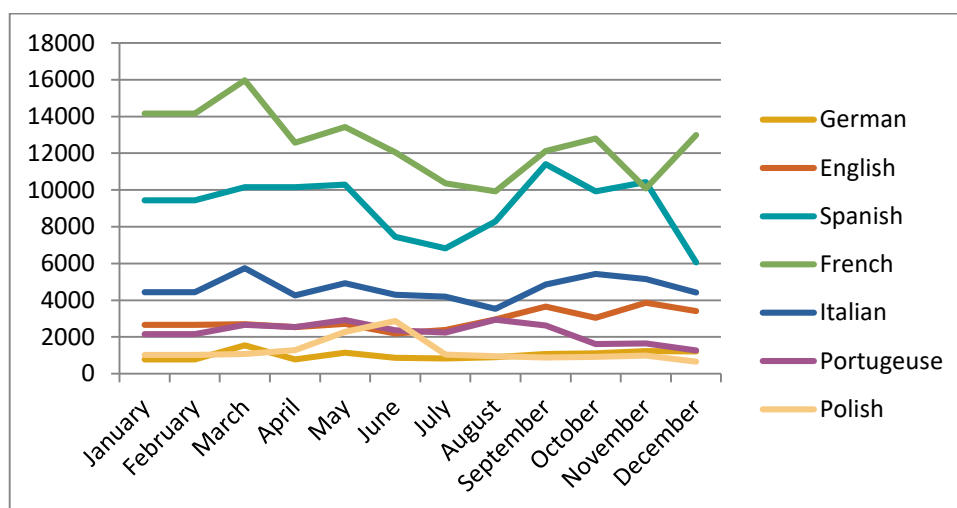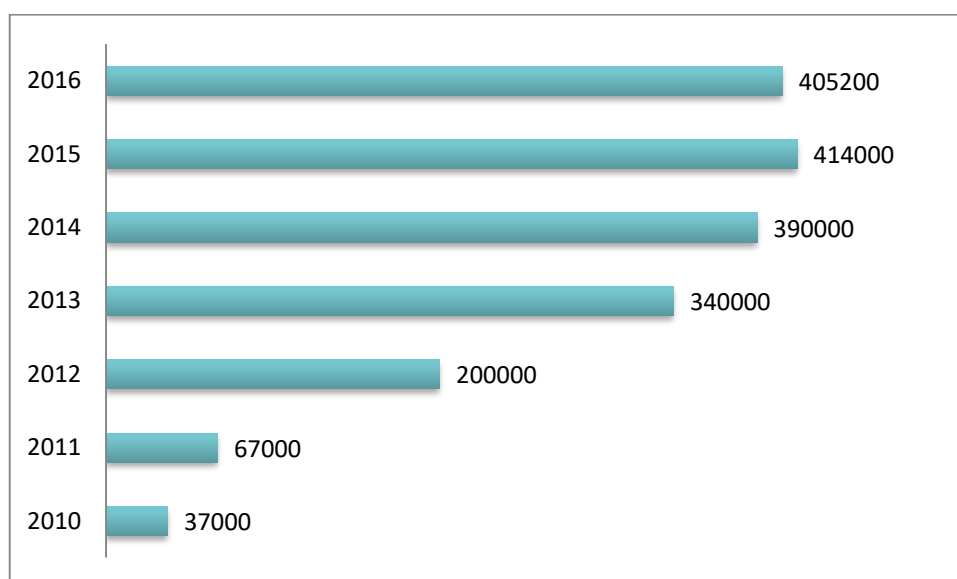

Figure 7 Downloads of the Orphanet emergency guidelines by language in 2016

Emergency guidelines were viewed more than **405,200** times in 2016 (Figure 8), versus approximately 414,000 in 2015 (Polish Emergency guidelines were excluded from this count in 2015 but included in 2016) (Figure 7).

Figure 8: Downloads of the Orphanet emergency guidelines since 2010 in all languages

Epidemiology:

5,299 diseases annotated with point prevalence data

Natural history:

5,248 diseases annotated with mode of inheritance

5,310 diseases annotated with age of onset

Mappings:

7,090 diseases mapped to ICD-10

4,390 diseases mapped to OMIM

2,884 diseases mapped to UMLS

1,168 diseases mapped to MedRA

1,761 diseases mapped to MeSH

Genes:

3,715 genes linked to 3,566 diseases, including:

3,713 genes interfaced with HGNC

3,500 genes interfaced with OMIM

3,458 genes interfaced with Genatlas

3,442 genes interfaced avec UniProt KB

2,243 diseases interfaced with **Pubmed**

2,630 diseases indexed with **clinical signs**

The Orphanet encyclopaedia contains the following summary texts:

4,089 in English

3,314 in Italian

3,299 in French

3,159 in German

3,074 in Spanish

1,182 in Portuguese

663 in Dutch

647 in Polish

424 in Greek

167 in Finnish

256 in Russian

103 in Slovak

5,321 **external links** for 5,070 diseases

In-house produced texts: 124 **articles for the general public** in French, 75 **emergency guidelines** in French, translated in German, English, Spanish, Italian, Portuguese, and Polish. 43 **Disability factsheets** in French

Link to external RD literature

539 Review articles

646 Clinical genetics reviews

331 Clinical practice guidelines

132 Guidance for genetic testing

864 General public articles

22 Emergency guidelines

Figure 9 The disease database content

3.3.2. GENERAL PUBLIC ENCYCLOPAEDIA

The general public encyclopaedia was initially a French project 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-four in-house French texts are available online. Eight have been translated into Spanish. Documents from this encyclopaedia are downloaded approximately 550,000 times per month, which corresponds to more than 6.6 million downloads in 2016 (Figure 10). This represents an increase of 8% compared to the 6.1 million downloads in 2015. 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).
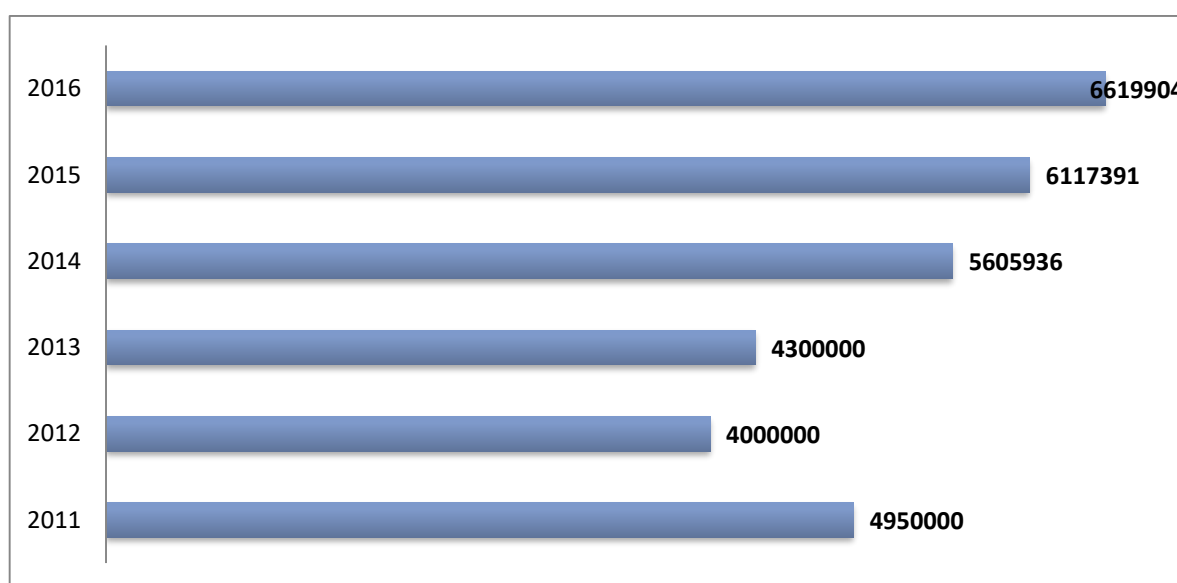
Figure 10 Downloads of the general Public encyclopaedia since 2011

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). In 2016 many of these texts were produced as stand-alone texts, independent of the General public encyclopaedia.

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 tabs "Encyclopaedia for professionals" and "Disability". Forty-three of these texts are available online since November 2013. They have been downloaded approximately 38,820 times in 2016 (Figure 11). This represents an increase of 61% compared to the 24,000 downloads in 2015. Translations into Spanish of these texts started in June 2016, with 4 translated in 2016.
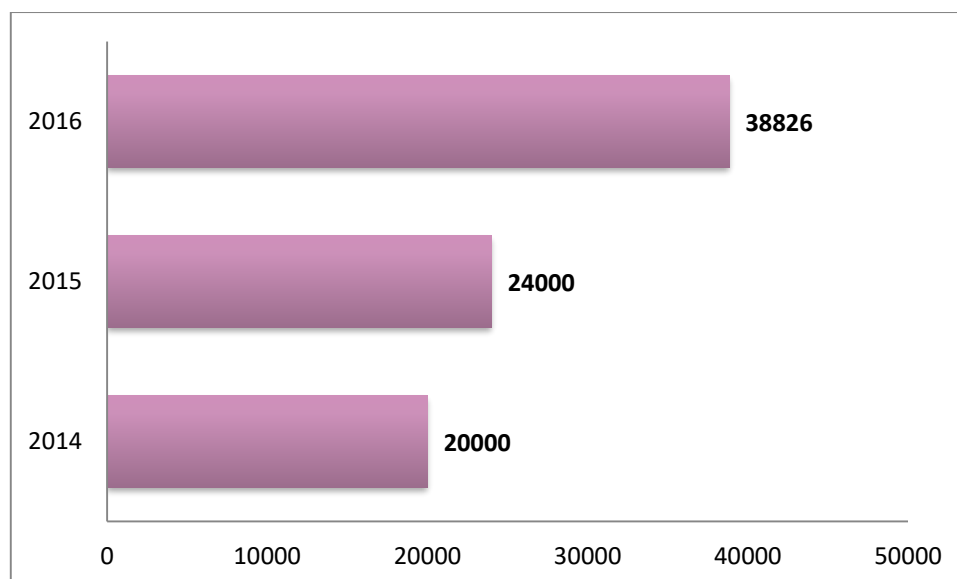
Figure 11 Evolution of number of downloads per year of the French Disability factsheets in since 2014

3.3.4. DIAGNOSTIC CRITERIA

Information on diagnostic criteria is presented in 26 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.

3.3.5. 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**
539 review articles (of which 228 were published in the Orphanet Journal of Rare Diseases) are available on the website.

- **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 646 articles from GeneReviews.

- **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[3]. The Orphanet website gives access to 331 best practice guidelines.

- **Guidance for genetic testing**
This collection comprises summary recommendations intended to disseminate the best practices in genetic testing. They include Gene Cards (published in the European Journal of Human Genetics). 132 recommendations are available via the website.

- **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. 864 articles are available on the website.

- **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. The website gives access to 22 external emergency guidelines in English.

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[3] *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

- **Disability factsheets**

20 disability factsheets are available in Danish, produced by Sjaeldenborger, the Danish Rare Diseases alliance.

	Article for general public	Review article	Clinical practice guidelines	Guidance for genetic testing	Clinical genetics review
Croatian	2	-	-	-	-
Czech	3	-	-	-	-
English	192	412**	120	131	646
Finnish	13	-	-	-	-
French	194*	52	102	1	-
German	64	30	86	-	-
Greek	8	-	-	-	-
Hungarian	1	-	1	-	-
Italian	30	34	1	-	-
Polish	6	-	-	-	-
Portugese	6	1	1	-	-
Romanian	5	-	-	-	-
Russian	8	-	1	-	-
Slovak	1	-	-	-	-
Spanish	27	10	19	-	-
Swedish	304	-	-	-	-

**including 228 Orphanet Journal of Rare Diseases reviews

* not including the in-house produced articles

Table 5 Total number of Orphanet external content: type of text per language

3.4.   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
- Mutation databases
- Biobanks
- Ongoing research projects
- Clinical trials
- Platforms

Data is collected 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. 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. Annual updates are managed either by the teams at country level, when they have sufficient funding for a dedicated professional, or by the coordinating team on behalf of the Orphanet national team.

The 35 countries in which Orphanet members collected data in 2016 are the following:
Argentina, Armenia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Morocco, the Netherlands, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tunisia, the United Kingdom and Western Australia. In 2016, Argentina, Bulgaria, Norway, and Turkey did not manage to update their data. Updates were received by the online registration tools for data regarding Denmark, Georgia, Lebanon and Luxembourg were managed at the coordinating team on behalf of the Orphanet contact points.

Data collection outside the Orphanet consortium:
Patient organisations in countries outside the Orphanet consortium can be registered in the database 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 mutation databases) funded by funding agencies in countries outside of the Orphanet consortium 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 fulfill inclusion criteria (Please refer to the technical procedures for an exhaustive list of inclusion criteria).

The catalogue of expert services in the Orphanet consortium contains the following data:
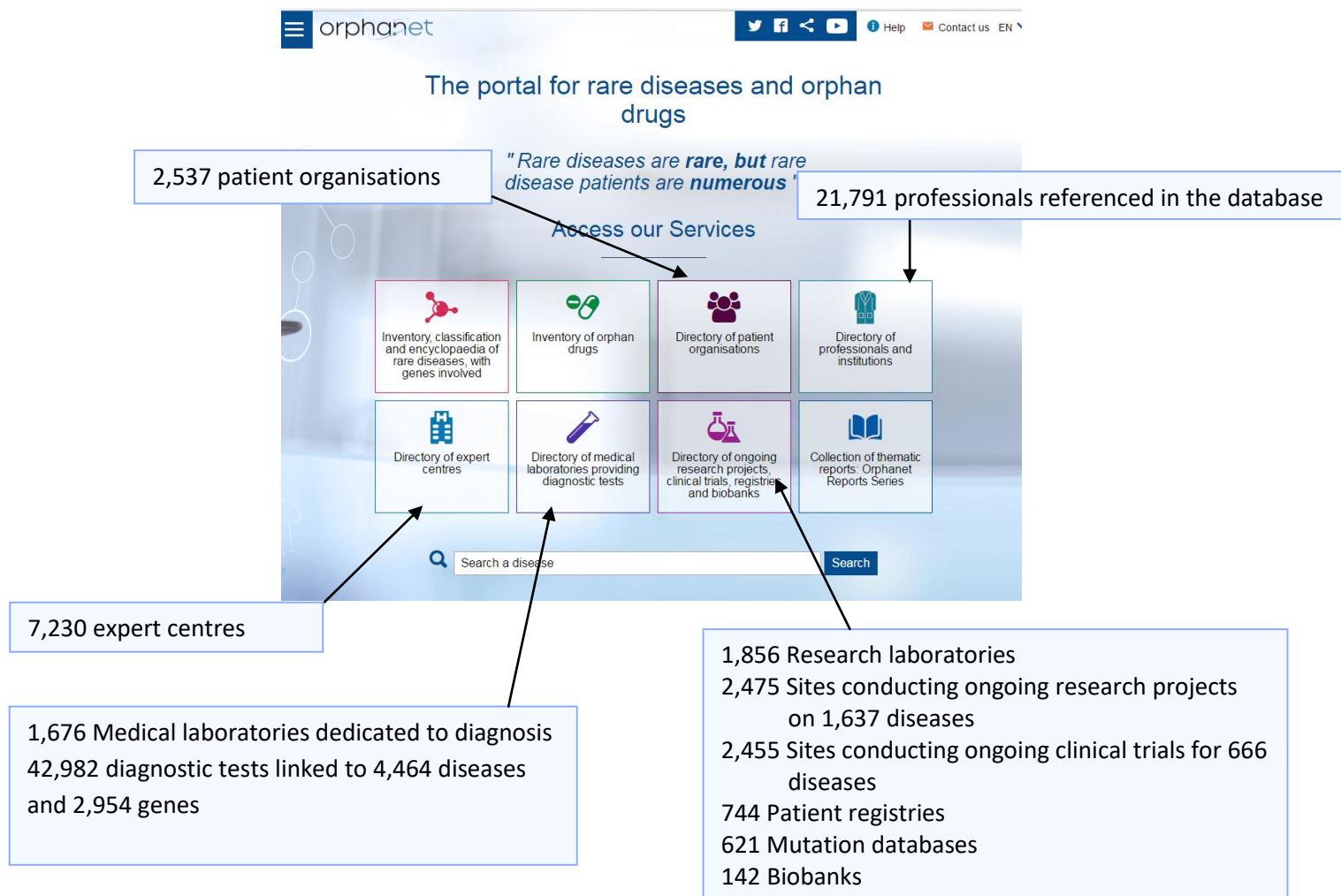
Figure 12 Directory of expert services[4]

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[4] Clinical trials: This number represents the total number of entries despite some of them are part of the same multinational clinical trial. Research projects : This number represents the total number of entries despite some of them are part of the same multicentric research project

3.4.1. 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, Cytogenetic European Quality Assessment Service (CEQAS) 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.

3.4.2. ADDITIONAL FUNCTIONALITIES IN 2016

The date of last update of all activites in Orphanet is now displayed on the website, in order to give users information on the last time this information was confirmed as being accurate, either by a professional or via an official source.

A new representation of diagnostic tests went live in 2016, expanding this dataset to give more information to user and allowing them to filter results by speciality/objective, technique, purpose, quality management data (accreditation and participation in EQA schemes), lab and test quality (accredited/participating in EQA), as well as the country in which the laboratory is located.

A link to EURORDIS' directory of specialised social services and links to Orphanet sources and procedures were added to the menu of services on each result page of the website, in order to help users find this information.

3.5. Orphanet content: Orphanet directory of orphan drugs

The list of orphan 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 included in the database because they have been tested in a clinical trial performed on a rare disease, but they do not have a 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 2016):

For Europe:
- **1287** Orphan Designations linked to **1007** substances and covering **485** diseases
- **240** Marketing Authorizations (of which **93** already had an Orphan Designation and **147** without Orphan Designation), covering **220** diseases

For the USA:
- **714** Orphan Designations linked to **588** substances and covering **399** diseases
- **302** Marketing Authorizations (of which **295** already had an Orphan Designation and **7** without Orphan Designation), covering **281** diseases

3.5.1. ADDITIONAL FUNCTIONALITIES IN 2016

The collection of information Orphan Drugs from Food and Drug Administration in the USA (FDA) is now complete.

3.6. Orphanet products: Orphanet Report Series

Orphanet Reports (ORS) are a series of texts 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.

The ORS are heavily downloaded: in 2016, more than 1,144,400 ORS were downloaded (Table 6). There was a decrease in downloads of Orphanet Report Series this year (Figure 13): this is most probably due to an over-evaluation of downloads in the previous year due to an unusual increase in access of some files by search engine robots.

	English	French	German	Spanish	Italian	Dutch	Polish	Portugueuse
List of rare diseases in alphabetical order	93415	316324	43336	45732	50661	9671	19129	6847
Prevalence of rare diseases by alphabetical list	45575	1181	6581	10674	6716	NA	NA	4014
List of orphan drugs in europe	26718	8750	2759	4972	4493	1031	NA	924
Prevalence of rare diseases by decreasing prevalence or cases	13994	14701	4182	22592	5402	NA	NA	6319
Activity Report 2015	39125		NA		NA	NA	NA	NA
Registries	32803	NA	NA	NA	NA	NA	NA	NA
Orphanet ICD10 coding rules	12589	NA	NA	NA	NA	NA	NA	NA
Orphanet linearisation rules	1018	NA	NA	NA	NA	NA	NA	NA
Research Infrastructures for rare diseases in Europe	10981	NA	NA	NA	NA	NA	NA	NA
Vivre avec une maladie rare en France	NA	121986	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 2016 by language
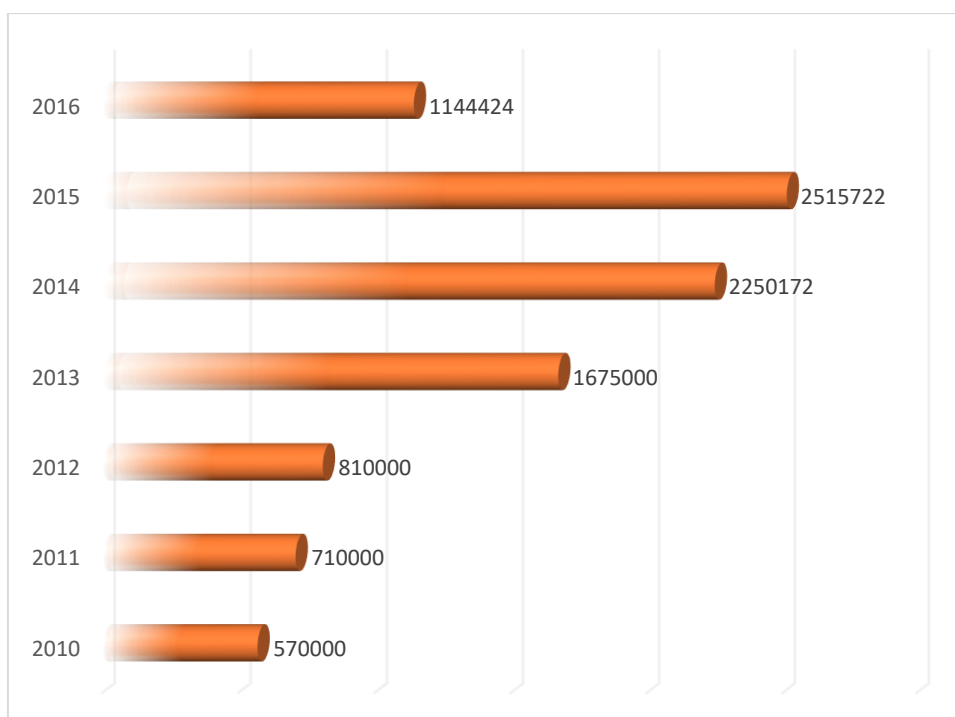
Figure 13 Number of downloads of the Orphanet Report Series in all languages since 2010

3.7.   Orphanet's IT infrastructure

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 fiber optic connection. This allows an excellent connectivity between production servers, development servers and backup environments. The architecture of the servers is represented in Figure 14.

Many production environments are in place: back office, pre-production, preservation and development environments. This makes the Activity Recovery Plan (PRA) of the Orphanet website highly efficient. Back-office tools used by the coordinating team in France, and other teams internationally, are accessed through VPN (Virtual Private Network) servers. No major problems were encountered in 2016 and the www.orpha.net website was highly available despite an increasing amount of visitors, which now reaches nearly 4 million pages viewed per month. We have made several updates for security reasons (PHP and servers OS).
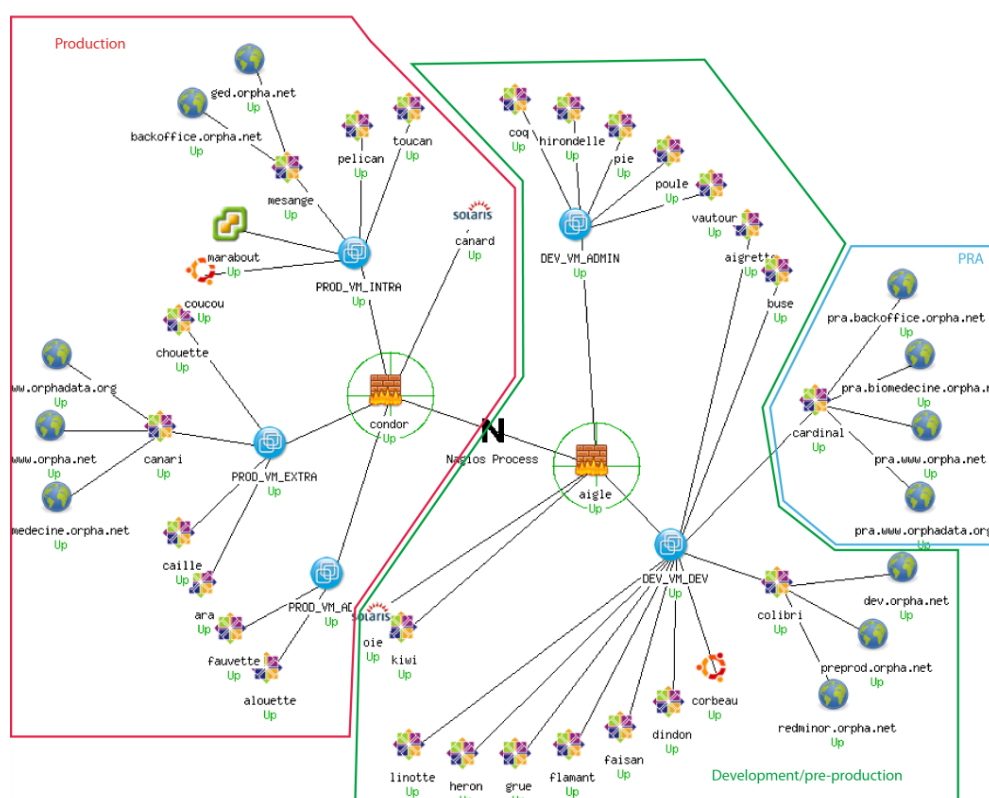
Figure 14 Orphanet's IT architecture in 2016

3.8. 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 (Figure 15). 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.

A new look website was launched to mark the 20th anniversary of Orphanet in 2017, with much of the redesign work taking place in 2016. One new feature is the 'burger menu' present on all pages, that allows users to access each of the products and services provided by Orphanet, no matter what page they are on. The popular Orphanet Report Series, which provides aggregated Orphanet data on a range of rare disease and orphan drug topics, has a dedicated icon block. OrphaNews, the newsletter of the rare disease community and a dissemination tool for RD-ACTION, is easily identified via a dedicated block, as are Orphadata and ORDO.
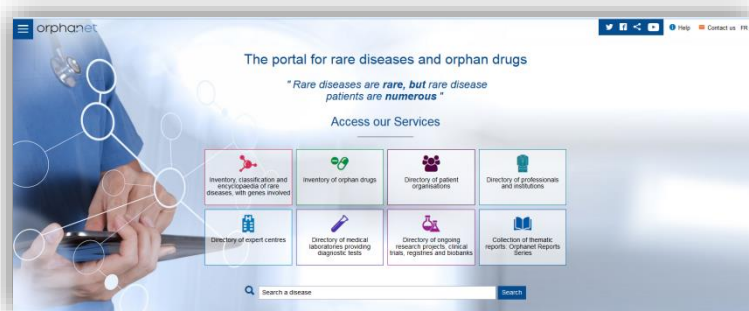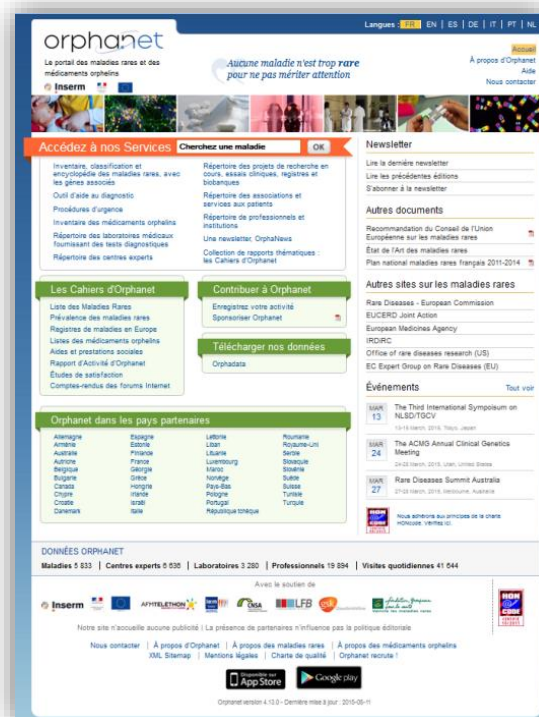
Figure 15 The Orphanet portal homepage in 2016 and the Orphanet portal homepage in 2017

To help users navigate the website, a list of our principal services is proposed on the "Help" page. Services are categorised to accommodate different user profiles. The new look and feel of the website was the first step in the process to improve access to the data in the Orphanet database.

3.8.1. 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 1,960,000 responses.

Users mainly access the www.orpha.net site through search engines, namely organic searches (54% of sessions according to Google Analytics), and Google alone accounts for almost 50% of queries (Figure 16). 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.

Other sites generating traffic to Orphanet through referrals represent 21% of visits. The remaining visits are made via direct access (bookmarks, 24%) and referrals.
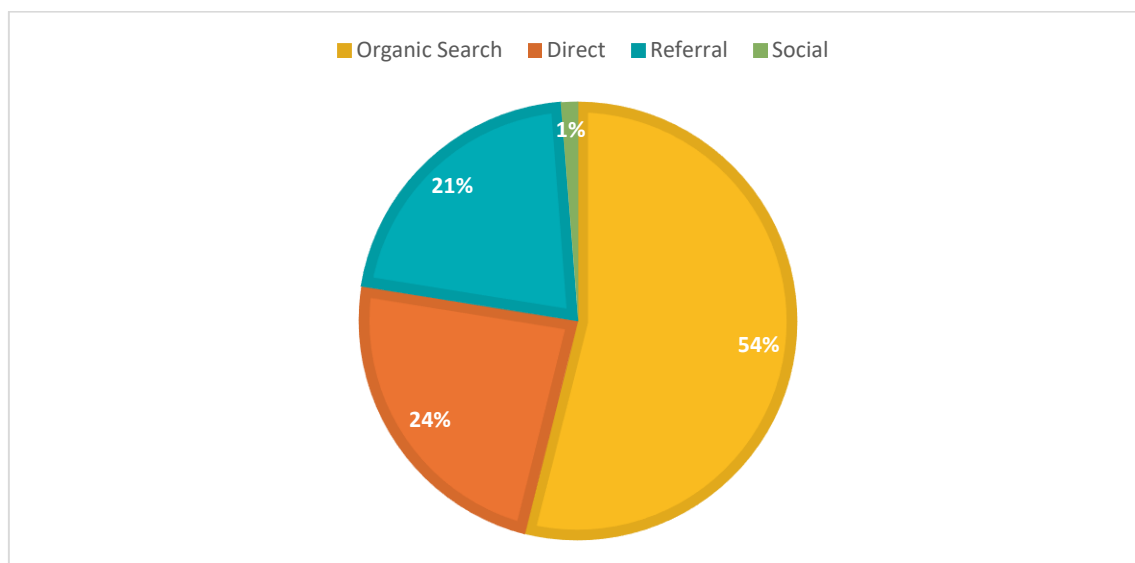
Figure 16 Distribution of the traffic sources
(Source: Google Analytics, 1ˢᵗ of January 2016 to 31ˢᵗ of December 2016)

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 300'000 different keywords generate traffic to the site.

Google Analytics allows users to trace visits made from mobile devices (Smartphone, tablets): these visits represented 28% of all visits during 2016, an increase when compared to other years (20% in 2015 and 2014, and 23% in 2013).

3.8.2. THE WEBSITE'S AUDIENCE

Orphanet website in numbers

- 47,5 million pages viewed
- More than 12 million PDFs downloaded
- Over 9 million visitors from 232 countries

In 2016, around 47.5 million pages were viewed, thus on average around 130,000 pages were viewed per day (Figure 17). This figure has increased in comparison to 2015 (82,000 pages viewed per day), representing a 59% increase.

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: each month, around 1 million PDF documents are consulted on the Orphanet website. This represents a figure of around 12,112,000 downloads in 2016. This is a decrease of around 2 million from 2015 which had a unusually high number of downloads, which can now be identified as being a result of robots accessing massively the PDFs.

The users come from 232 countries. The top ten countries are: France, Italy, Mexico, Spain, United States, Germany, Brazil, Canada, Colombia, and Belgium.
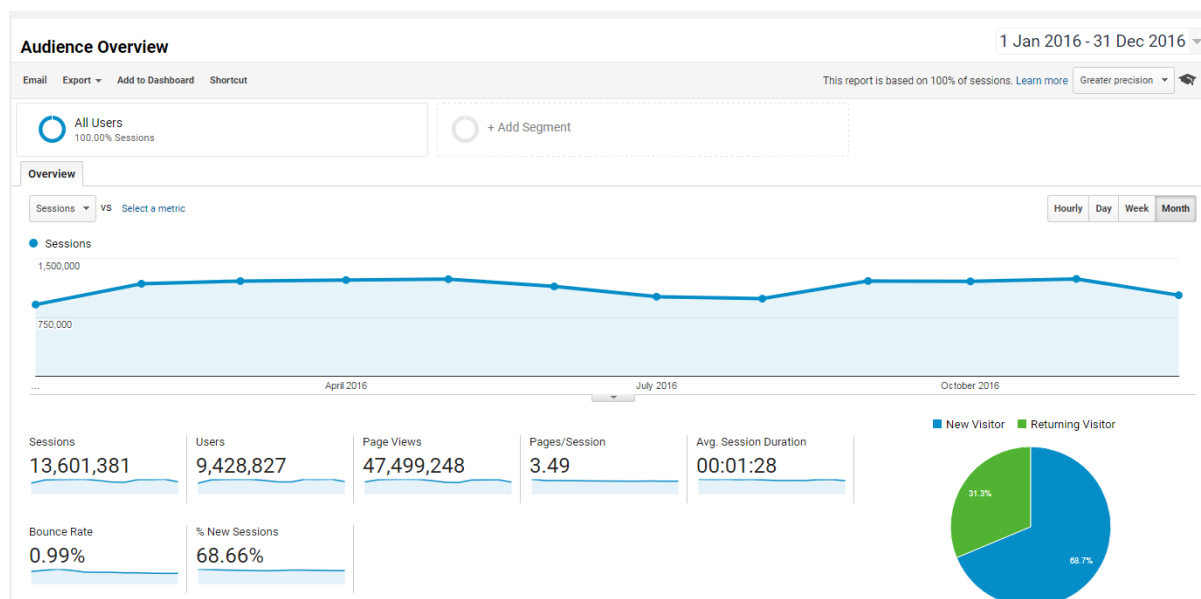
Figure 17 Orphanet website consultations in 2016
(Source: Google Analytics, 1ˢᵗ January 2016 to 31ˢᵗ December 2016)

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 increased by 464% in 2016 compared to 2015 (Figure 18), as did the number of users (by 877%) whereas the average session was nearly 60% shorter in 2016 compared to the previous year (1:28 minute versus 3:34 minutes). The number of pages viewed per session also decreased by 72% last year compared to the previous year. According to Google Analytics, users thus connected more often, and stayed for a shorter time on the site, viewing around 3.5 pages. These significant changes in the statistics are most probably a reflection of changes to the Google Analytics settings, in particular a change to their definition of a session.

Year	Sessions
2016	13601381
2015	2408303
2014	5422288
2013	7836100
2012	4414102
2011	3521390
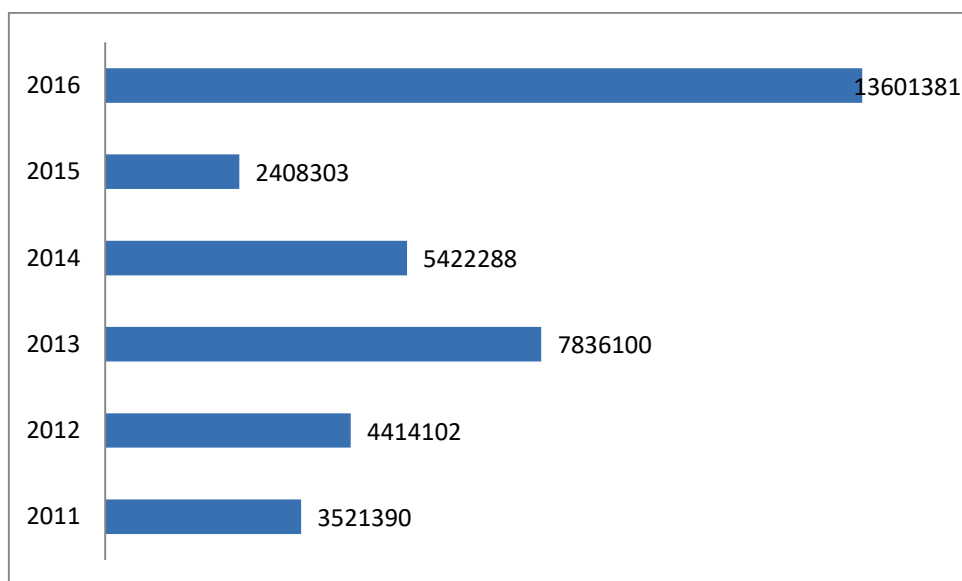
Figure 18 Evolution of number of sessions since 2016 (Source: Google Analytics)

3.8.3. 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 2016, 35 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.

3.9. Orphanet services: Orphanet Rare Diseases Ontology

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

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), 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.

In 2016, ORDO was downloaded 8,443 times, stable from the previous year.

3.10. 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.

Figure 19 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 seven languages: English, French, German, Italian, Portuguese, Spanish and Dutch. Part of the datasets are available freely via a Creative Commons licence, 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.
• A classification of rare diseases established by Orphanet, based on the literature and expert consensus classifications.
• 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)

Table 7 Products freely accessible on Orphadata

• 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 seven languages (English, French, German, Italian, Spanish, Portuguese, Netherlands)
• URLs of other websites providing information on specific rare diseases
• 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)
• 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

Orphadata provides a [guide](#) 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 [methodology of alignment of ICD10 coding rules for rare diseases](#) and the [methodology of linearisation](#).

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.

In 2016, **Orphadata products were downloaded more than 168,800 times**, with an average of 14,060 times per month. This represents a decrease of 16% compared to 2015 (Figure 21). This decrease is most likely explained by the transfer of the epidemiological data from the freely accessible part of the site, to access via signature of a DTA or licence agreement.
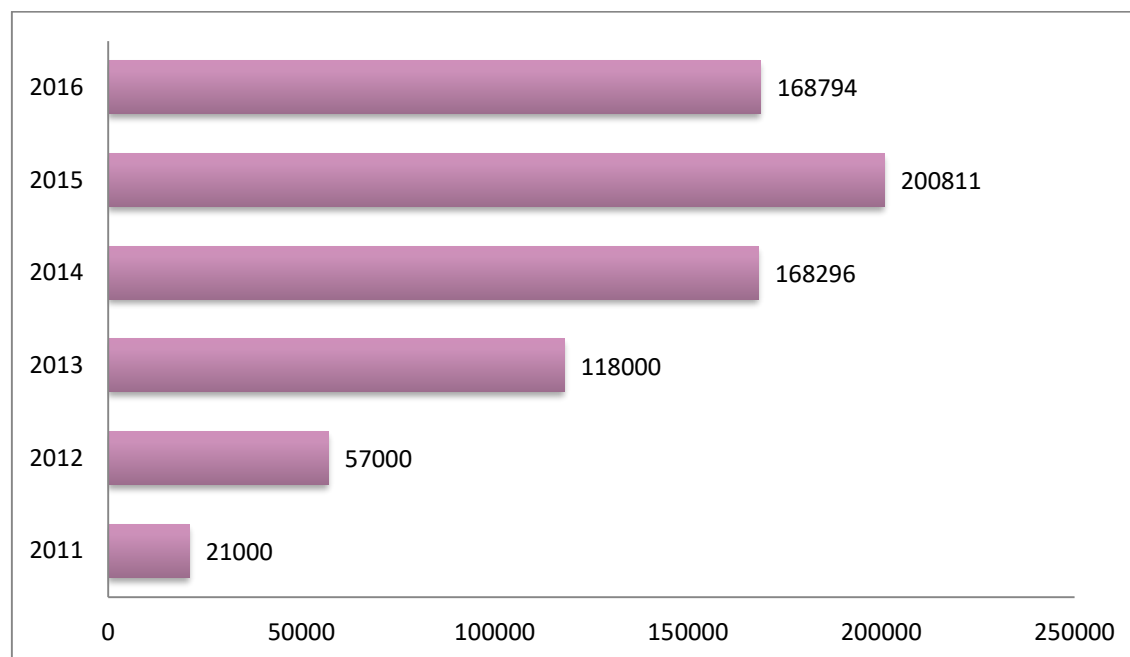
Figure 20 Number of downloads from the Orphadata website since mid-2011

The most requested Orphadata product in 2016 was the inventory of diseases with clinical signs (Figure 21).
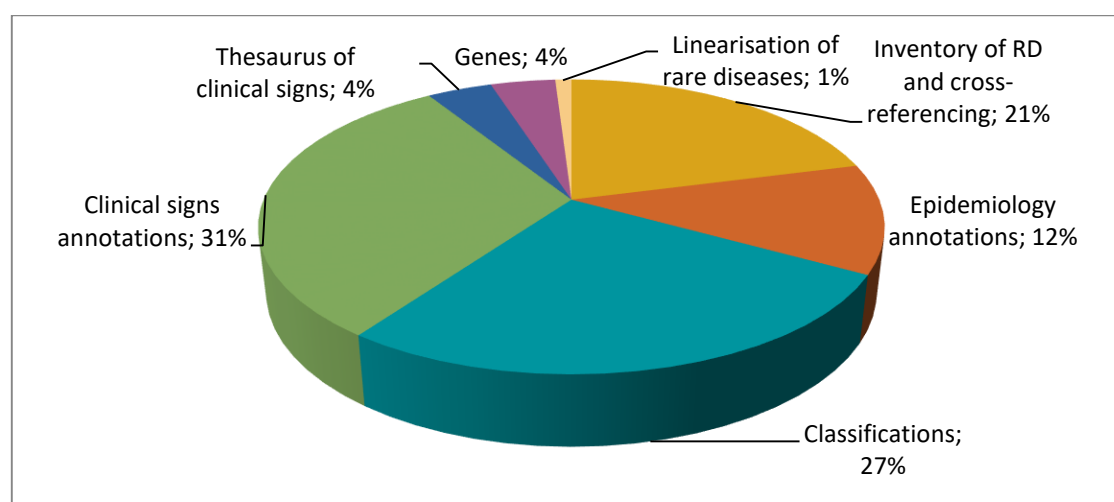
Figure 21 Distribution of the downloads of Orphadata freely available datasets in 2016. The epidemiological dataset, available via DTA or licence fee only from October 2016 is included. [total of 167,957 downloads]
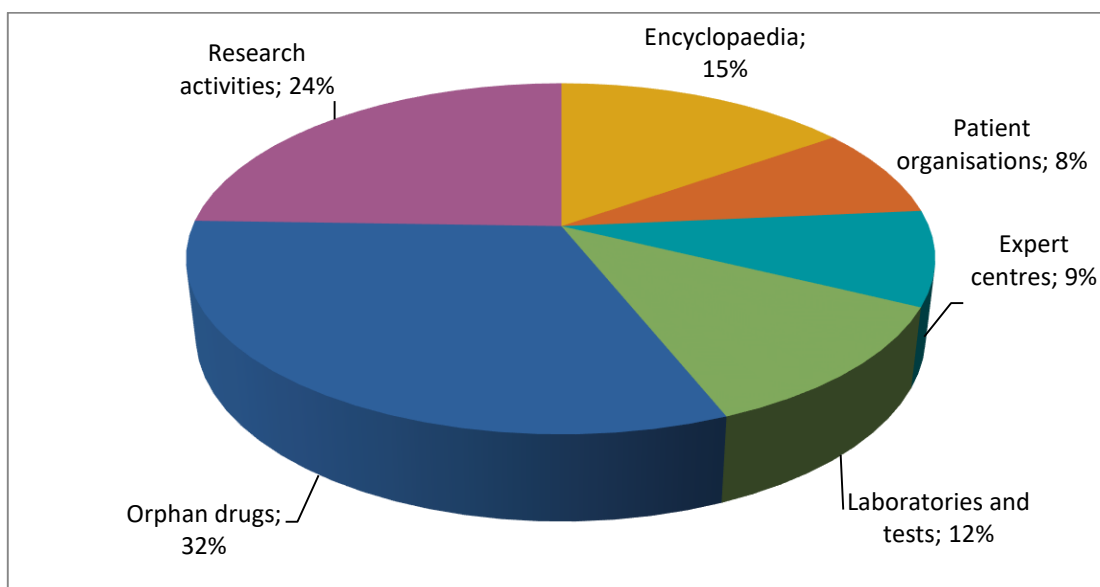
Figure 22 Distribution of the downloads of Orphadata Datasets accessible on demand in 2016 [total of 837 downloads]

3.10.1. ADDITIONAL FUNCTIONALITIES IN 2016

The Orphadata catalogue and user guide were updated in 2016. A SPARQL endpoint (beta version) was also made available for the freely-available data.

Due to the cost of producing the epidemiological dataset, it was decided to make this data available via a Data Transfer Agreement for academia and via a licence fee for private users as of October 2016. This was announced on the Orphadata website.

3.11. 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 review 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 is supported by the European Commission's DG SANTE RD-ACTION Joint Action N° 677024 and it is the dissemination tool of this Joint Action. OrphaNews France is supported by the French Muscular Dystrophy Association (AFM), while OrphaNews Italy is supported by Genzyme. At the end of 2016 the newsletter was transferred to a new tool (Figure 24) so as to improve the look and feel of the newsletter, navigation in the newsletter, and to provide

better search functions via a thesaurus of keywords: the first editions in this new format were published at the start of 2017.

Figure 23 OrphaNews homepage in 2016
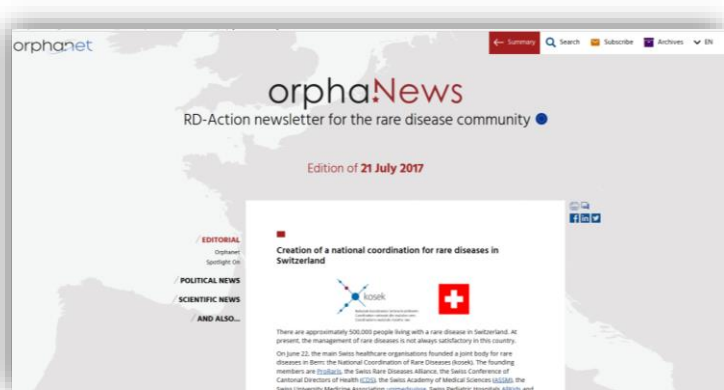
Figure 24 OrphaNews homepage in 2017

In 2016 OrphaNews in English had more than 16,000 subscribers. OrphaNews in French had more than 11'000 subscribers and OrphaNews in Italian had more than 7'000 subscribers.

3.12. Orphanet Services: Mobile applications

Orphanet data is available via two mobile apps.

Figure 25 Orphanet mobile app and Orpha Guides mobile app

Orphanet is an app allowing users to access the list of rare diseases, textual information concerning the diease and associated services, as well as Emergency Guidelines. The app is available via for iOS and Android. This application is available in all languages of the Orphanet website.

Orpha Guides is an app in French giving access to information on French national support mechanisms for patients and their families, as well as information concerning the functional consequences of over 100 rare diseases. The app is available for iOS and Android.

3.13. 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 current impact factor is 3.507.

4. Users

4.1. 2016 Orphanet user satisfaction survey

An online survey was carried out for 4 weeks in January 2017. The satisfaction of the website users was assessed by asking them to respond to a short online questionnaire. 4071 users replied to the survey.

The following results present the responses collected in all languages (Dutch, English, French, German, Italian, Portuguese and Spanish). More results from this survey are available in the Orphanet Report Series dedicated to the 2016 survey.

In what capacity are you consulting the Orphanet website TODAY?

This question aimed to determine the profile of Orphanet's users. Seven categories were proposed (i.e. health professional, patients/entourage, researcher, industry, health care manager/policy maker, and students), and a free text field was included for other types of users to enter their profession. Only one response was possible. Respondents from the 'other' category were reassigned to one of the seven proposed categories when appropriate.
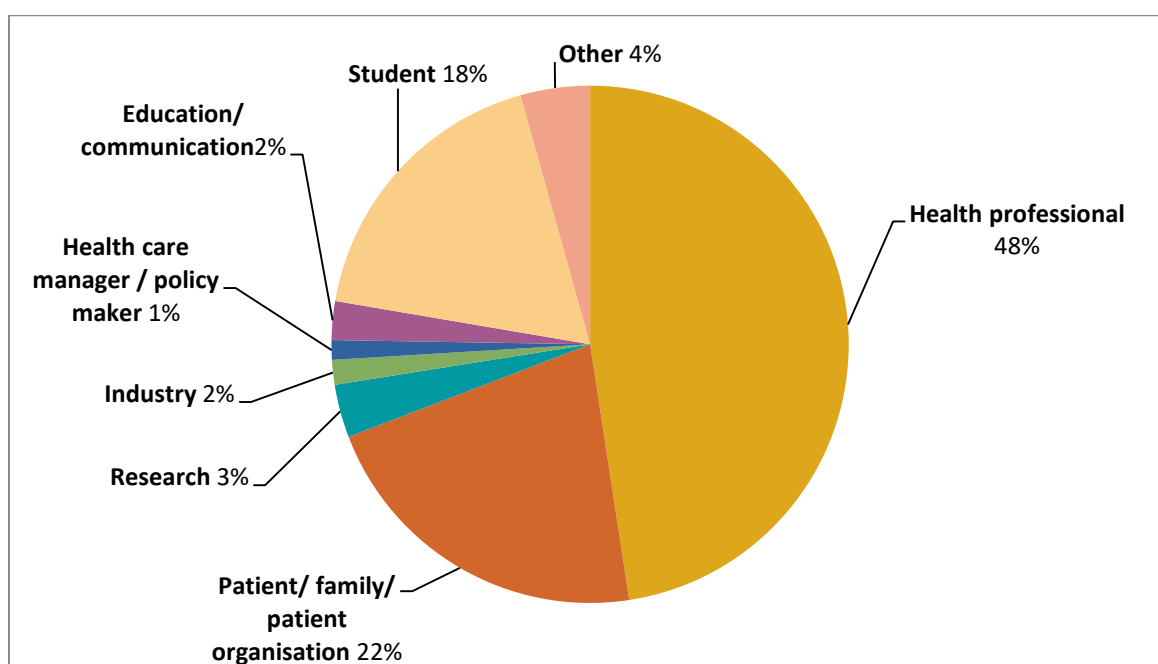
Figure 26 Types of Orphanet user (percentage of total respondents) n = 4010

The largest category of respondents is the health professional category (48%) (Figure 26). The second largest category of respondents is patients and their entourage (including patient organisations, alliances and support groups) with 22% of responses. Many students (18%) also use Orphanet. The 'other' category included respondents working in terminology standards,

biocuration, as well as non-related socio-professional categories and those generally interested in rare diseases but who did not state their professional category.

How often do you visit Orphanet?

Only one response was possible. Around 56 % of those answering the survey are regular users, whereas 20% were visiting Orphanet for the first time.
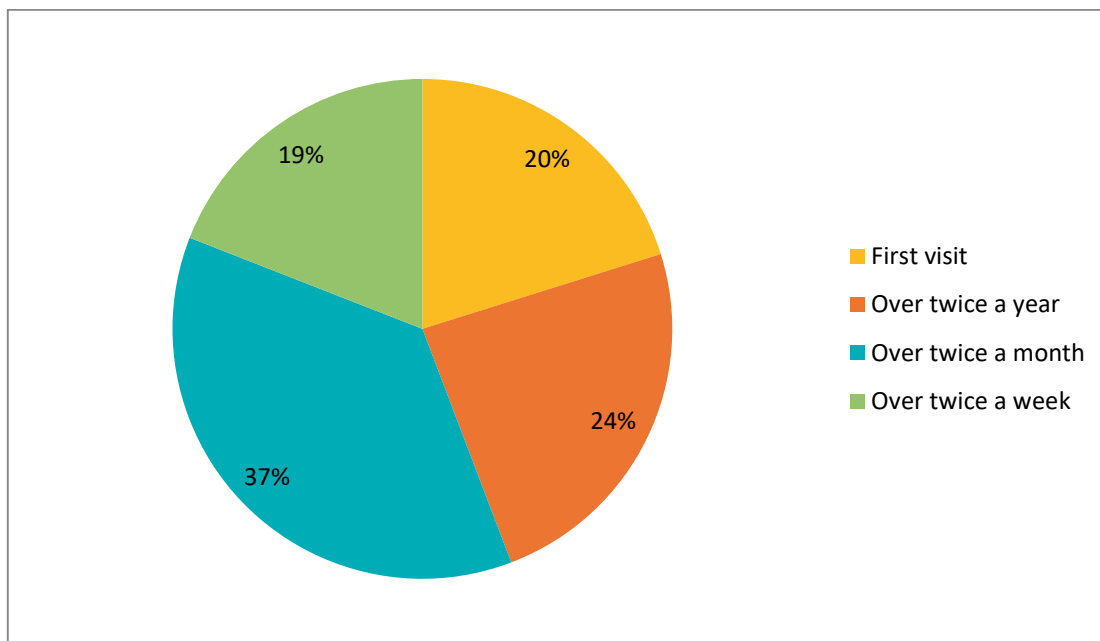
Figure 27 Visiting frequency of respondents (n=3646)

There were 6% less first time users this year compared to last year (26%), and 5% more users who use Orphanet twice a month.

What sort of information are you looking for during THIS CONNECTION to Orphanet?

This question aims to determine which kind of information visitors sought on Orphanet. More than one choice was possible.
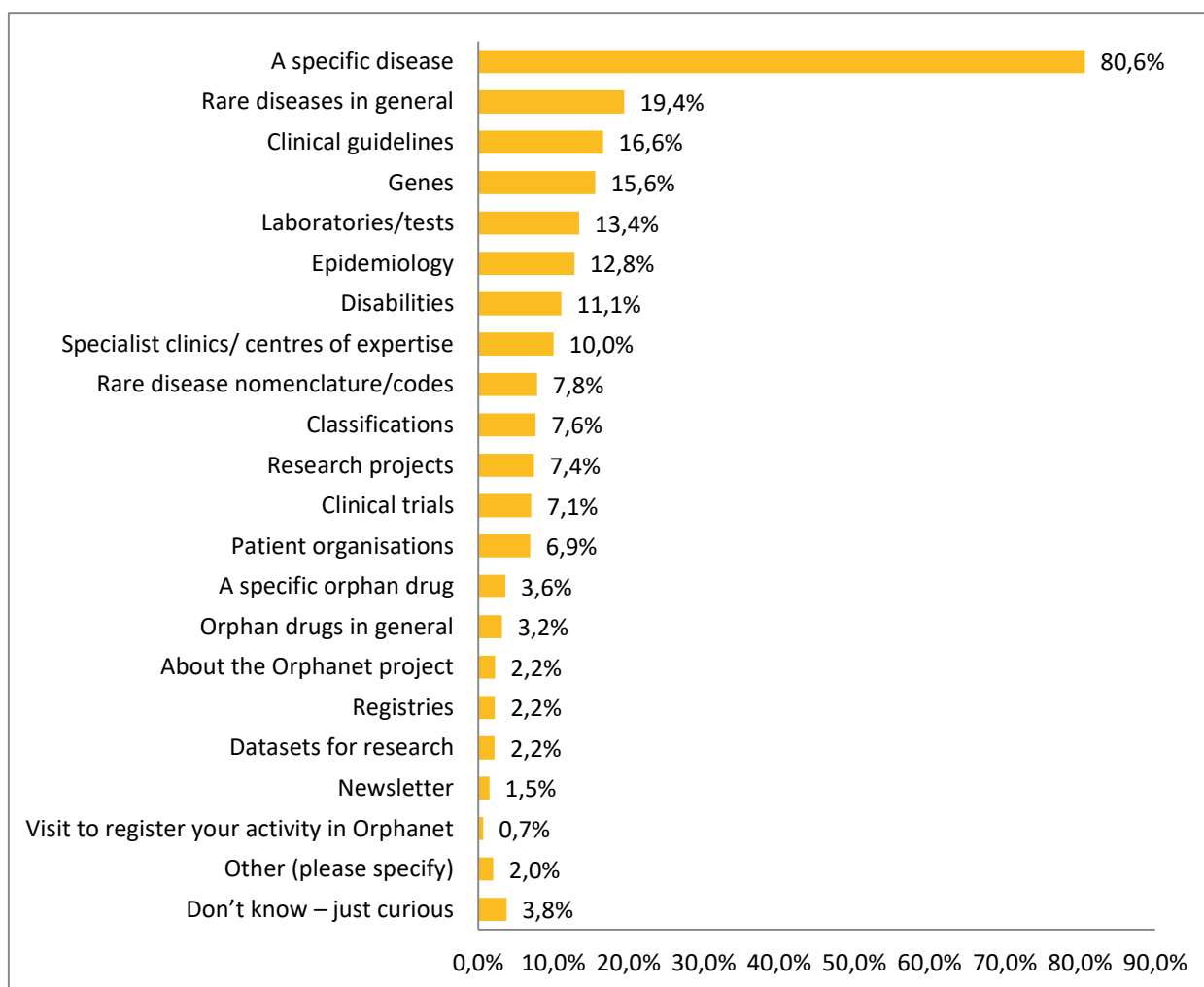
Figure 28 Information sought by respondents during their connection to Orphanet (percentage of total number of respondents n=3927)

The results show a clear trend: most of the respondents were looking for information for a specific disease (81%). Our visitors also look for information on rare diseases in general (20%) clinical guidelines (17%), genes (16%), laboratories/tests (13%) and epidemiology (13%). A smaller percentage of respondents were seeking information concerning other expert services: specialist clinics (10%), research projects (7%), on clinical trials (7%), patient organisations (7%). 8% of users were looking for information related to the nomenclature and coding of rare diseases and 8% were looking for information pertaining to the classification of rare diseases. Compared to last year's survey, general information on rare diseases had a 6 point progression.

The principle reason for visiting the site across all categories of users is information on a specific disease.

How useful would you rank the following Orphanet services for your own use?

The usefulness of Orphanet products was evaluated through this question. This question was asked to all respondents, except those consulting Orphanet for the first time as the aim was to assess the

usefulness of available tools and services for users' needs, based on their experience, and to also assess their knowledge of the existence of range of available services. Only one response was possible for each product for the 2600 respondents. For the first time a new scale was used for respondents to rate the services according to their utility for their own use: ++, +, -, - -. Two other options were given: 'I do not use this service', and 'I did not know Orphanet offered this service'. The results show that Orphanet products are highly appreciated but not sufficiently well known.

In order to assess the usefulness of Orphanet products for the needs for each respondent, an analysis of the results for this question was carried out. A product was deemed to be of use for a user if they answer if they answered '++' or '+' in the scale proposed to assess the usefulness of Orphanet's services. The percentage of these replies was calculated from the total number of replies to this question for this product, with the 'I don't use this service' and 'I didn't know Orphanet offered this service' answers subtracted from the total results beforehand so as to more faithfully represent the utility of the products, according to those aware of these services and using them (i.e. total replies = answers concerning the scale of utility '++', '+', '-', '- -').
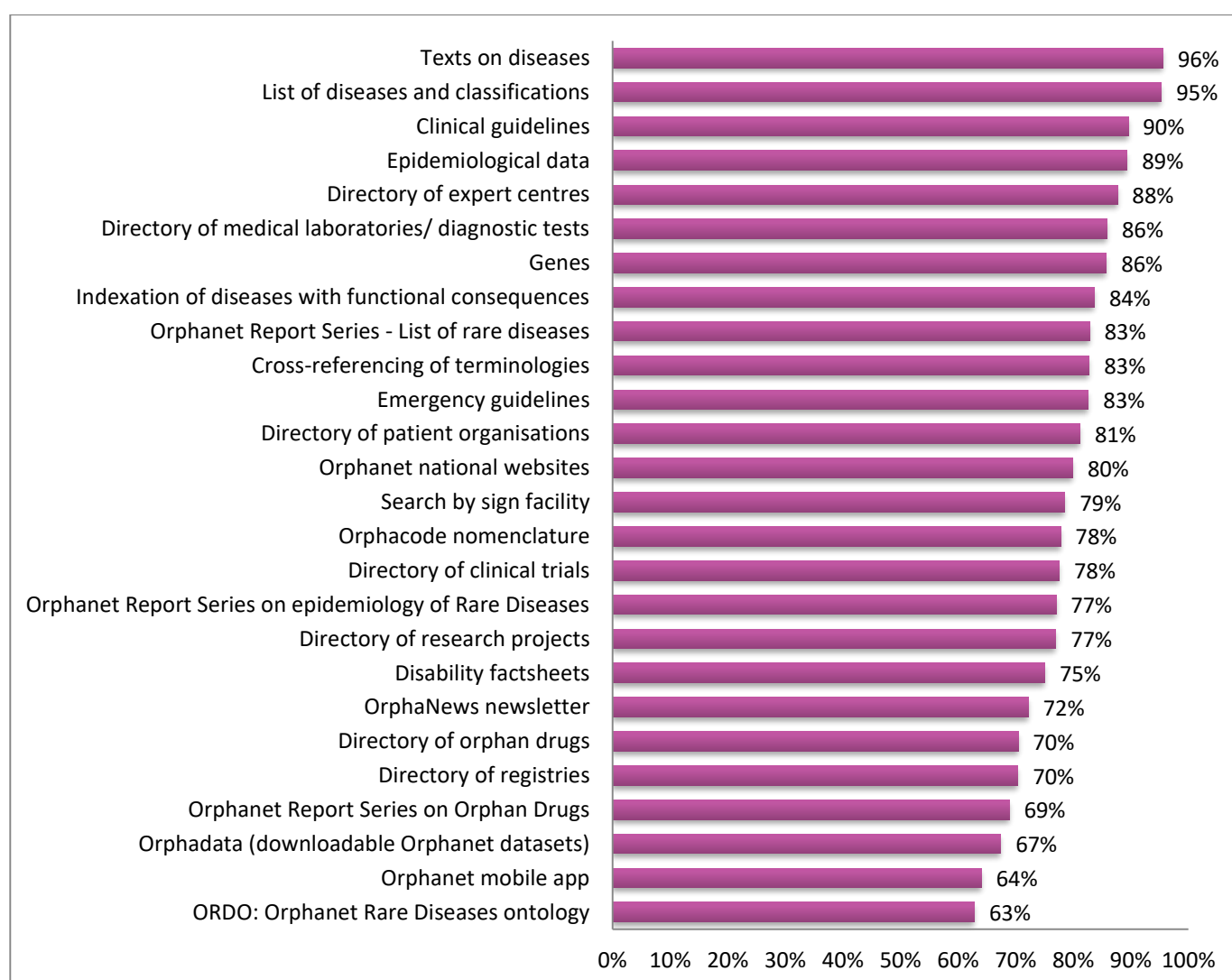
Figure 29 The most useful services offered by Orphanet according to respondents (answers '++' or '+' on the scale of usefulness).

The results show similar trends to previous years' surveys. The most useful Orphanet services, according to our users, are the texts on diseases (96%) and the list of diseases and classifications (95%). The data concerning the epidemiology of rare diseases is also highly appreciated (89%), as are the clinical guidelines made available via Orphanet (90%). The directory of expert centres were highly appreciated (88% of respondents who knew of, and used this service), as was the directory of medical laboratories (86%), and information on genes (86%). The indexation of diseases with the functional consequences of the disease is highly appreciated by 84% of respondents who knew of and used this service, which was launched online in June 2016.

An analysis of the answer 'I didn't know that Orphanet offered this service' highlights that our users are not sufficiently informed about our range of products and services.
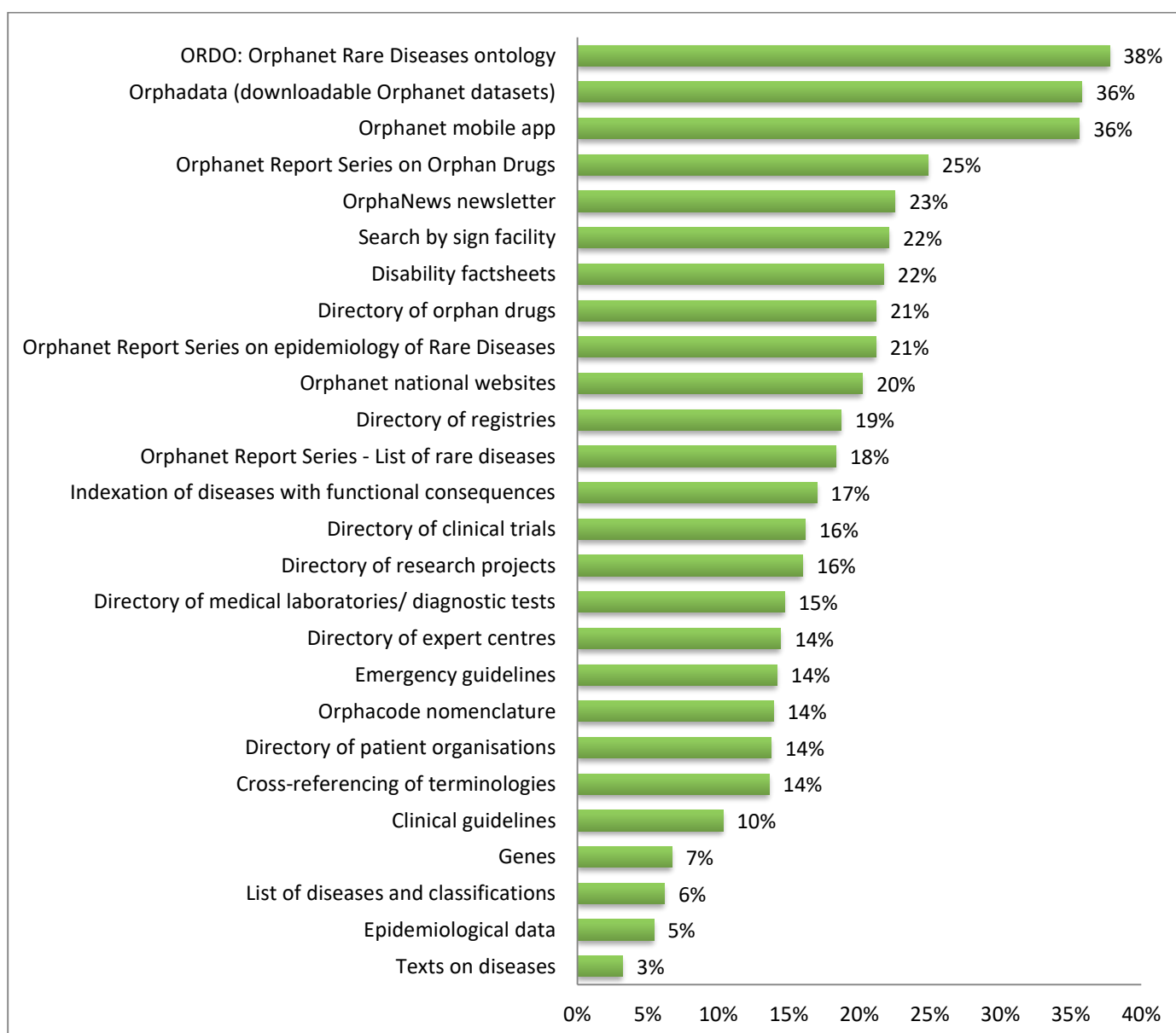
Figure 30 Least well-known Orphanet products (respondents answering 'I didn't know this service existed')

ORDO, the Orphanet Rare Disease Ontology, launched in 2013, is not known to 38% of our users, although amongst its users, it is well appreciated (63% highly appreciate this service): the targeted audience for this service is researchers, and in particular those in the bioinformatics sphere, which may explain why it is relatively unknown to those responding to the survey. Similarly, Orphadata, the website that allows users to download Orphanet datasets for research purposes, is fairly well appreciated but is one of the least well known services (36% of respondents). This service was launched in 2011, and is research orientated which may explain why it is not known or used by most of Orphanet's users. As previously seen, the Orphanet mobile app is not well known (36% of users answering this question did not know it existed, compared to 41% of respondents in last year's survey).

The most well-known products remain the texts on diseases with only 3% not aware of their existence; only 5% of respondents did not know about the epidemiological data made available by Orphanet, and only 6% of respondents did not know about the existence of the list of diseases and classification.

This analysis will help the Orphanet team structure outreach activities in the future, especially for newer services such as the Ontology and Orphadata.

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.

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.

Germany

Orphanet Germany is currently involved in two activities receiving financial support from the German Ministry of Health: (1) SE-ATLAS is a joint project by the Universities of Mainz, Orphanet-Germany, and the Centers for Rare Diseases in Frankfurt and Tübingen, aiming to innovate the presentation of health care facilities for patients with rare diseases in Germany by featuring an interactive geographical map. (2) PORTAL-SE is a sister project by the Universities of Hannover, Freiburg and Mainz, the Chamber of Physicians of Lower Saxony, and Orphanet-Germany, to conceptualise a central information portal facilitating access to information on all aspects of rare disease care in a user-group specific manner. Both of these projects do not intend to create new databases. Orphanet Germany will, according to the German Action Plan on Rare Diseases, remain 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 Centres, to coordinate the identification and documentation of Dutch centres of expertise for rare diseases together with Orphanet Netherlands and the VSOP (umbrella organisation of parent and patient organisations for genetic, congenital and rare disorders). The potential centres of excellence have been evaluated based on the EUCERD criteria established at the European level that 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 centre is ensured within the institute. The NFU published the procedure on the NFU website (in Dutch;

www.nfu.nl/patientenzorg/complexezorg/procedure-expertisecentra). In the first round, 288 potential centres from the University Medical Centres were evaluated, in the second round 125 potential centres from both University Medical Centres and non-university major "top-clinical" hospitals were assessed. The minister assigned from both rounds centres of expertise as official Dutch centres of expertise. These 302 centres are listed on the Orphanet website by the Dutch information scientist. The list can also be found on the Erfocentrum website www.erfelijkheid.nl.

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 prescriptionva delle prestazioni di assistenza ambulatoriale erogabili nell'ambito del Servizio sanitario nazionale"). The Decree sets up specific conditionons 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.

5.2.   Nomenclature and terminologies

5.2.1.   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 current 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.

A [mapping exercise](#) of the use of ORPHA codes in Europe is underway in the context of RD-Action and will be available in 2017. A number of countries have already taken some concrete steps in implementing ORPHA codes in their healthcare systems (Portugal, Germany, France, Belgium, Italy, Norway, Latvia, Czech Republic, Hungary, Cyprus, Switzerland) and national Orphanet teams are playing a key role in particular in the following countries:

France

In 2012, it was decreed that the French hospital system database would use ORPHA codes to code all hospitalised patients. The aim is to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways. The ORPHA code has been added in a dedicated part of the coding system, in addition to the ICD-10 derived code. Also because of the development of electronic health records in France, the French Ministry of Health has set up an advice committee for the codification of RD in which Orphanet plays a major role. A governmental memo was released in January 2016[5], 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. This will help in collecting data that is to be included in the BNDMR, which was partially deployed at the end of 2016. Coding with the ORPHA codes shall be extended to other sectors of the health system in the future.

Germany

In July 2013, a 3-year project started to revise the German ICD-10 (ICD-10GM). Orphanet Germany is a partner of this project by supplying the DIMDI (German Institute of Medical Documentation and Information) with the German translation of rare disease terms. The project intends to integrate the Orphanet classification of diseases by adding ORPHA codes and it also serves to expand the inventory of rare diseases within the ICD-10GM. Alignment of German disease terms within both database systems should lead to more congruence between both systems.

The Netherlands

The RIVM, the National Institute for Public Health and the Environment, that coordinates this project on behalf of the Ministry, started to compare the disease classification of the World Health Organization (WHO; WHO-FIC Update and Revision Committee) with the Orphanet classification. RIVM project leaders are working in close collaboration with Orphanet Netherlands on this subject within the work package 5 of the RD-ACTION project.

5.2.2. COLLABORATION WITH THE WHO

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

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

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. It included over 5,000 rare diseases and a proposal to include all Orphanet diseases in ICD11is being submitted. The beta version is available here for public consultation. A mapping file between ICD11 and ORPHA numbers is under production and will be released with the ICD11 release.

5.2.3. COLLABORATION WITH IHTSDO

Collaboration with the International **Health Terminology Standards Development Organisation** (IHTSDO) 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 alignment file will be available in 2019.

5.3. Catalogue of services

5.3.1. COLLABORATION WITH RD-CONNECT

A partnership has been established between Orphanet and RD-Connect. The latter is a European funded project (2012-2018) aimed at creating an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. This partnership will be focused on sharing data on biobanks and registries between Orphanet and RD-Connect in order to enrich both databases. The technical implementation of the partnership is planned for 2017.

5.3.2. 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.

5.3.3. SE-ATLAS

A collaboration is in place with SE-Atlas (https://www.se-atlas.de/) in order to improve the visibility of expert centres on rare diseases registered in Orphanet in Germany (see 5.2).

5.4.   Scientific collaborations and partnerships

5.4.1.   PARTNERSHIP WITH INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY (IUPHAR)

A partnership was established with **IUPHAR** at the end of 2011 to cross-link Orphanet with the IUPHAR database and the cross-linking is ongoing. This project is being expanded in order to take into account the evolutions of the IUPHAR database.

5.4.2.   PARTNERSHIP WITH THE INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

The INSERM unit that hosts the Orphanet coordinating team is a partner of an FP7 research support action entitled "**Support IRDIRC**".
IRDiRC was launched in April 2011 to foster international collaborations in rare disease research. IRDiRC unites 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. Orphanet hosts 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 Japan. In addition, Orphanet data is at the disposal of the IRDiRC working groups and their scientific committees and is analysed for them on request.
Orphanet also provides regular data analysis for the following indicators on the IRDiRC website: number of new RD on a monthly basis, number of genes linked to RD, number of RD for which there is a genetic test available and number of medicinal products with an orphan designation and marketing approval for the treatment of RD in the US and/or Europe.

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

Since 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 kicked-off in 2016 (www.jointactionrarecancers.eu). This Joint Action aims 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 is involved in a number of the work packages, in particular on issues such as the collection of epidemiological data of rare diseases, information on expert centres for rare diseases, clinical practice guidelines, and nomenclature and classifications. Cross-talk with the European Joint Action on Rare Diseases, RD-Action, coordinated by Orphanet, is also assured.

5.4.4. 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). The Ontology is updated twice a year.

5.4.5. Collaboration with the French Institute of Bioinformatics

Orphanet is the French Institute of Bioinformatics' 30th 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, 30 platforms are members, grouped into six regional centres across France. 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. 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.

Orphanet, in particular, participates in the ELIXIR pilot use case on rare diseases in the context of the EXCELERATE project: in 2016 Orphanet contributed to this use case by producing a report on the role of Orphanet, in particular the Orphanet nomenclature, as a vector for interoperability in the field of rare diseases. This project aims to build an ELIXIR registry of data resources and analysis tools that are critical for the development of rare disease research, implement a technical framework for the comparison and standardisation of services useful for rare disease communities, and collaborate with rare-disease communities in organising and running their training courses, workshops and jamborees. One of the principal goals of ELIXIR is to work towards the sustainability of resources and tools such as those offered by Orphanet, which makes this a strategic step in the right direction for Orphanet's future. In this context, Orphanet and ORDO are already cited in the ELIXIR Biosharing platform, a curated, informative and educational resource on inter-related data standards, databases, and policies in the life, environmental and biomedical sciences.

5.4.6. 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 are being 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) will be included in GARD for the diseases for which GARD does not have a text. This cross-Atlantic partnership will improve 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).

5.4.7. HARMONISING PHENOMICS INFORMATION FOR A BETTER INTEROPERABILITY IN THE RARE DISEASE FIELD (HIPBI-RD)

HIPBI-RD (www.hipbi-rd.net) is a three-year project financed via the E-Rare 3 ERA-NET mechanism. The project builds on three resources largely adopted by the RD community: Orphanet, and its ontology ORDO, HPO and PhenoTips. It aims to provide the community with an integrated, RD-specific informatics ecosystem that will harmonize the way phenomics information is stored in databases and in patient files worldwide, and thereby contribute to interoperability. This ecosystem will consist of a suite of tools and ontologies, optimized to work together, and available to clinicians and scientists through commonly used software repositories. Additionally, the ecosystem will improve and streamline the interpretation of variants identified through exome and full genome sequencing by harmonizing the way phenotypic information is collected.
Orphanet coordinates the project which includes partners from SickKids Toronto, La Charité Berlin, the European Bioinformatics Institute, and the Garvan Institute of Medical Research.

6. Funding

Orphanet's budget was approximately 2.9 million Euros in 2016, originating from 7 different contracts for the core activity funding and from various other contracts in some of the participating countries (Figure 31).
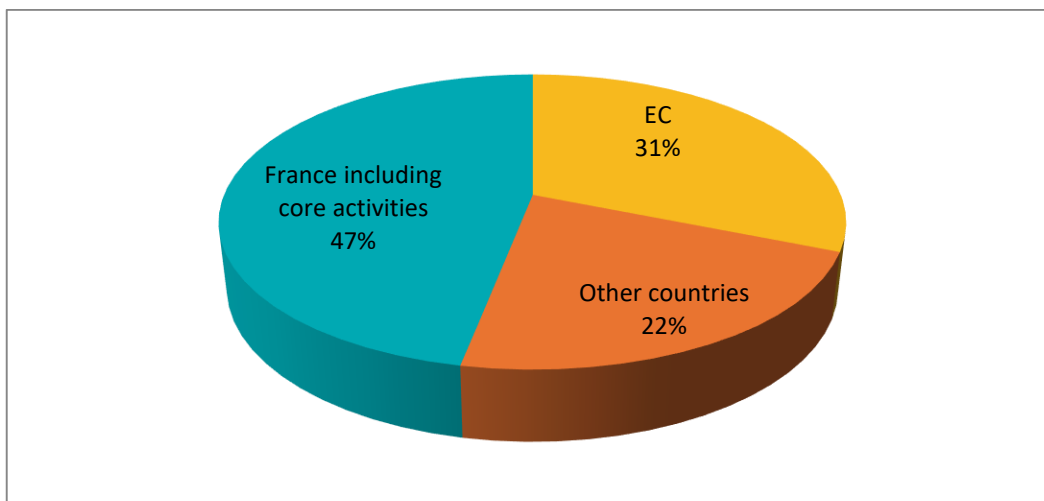
Figure 31 Orphanet's global budget 2016

6.1. Orphanet's core activity funding

Orphanet's core activities include the infrastructure, the coordination activities (management, management tools, quality control, rare disease inventory, classifications and production of the encyclopaedia) and communication. It excludes the collection of data on expert services in the participating countries.
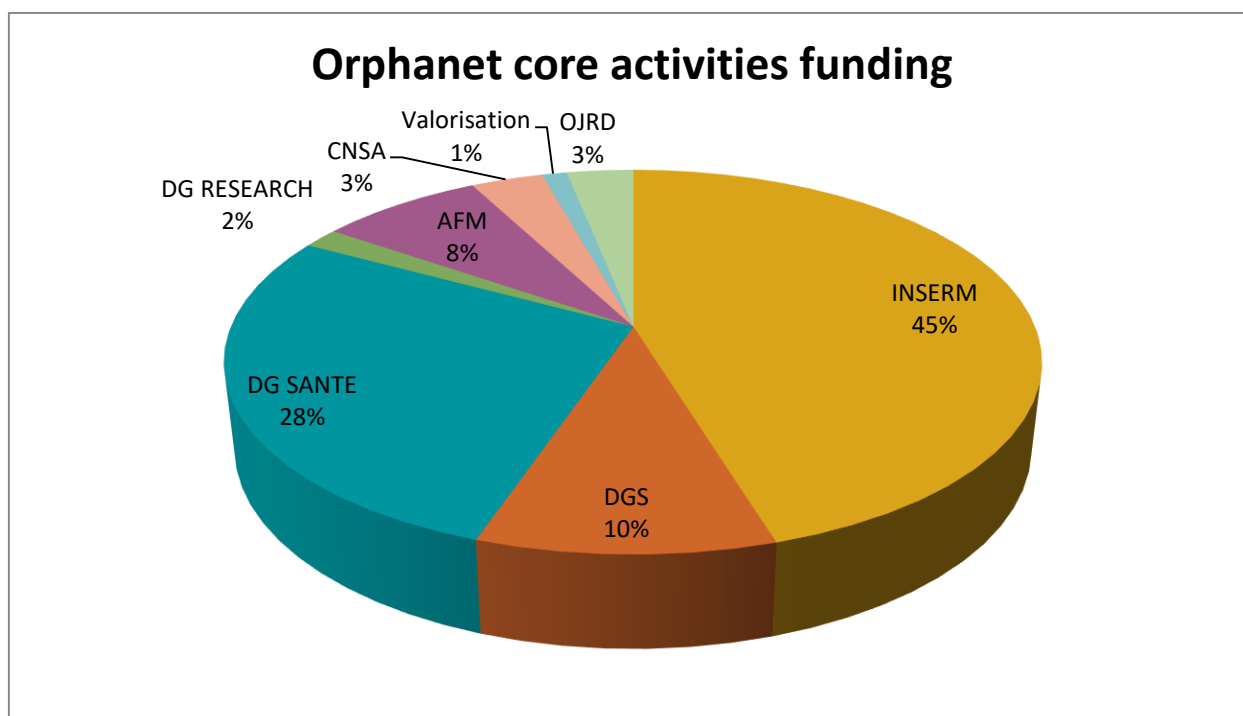
Figure 32 Orphanet core activities funding 2016

This budget (approx 1.5 million Euros) excludes the costs of infrastructure (office space) which are essentially covered by INSERM (Figure 32).

6.1.1. EUROPEAN FUNDING

The European Commission funds the inventory of rare diseases, the encyclopaedia, and the collection of data on expert services 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 2014, the DG Santé grant 20102206 (Orphanet Europe Joint Action) was extended for one year without additional funding. In 2015, Orphanet participated in the ECRIN Integrating Activity (ECRIN-IA, 284395), funded by the European Union Framework Program 7. From 2016 Orphanet coordinates the HIPBI-RD project (E-Rare3 ERA-NET joint call). Orphanet is also involved in the ELIXIR-EXCELERATE Project (H2020 Project N° 676559).

Orphanet consortium is funded by the DG Santé grant RD-ACTION Joint Action 677024 (2015-2018).

6.1.2. OTHER CURRENT FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY FUNDING

Instituts thématiques **Inserm** Institut national de la santé et de la recherche médica	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 licensing its data 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) and IT of the project through the EU Health Programme.
AFMTÉLÉTHON INNOVER POUR GUÉRIR	The "Association Française contre les Myopathies" finances OrphaNews France, the scientific literature survey, as well as data collection on clinical trials.

Table 9 Other current financial partnerships for core activity funding

6.1.3. 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.
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).
LOVD Leiden Open Variation Database	The LOVD (Leiden Open Variation Database) platform includes links to Orphanet's gene pages.
EuroGentest	EuroGentest financed the creation of a thesaurus of clinical signs to harmonise international phenotype nomenclatures. EuroGentest collaborates with Orphanet in the field of quality management of medical laboratories.
RD Connect	Orphanet and RD-Connect share information on biobanks and patient registries. Orphanet provides RD-connect with nomenclature of RD.
EMBL-EBI	Orphanet and EMBL-EBI have developed ORDO and in 2014, a new version of this ontology was launched (ORDO 2.0).
ihtsdo Delivering **SNOMED CT**	Collaboration with the International Health Terminology Standards Development Organisation (IHTSDO) is ongoing in order to include RD lacking in SNOMED-CT, and to provide alignments between ORPHA codes and SNOMED-CT terms
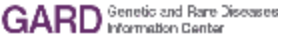
ifb excelerate	Orphanet is the 30th bioinformatics structure of the French Institute of Bioinfomatics, which is the French node of ELIXIR. Orphanet participates in the ELIXIR Use Case on Rare Diseases in the framework of the H2020 EU Project ELIXIR-EXCELERATE project N°676559.
GARD Genetic and Rare Diseases 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 activity

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 1.4 million Euros. Please refer to Figure 33 for an overview of funding of national activities.
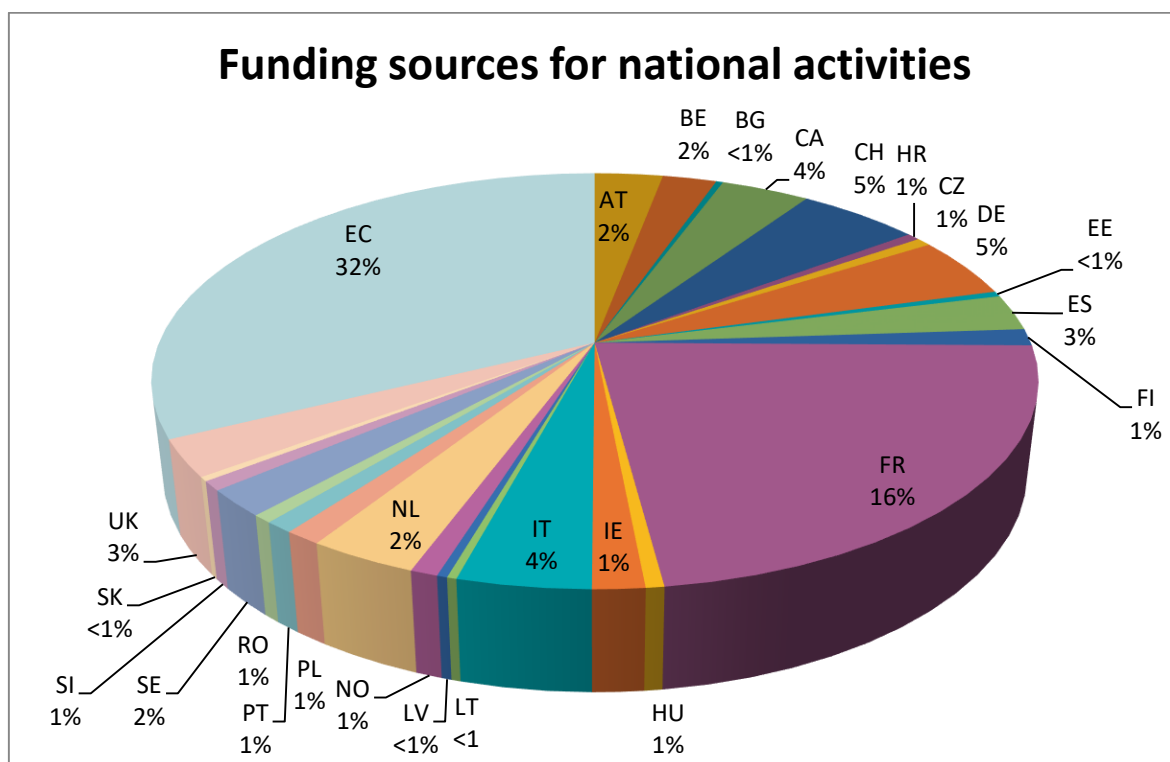
Figure 33 Funding sources for national activities in 2016

6.2.1. 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 in the RD-ACTION 677024 and hosts Orphanet Austria since 2004. It further provides part-time funding (in kind) for the work of the country coordinator.
MINISTERIUM FRAUEN GESUNDHEIT	The Austrian Ministry of Health and Women's Affairs provides funding to the RD-ACTION 677024 since June 2015.
BELGIUM	
federal public service HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT	The Federal Public Service Health, Food Chain Safety and Environment is beneficiary in RD-ACTION 677024
ISP WIV WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE	The "Wetenschappelijk Instituut Volksgezondheid – Institut Scientifique de Santé Publique" is a beneficiary in RD-ACTION 677024
	For the period 2014-2016, a convention between the Scientific Institute of Public Health (hosting the Orphanet team) and the National Institute of Health and Disability Insurance (NIHDI) includes financial support for the Orphanet project.
BULGARIA	
Bulgarian Association for Promotion of Education and Science BAPES	The Bulgarian Association for Promotion of Education and Science (BAPES) is a beneficiary in the RD-ACTION 677024 and hosts Orphanet Bulgaria's activities.
CANADA	
CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada	The Canadian Institute of Health Research is the host institution of Orphanet Canada, finances a position for an information scientist and provides additional administrative support for the project.
Santé et Services sociaux Québec	The Québec "Ministère de la Santé et des Services sociaux" finances a project manager position in Quebec and some administrative support.
Centre universitaire de santé McGill McGill University Health Centre	The Department of Medical Genetics of the McGill University Health Centre is the host institution of Orphanet-Quebec and provides the medical coordinator.
RQMO REGROUPEMENT QUÉBÉCOIS DES MALADIES ORPHELINES	Le "Regroupement québécois des maladies orphelines" provides the project coordinator and administrative support.

	Pfizer Canada finances different Orphanet-Canada outreach events (Café Scientifique, Booth, Presentation) and helps distribute Orphanet-Canada information through their network.
	Care4Rare finances a part-time position for an information scientist.
CROATIA	
	HSRB-The Croatian Alliance for Rare disease is a beneficiary in RD-ACTION 677024
CZECH REPUBLIC	
	The Charles University Prague - 2nd School of Medicine is beneficiary in RD-ACTION 677024
	The Czech Association of rare diseases finances the activity of the Czech team since April 2012.
	The Czech Medical Genetics society 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. They have a joint partnership for the development of the Czech National Plan for rare diseases following the Czech National Strategy from 2009. The first and second Czech National Plans (2012-2014 and 2015-2017) are 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.
ESTONIA	
	The University of Tartu is a beneficiary in RD-ACTION 677024
FINLAND	
	Rinnekoti Foundation is a beneficiary in RD-ACTION 677024
FRANCE	
	The "Fondation Groupama pour la santé" contributes to the development of the mobile application.
	The "LFB Biomédicaments" helps finance the development and update of emergency guidelines and the French encyclopaedia for the general public.

	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.
	The "Caisse nationale de solidarité pour l'autonomie" supports the annotation of rare diseases with the International Classification of Functioning, Disability and Health (ICF) and the Orphanet encyclopaedia of disabilities.
GERMANY	
	The Medical School of Hanover (MHH) supports data collection, and is a beneficiary in RD-ACTION 677024
	Amedes Medizinische Dienstleistungen GmbH is a private company who supported Orphanet Germany financially in 2016.
	Förderverein Orphanet Deutschland e.V., a charity founded by Orphanet Germany to support national activities, provides funding to the team.
	Humangenetik Freiburg, a private company, provides funding to support national activities
HUNGARY	
	Orszagos tisztifoorvosi hivatal - OTH is a beneficiary in RD-ACTION 677024
	Semmelweiss Egyetem is a beneficiary in RD-ACTION 677024
ITALY	
	The Italian Health Ministry finances Orphanet-Italy activities through current research funding.
	The Bambino Gesù Children's Hospital is a beneficiary in RD-ACTION 677024
	Genzyme, a Sanofi Company, finances OrphaNews Italia.
IRELAND	
	The Health Service Executive jointly funds Orphanet Ireland with RD-Action for the provision of a project manager, 0.5 information scientist, and part time administrative support.

	Shire Pharmaceuticals Ireland supported the start up of the National Rare Disease Office and Orphanet Ireland through the provision of a once-off unrestricted grant
LATVIA	
	"Centre for Disease Prevention and Control of Latvia" (Slimību profilakses un kontroles centrs) is a beneficiary in RD-ACTION 677024.
LITHUANIA	
	The Vilnius University Hospital, "Santariškių Klinikos" Centre for Medical Genetics is a beneficiary in RD-ACTION 677024
NETHERLANDS	
	The LUMC is a beneficiary in RD-ACTION 677024. It hosts Orphanet Netherlands and co-funds the work of Prof van Ommen.
	The Centre for Medical Systems Biology is a joint activity of six institutions in the Netherlands, led by LUMC and including VUMC. The CMSB co-funds the rare disease work of project manager Dr Petra van Overveld and of the chair of the Dutch Scientific Advisory Board, Prof Cornel.
NORWAY	
	The Norwegian Directorate of Health hosts part of Orphanet Norway's activities and contributes to the project by allocating the time of some professionals. It is beneficiary in RD-ACTION 677024
	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. It is beneficiary in RD-ACTION 677024
POLAND	
	The "Instytut Pomnik Centrum Zdrowia Dziecka" (Children's Memorial Health Institute) is beneficiary in RD-ACTION 677024. The CMHI 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.
	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 - Institute for Molecular and Cell Biology hosted Orphanet-Portugal from 2009 to June 2015

	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
	DGS - The Directorate-General of Health, at the Portuguese Ministry of Health, is 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" is a beneficiary in RD-ACTION 677024

SLOVAKIA	
	CUMS (UNIVERZITA KOMENSKEHO V BRATISLAVE) is a beneficiary in RD-ACTION 677024

SLOVENIA	
	The University Medical Centre Ljubljana is 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 and is beneficiary in the RD-ACTION 677024. CIBER (Institute of Health Carlos III, Ministry of Economy, Industry and Competitiveness) finances the main activities of the Spanish team. CIBER financed in 2016 an Annual Meeting in Madrid for the Orphanet National Scientific Committee, as well as other expenses, 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 is 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.

	Since 2011, Orphanet Switzerland is funded by the Swiss Conference of the Cantonal Ministers of Public Health. In 2015, the support financed an information scientist part time position.
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. It is a beneficiary in RD-ACTION 677024

Table 11 Partnerships providing funding for national activities

6.2.2. 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.
AUSTRIA	
	The "Gesundheit Österreich GmbH" (GÖG) is a collaborating stakeholder in the RD-ACTION
AUSTRALIA	
	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.
CYPRUS	
	The Department of Medical and Public Health Services is an associated partner in the Orphanet Europe Joint Action as of April 2011.

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 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.
MOROCCO	
INH	The National Institute of Hygiene hosts Orphanet Morocco's activities and contributes to the project by allocating the time of some professionals.
SERBIA	
ИМГГИ IMGGE	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	
PRINCIPE FELIPE CENTRO DE INVESTIGACION	The Príncipe Felipe Research Center (CIPF) hosts Orphanet Spain's activities.
Fundació per al Foment de la Investigació Sanitària i Biomèdica de la Comunitat Valenciana	The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) 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
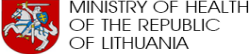
BELGIUM	
	A partnership exists with RaDiOrg.be, a EURORDIS member, which continued to play a role in the validation of data on Belgian patient organisations in Orphanet.
	The Orphanet team hosted by the Scientific Institute of Public Health collaborates internally with the Service "Infectious Diseases 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	
	The Ministry of Health of the Czech Republic officially supports Orphanet.
ESTONIA	
	The Ministry of Social Affairs of Estonia officially supports Orphanet.
FINLAND	
	The Ministry of Social Affairs and Health of Finland officially supports Orphanet.
	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
	The Ministry of Health officially supports Orphanet.
	The French High Authority for Health (HAS) and Orphanet cooperate for the online publication of the National Protocols for Diagnosis and Care (NHDP) produced by the HAS.
	The "Agence nationale de sécurité du médicament et des produits de santé" (ANSM) provides Orphanet with data on clinical trials in France.
	"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.
	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
	The "Allianz Chronischer Seltener Erkrankungen e.V." (ACHSE) works together with Orphanet Germany on information services for patients.
	The "Kindernetzwerk e.V. - für Kinder, Jugendliche und (junge) Erwachsene mit chronischen Krankheiten und Behinderungen" provides data on associations in Germany.
	The "Deutsche Gesellschaft für Humangenetik e.V." supports Orphanet by supplying the German team with addresses and information on laboratories and diagnostics.
	Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen (NAKOS) officially supports Orphanet.
	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 cooperates with Orphanet DE in including the disease terms from the German Orphanet nomenclature into the alpha-code of the ICD-10GM.
	HUNGARY
	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
ROYAL COLLEGE OF PHYSICIANS OF IRELAND	The Royal College of Physicians National Clinical Programme for Rare Diseases Clinical Advisory Group (Chair: Prof. Andrew Green) acts as Scientific Advisory Group for Orphanet Ireland
GRDO Genetic & Rare Disorders Organisation	The Genetic and Rare Diseases Organization (GRDO) (who together with MRCG and IPPOSI form the Irish National Alliance for Rare Disease) collaborate in the promotion of Orphanet and Rare Disease activities in Ireland. The Country Coordinator is a GRDO board member.
medical research charities group 'Unity is our Strength'	The Medical Research Charities Group (MRCG) collaborates in the endorsement and promotion of Orphanet and Irish Rare Disease activities.
IPPOSI Irish Platform for Patients' Organisations, Science and Industry	The Irish Platform for Patient Organizations, Science and Industry (IPPOSI) collaborate in the promotion of Orphanet and Rare Disease activities in Ireland. IPPOSI is also actively engaged in implementation of the RD-action WP5 in Ireland by providing links between the Orphanet Ireland team and eHealth and software developers.
ISRAEL	
State of Israel Ministry of Health	The Israeli Ministry of Health officially supports Orphanet.
ITALY	
ISTITUTO SUPERIORE DI SANITÀ	The "Istituto Superiore di Sanità" officially supports Orphanet.
TeleThon	Telethon collaborates with Orphanet for the collection of data concerning research projects.
UNIAMO FEDERAZIONE ITALIANA MALATTIE RARE ONLUS	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.it project by BURLO	Netgene collaborates with Orphanet for the diffusion of information on rare diseases.
FARMINDUSTRIA	Farmindustria promotes Orphanet publications.
Osservatorio Malattie Rare O.Ma.R.	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.
	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	
	The Ministry of Health of the Republic of Lithuania officially supports Orphanet.
NETHERLANDS	
	The Ministry of Health, Welfare and Sport of the Netherlands officially supports Orphanet Netherlands.
	The Erfocentrum provides information to the general public on mainly rare, genetic disorders. Collaboration has been established to increase the number of Dutch texts available on Orphanet and to list the Dutch designated centers of expertise for rare diseases for the public and for experts.
	The VSOP (umbrella organisation of parent and patient organisations for genetic, congenital and rare disorders) provides information regarding patient organisations dedicated to rare disease and participates in the designation of Dutch centers of expertise for rare diseases.
	The Dutch Federation of University Medical Centers (NFU) is, in collaboration with Orphanet NL and the VSOP, responsible for the inventorying and documentation of Dutch centers of expertise for rare diseases.
POLAND	
	The patient organisation, Ars Vivendi, provides patients and parents with information about Orphanet services and cooperates with Orphanet Poland.
ROMANIA	
	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.
	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.
	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	
	The Ministry of Health of Slovenia officially supports Orphanet.
SPAIN	
	The Spanish Ministry of Health, Social Services and Equality - Office for Health Planning and Quality officially supports Orphanet.
	The Institute of Health Carlos III (ISCIII) provides Orphanet with data on national research projects funded through the Health Strategic Action Calls.
	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.
	The University of Valencia has invited the Orphanet team to contribute to a class regarding RD information systems within the Rare Diseases course taught at this University's Medical School.
SWEDEN	
	The Ministry of Health and Social Affairs of Sweden officially supports Orphanet.
SWITZERLAND	
	The Health On the Net Foundation owns the domain www.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.
IG Seltene Krankheiten CI Maladies rares CI Malattie rare	Orphanet Switzerland is member of the « Community of Interest for Rare Diseases » launched in August 2011. This community brings together all the relevant stakeholders in the field of rare diseases in Switzerland in order to support the adoption and the implementation measures of the National Concept on Rare Diseases by the Swiss federal Office of Public Health.
TURKEY	
TURKEY Ministry of Public Health	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	
(DH) Department of Health	The Department of Health officially supports Orphanet.
Ataxia UK	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.
RARE DISEASE | UK	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.
Genetic Alliance UK Supporting. Campaigning. Uniting.	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 2016, A5-size flyers to present Orphanet and Orphanet services were updated when necessary and distributed:

- Orphanet in 3 languages (English, French 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

An A4 leaflet about Orphanet's achievements in 2015 was also printed and distributed at congresses.

An A4 leaflet explaining Orphanet's global positioning was also printed and distributed at congresses, in particular at the launch of the NGO Committee for Rare Diseases at the United Nations (CONGO) in November 2016.

7.2. Invitations to give lectures at conferences in 2016

Orphanet representatives, as specialists in the field of rare diseases, were invited to give lectures and to participate with poster presentations in more than 62 conferences worldwide in 2016. These lectures were mostly focused on presenting the Orphanet database (54), public health policies (2), and RD research (5). 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 2016

Orphanet booths were held in 17 different congresses in 2016 as indicated in the list below:

- Rare Disease Day Public Conference, Geneva University Hospitals, 29 February 2016 Geneva, Switzerland
- Rare Disease Day Conference organised by ProRaris, 27 February 2016, Zürich, Switzerland
- European Conference on Rare Diseases 2016, 26-28 May Edinburgh, United Kingdom
- European Human Genetics Conference 2016, 21-24 May, Barcelona, Spain
- French National Genetics Conference 8ème Assises de génétique humaine et médicale, 3-5 February 2016, Lyon, France
- International Congress of Personalized Health Care, 12-15 June 2016, Montréal, Québec, Canada
- Rare Disease Day Symposium, 29 February 2016, Hannover, Germany
- Canadian Association for Health Services and Policy Research (CAHSPR) 2016 Conference, 9-12 May 2016, Toronto, Ontario, Canada
- Swiss Society of General Internal Medicine, 25-27 May 2016, Basel, Switzerland
- Canadian Pediatric Society 2016 conference, 22-25 June 2016, Charlottetown, Prince Edward Island, Canada

- Eighth Annual Primary Healthcare Partnership Forum (PriFor), 29-30 June 2016, St. John's, Newfoundland, Canada
- International Society of Nurses in Genetics (ISONG) meeting, 4 & 5 August 2016, Dublin, Ireland
- 24th Karen Helene Ørstaviks Dysmorphology Meeting 2016, 24-25 August 2016, Bergen, Norway
- National Conference on Neuromuscular Disorders 2016, 12-13 September 2016, Tromsø, Norway
- Venous Thromboembolism conference, Mater Misericordiae University Hospital,16 September 2016, Dublin, Ireland
- Emerging Diagnostics in Modern Care Pathways: Endocrine Hypertension and Prostate Cancer conference, 30 September 2016, Dublin, Ireland
- Planète Santé 2016, 24-28 November 2016, Lausanne, Switzerland

7.4. Social media

The Orphanet coordinating team maintains a [Facebook page](#) (2,400 subscribers) and a [Twitter account](#) (@orphanet : 1,600 followers) as well as the [Orphanet Tutorials](#) Youtube channel.

The Orphanet Italy team also maintains a [Facebook page](#) (1,140 subscribers) and a [YouTube channel](#).

8. The Orphanet team in 2016

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Figure 34 Organisational chart

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