orphanet

2014 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

CNSA: French National Solidarity Fund for Autonomy

COMP : the Committee for Orphan Medicinal Products

DG Santé : Directorate General Health and Consumers

DIMDI: German Institute of Medical Documentation and Information

ECRIN: European Clinical research Infrastructure Network

EJHG: the European Journal of Human Genetics

EMA: the European Medicines Agency

EMBL - EBI: European Bioinformatics Institute

EMQN: European Molecular genetics Quality Network

EQA: external quality assessment

EUCERD: the European Union Committee of Experts on Rare Diseases

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

INSERM: the 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: the 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

UMLS: Unified Medical Language System

UniProtKB : Universal Protein Resource Knowledgebase

URL: uniform resource locator

WHO: World Health Organisation

1. Overview

1.1. Objective

Orphanet endeavours to provide the community at large with a comprehensive set of information and data on rare diseases and orphan drugs in order to contribute to the improvement of the diagnosis, care and treatment of patients with rare diseases.

1.2. Activities

Orphanet is currently the most comprehensive repertory 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 and healthcare professionals. Moreover, Orphanet database content is robust as it is expert validated, updated continuously and quality controlled. These unique features make Orphanet the reference in the field of RD as it allows different stakeholders, and in particular health professionals and researchers, to keep up to date with the constantly evolving knowledge concerning RD.

The site gives 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), Medical Dictionary for Regulatory Activities (MedRA),and associated genes, its 'identity card' includes the relevant prevalence class, age of onset class, mode of inheritance.
- An encyclopaedia covering more than 6600 rare diseases or group of diseases, written by science writers and reviewed by world-renowned experts. Abstracts are produced in English and are then translated into French, German, Italian, Portuguese, Spanish, Dutch, Polish, Slovak, Greek and Finnish. For some selected diseases, emergency guidelines and articles for general public are produced in French and translated.
- An inventory of review articles on rare diseases and of clinical guidelines.
- Quality articles published by other journals or learned societies. More than 1000 articles have been published, with the permission of authors and editors, comprising national and international clinical guidelines produced by learned societies that are not published in peer-reviewed journals but available as reports.
- An inventory of orphan drugs and of drugs intended for rare diseases, at all stages of development, from orphan designation to market authorisation.
- A directory of expert resources in the 39 partner countries, validated by national experts and providing information on: specialised expert centres and centres of expertise, medical laboratories, research projects, clinical trials, registries, networks, technological platforms and patient organisations.

A range of other services:

- A support-to-diagnosis tool (search by signs and symptoms).
- OrphaNews, the newsletter of rare diseases community in English covering both scientific and political news. This newsletter is also published in French and in Italian.
- Thematic studies and reports on overarching subjects: the "Orphanet Report Series" (ORS), published as PDF documents.

1.3. Main achievements of 2014

- **New data has been incorporated to offer more information on rare diseases and new functionalities have been added to make it easier for users to find the information they are looking for.** The additional data and tools aim to fine-tune and improve the accuracy of disease categorisation, disease epidemiology and the genetic contribution to disease ethiopathology. Most of the new data is accessible for download on Orphadata for reuse by investigators, policymakers and industry. The new data includes:

  o **A better categorisation of diseases and a better characterisation of their equivalence in other terminologies:**

  Entries in the diseases database are now characterised as diseases, syndromes, anomalies, particular clinical situations, group of disorders or subtypes. Users can now see whether a terminology's equivalence is exact or partial. This information improves interoperability between databases that use different nomenclatures. The alignment between Orphacodes and ICD-10 has now been completed.

  o **Extended genetic data**:

  Genetic entries have also been expanded to provide 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. In addition to the relationship between genes and diseases, functional information has been added, where available, on germline causal loss-of-function or gain-of-function mutations. Such information is of particular interest for therapeutic research.

  o **Large quantity of new and more accurate epidemiological data:**

  These new epidemiological entries are available for a large number of rare diseases and constitute a unique and global source of information which we hope are useful to all concerned users, namely policymakers, the research community and industrial actors involved in orphan drug development. These include incidence, point prevalence, birth prevalence and lifetime prevalence for a geographical area.

- **Release of the V2.0 of the Orphanet rare diseases ontology (ORDO) produced in collaboration with the European Bionformatic Institute (EMBL-EBI)**. The ontology is available on Bioportal, Orphadata and the EBI Ontologies Lookup Service. It represents a powerful research tool.

- **The directory of expert centres, medical laboratories, clinical trials, research projects, networks, registries, platforms, networks and patient organisations has been expanded and updated.**

- **Most of the Orphanet Report Series have been updated**: List of Rare Diseases, Prevalence of Rare Diseases, Lists of Orphan Drugs, Registries, Orphanet Activity Reports, and Satisfaction Surveys.

- **The Orphanet Activity report 2013 was translated into French, Italian and Spanish.**

- **Orphacodes have been implemented in national health information systems:** They are currently being used in the French and Italian (regional) health information systems. Orphacodes have been added to the German modification of the ICD-10 (ICD-10-GM) in order to be able to code all RD within the German coding system. Orphacodes are being piloted in

health information systems in Germany, Hungary, Latvia and Norway. Orphacodes are being used in centres of expertise in the Netherlands and Slovenia. The use of Orphacodes as a complement to existing coding systems is being explored in most EU Member States, as recommended by the European Commission Expert Group on Rare Diseases.

- **Availability of 85 summaries in Russian**
- **APP of the day!** On Rare Disease Day 2015 the Orphanet mobile application was "app of the day" on http://myhealthapps.net/ (a PatientView website).
- **Users are satisfied with the utility of the services provided by Orphanet:** in the 2014 satisfaction survey 75% of respondents stated that the services they used were very useful or useful.
- **Further actions to ensure transparency:** In addition to the **general SOPs** available online since last year and updated regularly, the procedures used for the indexation with ICD-10 and those used to carry out the linearisation of disorders, were published online. Indeed disorders can be multi-classified in Orphanet classifications. For analysis purposes, each disorder is attributed to a preferred classification (linearisation) by linking it to the head of classification entity. As some decisions could be made somewhat arbitrarily, a set of rules has been elaborated to make sure attributions are consistent. The list of Orpha signs and symptoms used to annotate the diseases, cross-referenced with other nomenclatures: HPO, PhenoDB, LDDB, were also made available online. .
- **The Orphadata user guide was also updated.**

2. Orphanet consortium

2.1. The Orphanet Europe Joint Action

Orphanet is mentioned in the documents of the European Union on rare diseases (The Commission Communication "Rare diseases: Europe's challenge" 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 rare diseases in the European Union and also as a strategic element of any national plan/strategy on rare diseases that each Member State is encouraged to develop by the end of 2013. It is also mentioned as a key tool for information on rare diseases in the Directive on the application of patients' rights in cross-border healthcare (2011).

In 2011, the Orphanet Europe Joint Action was launched under the EU Health Programme. This instrument combines funding from the European Commission and each of the participating Member States, as well as from Switzerland, as a collaborating partner. The Joint Action began on the 1st of April 2011 and ended on the 31st December 2014. The overarching aim of the Joint Action was to improve and adapt the presence of Orphanet in each participating country.

To ensure optimal governance of the Joint Action and efficient management of the workflow, and also to reflect the new involvement of the health authorities of the Member States, Orphanet's governance was organised through three different boards:

- The **Management Board** composed of country coordinators;

- The **Steering Committee** composed of representatives from the funding agencies/health authorities contributing to the funding of the core project (diseases database, encyclopaedia, database structure, infrastructures, and coordination of activities);
- The **International Advisory Board** composed of international experts.

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

In 2013, future funding instruments for Orphanet were discussed and several options were analysed: it was decided to prolong the Orphanet Europe Joint Action until December 2014. A new Joint Action for rare diseases activities (RD-ACTION) which will support, amongst other activities in the rare disease field, the Orphanet database, will start in early 2015 for a three-year period. During this next Joint Action, Orphanet will be evaluated and a sustainability plan for its activities will be defined.

2.2.   Expansion of the consortium

Since its creation, the quality of the data provided by Orphanet has built its reputation and as a result Orphanet has grown as a European consortium, gradually expanding into 35 neighbouring countries to the East and the South. In 2011, Orphanet went further west to include Canada. In 2012, the consortium expanded towards Australasia with the joining of Western Australia. In 2014 Georgia and Tunisia have joined the consortium. Discussions have started with other countries but the lack of resources at a central level to support the coordination, training and quality control workload generated by new partners prevents the expansion of the network until a sustainable economic model is found.

2.3.   List of partners and scope of their activity

2.3.1.   COORDINATING TEAM

The coordination of the consortium is managed by the coordinating team, Orphanet France, 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 and the production of the encyclopaedia, as well as 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 the designation stage to their marketing authorisation.

2.3.2.   PARTNERS

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 resources 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 can provide a suitable environment for the information scientists to work, in terms of documentation, secretarial facilities and access to the network.

The partners 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 when 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 and Greek teams are translating the encyclopaedia.

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

### 2.3.3. LIST OF ORPHANET PARTNER INSTITUTIONS

Joerg Schmidtke
Medizinische Hochschule Hannover
Hannover (DE)

Gert-Jan van Ommen
Leiden University Medical Center
Leiden (NL)

Dian Donnai
University of Manchester
Manchester (UK)

Andrew Green
National Centre for Medical Genetics
Dublin (IE)

Elfriede Swinnen
Scientific Institute Public Health & Federal Public Service Health
Brussels (BE)

Yolande Wagener
Ministère de la Santé du Luxembourg
Luxembourg (LU)

Ana Rath
INSERM US14
Paris (FR)

Jorge Sequeiros
Instituto de Biologia Molecular e Celular, University of Porto
Porto (PT)

Abdelaziz Sefiani
Institut National d'Hygiène
Rabat (MA)

Francesc Palau
CIBERER & Ministry of Health, Social Services and Equality
Valencia (ES)

Loredana D'Amato Sizonenko
Service of Genetic Medicine - Geneva University Hospitals
Geneva (CH)

Till Voigtländer
Medizinische Universität Wien & Gesundheit Osterreich Gmbh
Vienna (AT)

Borut Peterlin
University Medical Centre Ljubljana
Ljubljana (SI)

Bruno Dallapiccola
Bambino Gesù Children's Hospital
Rome (IT)

Ana Stavljenic-Rukavina
Zagreb University
Zagreb (HR)

Dragica Radojkovic
Institute of Molecular Genetics and Genetic Engineering
Belgrade (RS)

John Rosendahl Oestergaard
University Hospital of Aarhus
Aarhus (DK)

Stein Are Aksnes
Norweigan Directorate of Health
Oslo (NO)

Désirée Gavhed
Karolinska Institutet
Stockholm (SE)

Micheil Innes
Mc Gill University
Montreal (CA)

Hugh Dawkins
Governement of Western Australia
Perth(AU)

Riitta Salonen
Rinnekoti Foundation
Helsinki (FI)

Vallo Tillmann
Tartu University
Tartu (EE)

Jana Lepiksone
Disease Prevention and Control Centre of Latvia
Riga (LV)

Vaidutis Kucinskas
Vilnius University Hospital
Vilnius (LT)

Krystyna Chrzanowska & Malgorzata Krajewska-Walasek
Children's Memorial Health Institute
Warsaw (PL)

Milan Macek
Charles University Prague - 2nd School of Medicine
Prague (CZ)

László Kovács
Children's University Hospital of Bratislava
Bratislava (SK)

Kristine Hovhannesyan
Center of Medical Genetics and Primary Health Care
Yerevan (AM)

Cristina Rusu
Universitatea de Medicina si Farmacie «Gr.T.Popa» Iasi
Iasi (RO)

Veronika Karcagi (until June 2014)
National Institute for Health Development
Budapest (HU)

André Mégarbané
Université Saint Joseph
Beirut (LB)

Violetta Anastasiadou
Archbishop Makarios III Hospital
Nicosia (CY)

Annick Rotshild
Chaim Sheba Medical Center
Kfar Sava (IL)

Ugur Özbek
University of Istanbul
Istanbul (TR)

Rumen Stefanov
Bulgarian Association for Promotion of Education and Science
Plovdiv (BG)

Helen Michelakakis
Institute of Child Health
Athens (GR)

Associated partners
Collaborating partners
Other partners

Fig.1 The Orphanet consortium in 2014

3. Orphanet: Products and Services

Fig.2 Orphanet relational database

Orphanet is an evolutive relational knowledge database with added value as scientific content produced in-house is expert-validated and integrated to other available resources as shown in the diagram presented in Figure 2 and described hereafter.

Entries in the Orphanet diseases database correspond to rare diseases, rare forms of common diseases, or, in some particular cases, non-rare diseases considered to be orphan because their diagnosis or management remains particularly difficult or information on these diseases is very often requested of Orphanet.

The updating of the scientific content of the database is based on a literature survey of international journals that helps to identify new syndromes, genes or treatments, update classifications of diseases, and is the basis for the production of various texts (encyclopaedia, guidelines, etc.). All texts are produced in collaboration with internationally recognised experts, learned societies and patient organisations.

All the teams that make up the Orphanet consortium are responsible for the collection, validation and submission of data on expert resources. To publish data which are relevant and accurate (complete, valid, 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. 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 3). Indeed, the typeface is magnified and
information is organised in easy-to-spot blocks that allow
users to more readily navigate the site. The disease search
function is in the centre of the homepage, while the tabs
for Orphanet's other principal resources are organised
into a table of contents. The popular Orphanet Report
Series, which address relevant rare disease and orphan
drug topics, are highlighted in a specific area. Finally,
OrphaNews, the newsletter of the rare disease
community, produced jointly by Orphanet and the
Commission Expert Group on Rare Diseases (via the
EUCERD Joint Action) is easily identified near the top right
of the homepage.

Fig.3 The Orphanet portal homepage in 2014

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.

3.1.1. 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 4,970,000 responses.
Users mainly access the www.orpha.net site through search engines (76.9% of visits according to
Google Analytics) and Google alone accounts for 73.5% of queries (figure 4). Other sites generating
traffic to Orphanet represent 4.9% of visits. The remaining visits are made via direct access
(bookmarks, 17,9%). Organic search corresponds to listing on search engine results pages that appear
because of their relevance to the search terms, as opposed to them being advertisements.
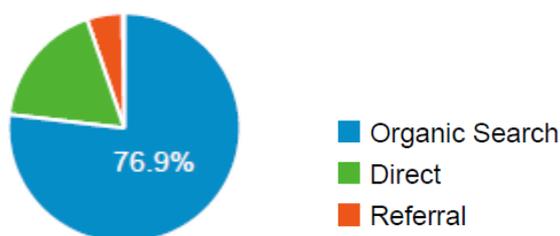

Fig. 4 Distribution of the traffic sources
(Source: Google Analytics, 1ˢᵗ of January 2014 to 31ˢᵗ of December 2014)

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 (smartphones, tablets): these visits represented 20% of all visits during 2014: in 2013, 23% of visits were from mobile devices and in 2012, it represented only 12%.

3.1.2. THE WEBSITE'S AUDIENCE

In 2014, around 32.4 million pages were viewed, thus on average around 90,000 pages viewed per day (figure 5). This figure has increased by 64% in comparison to 2013 (54,000 page viewed per day). This significant increase can perhaps be explained by a number of changes made to Google's algorithms since September 2012, which seems to have improved the referencing of Orphanet in Google and by the several improvements of services and products implemented during the years.

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 950,000 PDF documents are consulted on the Orphanet website. This represents more than 11,824,447 downloads in 2014, which is higher than in 2013 (around 10,000,000 downloads).

The users come from 226 countries. The top ten countries are: France, Italy, United States, Germany, Spain, Mexico, Brazil, Canada, Belgium and Switzerland.

At the end of July 2014, the way in which a session is counted changed at Google, thus explaining the increase in numbers of pages seen/sessions and a reduction in the number of sessions. Globally since 2011 the numbers of users has increased 3 times (Figure 6).

3.1.3. ORPHANET NATIONAL WEBSITES

In order for Orphanet to become an instrument in national plans or strategies for rare diseases, the international portal in seven languages has evolved towards customised websites by each country in their national language(s).
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 2014, 39 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.

Audience Overview

All Sessions
100.00%

Overview

|		
Sessions	Users	Pageviews
5,422,288	3,667,003	32,425,302
Pages / Session	Avg. Session Duration	Bounce Rate
5.98	00:02:05	2.04%
% New Sessions		
63.18%		

New Visitor Returning Visitor

36.8%   63.2%
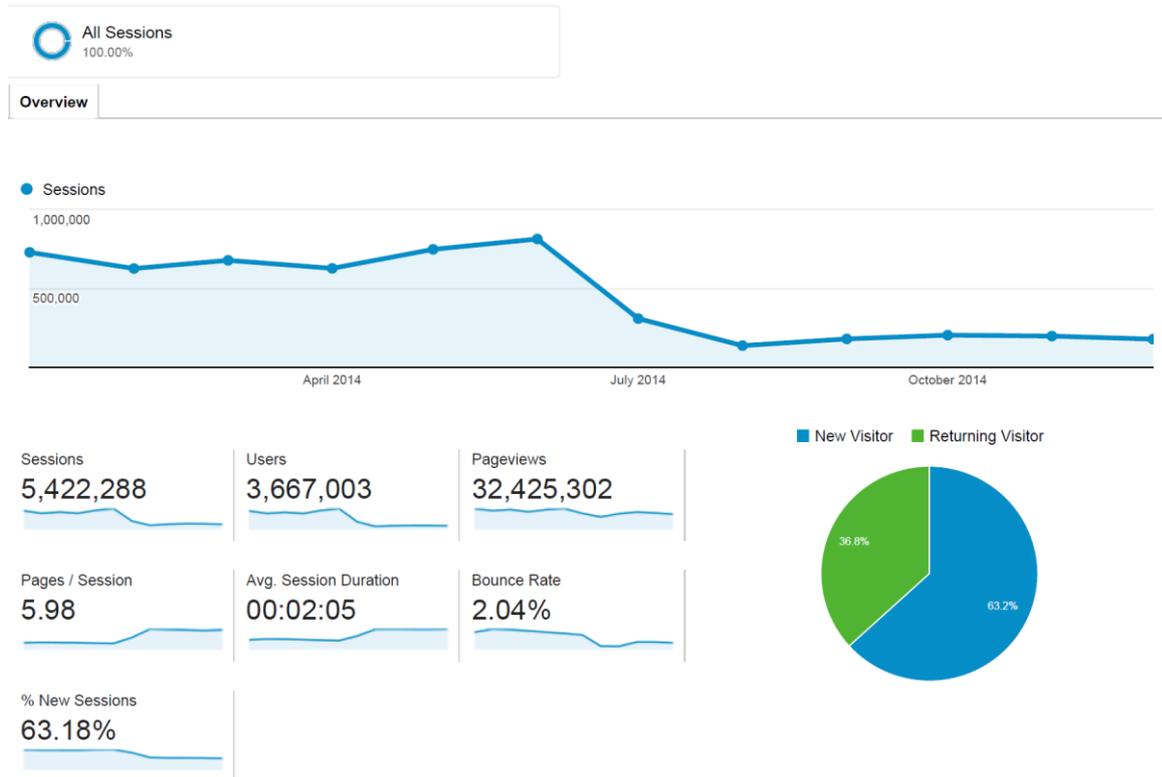
Fig.5 Orphanet website consultations in 2014[1]
(Source: Google Analytics, 1st January 2014 to 31st December 2014)

Pageviews Users

Year	Pageviews	Users
2014	32,425,302	3,667,003
2013	19,691,139	5,601,866
2012	12,207,186	3,116,967
2011	11,245,243	2,543,517
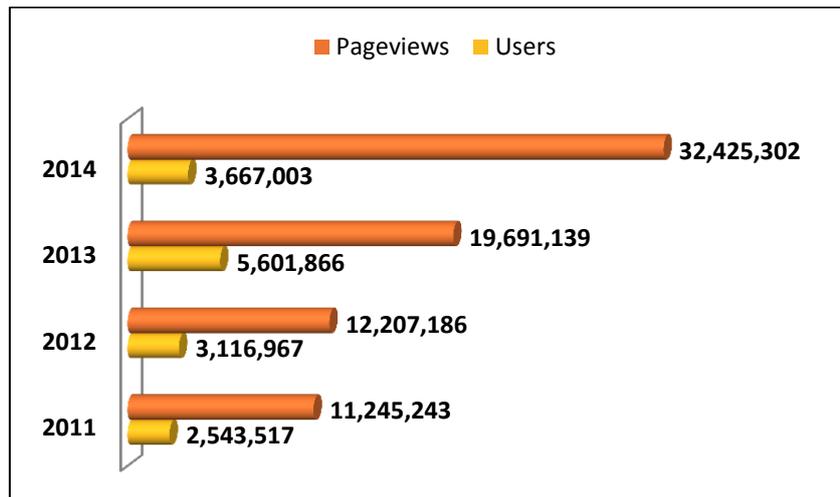
Fig.6 Number of page views and users of the Orphanet website since 2011

3.2. The Orphanet servers

The production servers are located to the largest civil data centre in France, the CINES (Centre Informatique National de l'Enseignement Supérieur). To ensure structural security, the development servers are located in an 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 7.

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 and deployed VPN clients to the teams.

No major problems were encountered in 2014 and the www.orpha.net website was highly available despite an increasing amount of visitors, which now reaches over 3 million pages viewed per month.
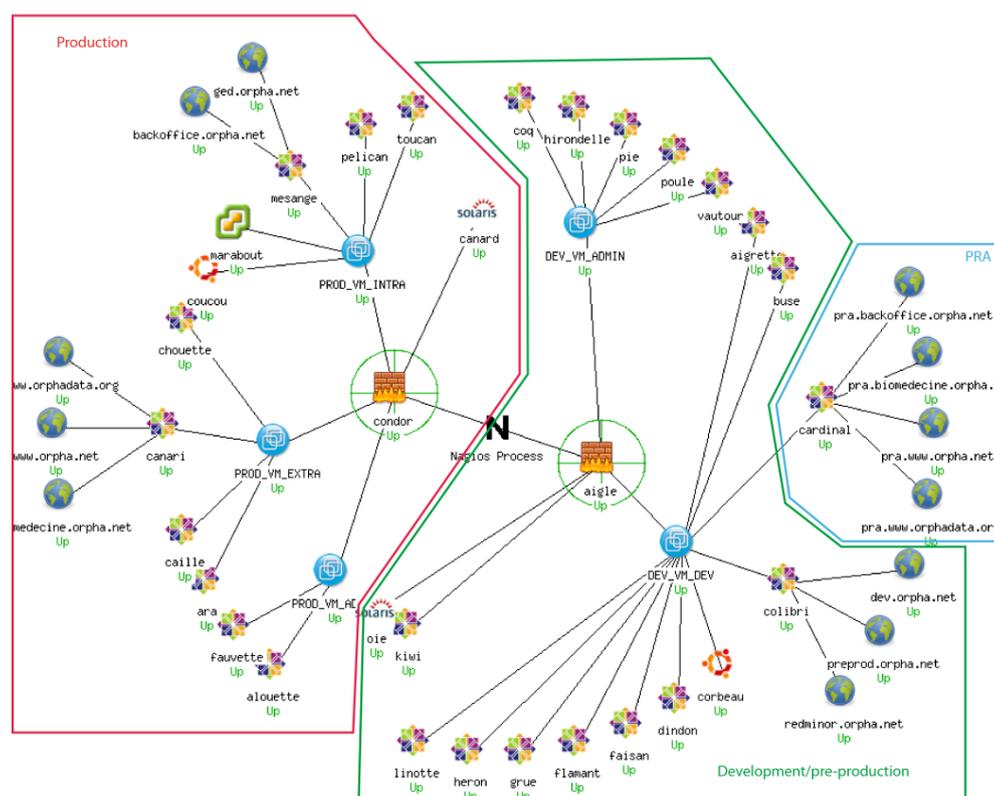
Fig. 7 The Orphanet IT architecture in 2014

3.3. Orphanet inventory of rare diseases

Orphanet provides a comprehensive inventory of rare diseases classified according to a polyhierarchical classification system of rare diseases. As new scientific knowledge issues arise, the Orphanet RD inventory and classification system is maintained with regular additions/updates of diseases employing two non-exclusive sources: documented sources and/or expert advice (Figure 8). The diseases database contains 9,539 diseases or groups of diseases and their synonyms as of 2014. 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 etiological criteria when diagnostically or therapeutically relevant. The Orphanet classification provides the scope and level of granularity needed by health professionals and can be viewed directly on the www.orpha.net website and/or extracted from Orphadata in XML format.
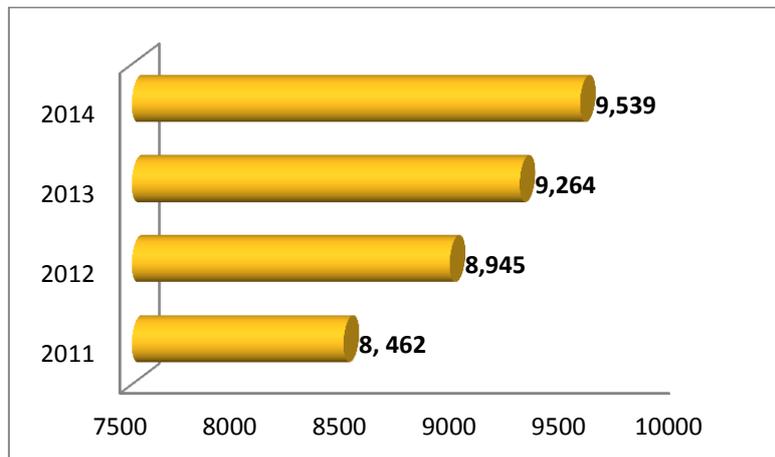

Fig. 8 Evolution of the inventory of RD since 2010

Within this classification entries are diseases, syndromes, anomalies, malformations, particular clinical situations, groups of diseases and disease sub-types. From 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 the literature.

Rare diseases are indexed with ICD-10 codes (see Table 2). This 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 indexation procedure. The ICD-10 indexation is manually curated.

Indexation by clinical signs uses an in-house thesaurus of phenotypic terms and is carried out with the aim of supplementing the Orphanet assistance-to-diagnosis tool. For each phenotypic term associated with a rare disease, the frequency of its occurrence (very frequent, frequent and occasional) is annotated. The search facility to retrieve diagnoses through signs and symptoms is available for 2,689 RD as of 31 December 2014.

Disease 'identity cards' have been improved with additional mappings and indexations. Diseases are mapped to one or more OMIM numbers (please refer to table 2). Exact mappings between the Orpha nomenclature and other terminologies (UMLS, MeSH and MedDRA) are available online (see Table 1). Mappings to SNOMED-CT are produced in collaboration with IHTSDO and will be 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 now 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 diseases
UMLS	2,969
MeSH	1,816
SNOMED CT	2,725
MedDRA	1,229
OMIM	4,229

Table 1. Number of mapped diseases per terminology as of 31 December 2014

Codes	Indexed diseases
ICD-10	6,657

Table 2. Number of indexed diseases with
ICD-10 codes as of 31 December 2014

Information on epidemiological data is available. Disease hereditary patterns and age of onset categories have been refined for more accurate information. Prevalence, annual incidence, prevalence at birth and lifetime prevalence data are now available for download on www.orphadata.org, in addition to prevalence intervals already available. Minimum, maximum and mean figures for each item are documented according to geographic zones where the information is available. The number of cases or families reported in the literature is also indicated for very rare diseases. Data sources and validity are supplied for all these datas. These new epidemiological data are available for 4,726 rare diseases and constitute a unique and global source of information which we hope are useful to all concerned users, namely policymakers, the research community and industrial actors involved in orphan drug development.

3.3.1   ORPHANET RARE DISEASES ONTOLOGY

In January 2014 the Orphanet Rare Disease ontology (ORDO) was released on three websites Bioportal, Orphadata and the EBI Ontologies 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 a nosology (classification of rare diseases), relationships (gene-disease relations, epidemiological data) and connections with other terminologies (MeSH, UMLS, MedDRA), databases (OMIM, Universal Protein Resource Knowledgebase (UniProtKB), Human Genome Organisation Gene Nomenclature Committee (HGNC), ensembl, Reactome, IUPHAR, Genatlas) or classifications (ICD-10). 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) view. ORDO is updated monthly and follows the OBO guidelines on

deprecation of terms. It constitutes the official ontology of rare diseases. ORDO Version 2.0 was launched at the end of 2014 to include new content from Orphanet including complete epidemiological data, mappings and genetic annotations as indicated below. 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 to associate new contents and to establish new research hypothesis on data that were not initially related.

3.4 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 tests, mutation databases and/or research projects. The data registered includes: indexation with the main name and symbol of the gene (from HGNC), its synonyms, and its HGNC, UniProtKB, Genatlas and OMIM references (in order to cross-reference these websites). Moreover, genes are now cross-referenced with 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) database. The relationship between a gene and a disease is qualified according to the role that the gene plays in the pathogenesis of a disease.

3.4.1 ADDITIONAL FUNCTIONALITIES IN 2014

Genetic entries have also been expanded to provide 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. Genes are also annotated as 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 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.
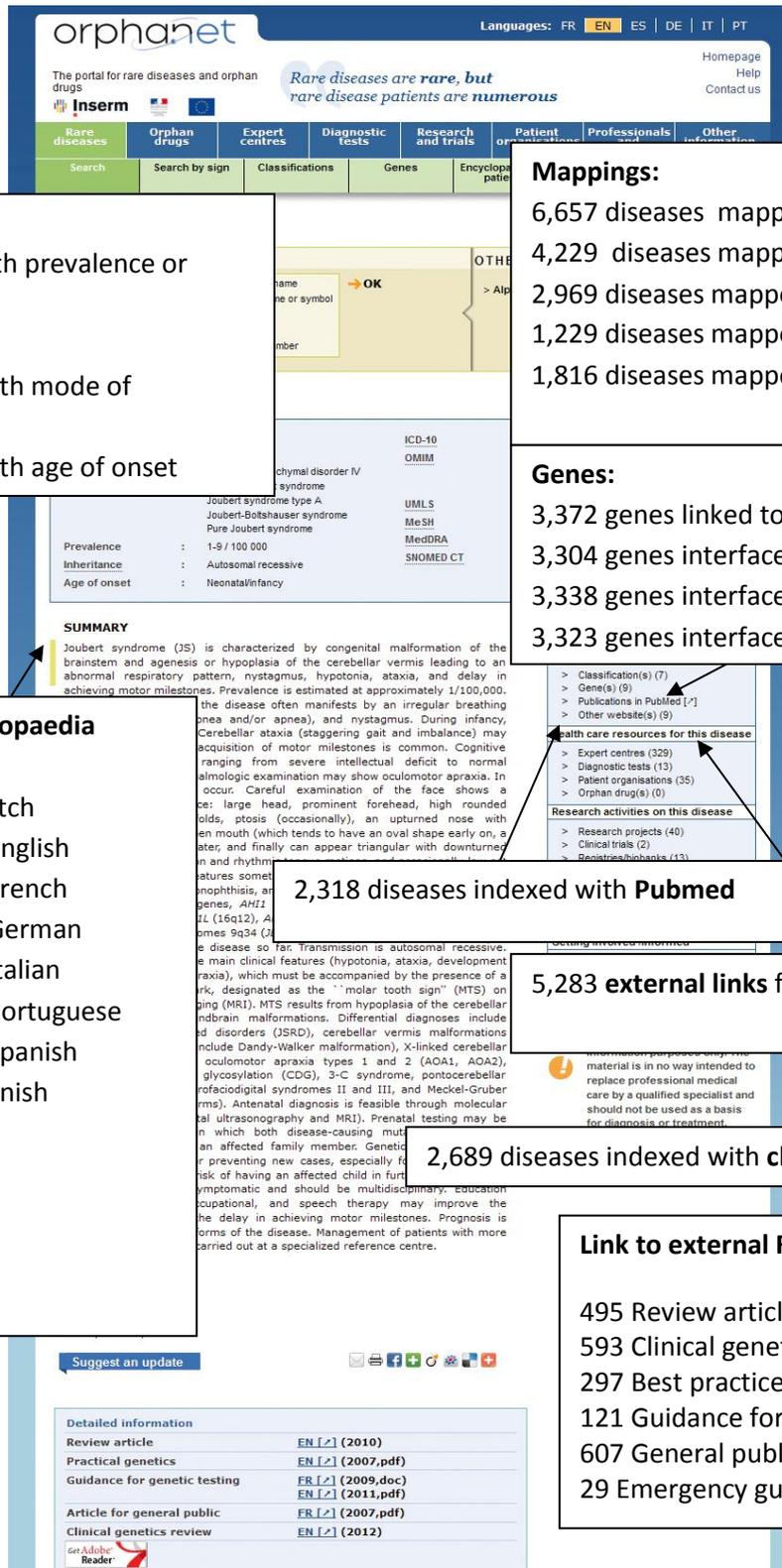
Epidemiology:
4,726 diseases annotated with prevalence or incidence data

Natural history:
4, 508 diseases annotated with mode of transmission
4, 541 diseases annotated with age of onset

Mappings:
6,657 diseases mapped to ICD-10
4,229 diseases mapped to OMIM
2,969 diseases mapped to UMLS
1,229 diseases mapped to MedRA
1,816 diseases mapped to MeSH

Genes:
3,372 genes linked to 3312 diseases, including:
3,304 genes interfaced with UniProt KB
3,338 genes interfaced with OMIM
3,323 genes interfaced with Genatlas

The Orphanet encyclopaedia contains:
367 summaries in Dutch
3,969 summaries in English
3,235 summaries in French
3,100 summaries in German
3,265 summaries in Italian
1,235 summaries in Portuguese
2,907 summaries in Spanish
307 summaries in Finnish
435 in Greek
476 in Polish
103 in Slovak
85 in Russian

2,318 diseases indexed with **Pubmed**

5,283 **external links** for 3,775 diseases

2,689 diseases indexed with **clinical signs**

Link to external RD literature

495 Review articles
593 Clinical genetics reviews
297 Best practice guidelines
121 Guidance for genetic testing
607 General public articles
29 Emergency guidelines

140 **articles for the general public** in French, 64 **emergency guidelines** in French, German, English, Spanish, Italian, Portuguese, and Polish. 24 **Disabilities factsheets** in French

Fig. 9 The disease database content as of 31 December 2014

3.5 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.

3.5.1 HEALTH PROFESSIONALS ENCYCLOPAEDIA

- **Summary information**

The textual information on a disease can be provided as an abstract, definition or as automatically generated texts.

The Orphanet texts are unique, originally written in English by a member of the Paris-based editorial team and abstracts and definitions are reviewed by an invited world-renowned expert. Additional information on the diseases (i.e. annotations on epidemiological data, clinical signs, functional consequences of the disease, genes, etc.) is requested from the expert if not already documented in the database, or validation of the existing data is requested. Abstracts and definitions are structured in up to 10 sections : Definition of the disease – Epidemiology – Clinical description – Aetiology – Diagnostic methods – Differential diagnosis – Antenatal diagnosis (if relevant) – Genetic counselling (if relevant) – Management and treatment – Prognosis.

As of December 2014, summary information for 3,969 RD is available online.

They are systematically translated into the six other languages of the website (French, Italian, Spanish, German, Portuguese and Dutch). In addition, as of 31 December 2014, 307 abstracts are available in Finnish, 476 in Polish, 103 in Slovak and 435 in Greek. For additional 2661 entries in the disease inventory textual information is provided through automatically generated texts (for diseases labelled as a group of diseases, deprecated entries, subtype of disorders, particular clinical situation 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 accessible from 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: 64 emergency guidelines in French are now online. They are being translated into six languages (English, German, Italian, Portuguese, Spanish and Polish). Currently, 21 emergency guidelines are available in English, 36 in Italian, 26 in German, 23 in Spanish, 19 in Portuguese, and 18 in Polish.
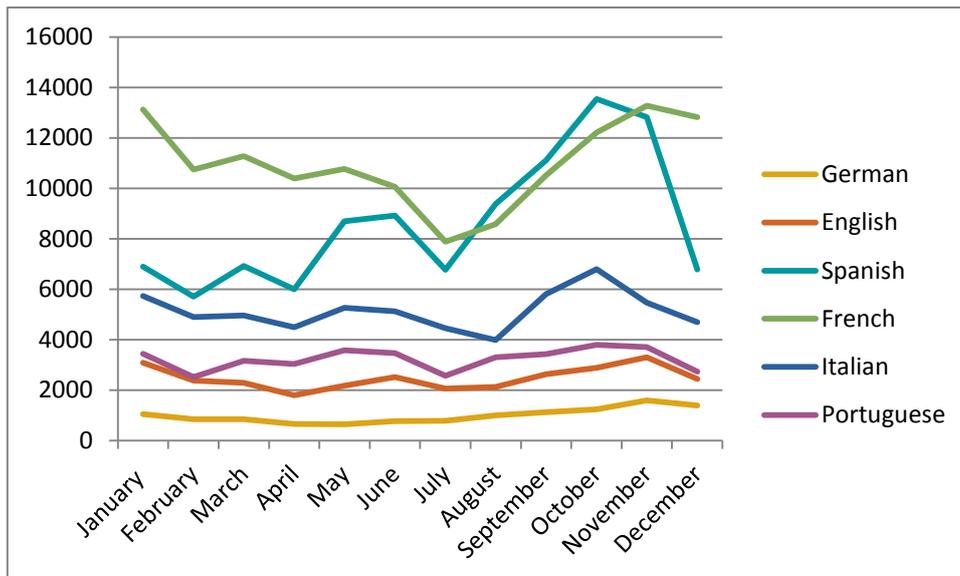
Fig. 10 Downloads of the emergency guidelines by language in 2014

Emergency guidelines were viewed approximately 380,000 times in 2014, versus 340,000 in 2013, representing an increase of 11% in one year (figure 11).

The ratio of the number of consultations for each language to the number of guidelines shows that this collection is a success in several languages such as French, Italian, Spanish and Portuguese (figure 10). On the other hand, the disappointing number of consultations in English can be explained by the existence of a larger number of equivalent documents elsewhere in this language that are produced by learned societies. To avoid dissipation of time and work, Orphanet has established collaborations with these learned societies to provide links to these already existing and valuable resources (please refer to 0). In addition, consultation of the guidelines in Polish reached 9,000 downloads in 2014.
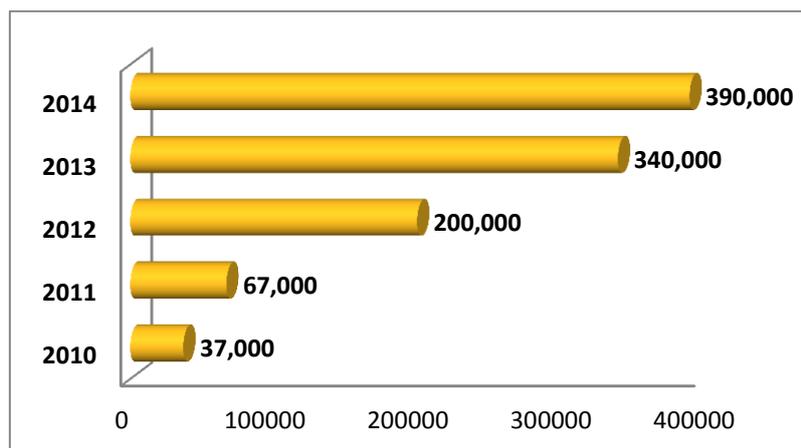
Fig. 11 Downloads of the emergency guidelines since 2010 in all languages

3.5.2 GENERAL PUBLIC ENCYCLOPAEDIA

The general public encyclopaedia was initially a French project intended to give complete, honest, and up-to-date information to patients and their relatives on the diseases that concern them.

Starting from 2011, the general public encyclopaedia texts have been enriched with paragraphs on 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.

As of 31 December 2014, 140 in-house French texts are available online. Documents from this encyclopaedia are downloaded more than 467,000 times per month, which corresponds to more than 5.6 million downloads in 2014 (figure 13). This represents an increase of 25% compared to the 4.3 million downloads in 2013.
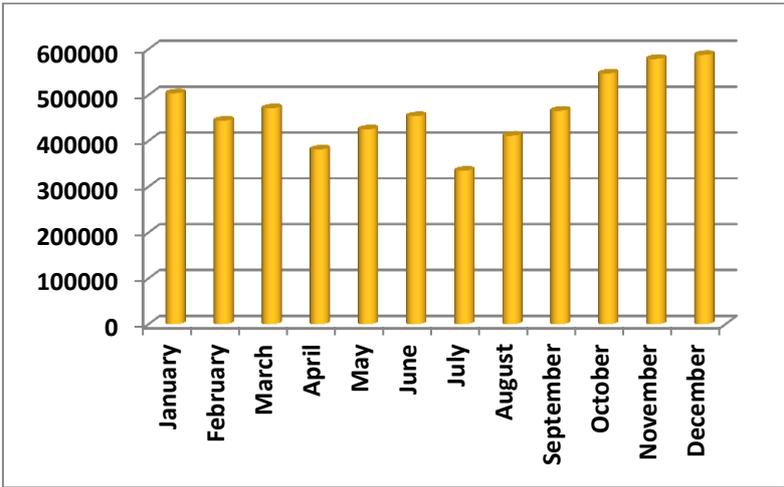
Fig. 12 Total number of downloaded Orphanet general public encyclopaedia texts in 2014
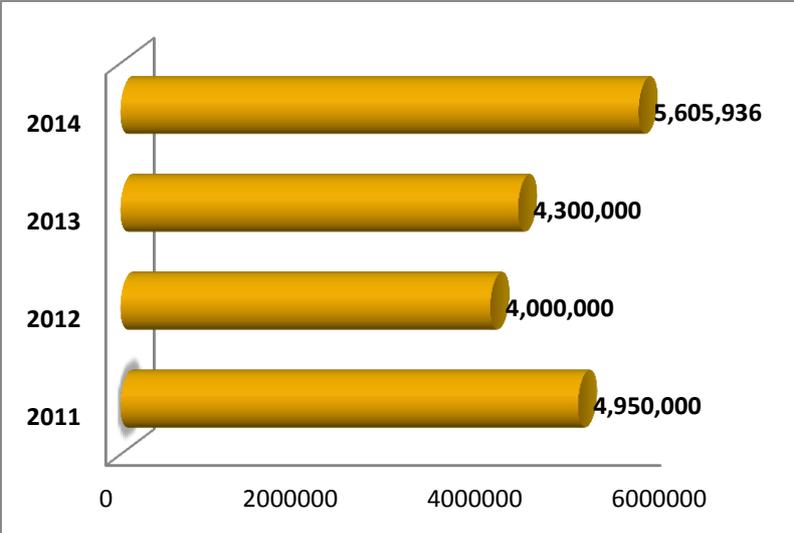
Fig. 13 Downloads of the general Public encyclopaedia since 2011

3.5.3 DISABILITIES ENCYCLOPAEDIA

As part of the collaboration between CNSA (French National Solidarity Fund for Autonomy) and INSERM, Orphanet now provides a new collection of texts named "**disability factsheets**" in the Orphanet Encyclopaedia of Disability devoted to the disabilities associated with each rare disease. This new 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 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).

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 "Encyclopaedia for general public." 24 of these texts are available online since November 2013. They have been dowloaded approximately 20,000 times in 2014.

3.5.4 ADDITIONAL PRODUCTS IN 2014

Information on diagnostic criteria is presented in 13 concise documents intended to avoid serial misdiagnosis and facilitate early therapeutic management. This information is extracted from peer-reviewed journals and validated by international experts, with reference to the original paper given at the top of the page.

3.5.5 LINKS TO EXTERNAL RARE DISEASES LITERATURE

With the purpose of expanding the number of articles available online and to disseminate articles matching Orphanet's quality criteria, the editorial team is also in charge of identifying articles suitable for publication on the website produced by other journals or learned societies. Authorisations from the copyright holder are requested so as to give access to the full text.

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

- **Review articles**
As of 31 December 2014, 495 review articles (excluding those published in the Orphanet Journal of Rare Diseases) were available on the website.

- **Clinical Genetics Review**
These are peer-reviewed disease descriptions focus on genetic aspects with an implication in the diagnosis, management, and genetic counselling of patients and families with specific inherited conditions.
As of 31 December 2014, the clinical genetic review collection comprised 593 articles from GeneReviews.

- **Best 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 and published either in scientific journals or on learned societies or health agency websites. A methodology of assessment has been

developed to review the guidelines based on the AGREEII instrument in order to link only the most accurate ones. As of 31 December 2014, 297 best practice guidelines were available on the website.

- **Guidance for genetic testing**

This collection comprises summary recommendations intended to disseminate best practice in genetics testing. They include Gene Cards (published in the EJHG). As of 31 December 2014, 121 recommendations were available on the website.

- **Articles for general public**

Publication of general public-intended texts, externally produced by expert centres or patient organisations (produced in compliance with a reliable methodology), in all languages are now selected.

607 articles are available on the website as of 31 December 2014.

- **Emergency guidelines**

Orphanet has established acollaboration with the British Inherited Metabolic Disease Group (BIMDG) to provide links to the emergency guidelines they produce. Currently 23 external emergency guidelines are available in English and in other languages.

- **Disabilities factsheets**

21 additional disability factsheets in Danish are available produced by Sjaeldenborger the Danish Rare Diseases alliance.

Language	External review articles	Clinical genetics review	Best practice guidelines	Guidance for genetic testing	General public articles
English	392**	593	103	120	179
French	62	---	91	1	22*
German	5	---	82	---	33
Italian	33	---	1	---	24
Portuguese	---	---	---	---	6
Spanish	2	---	16	---	16
Dutch	---	---	2	---	2
Hungarian	---	---	1	---	
Greek	1	---	1	---	5
Russian	---	---	---	---	5
Polish	---	---	---	---	2
Swedish	---	---	---	---	294
Arabic	---	---	---	---	4
Croatian	---	---	---	---	2
Czech	---	---	---	---	2
Finnish	---	---	---	---	13
Total	**495**	**593**	**297**	**121**	**607**

* not including the in-house produced
Table 4. Total number of Orphanet external content in 2014: type of text per language

3.6. Orphanet directory of expert resources

Orphanet provides a directory of:
- Centres of expertise/genetic counselling clinics
- Medical laboratories
- Patient organisations
- Clinical trials
- Patient registries
- Mutation registries
- Biobanks
- Ongoing research projects
- Platforms
- Networks

Data is collected either from national official sources, or proactively from non-official sources by information scientists in each country. 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 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 against the criteria of relevance for rare diseases, coherence across the database and proper indexing with 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 resources they are involved in.

The 39 countries in which Orphanet collects data are the following:
Armenia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Ireland, Israel, Italy, Latvia, Lebanon, Lithuania, Luxembourg, Morocco, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tunisia, Turkey, the United Kingdom and Western Australia. Additionally, are collected from countries outside the consortium research-related activities (research projects, clinical trials, infrastructures, patient registries, biobanks and mutation databases) for which the funding bodies belong to the IRDIRC consortium (i.e. USA and South Korea).

Data collection and/or 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.
In 2014, all countries managed both data collection and updates at country level except: Bulgaria, Cyprus, Denmark, Georgia, Lebanon, Luxembourg, Norway, Romania and Turkey.

The directory of expert resources in 39 countries in the Orphanet consortium contains the following data:
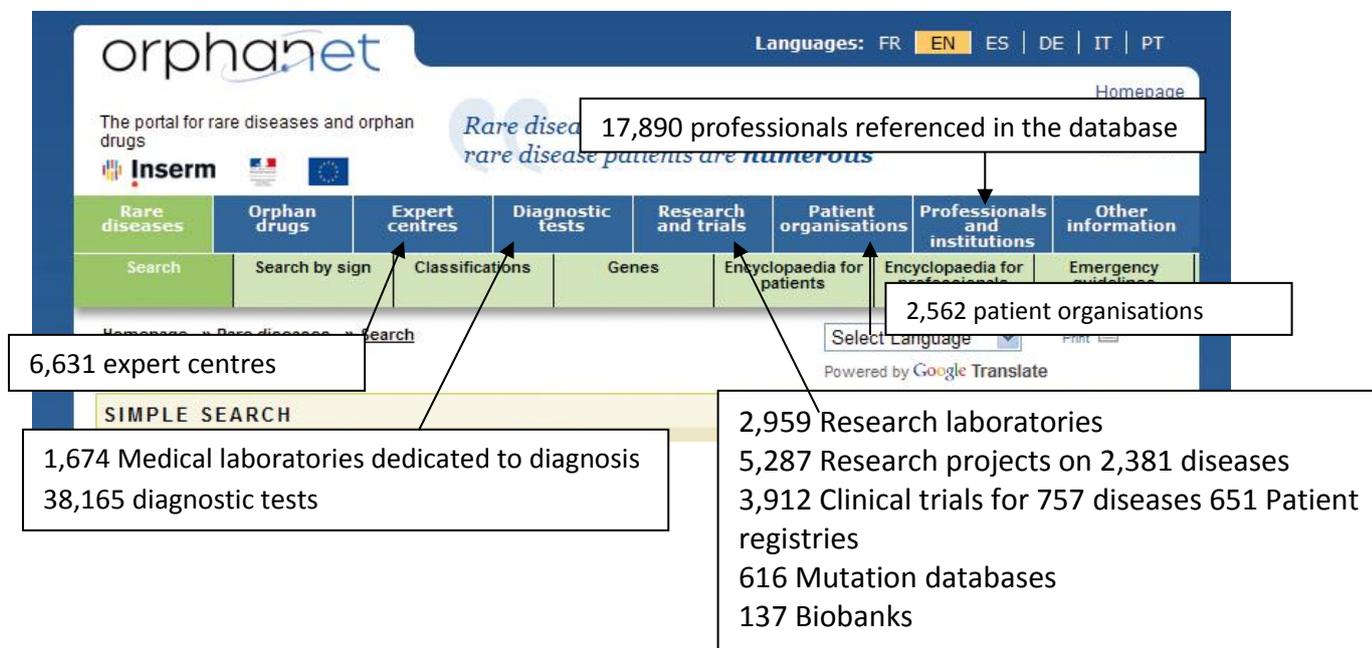
Fig.14 2014 Directory of expert resources in 39 countries

3.6.1 ADDITIONAL FUNCTIONALITIES IN 2014

It is now possible to indicate if an expert centre has two heads of clinic, and if it has both a medical management and genetic counselling role.

The research-related activities funded by an International Rare Diseases Research Consortium (IRDiRC) member as also marked with an IRDiRC logo.

3.6.2 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 that 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 is validated by Orphanet upon reception of an EQA participation certificate; otherwise the information provided on the Orphanet website is deemed 'not validated' and associated with a [!] sign.

3.7 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 are 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).

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:

For Europe:
-   1219 substances linked to 1198 orphan designations (regarding 548 diseases).
-   187 European marketing authorisations (of which 83 already had an orphan designation and 104 had no previous without orphan designation) (regarding 199 diseases).

For the USA:
- 786 substances linked to 896 orphan designations (regarding 419 diseases)
- 193 USA marketing authorisations after orphan designation (regarding 187 diseases)

3.8 Orphadata

Since Orphanet is 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.

On this website, the whole Orphanet dataset has been directly accessible in a reusable format since June 2011. Orphadata was developed within the context of the Rare Diseases Portal project and the Orphanet Europe Joint Action contract funded by DG Santé. The dataset is a partial extraction of the data stored in Orphanet and is updated monthly.

Freely accessible in six languages (English, French, German, Italian, Portuguese and Spanish) the Orphadata dataset encompasses:

• An inventory of rare diseases, cross-referenced with OMIM, ICD-10, MeSH, MedDRA, UMLS, and with genes in HGNC, OMIM, UniProtKB, IUPHARand Genatlas. Annotations on typology of diseases and genes and of genes-diseaes relationships. definitions for RD
• A classification of rare diseases established by Orphanet, based on the literature and expert classifications
• Epidemiology data related to rare diseases in Europe based on the literature
• A list of signs and symptoms associated with each disease, with their frequency class within the disease
• The list of Orphanet signs and symptoms used to annotate the diseases, cross-referenced with other terminologies: HPO, PhenoDB, LDDB.
• Linearisation of RD : for analysis purposes, each disorder is attributed to a preferred classification (linearisation) by linking it to the head of classification entity. As some decisions could be made somewhat arbitrarily, a set of rules has been elaborated to make sure attributions are consistent.
• Orphanet Rare Diseases Ontology (ORDO)

Table 5 . Products freely accessible on Orphadata

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.

• 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 six languages (English, French, German, Italian, Spanish, Portuguese)
• URLs of other websites providing information on specific rare diseases
• A directory of specialised services, providing information on centers of expertise, medical laboratories, diagnostic tests, research projects, clinical trials, patient registries, mutation databases, biobanks and patient organizations in the field of rare diseases, in each of the countries in Orphanet network.

Table 6 . Products accessible on Orphadata after signature of a Data Transfer Agreement

Orphadata provides a guide for users that defines and describes the elements of the dataset.

In 2014, **Orphadata products were downloaded more than 168,000 times**, with an average of 14,000 times per month. This represents an increase of 800% since its release mid-2011 (Figure 15).
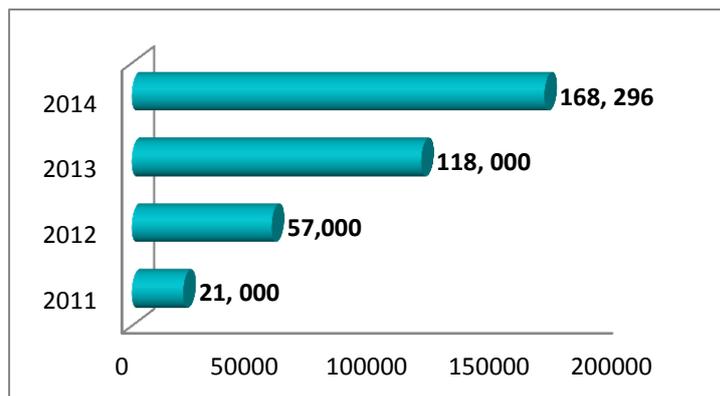
Fig. 15 Number of downloads from the Orphadata website since mid-2011

The most requested Orphadata product is the inventory of diseases with clinical signs (figure 16).
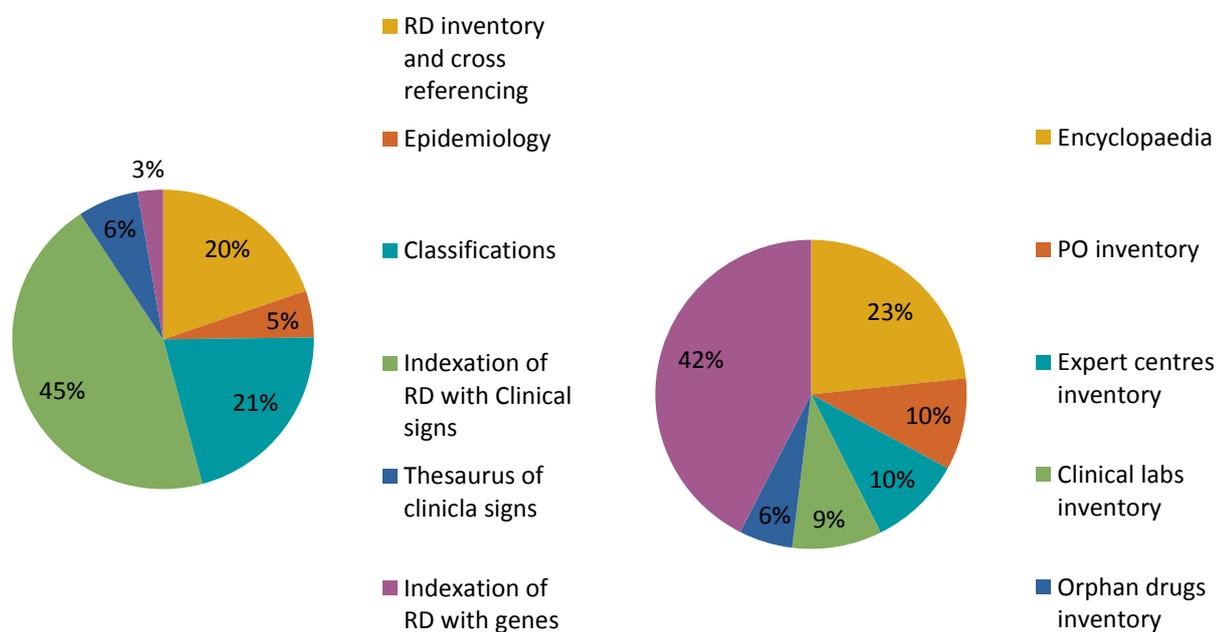

Fig. 16.Distribution of the downloads of Orphadata datasets in 2014
a) Freely available datasets [total of 166933 downloads]

b) Datasets accessible on demand [total of 1363 downloads]

3.8.1. ADDITIONAL FUNCTIONALITIES IN 2014

In late 2014, Orphadata provided access to Orphanet's newly incorporated data (as described in the additional products in 2014 sections previously) and an updated user guide was also released online.

3.9. Orphanet Report Series

Orphanet Reports are a series of texts (ORS) 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 other page of the Orphanet's website.

New versions of these publications are advertised in OrphaNews.

The ORS are heavily downloaded: in 2014, more than 2,250,000 ORS were consulted (table 7). This represents an increase of 34% compared to 2013 (approximately 1,675,000 downloads) (figure 17).

Title	English	French	German	Italian	Portuguese	Spanish	Dutch
Activity Report 2012	52,275	1,542	n.a.	4,720	n.a.	5,327	n.a.
Activity Report 2013	86,737	9,732	n.a.	7,484	n.a.	3,670	n.a.
List of orphan drugs in Europe	153,747	39,760	n.a.	22,693	3,822	27,957	11,082
List of RD in alphabetical order	273,313	251,118	n.a.	38,155	7,636	152,367	n.a
Prevalence of RD by alphabetical list	158,346	39,857	19,222	17,816	15,711	68,784	n.a
Prevalence of RD by decreasing prevalence or cases	47,044	33,453	9,788	12,983	25,040	35,150	n.a.
Diseases registries in Europe	71,574	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Research Infrastructures for RD in Europe	15,592	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Table 7. Number of downloads of selected Orphanet Report Series in 2014 by language

n.a. ORS not available in this language

Comparison of the number of downloads of the ORS translated in all 6 languages shows that this collection is most heavily downloaded in English and French.
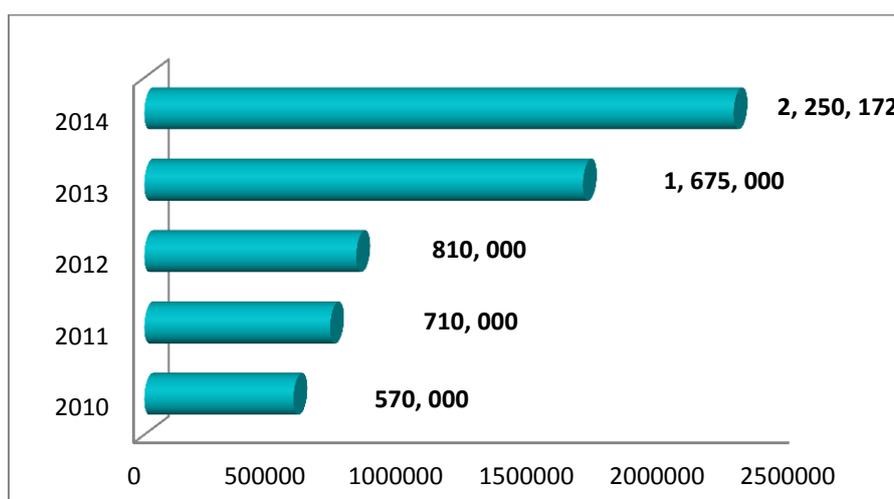

Fig. 17 Number of downloads of the Orphanet Report Series in all languages since 2010

3.10. The Orphanews Newsletter

A literature review is performed twice a month in order to update the database and to collect news to report in OrphaNews, a bi-monthly electronic newsletter, to which the subscription is free. OrphaNews presents an overview of scientific and political news about rare diseases and orphan drugs. It is the communication tool of the Rare Disease community and is produced jointly by Orphanet and the Commission Expert Group on Rare Diseases through support provided by the EUCERD Joint Action, co-funded in the framework of the European Union Health Programme.

Fig. 18 Orphanews homepage

OrphaNews in English has more than 15,700 subscribers. Orphanews in French has more than 9,400 subscribers and OrphaNews in Italian has more than 4,600 subscribers.

3.11. Orphanet Journal of Rare Diseases

Orphanet Journal of Rare Diseases (OJRD) is an open access, online journal that encompasses all aspects of rare diseases and orphan drugs. The journal publishes high quality reviews on specific rare diseases. In addition, the journal may consider articles on clinical trial outcome reports, either positive or negative, and articles on public health issues in the field of rare diseases and orphan drugs. OJRD was indexed in Medline at the end of its first year of existence (2006) and was selected by Thompson Scientific after only two years in publication. Its current impact factor is 3.96. In 2014, 495 publications were submitted to the journal. Of these, 214 were accepted for publication.

4   Users

4.1.   Types of users and use

2014 Orphanet user satisfaction survey

An online survey was carried out for 5 weeks from 18 December 2014 to 22 January 2015. The satisfaction of the portal users was assessed by asking them to respond to a short online questionnaire.

The following results present the responses collected in all languages (Dutch, English, French, German, Italian, Portuguese and Spanish). For this analysis, the users who answered "other" in

question 1 were not reattributed to another category. More results from this survey, with reattribution, will be available in the Orphanet Report Series dedicated to the 2014 survey.

QUESTION 1

IN WHAT CAPACITY ARE YOU CONSULTING THE ORPHANET WEBSITE TODAY? PLEASE SELECT A CATEGORY.

(N=3224)
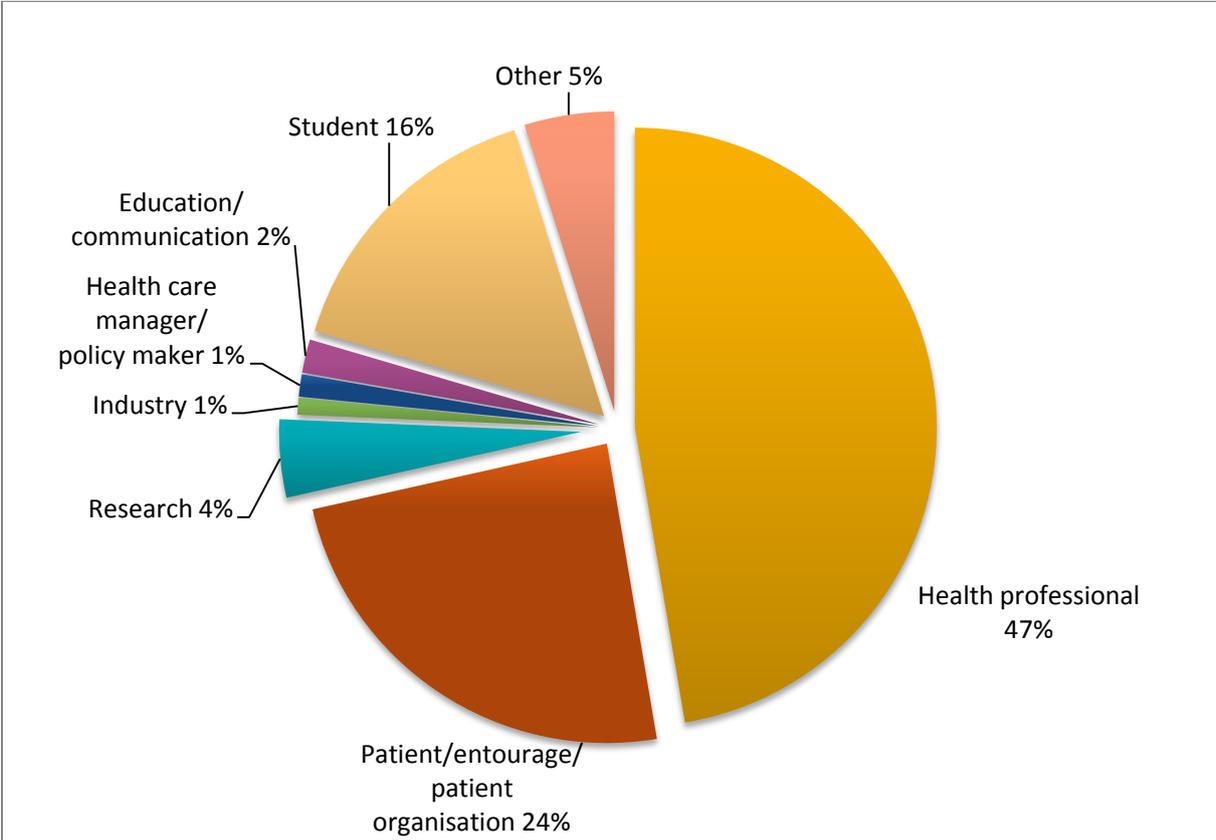
Fig. 19 Distribution of the 2014 user survey respondents amongst the proposed categories

The largest category of respondents was the health professionals' category (47%). The second largest category of respondents was patients and their entourage (including patient organisations, alliances and support groups) with 24% of responses.

Then, for each category, respondents were asked to choose the sub-category that would best describe them. The results for health care professionals (Fig. 20) and researchers (Fig. 21) are presented below. The majority of users in the health care professionals sub-category (Figure 20) were hospital specialists (40%), followed by general practitioners (12%). Experts in the field of rare diseases represented 4% of respondents to this question.
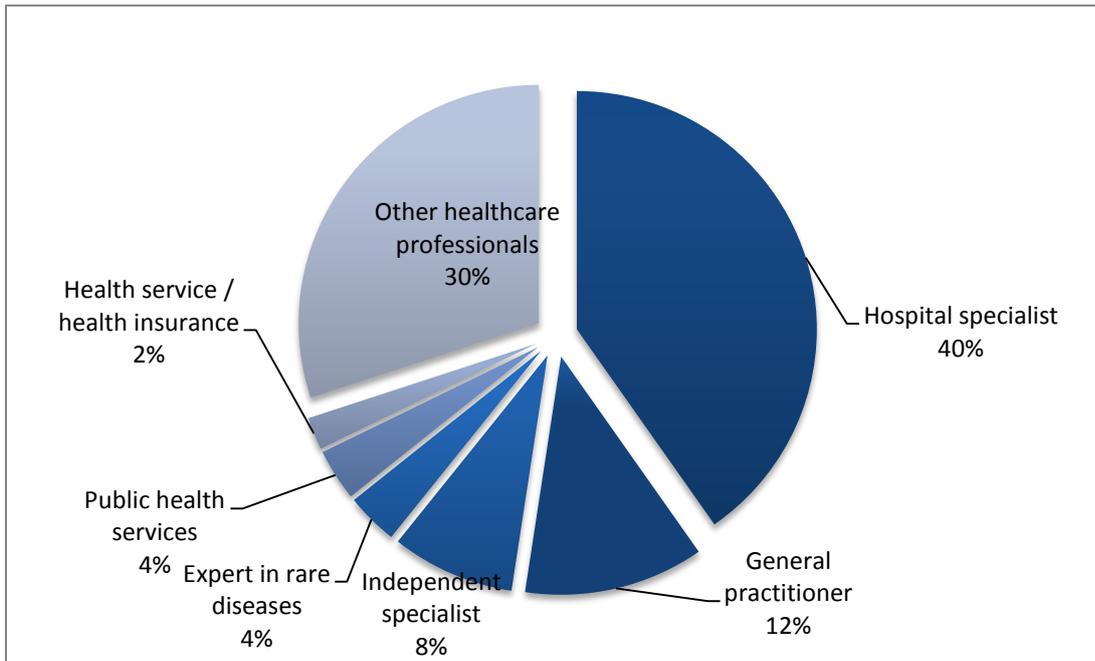
Fig. 20 Distribution of the 2014 user survey respondents in the health care professional category

The majority of users coming from the field of research (Figure 21) were academic, clinical researchers (40%), with those working in basic research also fairly well represented (19%).
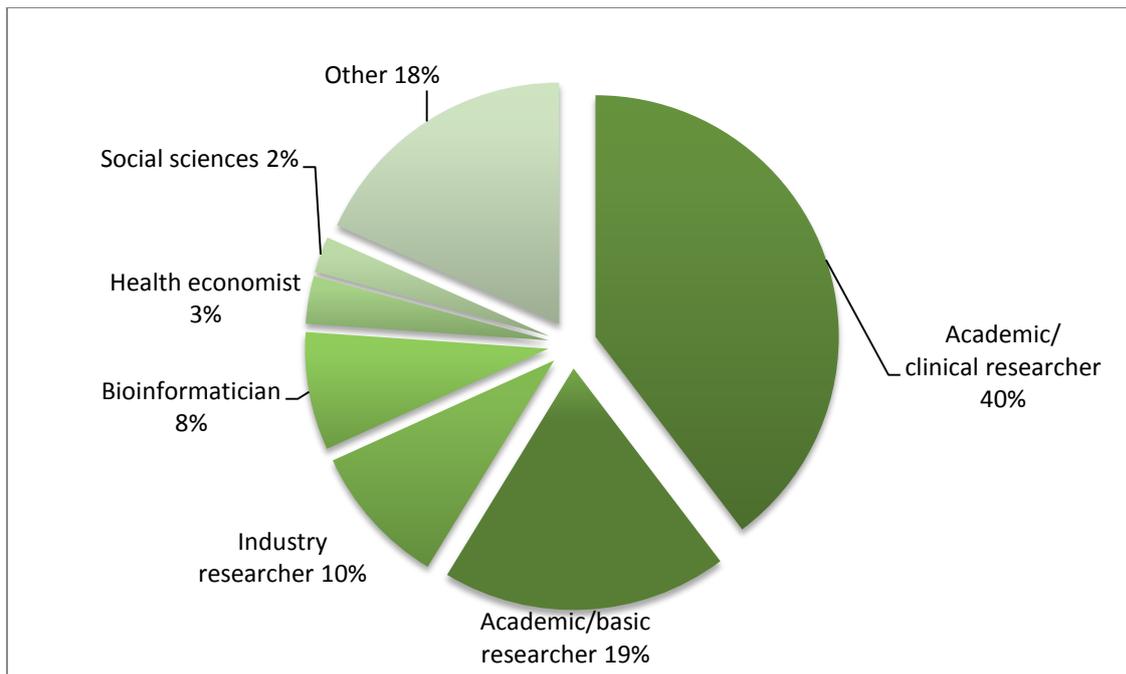

Fig. 21 Distribution of the 2014 user survey respondents in the research category

QUESTION 2

HOW OFTEN DO YOU VISIT ORPHANET? (N=3151)

Over 75% of those who answered this survey are regular users whereas 25% were visiting Orphanet for the first time.

QUESTION 3

WHAT SORT OF INFORMATION ARE YOU LOOKING FOR DURING THIS CONNECTION TO ORPHANET? (N=3136)

As in previous years, most users are looking for information on a specific rare disease (87% of respondents). They are also looking for information on rare diseases in general, followed closely by information on expert services including laboratory tests (16%), specialist clinics (12%), research projects (12%), as well as clinical trials (11%) and patient organisations (10%).
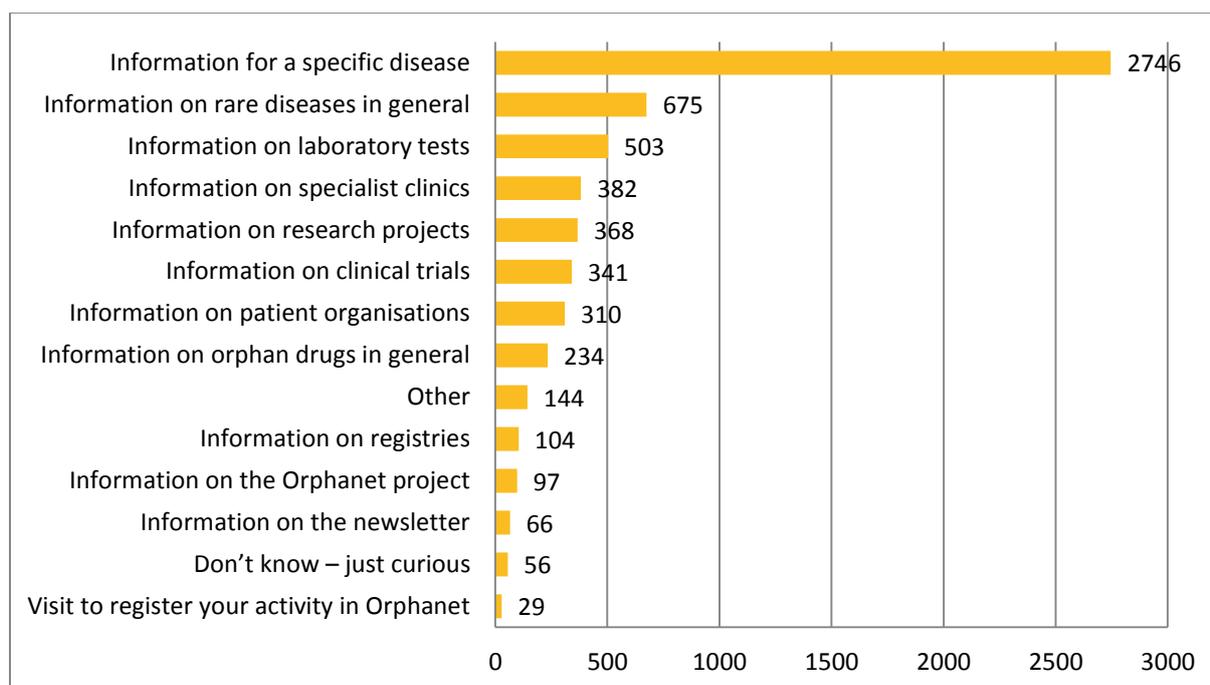
Fig. 22 Information sought on Orphanet by the 2014 user survey respondents

QUESTION 6

HAVE YOU DOWNLOADED THE ORPHANET APPLICATION? (N=3113)

Answer options	Response percent	Response count
Yes	7,1%	222
No	92,9%	2891

Table 8. Download of the Orphanet application by the 2014 user survey respondents

The respondents accessing Orphanet via a mobile device to whilst answering the survey have increased from 10 to 15% in the past year. This reflects the trends identified with Google Analytics concerning the increase in use of the site via mobile devices. However, only a small percentage of respondents have downloaded the Orphanet mobile application suggesting that most users a majority of mobile device users navigate the site via a traditional web browser.

QUESTION 8

HOW USEFUL ARE ORPHANET'S PRODUCTS FOR YOUR OWN USE? (N=2852)

The usefulness of Orphanet products was evaluated through this question. Only one response was possible for each product. The results show that Orphanet products are highly appreciated, but some are not sufficiently well known, in particular the more recent products, such as the Orphanet Rare Disesases Ontology and Orphadata.

Orphanet product	Very useful	Useful	Fairly useful	Not useful	No opinion	I didn't know Orphanet offered this service
Texts on diseases	1636	691	179	18	62	153
List of diseases and classifications	1527	689	158	31	96	273
Emergency guidelines	768	565	302	99	256	624
Search by sign facility	750	602	278	98	236	639
Orphanet Report Series on epidemiology of Rare Diseases	628	582	261	67	253	731
Directory of patient organisations	621	621	386	107	294	530
Directory of medical laboratories	585	498	350	147	315	649
Directory of clinics	547	549	373	109	315	662
Directory of orphan drugs	530	559	279	120	346	664
Directory of clinical trials	518	578	370	112	313	645
Directory of research projects	517	595	371	105	322	633
Orphanet Report Series on Orphan Drugs	445	491	260	93	345	838
Orphanet national websites	414	470	269	80	380	845
OrphaNews newsletter	341	375	276	105	403	947
Directory of registries	336	515	339	131	416	737
Orphadata (downloadable Orphanet datasets)	317	331	211	76	362	1168
ORDO: Orphanet Rare Diseases ontology	262	308	218	75	415	1159

Table 9. Opinion of the 2014 user survey respondents on the utility of Orphanet products for their needs (all languages except Dutch)

The usefulness of Orphanet's products for the needs for those answering the survey were calculated using the percentage of 'very useful' and 'useful' replies. The 'no opinion' and 'I didn't know Orphanet offered this service' answers were subtracted from the total results to calculate this percentage to more faithfully represent the utility of the products, according to those aware of the services.

Product	Percentage
Texts on diseases	92%
List of diseases and classifications	92%
Orphanet Report Series on epidemiology of Rare Diseases	79%
Search by sign facility	78%
Emergency guidelines	77%
Directory of orphan drugs	73%
Orphanet Report Series on Orphan Drugs	73%
Orphanet national websites	72%
Directory of patient organisations	72%
Directory of research projects	70%
Directory of clinical trials	69%
Directory of clinics	69%
Orphadata (downloadable Orphanet datasets)	69%
Directory of medical laboratories	69%
ORDO: Orphanet Rare Diseases ontology	66%
OrphaNews newsletter	65%
Directory of registries	64%

Fig. 22 Most useful Orphanet products in the opinion of the 2014 user survey respondents

The most useful service, according to our users, remains the list of diseases and classifications and the texts on diseases (according to 92% of respondents aware of this service). The Orphanet Report Series on the epidemiology is also well appreciated (79%), as is the search by sign facility (78%). The data concerning orphan drugs is popular with those who use it (73%) as is the corresponding Report Series (73%).

5   Network: Orphanet's national and international collaborations

5.3 Collaboration with the WHO

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

Orphanet has been entrusted as the operating institution to prepare the proposal for ICD-11 related to rare diseases. The Rare Diseases Topic Advisory Group (RD-TAG) has therefore

managed the process of the preparation and peer-review of proposals in order to include rare diseases in every relevant chapter of the ICD-11. In 2013, the beta version of ICD-11 was released. It includes over 5,000 rare diseases. The beta version is available here for public consultation. The final version is not expected before 2018.

5.4 Collaboration with Health Authorities

5.4.1 NATIONAL PLANS

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 inventorising and documentation of Dutch centres of expertise for rare diseases. Orphanet Netherlands was asked to perform the validation of the centres of expertise identified by the NFU. The validation procedure, according to the EUCERD recomendations, applied by Orphanet Netherlands entails validation by medical specialists via the Orphanet Netherlands Scientific Advisory Board as well as validation by patient organisations via the VSOP, the National Patient Alliance for Rare and Genetic Disorders. This validation is ongoing. The minister will assign the Center of Expertise listed in this catalogue as official Dutch centres of expertise.

5.4.2 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 Orphacode. It is composed of a unique and stable Orpha number for each rare disease of the inventory.

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 Orphacodes at 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 Orphacodes as a complement to existing coding systems will be provided via a dedicated work package of the future Joint Action for rare diseases (RD-Action).

A number of countries have already taken some concrete steps in implementing Orphacodes in their healthcare systems and national Orphanet teams are playing a key role in the following countries:

France

In 2012, it was decreed that the French hospital system database would use Orphacodes to code all hospitalised patients. The goal is to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways. The Orphacode has been added in a dedicated part of the coding system, in addition to the ICD-10 derived code. The French Ministry of Health issued a directive to rare disease reference centres and competence centres in order to include Orphacodein patient records. This will help capturing data to be included in the French Rare Diseases Data Repository [BNDMR](#) , which is in development. Coding with the Orphacodes should 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 partnering in this project by supplying the DIMDI (German Institute of Medical Documentation and Information) with the German translation of the rare disease terms. The project intends to integrate the Orphanet classification of diseases by adding Orphacodes 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.

5.4.3 EXPERT RESOURCES DOCUMENTATION

The Orphanet Belgian team is piloting a nation-wide survey on behalf of the Ministry of Health to document Belgian expertise for rare diseases.

5.5 Scientific collaborations and partnerships

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.

5.5.1 PARTNERSHIP WITH THE INTERNATIONAL CONSORTIUM OF HUMAN PHENOTYPE TERMINOLOGIES (ICHPT)

A collaboration between Orphanet, HPO (Human Phenotyp Ontology) and OMIM was established to prepare a proposal for a core set of terms to describe human phenomes. A consortium of partners was set up: the **ICHPT**. There is now an agreement on 2,372 terms which are proposed to be adopted by all existing terminologies. This core terminology will be made available on a dedicated website in 2015, and mappings with other phenotype terminologies in use (HPO, PhenoDB, LDDB, SNOMED CT, Elements of Morphology amongst others) will be provided in order to ensure inter-operability between databases and patient data worldwide. This project, now overseen by the IRDiRC, was initiated and coordinated by Orphanet.

5.5.2 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. In particular a scientific collaboration has been undertaken in order to explore the relationships between RD, genes and druggable targets.

5.5.3 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**".
The IRDiRC was launched in April 2011 to foster international collaborations in rare disease research. IRDiRC teams up 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. In addition, Orphanet

data is at the disposal of the IRDiRC working groups and their sicentific 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, numbe rof 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.

5.5.4   PARTNERSHIP WITH EUROPEAN CLINICAL RESEARCH INFRASTRUCTURE NETWORK

Since 2012, Orphanet is involved in **European Clinical Research Infrastructure Network Integrated Activities (ECRIN-IA)** as the leader of the work package on Rare Diseases. ECRIN (European Clinical research Infrastructure Network) is a network dedicated to fostering clinical research and to help organise multinational clinical trials mainly directed towards academics.

5.5.5   PARTNERSHIP WITH RARECARENET

Since mid-2013, Orphanet has a partnership with **RareCareNet**, providing them with information on expert centres and rare cancer patient organisations. RareCareNet provides Orphanet with information on the epidemiology of rare cancers, and a common effort is currently performed in order to agree on the classification for rare cancers.

5.5.6   COLLABORATION WITH IHTSDO

Collaboration with the International **Health Terminology Standards Development Organisation** (IHT-SDO) is ongoing in order to include RD lacking in SNOMED-CT, and to provide alignments between Orphacodes and SNOMED-CT terms. It will help identification of patients with RD in health information systems in countries having adopted SNOMED-CT.

5.5.7   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 and cross-referencing are 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).

6   Funding

Orphanet's budget was approximately 3,2 M Euros in 2014, originating from 6 different contracts for the core activity funding and from various other contracts in some of the participating countries.
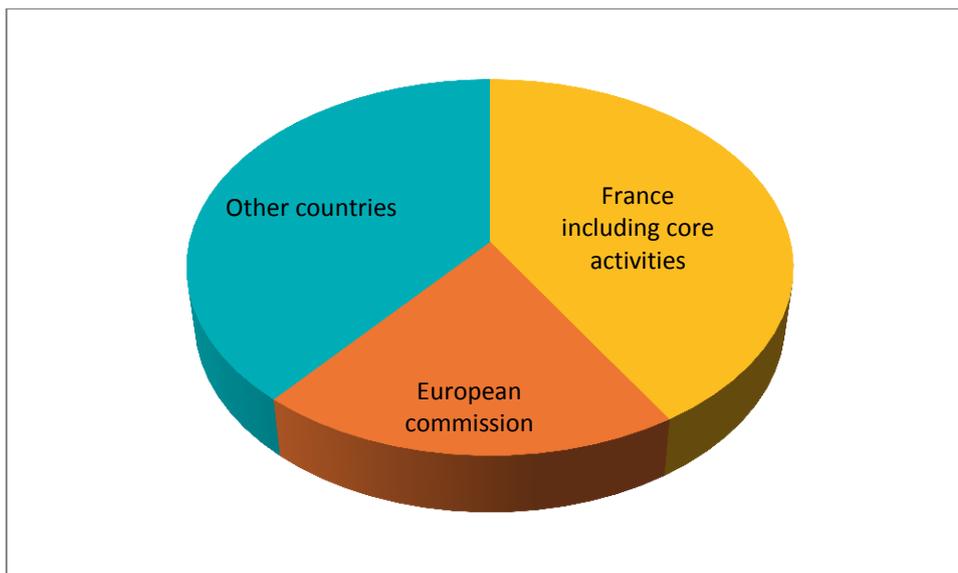
Fig. 23 Orphanet's global budget 2014

6.3 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 resources in the participating countries.
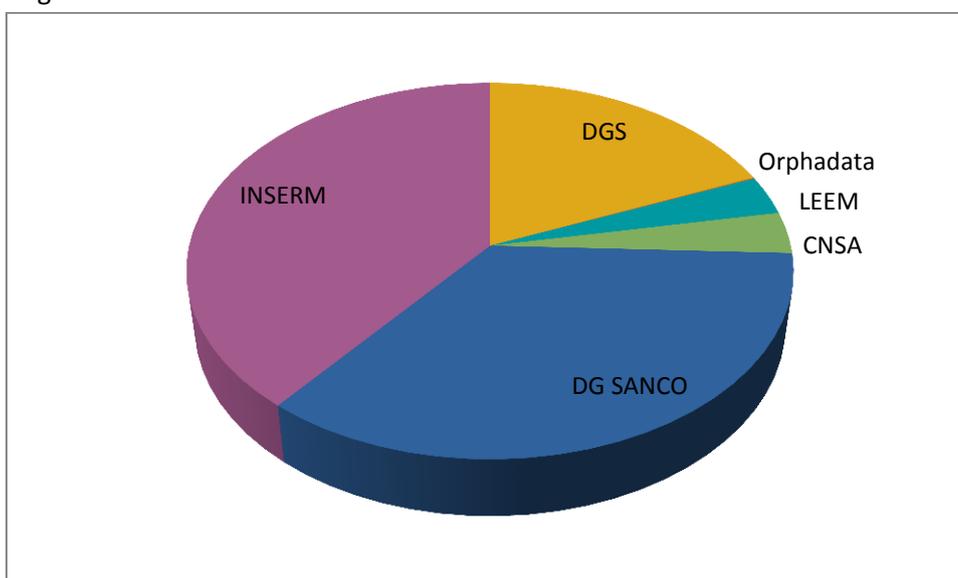

Fig. 24 Orphanet core activities funding 2014

This budget (approx 1.5M Euros) excludes the costs of infrastructure (office space) which are essentially supported by INSERM.

In the last 10 years, the funding of Orphanet's core activities has quadrupled reflecting the growth of the project. It is translated by the increase in manpower needed to provide and validate the growing amount of data.

6.3.1 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).

In 2014 Orphanet coordinating team was funded by the DG Sanco grant 20133305 (Operating Grant Orphanet). The DG Sanco grant 20102206 (Orphanet Europe Joint Action) was extended one year without additional funding.

6.3.2 OTHER CURRENT FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY FUNDING

Inserm	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 licencing its data and in providing advice concerning intellectual property.
République Française	The French Directorate General for Health finances Orphanet's core activities (DGS).
European Commission	The European Commission finances the database of diseases, the encyclopaedia in English, coordination, communication and IT of the project through the EU Health Programme.
CNSA	The "Caisse nationale de solidarité pour l'autonomie" supports the indexing of rare diseases with the International Classification of Functioning, Disability and Health (ICF) and the Orphanet encyclopaedia of disabilities.
AFM	The "Association Française contre les Myopathies" finances OrphaNews France and OrphaNews Europe, as well as data collection on clinical trials.
leem Fondation	The "Fondation des Entreprises du Médicament" finances the collection of data on orphan drugs and clinical trials.
gsk GlaxoSmithKline	Glaxo Smith Kline finances the extension of the database's disease annotation and free access to this data.

6.3.3 CURRENT NON FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY FUNDING

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), and OMIM has added Orphanet to the list of external links provided on its website.
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 has been updated with links to Orphanet's gene pages.
EuroGentest	EuroGentest financed the creation of a thesaurus of clinical signs to harmonise international phenotype nomenclatures.EuroGenetest 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).

6.4 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

6.4.1 PARTNERSHIPS PROVIDING FUNDING FOR NATIONAL ACTIVITIES

Institutional partners host Orphanet national team activities and contribute to the project by allocating a budget and the time of some of their professionals. For European countries, this kind of partner is defined as an "associated partner". Other partners such as Switzerland and Canada also allocate a budget and the time of some professionals. Globally this budgets reaches 1,35 M Euros. Please refer to Figure 29 for an overview of funding of national activities.
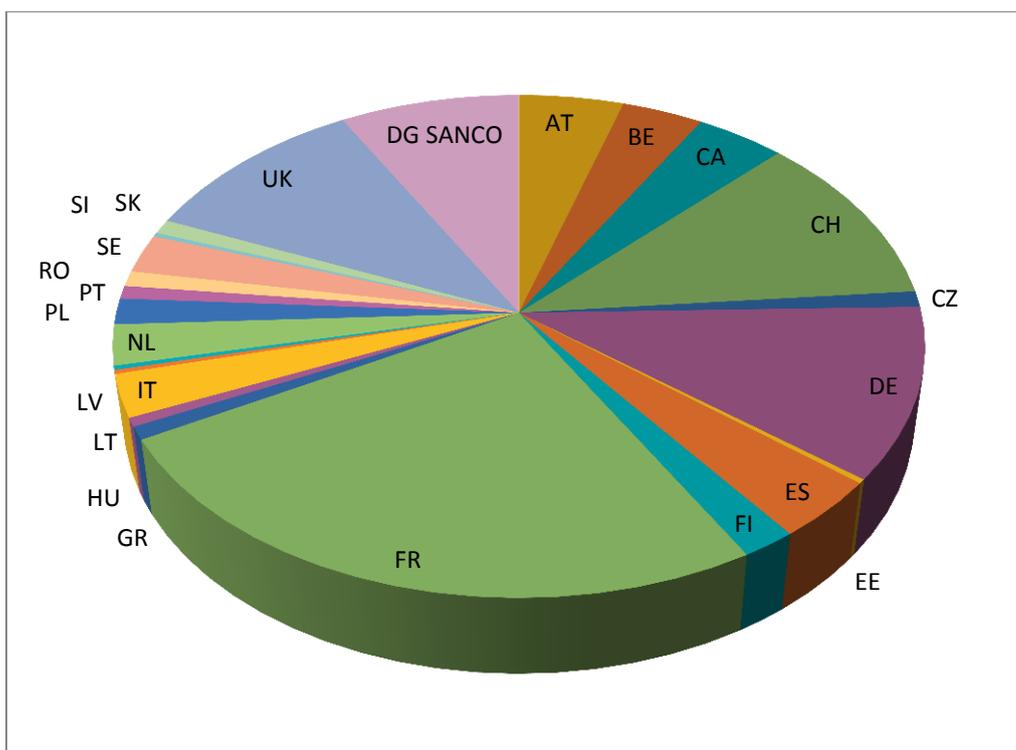
Fig. 25 Funding sources for national activities in 2014

AUSTRIA	
Gesundheit Österreich GmbH	The "Gesundheit Österreich GmbH" (GÖG) is an associated partner in the Orphanet Europe Joint Action as of April 2011.

MEDIZINISCHE UNIVERSITÄT WIEN	The Medical University of Vienna is an associated partner in the Orphanet Europe Joint Action as of April 2011 and hosts Orphanet Austria since 2005. It further provides part-time funding (in kind) for the work of the country coordinator.
BUNDESMINISTERIUM FÜR GESUNDHEIT	The Austrian Ministry of Health provides funding to the Orphanet Europe Joint Action as of April 2011.

BELGIUM

federal public service HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT	The Federal Public Service Health, Food Chain Safety and Environment is an associated partner in the Orphanet Europe Joint Action as of April 2011.
ISP WIV WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE	The "Wetenschappelijk Instituut Volksgezondheid – Institut Scientifique de Santé Publique" is an associated partner in the Orphanet Europe Joint Action as of April 2011.

CANADA

CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada	Canadian institute of Health Research is the host institution of Orphanet Canada, finances a position for the project manager 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.

CYPRUS

	The Department of Medical and Public Health Services is an associated partner in the Orphanet Europe Joint Action as of April 2011.

CZECH REPUBLIC

CHARLES UNIVERSITY	The Charles University Prague - 2nd School of Medicine is an associated partner in the Orphanet Europe Joint Action as of April 2011.
česká asociace pro vzácná onemocnění	Czech Association of rare diseases finances the activity of the Czech team since April 2012.

ESTONIA

	The University of Tartu is an associated partner in the Orphanet Europe Joint Action as of April 2011.
FINLAND	
	Rinnekoti Foundation is an associated partner in the Orphanet Europe Joint Action as of January 2013.
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 development of the French encyclopaedia for the general public with information on the functional consequences of rare diseases, as well as the production of fact sheets on rare disabilities not necessarily related to rare diseases.
	The INVS, Institut de Veille Sanitaire, supports Orphanet.
GERMANY	
	The Federal Ministry of Health Germany provides funding to the Orphanet Europe Joint Action as of April 2011.
	The Medical School of Hanover (MHH) supports data collection, and is an associated partner in the Orphanet Europe Joint Action as of April 2011.
GREECE	
	The Institute of Child Health, Athens is an associated partner in the Orphanet Europe Joint Action as of April 2011.
HUNGARY	
	The National Institute for Health Development ("*Országos Egészségfejlesztési Intézet*") is an associated partner in the Orphanet Europe Joint Action as of August 2012.
ITALY	

|	
	The Italian Health Ministry finances Orphanet-Italy activities through current research funding.
	The Bambino Gesù Children's Hospital is an associated partner in the Orphanet Europe Joint Action as of April 2011.
	Genzyme Italia finances OrphaNews Italia.
LATVIA	
	"Centre for Disease Prevention and Control of Latvia" (Slimību profilakses un kontroles centrs) is an associated partner in the Orphanet Europe Joint Action as of April 2012.
LITHUANIA	
	The Vilnius University Hospital, "Santariškių Klinikos" Centre for Medical Genetics is an associated partner in the Orphanet Europe Joint Action as of April 2011.
NETHERLANDS	
	The "Leids Universitair Medisch Centrum" is an associated partner in the Orphanet Europe Joint Action as of April 2011. It hosts Orphanet Netherlands and co-funds the work of prof. dr. 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 the country coordinator, prof. dr. Van Ommen, and the chair of the Dutch Scientific Advisory Board, prof. dr. Cornel. From April 2011 on the CMSB also funds the work of the project manager.
POLAND	
	The "Instytut Pomnik Centrum Zdrowia Dziecka" (Children's Memorial Health Institute) is an associated partner in the Orphanet Europe Joint Action as of April 2011. 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 encyclopedia in Polish and contributes to translation of the Orphanet international website
PORTUGAL	
	IBMC - Institute for Molecular and Cell Biology is the host institution of Orphanet-Portugal since 2009 and is a partner in the Orphanet Europe Joint Action as of April 2011; it partly funds the national activities, namely the full salary of the project coordinator.

	ICBAS - Instituto de Ciências Biomédicas Abel Salazar, the Biomedical Sciences Institute at the University of Porto, is an Orphanet partner since 2009; it is responsible for the full salary of the national coordinator, a full-time Professor at that institution.
	DGS - The Directorate-General of Health, at the Portuguese Ministry of Health, officially supports Orphanet-Portugal, and provided a specific grant for 2012, including part of the salary of the information scientist, as well as dissemination materials and activities, among others.
	The pharmaceutical company Pfizer supports financially the Orphanet-Portugal, through some planned activities.
	The pharmaceutical company Biomarin supports financially the Orphanet-Portugal, through some planned activities.
ROMANIA	
	The "Universitatea de Medicina si Farmacie "Gr.T.Popa" Iasi" is an associated partner in the Orphanet Europe Joint Action as of April 2011.
SLOVAKIA	
	The Children's University Hospital in Bratislava is an associated partner in the Orphanet Europe Joint Action as of April 2011.
SLOVENIA	
	The University Medical Centre Ljubljana is an associated partner in the Orphanet Europe Joint Action as of April 2011.
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 an associated partner in the Orphanet Europe Joint Action as of April 2011. CIBER (Institute of Health Carlos III, Ministry of Economy and Competitiveness) finances the main activities of the Spanish team.
SWEDEN	
	The "Karolinska Institutet" is an associated partner in the Orphanet Europe Joint Action as of April 2011.
	Karolinska University Hospital of Stockholm supports the Orphanet Sweden activities.
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. The support finances the position of the coordinator (part-time), two information scientists (1 full-time from April 2011 and 1 part-time) and a webmaster from the Health On The Net Foundation (HON).

TURKEY	
	The Association of Research-Based Pharmaceutical Companies gives non-restricted support for the Turkish translation of the Orphanet webpage and the document including over 10,000 rare genetic diseases together with their detailed description. They supported the creation of the Orphanet-Turkey website and help Orphanet Turkey to prepare and print leaflets representing Orphanet, Orphanet-Turkey and their activities 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
	The University of Manchester has been an associated partner in the Orphanet Europe Joint Action from April 2011 until August 2014.
	Nowgen in Manchester has hosted Orphanet-UK's activities and contributes to the project by allocating the time of some professionals until August 2014

6.4.2 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. For European countries, this kind of partner is defined as a "collaborating partner", for other countries it is referred as other partnerships (as indicated in detail in fig.1).

ARMENIA	
	The Center of Medical Genetics and Primary Health Care hosts Orphanet-Armenia's activities and contributes to the project by allocating the time of some professionals.

AUSTRALIA	
	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.
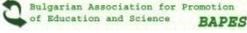
BULGARIA	
	The Bulgarian Association for Promotion of Education and Science (BAPES), hosts Orphanet Bulgaria's activities and contributes to the project by allocating the time of some professionals.
CROATIA	
	The Zagreb University hosts Orphanet Croatia's activities and contributes to the project by allocating the time of some professionals.
IRELAND	
	The Our Lady's Children's Hospital, Crumlin hosts Orphanet Ireland's activities and contributes to the project by allocating the time of some professionals.
	Nowgen in Manchester, UK hosted Orphanet Ireland's activities and has contributed to the project by allocating the time of some professionals until Augsut 2014..
ISRAEL	
	The Meir Medical Center of Israel hosts Orphanet Israel's activities and contributes to the project by allocating the time of some professionals since June 2013.
LEBANON	
	The Saint Joseph University hosts Orphanet Lebanon's activities and contributes to the project by allocating the time of some professionals.
LUXEMBOURG	
	The Ministry of Health of Luxembourg hosts OrphanetLuxembourg's activities and contributes to the project by allocating the time of some professionals.
MOROCCO	
	The National Institute of Hygiene hosts Orphanet Morocco's activities and contributes to the project by allocating the time of some professionals.
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.
	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.
SERBIA	

	The Institute of Molecular Genetics and Genetic Engineering , University of Belgrade, hosts Orphanet Serbia's activities and contributes to the project by allocating the time of some professionals.
TURKEY	
	The Istanbul University hosts Orphanet Turkey's activities and contributes to the project by allocating the time of some professionals.

6.4.3 NON-FINANCIAL PARTNERSHIPS

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, are 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 ASM-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 diseases patients in Bulgaria, as well as to list the Bulgarian patient associations on the Orphanet database.

CZECH REPUBLIC	
	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 counselling 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 Czech National Plan is developed under the auspices of the Ministry of Health - Department of Medical Services.
	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 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 patients and professionals with a quota of airline tickets for patients to travel to medical experts or experts to patients with rare diseases. Orphanet provides expertise on the merits of applications.
	Orphanet has delegated to "Maladies Rares Info Services", the French helpline for information on rare diseases - 0810 69 19 20, the role of replying to unsolicited electronic messages received by Orphanet.

GERMANY	
	The Federal Ministry of Health Germany officially supports Orphanet.
	The "Allianz Chronischer Seltener Erkrankungen e.V." (ACHSE) works together with Orphanet Germany on informational 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.
GREECE	
	The Ministry of Health and Social Solidarity of the Hellenic Republic officially supports Orphanet.
HUNGARY	
	The State Secretary of Health within the Ministry of Human Resources officially supports Orphanet.
ISRAEL	
	The Israeli Ministry of Health officially supports Orphanet.
ITALY	
	The "Istituto Superiore di Sanità" officially supports Orphanet.
	Telethon collaborates with Orphanet for the collection of data concerning research projects.

	Uniamo, the Italian Federation of support groups on rare diseases, collaborates with Orphanet in the organization and promotion of events dedicated to rare diseases, in order to increase public awareness on this particular issue.
	AIFA collaborates with Orphanet for the collection of data concerning clinical trials.
	Netgene collaborates with Orphanet for the diffusion of information on rare diseases.
	Farmindustria promotes Orphanet publications.
	Osservatorio Malattie Rare (O.Ma.R.) collaborates with Orphanet for the diffusion of information on rare diseases and the promotion of events
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.
	The Erfocentrum provides information to the general public on genetic, mainly rare, disorders. Collaboration has been established to increase the number of Dutch texts available on Orphanet.
	The VSOP (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties) provides information regarding patient organisations dedicated to rare disease and participates in the validation of information on Dutch expert centres.
	The Dutch Federation of University Medical Centres and Orphanet NL collaborate in establishing a comprehensive list of Dutch expert centres.
POLAND	

	The patient organisation, Ars Vivendi, provides patients and parents with information about Orphanet services and cooperates with Orphanet Poland.
PORTUGAL	
	INFARMED - the National Authority for Medicines and Health Products, collaborates with a regularly updated list of orphan drugs approved and available in Portugal, as well as its quantities used.
	ACSS - the Central Administration of Health System acknowledges that Orphanet-Portugal is the reference source of information on rare diseases and orphan drugs in Portugal.
	CES - the Social Studies Center, at the School of Economics at the University of Coimbra, has been collaborating in the update and validation of the list of *bona fide* patient associations in the country
	NEDR - the Nucleus for Study of Rare Diseases of the Portuguese Society of Internal Medicine collaborates in the update and validation of activities about rare diseases ongoing in Portugal.
	Aliança - the Portuguese Alliance of Rare Diseases Organizations has been collaborating in several joint activities with Orphanet-PT, including the update and validation of Patient Associations and the joint organisation of the Rare Diseases Day each year.
	FCT - The "Fundação para a Ciência e a Tecnologia" collaborates by updating information on research projects and clinical trials taking place in the field of rare diseases and/or orphan drugs ongoing in Portugal. The Orpha number is requested in every project in the life sciences dealing with rare diseases.
	SPGH - The Portuguese Society of Human Genetics collaborates by updating information on professionals, genetic counselling clinics, medical labs and diagnostic tests available in the country.
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 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.
	Orphanet Slovenia collaborates with the Institute of Genomic Research and Education IGRE with the aim of disseminating information about the Orphanet project and web services on the national level.
SPAIN	
	The Spanish Ministry of Health, Social Services and Equality - Office for Health Planning and Quality is an associated partner in the Orphanet Europe Joint Action as of April 2011.
	The Príncipe Felipe Research Center hosts Orphanet Spain's activities.
SWEDEN	
	The Ministry of Health and Social Affairs of Sweden officially supports Orphanet.
SWITZERLAND	
	The Health On the Net Foundation supports the technical aspect of the project by developing online forms to collect data. In addition, it hosts the website www.orphanet.ch and helps to update the homepage.
	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.
	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 develop, in collaboration with the Federal Office of Public Health, a national strategy for rare diseases.
TURKEY	

	The Turkish Ministry of Health officially supports Orphanet. It collaborates with Orphanet Turkey for data collection and the dissemination of Orphanet in Turkey.
UNITED KINGDOM	
	The Department of Health officially supports Orphanet.
	Ataxia UK and Orphanet cooperate in the exchange of information, in the validation and online publication of research projects regarding Ataxia and in the endorsement and boosting of Orphanet and Ataxia UK activities.
	Dyscerne and Orphanet cooperate in endorsing and boosting Dyscerne and Orphanet activities, raising standards in the diagnosis and management of rare dysmorphic conditions, improving dissemination of information on these conditions, developing and sharing information and educational tools for healthcare professionals.
	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 regarding patient organisations in the UK.
	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 patient organisations in the UK.
	ERNDIM is a post-validator of information on Orphanet UK regarding medical laboratories performing biochemical diagnosis of rare diseases.

7 Communication

7.3 Communication documents

In 2014, 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)

- Orphacodes (English)
- Orphanet database structure and main products (English)
- Orphanet rare disease ontology

An A5 leaflet about Orphanet - Italy was also printed in February 2014.

7.4 Invitations to give lectures at conferences in 2014

Orphanet representatives, as specialists in the field of rare diseases, were invited to give lectures and to participate in more than 50 conferences worldwide. These lectures focused on presenting the Orphanet database (37), public health policies (5), RD research (4), orphan drugs (1), and medical and genetic approaches (10 presentations).

7.5 Booths at conferences in 2014

Orphanet booths were held in 7 different congresses in 2014 as indicated in the lsit below:
- 25th Annual Meeting of the German Society of Human Genetics in Cooperation with the Austrian Society of Human Genetics and the Swiss Society of Medical Genetics", Essen, Germany, 19-21th March
- 2nd Spring Meeting with Patient Organisations, in collaboration with Telethon Foundation, Bambino Gesù Children's Hospital, April 5, 2014, Rome
- European Conference Of Human Genetics 2014 31 May-3 June, Milan, Italy
- American Society of Human Genetics, San Diego, USA, 18-21 October 2014
- e-Health Forum 2014, Athens, 12-14 May
- Postgraduate Research Student Showcase, Manchester, 2 July 2014
- CCMG Annual Meeting, November 6th-8th, Vancouver

8 The Orphanet team as of December 2014

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