

## CEMARA an information system for rare diseases

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### Abstract

Rare diseases cover a group of conditions characterized by a low prevalence, affecting less than 1 in 2,000 people; 5000 to 7000 rare diseases have been currently identified in Europe. Most diseases do not have any curative treatment. They represent thus an important public health concern. CEMARA is based on a n-tier architecture. Its main objective is to collect continuous and complete records of patients with rare diseases, and their follow-up through a web-based Information System, and to analyse the epidemiological patterns. In France, 41 out of 131 labelled Reference Centres (RC) are sharing CEMARA. Presently 56,593 cases have been registered by more than 850 health care professionals belonging to 171 clinical sites. The national demand of care was explored in relation with the offer of care in order to reach an improved match. Within 2 years, CEMARA stimulated sharing a common platform, a common ontology with Orphanet and initiating new cohorts of rare diseases for improving patient care and research.

**Keywords:** Rare diseases, information system, ontology, public health, Thesaurus.

### Introduction

Rare diseases cover a group of conditions characterized by a low prevalence, affecting less than 1 in 2,000 people. According to this criterion, 5000 to 7000 rare diseases have been currently identified. Three to 4% of children and 6% of the population in Europe are affected. Rare diseases are often chronic, progressive, degenerative, life-threatening and disabling. It is thus a true public health concern since most diseases do not have any curative treatment. In France, the Ministry of Health has initiated in 2004 a National Rare Diseases Plan; 131 Reference Centres (RCs) were then labelled for a given disease or group of diseases. Among their missions, the RCs lead the management networks and are involved in the epidemiological monitoring of pathologies they are in charge of, in order to

better assess the distribution of rare conditions on the territory, as well as their social, educational and familial repercussions. To support RCs networking, an information system named CEMARA (CENTRES MALADIES RARES), was developed. The main objective of CEMARA is to contribute to the missions of the RCs regarding the registration and description of their activities, collecting continuous and complete records of all patients presenting with a rare disease in France and their follow-up, coordinating the network of correspondents, and analyzing the epidemiological patterns.

### Material and Methods

#### Professional network

Thirty three centres are presently active members of the CEMARA network in France (Figure 1) and 16 additional centres joined CEMARA in 2009. Each centre is composed of one or more clinical units, managed by a coordinator. The RCs have been described elsewhere [1].

#### Ontology for rare diseases: Orphanet classification

Orphanet<sup>1</sup> [2] is member of the European Rare Disease Task Force<sup>2</sup> and in charge of the topical advisory group for rare diseases for the World Health Organization. Orphanet database provides an ontological support to experts for each field of CEMARA. Thus, specific thesauri were designed. The specificity of our collaboration provided a shared ontology for each thesaurus of CEMARA. A grammatical and lexical uniqueness for labelling each disease includes the management of synonyms and eponyms. The associated nosography helps health professionals to share common terms.

Regarding gene mutations we use GENATLAS<sup>3</sup>, which contains relevant information with respect to gene mapping and

<sup>1</sup> Orphanet : <http://www.orpha.net>

<sup>2</sup> Rare Disease Task Force : <http://www.rdtf.org/>

<sup>3</sup> GENATLAS <http://www.dsi.univ-paris5.fr/genatlas/>

genetic diseases. A specific link was also developed with this database. OMIM codes are also provided.

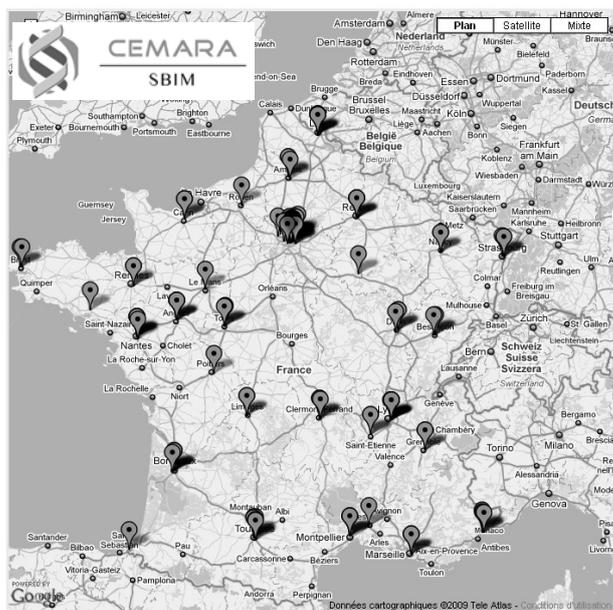


Figure 1: CEMARA network of the first 33 centres for rare diseases

## Information System (IS): Design and Implementation

The IS of CEMARA has been described elsewhere [1]. Briefly, it collates in a standardized representation a minimal patient record. CEMARA IS has been based on a n-tier architecture. At the client side, CEMARA relies on existing local Internet networking facilities and on a widely spread computer configuration in medical settings. Via a web browser, the client tier connects to the middle tier, which is connected to several databases: the production database, the geographical dictionary database, and the thesaurus database. The data warehouse and the geographical information system are not yet connected [3]. Their framework is close to an already available application for end-stage renal disease [4]. The middle tier supports client services through Web containers and business logic services through component containers. Business logic components in the middle ware support transactions toward the databases.

CEMARA fulfils several requirements: scalability, portability, reliability, accessibility and cost effectiveness oriented toward non-proprietary software [1].

Maintenance and evolutions are made centrally, which reduce deployment costs and delays. The structure of the production database was built according to a “beehive-like” structure.

The implementation began as of May 2007, initiated by fifteen centres. Coordinators were trained and on-site trainings were also provided for the rare diseases professionals. A technical assistance was also available.

### Data entry sheets

All centres share a common core data set. It comprises identification data for the index case and family members,

diagnosis, context and medical activity. According to the European Directives and French protection Act, permission was obtained from the “Commission Nationale de l’Informatique et des Libertés”<sup>4</sup> to identify patients on the basis of: name, surname, birth date, date of death, place of birth and municipality of residence. The respect of privacy, confidentiality and security [5] was ensured. An identification module warrants identity doubles using a double-entry prevention function [6].

Figure 2: CEMARA data entry sheet: patient identification.

Medical activities and mode of recruitment are recorded. Optional information is related to antenatal or neonatal data. Diagnosis is recorded using Orphanet classification cited above, as well as the circumstances of the diagnosis. A description of chromosomal abnormalities is also possible. Additional keywords are available for describing atypical signs and symptoms, or for patients presenting with a still unknown diagnosis. Several diagnoses may be provided for a given patient, if need be. Complementary information for specific diseases are described in the so called “petals”, attached to the core data set, and focused on specific data collection. Petals are dedicated to follow-up specific diseases such as ichthyosis, nephronoptosis, nephrotic syndromes, cystinosis, juvenile chronic arthritis, rhombencephalosynapsis, rare congenital deafness, Turner syndrome, or neonatal diabetes.

## Results

### Demand of care

As of September 23<sup>rd</sup> 2009, the data set included 56.593 records comprising 29,241 male patients (1,605 foetuses) and 25,900 females (1,431 foetuses). Gender was indeterminate in 1452 foetuses. Median age of patients born alive was 9.2 years, (range: from birth to 87 years). Patients were mainly enrolled via outpatient clinics (39,402) or hospital wards

<sup>4</sup> CNIL : <http://www.cnil.fr/english/the-cnil/>

(3,460). They were predominantly referred to CRs by paediatricians (20,646) and medical specialists (13,084). For foetuses, their mothers were mainly referred by gynaecologists (3,074) and by centres for prenatal diagnosis (1,012). Foetal cases were described during pregnancy (3,162), or after spontaneous miscarriage or termination of pregnancy (1,619). Figure 3 shows the heterogeneous distribution of patients with rare diseases according to departments per 10<sup>5</sup> inhabitants; in mean, 86 patients / 10<sup>5</sup>.

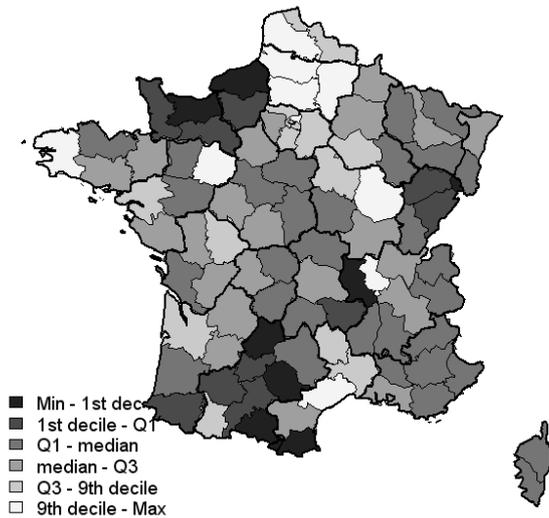


Figure 3- Distribution of patients with rare diseases according to French departments per 100,000 inhabitants

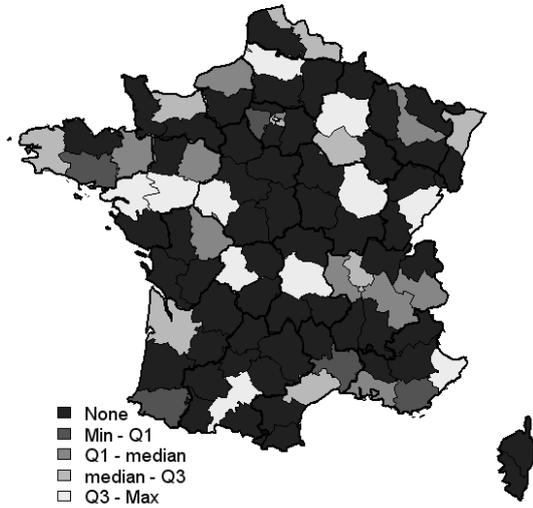


Figure 4- Distribution of CEMARA clinical sites in the French departments, according to departments' population

Table 1 and table 2 summarize the 10 most frequent diagnoses for the 4 centres of rare renal diseases (5,789 patients) and the 8 centres of rare developmental defects during embryogenesis (3,938 foetuses and 28,636 patients), respectively. They cover a broad spectrum of developmental anomalies<sup>5</sup>.

### Offer of care

Close to 850 members are presently registered in 171 clinical units of the 33 active registered RCs. All gave their consent and signed the confidentiality charter of the network. Figure 4 represents the distribution of CEMARA RCs offer of care. The offer of care is present in 35 departments out of 95. A median of 2 clinical units by region cater for patients except in Paris where there are 50 clinical units.

Table 1 – Ten most currently registered diagnoses by the 4 centres for rare renal diseases (879 unknown diagnoses).

Diagnoses (n)
Nephrotic syndrome, steroid-sensitive (534)
Polycystic kidney disease, autosomal dominant (306)
Posterior urethral valve (285)
Renal agenesis, unilateral (244)
Renal dysplasia, multicystic, unilateral (228)
Renal hypoplasia, bilateral (208)
Berger disease (172)
Renal dysplasia (152)
Hydronephrosis congenital (138)
Henoch-Schoenlein purpura (135)

Table 2 – Ten most currently registered diagnoses by the 8 centres for rare developmental defect during embryogenesis (1,552 “unknown diagnoses” for foetuses and 6,582 for patients).

Diagnoses (n)	
For foetuses	
Trisomy 21 (153)	
Spina bifida (84)	
Trisomy 18 (80)	
Anencephaly (44)	
Turner syndrome (42)	
Osteogenesis imperfecta (40)	
Holoprosencephaly (36)	
Isolated corpus callosum agenesis (36)	
Trisomy 13 (35)	
Cleft lip with or without cleft palate (30)	
For patients	
Neurofibromatosis type 1 (575)	
Marfan syndrome (509)	
Trisomy 21 (444)	
Noonan syndrome (416)	
Osteogenesis imperfecta (373)	
Intellectual deficiency with developmental anomaly, rare (336)	
Fragile X syndrome (307)	
Steinert myotonic dystrophy (203)	
Beckwith-Wiedemann syndrome (200)	
Cleft lip with or without cleft palate (200)	

<sup>5</sup> <http://www.feclad.org/anomalies.html>

Institutional collaborations were developed with the Ministry of Health, the National Institute for Health Surveillance for epidemiological survey, with the French National Authority for Health<sup>6</sup> and the National Health Insurance Fund concerning the design of national protocols for diagnoses, treatment and follow-up, as well as for cost analyses, with associations of patients, university hospitals, for the coordination and networking of clinical correspondents.

## Discussion

As of June 9, 2009, a recommendation of the European Council called for concerted action at EU and national levels in order to:

- Ensure that rare diseases are adequately coded and classified
- Enhance research in the field of rare diseases;
- Identify Centres of Expertise by the end of 2013 and foster their participation into European Reference Networks;
- Support the pooling of expertise at European level;
- Share assessments on the clinical added value of orphan drugs
- Foster patient empowerment by involving patients and their representatives at all stages of the decision-making process;
- Ensure the sustainability of infrastructures developed for rare diseases.

This recommendation was welcome since many patients with rare disease continue to advocate their need to overcome common obstacles.

An important challenge is thus to collect pertinent information on rare diseases in order to better assess the demand of care and adapt the offer of care.

### CEMARA: networking rare disease reference centres

In this perspective, we have built a secured web-based network of professionals. CEMARA offers a secured information system via Internet for rare diseases. The platform is shared by 33 rare diseases centres in France, and recently 16 added centres joined the network in 2009. It helped networking 850 health care professionals belonging to 171 clinical sites who recorded 56,593 cases since 2 years. During this period, it stimulated sharing a common platform, a common ontology with Orphanet and initiating new cohorts of rare disease for improving patient care and research.

We developed a simple core data set to enable registering easily all patients presenting with a rare disease. Within 2 years of data collection, 56,593 cases were declared. More recently 16 new centres joined the previous 33 CEMARA centres. A pattern of the demand of care could thus be initiated.

As expected, the number of patients per diagnosis is limited, even for the most prevalent diagnoses (tables 1 and 2). Moreover, for rare developmental defects during embryogenesis, nearly 1 out of 4 records are classified as “unknown diagnosis”. It means that no diagnosis has been reached, which is a common occurrence for patients with multiple malformations, whose syndrome do not fit with currently delineated entities. It

is less frequent for rare renal diseases where 1 out of 6 records remained however with a not yet identified diagnosis.

Other networks for rare diseases have been proposed. For instance, the European Society for ImmunoDeficiencies (ESID<sup>7</sup>) promotes research on causes, mechanisms and treatment of primary immunodeficiencies (PID) [7]. ESID developed an Online Database network for PID. The French National Immunodeficiency Centre, CEREDIH<sup>8</sup>, belongs to this network. RAMEDIS [8] enables reporting cases of rare metabolic diseases. It is a platform independent, web-based information system. Developed in close cooperation with clinical partners, it allows collecting symptoms, laboratory findings, therapy and molecular data. Comparing and analyzing data was made possible by the use of standardized medical terms and conditions. The British Paediatric Orphan Lung Disease<sup>9</sup> (BPOLD) [9] was dedicated to nine rare lung diseases in children in the UK. This registry is oriented toward describing epidemiological data, prevalence and incidence of these rare lung diseases. It also informs on research projects in order to improve treatment strategies.

The Tumori Rari in Età Pediatrica (TREP) project [10] was launched in 2000. It is an Italian cooperative project focusing on rare pediatric tumors. It is oriented towards improving clinical management, networking professionals and stimulating basic research on very rare solid malignancies in childhood (annual incidence < 2/million). Though an electronic web-based data management system is not yet available, in the near future it will support this multidisciplinary experience, a network of professionals sharing a common structured framework including practical management schemes and research project.

### Demand of care for rare diseases: patients' expectations

The demand of care is multiple and complex as illustrated by two recent EurordisCare surveys which investigated patients' experiences and expectations regarding access to diagnosis and to health services [11]. The results of Eurordis Care2 showed that much remains to be done. For instance, 1 patient out of 4 reported a delay of 5 to 30 years to a confirmatory diagnosis of their disease from the time of first symptoms; misdiagnosis was reported in 4 out of 10 cases; 1 out of 4 of patients had to travel to a different region to obtain a diagnosis. Genetic counselling was provided in only 50% of cases which is low since most rare diseases are of genetic origin.

Over the two-year period preceding EurordisCare3, in mean, a patient required more than nine different medical services (from 4 to 12, according to the disease). One patient out of 4 patients reported difficult or even impossible access to services. The greatest barrier in accessing essential medical services was a lack of referral. Three out of 10 respondents required the assistance of a social worker in the 12 months preceding the survey. More than one-third experienced difficulty or even failed to find such assistance. Twenty-nine percent of respondents reported a patient in their family had to reduce or stop professional activity as a result of their disease and an

<sup>7</sup> <http://www.esid.org/>

<sup>8</sup> <http://www.ceredih.fr/>

<sup>9</sup> <http://www.bpold.co.uk/>

<sup>6</sup> [http://www.has-sante.fr/portail/jcms/c\\_5443/english?cid=c\\_5443](http://www.has-sante.fr/portail/jcms/c_5443/english?cid=c_5443)

additional 30% of respondents reported one member in the family had to reduce or stop professional activities to take care of a relative with a rare disease. The majority of patients reported a reluctance of professionals to treat them due to the complexity of their disease.

### Federating Reference centres

These two studies confirmed that a lot remained to be done. The offer of care has to be organized in order to match the demand. CEMARA faced this major goal. It appeared as an efficient platform to gather useful information to aid promoting a better identification of the demand of care, a necessary step to better adapting the offer of care. To date, the offer of care described by CEMARA shows that it covers 1 out of 3 departments for a demand for care which covers the whole French territory. Thus, much remains to be done to allow each patient to benefit an appropriate access to care.

Federating the RCs in France is an important challenge for reinforcing European Reference Networks. The Rare Disease Task Force<sup>10</sup> (RDTF) at the European level contributes to networking professionals through its two main goals:

- advise and assist the European Commission Public Health Directorate in promoting the optimal prevention, diagnosis and treatment of rare diseases in Europe, in recognition of the unique added value to be gained for rare diseases through European co-ordination,
- provide a forum for discussion and exchange of views and experience on all issues related to rare diseases.

The Alliance Maladies Rares<sup>11</sup>, the Association Française contre les Myopathies<sup>12</sup> (AFM) or EURORDIS<sup>13</sup> strongly stimulate a better knowledge for rare diseases and attaining the most appropriate offer of care.

### Conclusion

An information system shared by professionals appeared a valuable support to better matching the offer of care to the demand. In this perspective, CEMARA proposed a secured information system via Internet for rare diseases centres. The platform is now shared by 49 rare diseases centres in France. It helped networking health care professionals. They share a web-based secured beehive-like platform and a common ontology with Orphanet. It also helped initiating new cohorts of rare diseases for improving patient care and research.

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### References

- [1] Messiaen C, Le Mignot L, Rath A, Richard JB, Dufour E, Ben Saïd M, Jais JP, Verloes A, Le Merrer M, Bodemer C, Baujat G, Gerard-Blanluet M, Bourdon-Lanoy E, Salomon R, Ayme S, Landais P. *Stud Health Technol Inform*. 2008;136:51-6.
- [2] CEMARA et Orphanet : une collaboration au service des centres de référence.  
<http://www.orpha.net/actor/Orphanews/2007/070321.html>
- [3] Richard JB, Toubiana L, Le Mignot L, Ben Saïd M, Mugnier C, Le Bihan-Benjamin C, Jais JP, Landais P. A Web-based GIS for health care decision-support. *AMIA Annu Symp Proc*. 2005:365-9.
- [4] Landais P, Simonet A, Guillon D, Jacquelinet C, Ben Saïd M, Mugnier C, Simonet M. SIMS REIN: a multi-source information system for end-stage renal disease. *CR Biol*. 2002; 325:515-28.
- [5] Rindfleish TC. Privacy, Information Technology and Health Care. *Communications of the ACM* August 1997; 40:93-100.
- [6] Le Mignot L, Mugnier C, Saïd MB, Jais JP, Richard JB, Le Bihan-Benjamin C, Taupin P, Landais P. Avoiding doubles in distributed nominative medical databases: optimization of the Needleman and Wunsch algorithm. *Stud Health Technol Inform*. 2005; 116:83-88.
- [7] Guzman D, Veit D, Knerr V, Kindle G, Gathmann B, Eades-Perner AM, Grimbacher B. The ESID Online Database network. *Bioinformatics*. 2007 ;23:654-5.
- [8] Töpel T, Hofestädt R, Scheible D, Trefz F. RAMEDIS: the rare metabolic diseases database. *Appl Bioinformatics*. 2006 ;5:115-8.
- [9] Laverty A, Jaffé A, Cunningham S. Establishment of a web-based registry for rare (orphan) pediatric lung diseases in the United Kingdom: the BPOLD registry. *Pediatr Pulmonol*. 2008 ;43:451-6.
- [10] Pastore G, De Salvo GL, Bisogno G, Dama E, Inserra A, Cecchetto G, Ferrari A; TREP Group; CSD of Epidemiology Biostatistics, AIEOP. Evaluating access to pediatric cancer care centers of children and adolescents with rare tumors in Italy: the TREP project. *Pediatr Blood Cancer*. 2009 ;53 :152-5.
- [11] The Voice of 12,000 Patients, <http://eurordiscarebook.eurordis.org/>

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<sup>10</sup> <http://www.rdtf.org/testor/cgi-bin/OTmain.php>

<sup>11</sup> <http://www.alliance-maladies-rares.org/>

<sup>12</sup> [http://www.afm-france.org/ewb\\_pages/1/la\\_une.php](http://www.afm-france.org/ewb_pages/1/la_une.php)

<sup>13</sup> [http://www.eurordis.org/secteur.php3?id\\_rubrique=1](http://www.eurordis.org/secteur.php3?id_rubrique=1)