
REPORT
ON RARE DISEASE RESEARCH,
ITS DETERMINANTS IN EUROPE
AND THE WAY FORWARD

May 2011



HEALTH-F2-2008-201230



SEVENTH FRAMEWORK
PROGRAMME

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More information on the RDPlatform project can be found at www.rdplatform.org.

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INTRODUCTION

This report was prepared in the context of the RareDiseasePlatform project¹ (RDPlatform) which is a three-year support action project of the European Union's Seventh Framework Programme (HEALTH-F2-2008-201230): the project began in May 2008 and ended in April 2011.

RDPlatform was dedicated to developing a platform to help researchers in the field of rare diseases (RD) set up efficient, multidisciplinary teams to tackle RD research challenges. This project was intended to offer the opportunity for potential multinational teams to exchange ideas and strategies in order to structure future research proposals in the 27 EU member states.

RDPlatform produced an inventory of publicly funded research projects in the field of RD and orphan drugs, accessible through the research tab of the Orphanet website². Data were collected in thirteen countries. So far, the database contains 4 212 ongoing research projects for about 2 131 different RDs. In addition 1 459 clinical trials are ongoing at country level, in 27 countries for 409 diseases (corresponding to 1 236 unique trials). Disease and product registries have also been identified. So far, 514 registries have been listed³. The research networks funded by the European Commission (EC) have also been registered⁴.

One of the objectives of RDPlatform was to organise two workshops with top experts to analyse areas in need of collaborative research projects, based on an analysis of the current situation, thanks to the data collected. The first workshop took place in Paris, on 3 December 2009, the second on 20 January 2011. These two workshops were intended to establish the outlines of a position paper to be submitted to the European Commission by April 2011.

A first 2009 report analysed the data collected by Orphanet⁵. This report is more comprehensive as it includes, in addition to the analysis of the data collected by Orphanet, an analysis of the literature in the field of research and R&D.

The goal of this report is to highlight the state of the art of R&D in Europe in the field of RD, the initiatives and incentives that have already been foreseen, the policy decisions that have supported these evolutions, the lessons learnt from European policy and experience in regards to the rest of the world, and to propose areas for action in the future. The report does not address the issue of rare infectious diseases, which are neglected diseases more than rare diseases at a worldwide level. It was felt that this was a separate issue.

This report was drafted by the coordinating team of the RDPlatform project, sent for review to a large group of experts and finally discussed during a workshop which took place in Paris on the 20 January 2011. The consulted experts were those who are or were principal investigator of EC funded projects in the field, or principal investigators of European projects funded by E-Rare. In addition, a sub-set of these experts was invited to attend the workshop for more in-depth discussion, on a voluntary basis.

1. RARE DISEASES AS AN ISSUE IN RESEARCH

1.1. Definition of rare diseases

Rare diseases (RDs) are diseases of such low prevalence (less than 5 people affected per 10 000 in the European Union, as defined by the European Orphan Drug regulation) that special combined efforts are needed to address them so as to prevent significant morbidity and premature mortality. Most RDs are lifethreatening or chronically debilitating diseases which result in a considerable reduction in an individual's quality of life or socio-economic potential.

According to the Orphanet inventory of RDs, there are between 6 000 and 8 000 distinct rare diseases identified today, depending on the definition applied to define what a disease entity is. The true prevalence of RDs is unknown as there is no source of data at the population level. Prevalence data quoted in articles and policy documents have no documented sources.

When considering the published data by disease as listed by the Orphanet Report series “Prevalence of RDs”⁶, the distribution of RD prevalence tends towards very low numbers. Of the 6 000 RDs listed in Orphanet, only 105 have a prevalence ranging from 5 to 1 in 10 000, and 233 have a prevalence ranging between 1 in 10 000 and 1 in 100 000. Another 1 000 RDs probably have a prevalence of around 1 per million, all the other ones affecting only a few patients worldwide, usually due to a single mutation segregating in family members (see Figure 1).

This data is extracted from the literature and cannot be considered as well-established since the quality of the methodology applied to assess the prevalence of single RDs is mostly poor, but it is the best information available to date. If accepted, this means that 350 RDs affect 80% of the patients and 1 500 RDs affect 95% of the patients. If these individual prevalence estimates are summed up, the total prevalence is in the range of 2 to 3%. The estimated numbers have to be validated by data from RD patient population registries which have started to be established in some countries.

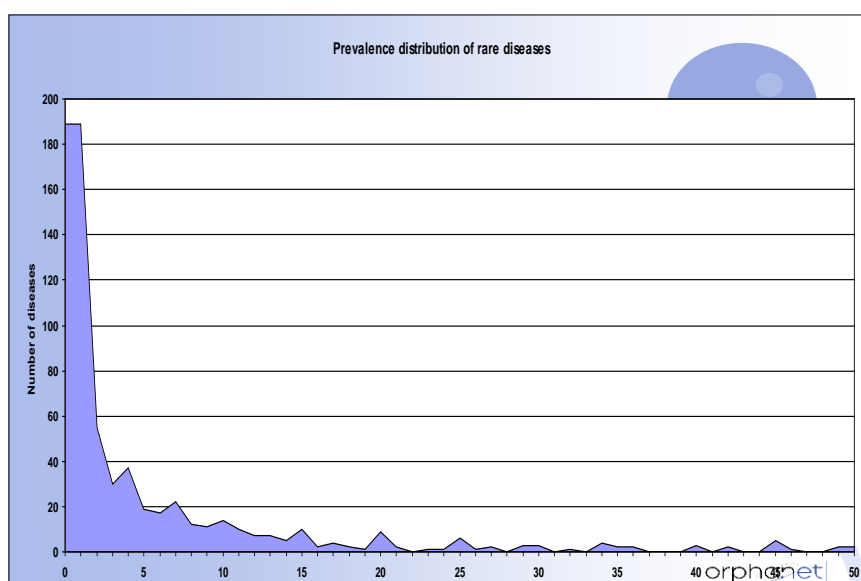


Figure 1: Distribution of prevalence rates of individual RDs (data extracted from Orphanet)
Expressed for 100 000 people, equal to or lower than the threshold for rarity as defined in the EU
(5 per 10 000 in principle, which is 50 per 100 000 here)

The definition of a rare disease as having a prevalence of 5 in 10 000 first appeared in EU legislation in Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products⁷. The Community action programme on rare diseases including genetic diseases for the period 1 January 1999 to 31 December 2003 then applied this definition to the field of public health.

1.2. Specificities of research in the field of RD

There is a strong need for research into RDs since most patients have so far unmet medical needs. It is considered as an area requiring specific initiatives to attract interest from researchers and from Industry. It is also an area where experts are very rare.

1.2.1. Identification of the genetic mechanisms of RDs

The R&D landscape in the field is contrasted. RDs were instrumental in establishing the Human Genome mapping during the 90s, then again in cloning genes, as most RDs are Mendelian disorders. Even today, high-impact journals continue to publish articles on new genes identified by exome sequencing, mostly related to RDs. Therefore, it can be said that RDs are not orphan when it comes to identifying the underlying genetic mechanism, as it is still of high interest for the biomedical research community to dissect genetic mechanisms. This results in an improvement in the testing possibilities for many RDs.

1.2.2. Natural history of RDs

In contrast, the natural history of RDs is very often poorly understood, due to the rarity of patients, which is an obstacle to collecting enough data to conduct a proper study, also due to the high phenotypic heterogeneity of RDs and the lack of scientific interest for this stage in research. It is difficult to use medical records data to conduct clinical studies as RDs are invisible in health information systems due to the lack of specific codes in the International Classification of Diseases (ICD10). For a few RDs only, systematic collection of clinical data is taking place, at regional, national, European or global level. This situation is an obstacle to the development of therapies and to the establishment of good clinical practice guidelines.

1.2.3. RDs as models for common diseases

Most RDs result from a dysfunction of a single pathway due to a defective gene. Understanding the impact of a single defect may therefore yield insights into the more complex pathways involved in common diseases which are generally multifactorial. This was already stated in 1657 by William Harvey: *“Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease”*. Research on RDs may help to elucidate the complex pathways underlying common diseases. Therefore, stimulating RD research can lead to scientific breakthroughs applicable to common conditions as was the case with the study of homozygous familial hypercholesterolemia which led to the development of statins⁸.

Strategies for the treatment of RDs, with restricted patient populations, are also cited as models for personalised medicine. For these reasons, interest in the field has increased significantly these last few years.

1.2.4. RDs as a driver for innovation

This has led to the involvement of the pharmaceutical and of the biotechnology Industry in developing new treatments where there are unmet needs. Both innovative therapies (gene and cell therapy, enzyme-replacement therapy, exon-skipping approach) and classical ones with small molecules prove to be efficient in treating RDs. Currently, 20% of all innovative products obtaining a marketing authorisation in Europe are developed for an RD.

2. INITIATIVES AND INCENTIVES TO BOOST RESEARCH IN THE FIELD OF RDs

The European Commission has a global approach to the field of rare diseases and orphan drugs in the areas of research, public health, regulatory aspects of pharmaceuticals and access to treatment. Three Directorates General of the European Commission are implicated in initiatives and/or incentives at European Union level in the field of rare diseases and orphan drugs: the Directorate General Enterprise and Industry, the Directorate General Health and Consumers, and the Directorate General Research. European cooperation aims to bring together the scarce resources for rare diseases fragmented across EU Member States. European action aims to help patients and professionals collaborate across Member States so as to share and coordinate expertise and information. This will be achieved through, for example, networks linking centres of expertise in different countries, and by making use of new information and communication technologies ("E-Health"). The European Commission (EC) aims to develop successful existing actions, such as the previous health programme on rare diseases, the Research and Technological Development Framework Programmes, and the specific regulatory framework already in place to provide additional incentives for the development of 'orphan' drugs for these conditions.

2.1. Initiatives and incentives at the level of the European Commission

2.1.1. European Commission & EMA⁹

The European Commission is responsible for proposing pharmaceutical legislation. The European Parliament and the Council, as the Community legislators, then adopt and maintain legislation in this field.

2.1.1.1. Orphan Medicinal Product Regulation¹⁰

The orphan medicinal product regulation (Regulation (EC) No 141/2000) was adopted in December 1999 and came into force in the European Union in 2000. Nine years after its implementation, the Committee for Orphan Medicinal Products (COMP¹¹) celebrated its 100th meeting in April 2009.

The Orphan Drug Regulation addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions; without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides for incentives for products receiving an orphan designation. The incentives contained in the legislation aim to assist sponsors receiving orphan drug designations in the development of medicinal products with the ultimate goal of providing medicinal products for rare diseases to patients.

Since 2000, there is a Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA). The COMP is comprised of health professionals representing each of the Member States, three patient representatives, and three other representatives nominated by the EC after recommendation from the EMA. The Committee meets once a month and is responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10 000 persons in the European Union. The Commission adopts decisions on designation based on an opinion from the COMP. The COMP is also responsible for advising the European Commission on the establishment and development of a policy on orphan medicinal products in the EU, and assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products. This regulation has been instrumental in boosting R&D in the field, as described in the next section.

2.1.1.2. Other regulations impacting on R&D in the field of RDs

Other EU regulations have a strong impact on the R&D process in the field of RDs:

- The Regulation on Clinical Trials¹², which is considered to have had a negative impact as a result of increasing the costs of trials to such an extent that academic clinical trials were no longer possible, even though there is a significant need for them for RDs. This directive is currently being revised.
- The Regulation on Advanced Therapies¹³. The lack of an EU-wide regulatory framework in the past led to divergent national approaches which hindered patients' access to products, hampered the growth of this emerging industry, and ultimately affected the EU's competitiveness in a key biotechnology area. A centralised marketing authorisation procedure enables beneficial pooling of expertise at the European level and provides direct access to the EU market. The European Medicines Agency (EMA) formed the Committee for Advanced Therapies (CAT) – the EMA's sixth scientific committee, following new European Union legislation concerning the regulation of advanced-therapy medicinal products (ATMPs) – a promising area for the field of rare diseases. The CAT met for the first time on 15 January 2009. Three types of advanced-therapy products are defined in the EU legislation: gene therapy products, somatic cell therapy products, and tissue engineered products. Similar to the COMP, the CAT *“prepare[s] a draft opinion on each advanced-therapy medicinal product submitted to the EMA for evaluation as part of a marketing authorisation application, prior to the adoption of a final opinion by the Committee for Medicinal Products for Human Use (CHMP), which retains overall responsibility for scientific evaluation of human medicines at the EMA”*. The CAT has now released its Work Programme for 2010-2015 with the overarching goal of bringing more advanced-therapy products to the market. Measures,

some of which are already underway, include “training and early dialogue” with relevant stakeholders and an examination of the existing regulatory framework with an eye to making it “...more accessible for small and medium-sized enterprises, academia, patient groups, hospitals, charity foundations and trusts developing ATMPs”.

- The regulation on Medicinal Products for Paediatric Use ¹⁴ provided an incentive to Industry to develop paediatric forms of medicinal products. This is very relevant for RDs as two-thirds of them occur in children.

2.1.1.3. EMA - FDA joint effort to promote good clinical practices

As part of the ongoing confidentiality agreement between the European Commission, the European Medicines Agency, and the US Food and Drug Administration, a new initiative was launched for an 18 month pilot phase on 1 September 2009. The Good Clinical Practice Initiative - a reflection of both the increasing globalisation of clinical studies and limited inspection resources - defines its objectives as “the sharing of information on inspection planning, policy and outcomes and the conduct of collaborative inspections”. The small patient populations typically available for rare disease medicinal product trials mean that these trials require international participation. By harmonising inspection procedures, the new initiative is expected to play a key role in ensuring that trials are conducted under safe, ethical, and uniform conditions. One of the principle objectives for the pilot phase of the initiative includes the exchange of Good Clinical Practice-related information.

2.1.2. Actions of the European Commission in the field of Public Health

The first Community action programme on rare diseases, including genetic diseases, was adopted by the European Commission for the period 1 January 1999 to 31 December 2007. The aim of the programme was to contribute, in co-ordination with other Community measures, to ensuring a high level of health protection in relation to rare diseases. As a first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases.

Rare diseases are now one of the priorities in the second programme of the Community action in the field of health (2008-2013)¹⁵. According to the DG Public Health Work Plans for the implementation of the Public Health Programme, the two main lines of action are the exchange of information via existing European information networks on rare diseases, and the development of strategies and mechanisms for information exchange and co-ordination at EU level, to encourage continuity of work and transnational co-operation. In the field of rare diseases, DG Public Health prioritises networks¹⁶, which centralise information on as many rare diseases as possible - not just a specific group or a single disease - to improve information, monitoring and surveillance. Although this programme is not intended to provide support to research activities, it does so indirectly as it provides funding for:

- the establishment of European registries, and more generally for the collection of clinical data which is one of the critical areas in R&D;
- the inventory and classification of RDs;
- the development of health indicators and development of comparable epidemiological data at the EU level.

A list of projects concerning rare diseases supported by the DG Public Health and Consumers is available in the Orphanet Report Series (European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases & European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases)¹⁷.

2.1.3. Actions of the European Commission in the field of Research

Research on rare diseases has been supported for more than twenty years through past Framework Programmes for research, technological development and demonstration activities¹⁸.

During the Fifth Framework Programme for Research (FP5: 1998-2002) the thematic programme “Improving the quality of life and management of living resources” included, amongst other topics, fundamental and clinical research in the field of rare diseases. Support was provided for multinational research into rare diseases, applying advances in modern technology to diagnosis, treatment, prevention and surveillance through epidemiology. Forty seven projects were funded for about € 64 million in total.

Under the subsequent Sixth Framework Programme for Research (FP6: 2002–2006), one of the seven thematic areas supported projects focusing on “Life sciences, genomics and biotechnology for health”. This thematic area stimulated and sustained multidisciplinary research to use the full potential of genome information to underpin applications to human health. In the field of applications, the emphasis was on research aimed at bringing basic knowledge through to the application stage (translational approach), to allow real, consistent and coordinated medical progress at the European level and to improve quality of life. This thematic area was twofold, one of the aspects being the fight against major diseases, including rare diseases. FP6 saw a significant increase in the funding for rare disease projects: around € 230 million for a total of 59 projects, also including an ERA-Net project (E-Rare). Overall this allowed for the mobilization of researchers to tackle the fragmentation of research and the production of new knowledge, but also a better coordination of research at the EU level, and the fostering of dialogue with all stakeholders, including patients.

The Seventh Framework Programme of the European Union for research, technological development and demonstration activities (FP7, 2007-2013¹⁹) has a total budget of € 54.582 billion and is composed of four main Specific Programmes – “Cooperation”, “Ideas”, “People” and “Capacities” – including cross-cutting issues such as support for SMEs, international cooperation, the contribution of research to EU policy, and the inclusion of societal considerations (see Figure 2).

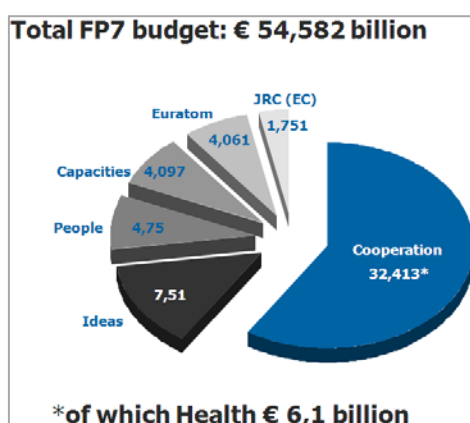


Figure 2: Breakdown of the FP7 budget among the 6 programmes.

Source: Presentation by C. Berens - RDPlatform workshop (Paris, 3 December 2009)

The “Cooperation” Specific Programme of FP7 is sub-divided into 10 Thematic Priorities, which includes the Health theme (€ 6.1 billion). This specific Programme is designed to gain or strengthen

leadership in key scientific and technological areas by supporting transnational co-operation between universities, industry, research centres, public authorities and stakeholders across the European Union and the rest of the world.

Research on rare diseases features under the heading of the Health theme and is funded through Sub-theme 2 (Translating research for human health).

The European Commission has already published several calls for proposals for the Health theme, and the rare diseases area was open to proposals in the 1st, 3rd and 4th calls.

Specifically, the focus for rare disease collaborative research in FP7 is on pan-European studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions. This sector includes rare Mendelian phenotypes of common diseases. Supported projects should help in identifying and mobilising the critical mass of expertise in order (i) to shed light on the course and/or mechanisms of rare diseases, or (ii) to test diagnostic, preventive and/or therapeutic approaches, to alleviate the negative impact of the disease on quality of life of the patients and their families, as appropriate, depending on the level of knowledge concerning the specific (group of) disease(s) under study.

The European Commission has already published several calls for proposals covering research on rare diseases in various thematic areas of FP7. For the period 2007–2010, 50 research projects with an EU contribution of over € 237 million are being supported. They will ultimately lead to better diagnostic methods, new treatments, better care and prevention strategies for rare diseases. Of these, 17 projects are specifically aimed at supporting research on the natural history and pathophysiology of rare diseases (for a total of € 71 million), and 8 projects cover the preclinical and clinical development of orphan drugs (for a total of € 36 million).

In addition to the “Activities” mentioned earlier, research on RDs is also present in other parts of the Health Theme, but the keyword “rare disease” does not appear in their titles.

Some examples are:

- HEALTH-2007-1.2-6: High throughput molecular diagnostics in individual patients for genetic diseases with heterogeneous clinical presentation
- HEALTH-2007-1.4-5: Gene therapy tools targeting the central nervous system
- HEALTH.2010.2.4.1-5: Structuring clinical research on rare cancers in adults

The budget related to these RD-relevant projects funded under other sections of the Health Theme amounts so far to about an additional € 127 million.

The last call for proposals in 2010 provided further opportunities to research projects on rare diseases under regenerative medicine and cancer:

- HEALTH.2011.1.4-1: Regenerative medicine clinical trials
- HEALTH.2011.2.4.1-1: Investigator-driven treatment trials for rare cancers

The future calls for proposals for RD research will try to fill the gaps in the research portfolio bearing in mind the EU added value and the EU research potential. They will be based on:

- results from previous calls
- contribution to EU policy objectives

- priorities discussed with:
 - The Health Theme Advisory Group (scientific community representatives, providing independent advice for the implementation of a Theme)
 - The Health Theme Programme Committee (Member States representatives)

A full list of projects concerning rare diseases supported by the Framework Programmes is available in the Orphanet Report Series (European collaborative research projects funded by DG Research and by E-Rare in the field of rare diseases & European clinical networks funded by DG Sanco and contributing to clinical research in the field of rare diseases)²⁰. The list contains projects that have been funded thanks to specific calls on rare diseases and also projects on rare diseases that have been funded through non-specific calls.

2.2. Initiatives and incentives at the level of European countries

2.2.1. E-Rare: national research programmes on rare diseases coordinated at the European level

E-Rare was an FP6 funded ERA-Net programme for research on rare diseases²¹. The ERA-Net scheme aims to step up the cooperation and coordination of research activities carried out at national or regional level in the Member States and Associated States through the networking of research activities conducted at national or regional level, and the mutual opening of national and regional research programmes. The scheme aims to help develop a European Research Area by improving the coherence and coordination of such research programmes across Europe. The scheme will also enable national systems to take on tasks collectively that they would not have been able to tackle independently. Both networking and mutual opening require a progressive approach. The ERA-NET scheme therefore has a long term perspective that must also allow for the different ways in which research is organised in different Member States and Associated States.

E-Rare is a network of sixteen partners – public bodies, ministries and research funding organisations – from twelve countries (Austria, Belgium, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Portugal, Spain and Turkey) responsible for the development and management of national/regional research programmes on rare diseases. This project helps develop synergies amongst the national and/or regional research programmes on rare diseases in participating countries, to establish a common research policy on rare diseases and to coordinate their national/regional research programmes, notably through the setting up of joint strategic activities and transnational calls for proposals.

One of the achievements of E-Rare is the development of a framework and tools for the implementation of transnational research funding. Two Joint Transnational Calls (JTC) for research on RDs have been launched in the past.

A first transnational call for proposals was launched by E-Rare in 2007²²: A total of 502 research groups in 6 countries (France, Germany, Italy, Israel, Spain and Turkey) applied in 123 eligible projects and 13 projects were selected for funding.

The second joint transnational call²³ was launched at the end of 2008/beginning of 2009: an increase in the number of research groups (566), countries (10: The Netherlands, Portugal, Austria and Greece participated together with the other countries), and projects (137) was observed during the second call. 16 transnational research consortia with 75 participating research teams from 10 countries were funded via this call for a total research budget of € 9.6 million.

The average rate of success for the E-Rare funded projects is 10% (13/123 consortia funded in 2007 and 16/137 in 2009), which is the result of the very open nature of the call topics and the high interest of rare disease researchers in international collaboration. In addition, the success rate is also partially dependent on the particularity of the E-Rare funding rules. Indeed, the fact that each call partner country funds its own national research group means that in addition to fulfilling the scientific competitiveness requirements, the proposals need to match the funding availability at national level. Details on this issue are available in Figure 3:

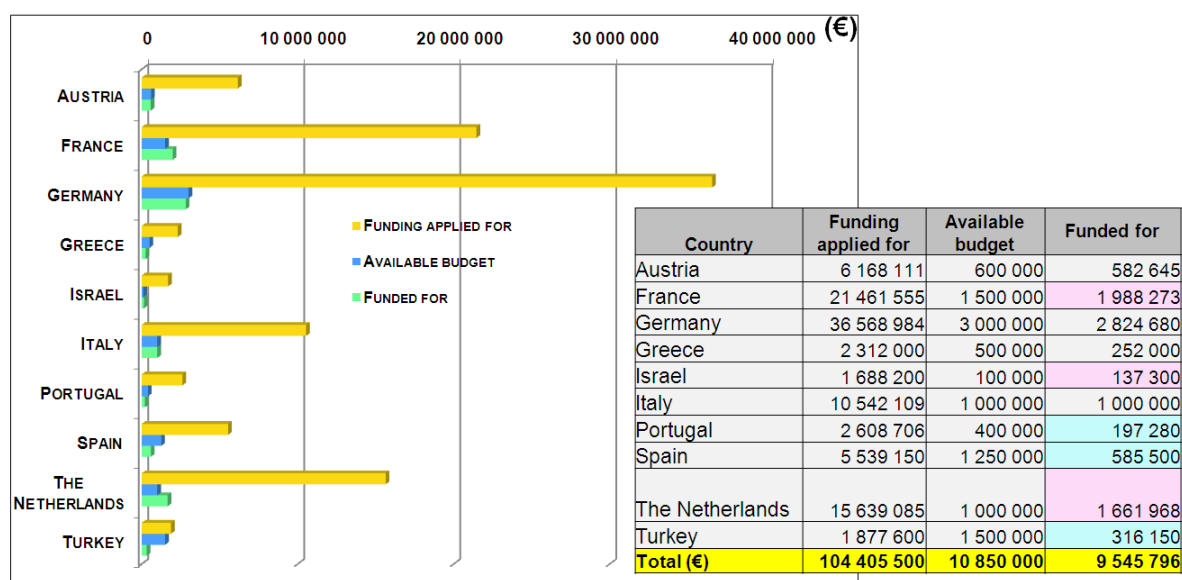


Figure 3: E-Rare JTC 2009: Funding and needs by country.

Source: Presentation by Sophie Koutouzov - RDPlatform workshop (Paris, 3 December 2009)

The proposals in the JTC include broad scientific scopes and approaches which meet the needs of the RD research: clinical studies (epidemiology / natural history of diseases, registries, databases, biomarkers, diagnosis / prognosis markers), human and social sciences, genetics and pathophysiology and pre-clinical research. Only rare drugs effects and clinical trials were excluded. All medical domains were concerned, with an over representation of Haematology/Immunology. Rare cancers and rare infectious diseases were excluded.

In conclusion, the success of the E-Rare JTC (2006-2010) in terms of the quantity of applications reflects the expectations and needs of the transnational RD research community. The JTC general process can be considered as successful, with 120-150 proposals and a great flexibility in the inclusion of new partners. Additionally, it should be noted that the translational call has helped leverage funds from agencies in countries without national RD plans. In the future, stronger involvement of national stakeholders would be a valuable contribution to the goal that the national

plans include the national participation in the E-Rare projects, as an efficient means of funding RD research.

An extension of E-Rare (E-Rare 2) is funded today under the FP7 for the period 2010-2014. The main goal will be the development of a joint translational RD research programme, with wider European collaboration, an increase in communication, the creation of indicators, the launch of yearly JTCs, the development of a strategic research policy (to increase national funding), and the elaboration of plans for the sustainability of the E-Rare network. The first E-Rare 2 call²⁴ (and the third call since the E-Rare project first began in June 2006) is now ongoing. Nine countries have joined this call: Austria, Belgium, France, Germany, Greece, Israel, Italy, Spain and Turkey.

2.2.2. Initiatives and Incentives at the Member States level

2.2.2.1. AUSTRIA

Research activities

Currently, there is no specific and explicit funding policy for rare diseases in Austria. In theory, funding is available through grant applications at different funding bodies (for instance, the *Fonds zur Förderung der wissenschaftlichen Forschung (FWF)*, the *Nationalbank*, or minor resources such as the *Fonds des Bürgermeisters der Bundeshauptstadt Wien*). However, funding follows a bottom-up approach, meaning that applications from all medical disciplines and, in some instances, totally unrelated medical, as well as non-medical, research fields compete with each other in a peer-review selection process, eventually resulting in a selection bias towards projects addressing more common diseases.

An alternative source of funding is provided by occasional project calls launched by the Austrian Ministry of Science. In the past 4 years, one of these calls was dedicated to rare diseases. Moreover, some fundraising patient organisations finance rare disease research projects. One strategic priority in the Austrian national plan will be the implementation of a defined, separate funding budget in the main existing research bodies, which will be specifically dedicated to research on rare diseases, as mentioned in the National Plans segment (“Establishing selective funding for research on rare diseases”).

E-Rare

Austria was not an official partner in the E-Rare consortium before 2009 and did not participate in the first E-Rare Joint Transnational Call in 2007. The *Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund)*²⁵ joined the second E-Rare Joint Transnational Call in 2009, and around € 580 000 of funding was granted for Austrian teams participating in 3 projects. Austria will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

Austrian teams participate, or have participated, in the following European Reference Networks for rare diseases: EUROHISTIONET, NEUROPED (main partner), Paediatric Hodgkin Lymphoma Network and PAAIR. Austrian teams participate, or have participated, in European research projects for rare diseases including: BNE, CLINIGENE, EMSA-SG, EMINA, ENRAH, ENCE-PLAN, EURIPFNET, EUROTRAPS, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EURO-IRON1, GENESKIN,

LYMPHANGIOGENOMICS, MYELINET, NEUTRONET, NEUROPRION, PERXISOMES, PNSEURONET, PROTHETS, PULMOTENSION, PWS, RHORCOD, RD PLATFORM, SIOPEN-R-NET and SARS/FLU-VACCINE. Austrian teams contribute to the following European registries: AIR, EUROCAT, EMSA-SG, EUROCAT and ENRAH. Austria contributes to the EUROPLAN project. Austria is part of the SOPEN-R-NET research network.

2.2.2.2. BELGIUM

Research activities

There are no specific research programmes for rare diseases in Belgium. The FNRS (National Fund for Scientific Research)²⁶, however, provides funding for applied research on rare diseases and has also created a contact group to foster public information. Rare disease research also benefits from initiatives such as programmes to stimulate translational R&D. Some fundraising patient organisations also finance rare disease research.

E-Rare

The FNRS is a full, contracting member, of the E-Rare consortium, participating in the whole decision and implementation process of E-Rare although Belgium did not participate in E-Rare's first two Joint Transnational Calls. The Research Foundation Flanders (FWO)²⁷ and Fund for Scientific Research (FNRQ) will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

Belgian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, EPNET, EPI, ENERCA, EUROHISTIONET, NEUROPED, PAAIR, EN-RBD and TAG. Belgian teams participate, or have participated, in the following European research projects for rare diseases, including: ANTIMAL, CONTICANET, CHEARTED, ESDN, ENRAH, EURAMY, EUREGEN, EUROCAT-CF, EUROSCA, EVI-GENORET, FASTEST-TB, EUNEFRON, EUROAGENTEST, EUROGLYCANET, GENESKIN, GEN2PHEN, HUE-MAN, KALADRUG-R, LEISHMED, IMMUNOPRION, MITOTARGET, MYASTAID, NANOTRYP, NEOTIM, NEUROPRION, PEROXISOMES, PULMOTENSION, PWS, RATSTREAM, RD PLATFORM, SIOPEN-R-NET, STEM-HD, TB-DRUG OLIGOCOLOR and WHIPPLE'S DISEASE. Belgian teams contribute to the following European registries: EUROCAT, AIR, ECFS, RBDD, ESID, ENRAH, EUNEFRON and EURECHINOREG. Belgium contributes to the EUROPLAN project.

2.2.2.3. BULGARIA

Research activities

In Bulgaria, there is no specific call for rare diseases at the national fund for research, although rare disease related projects can apply. The National Plan does not include any official policies to stimulate research on rare diseases; it only aims to encourage partnerships. The possibility of establishing a public-private fund for rare disease research is being explored following discussions at the National Conference on Rare Diseases (28-30 May 2010) which concluded that there is a lack of rare disease research in Bulgaria at present.

E-Rare

Bulgaria is not currently a partner of E-Rare.

Participation in European projects

Bulgaria participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne and Care-NMD. Bulgaria participates, or has participated, in European rare disease research projects, including: EUROGLYCANET. Bulgaria contributes to the following European registries: EUROCARE CF and TREAT-NMD. Bulgaria contributes to the EUROPLAN project.

Discussions at the National Conference on Rare Diseases (28-30 May 2010) highlighted the need to make European rare disease research projects and topics better known amongst researchers and academics in order to set up partnerships.

2.2.2.4. CYPRUS **Research activities**

Funding opportunities for rare disease research are offered by the Cyprus Research Promotion Foundation and the Cyprus Institute of Neurology and Genetics. The Telethon is an international charitable institution which is organised by the Cyprus Institute of Neurology and Genetics (CING) to support scientific research into gene therapy for neuromuscular diseases. A large proportion of net revenue from the Telethon (approximately 30%) is allocated to the Association for Patients with Muscular Dystrophy and the rest supports specific research projects conducted at the Institute. The selection of these investigations is made with the help of an independent international scientific committee.

In Cyprus, preparation of the approval of clinical trials using lentivirus vectors for gene therapy in B-Thalassemia is underway.

E-Rare

Cyprus is currently not a member of E-Rare and does not participate in their calls.

Participation in European projects

Cyprus participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ENERCA and TAG. Cyprus participates, or has participated, in European rare disease research projects including: EUROPEAN LEUKEMIA NET, Ithanel, LEISHMED and MYELINET. Cyprus contributes to the following European registry: EUROCARE CF. Cyprus contributes to the EUROPLAN project.

2.2.2.5. CZECH REPUBLIC **Research activities**

Rare diseases research is conducted through several funding bodies: the internal grant agency of the Czech Ministry of Health (www.mzcr.cz), the grant agency of the Czech Republic (www.gacr.cz), and the grant agency of the Charles University Prague (www.gauk.cz). Currently, 15 different research projects in the field of rare diseases are registered with Orphanet, focusing on 30 different rare disorders. At least three projects target specific genes.

E-Rare

The Czech Republic is not currently a partner of the E-Rare research programme on rare diseases. However, negotiations with the E-Rare2 project are underway.

Participation in European projects

Teams in the Czech Republic participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, EPNET/EPI, ENERCA Paediatric Hodgkin Lymphoma Network, NEUROPED, PAAIR and Care-NMD. Teams in the Czech Republic participate, or have participated, in European rare disease research projects, including: CLINIGENE, ENCE PLAN, EUMITOCOMBAT, EURO-PADNET, EUROCARE-CF, EUROPEAN LEUKEMIA NET, EUROAGENTEST, EUROGLYCANET, HUE-MAN, MYORES, NEUROSIS, PNSEURONET, RD PLATFORM, SARS/FLU VACCINE, SCRIN-SILICO and SIOPEN-R-NET. Teams in the Czech Republic contribute to the following European registries: EUROCARE CF, EUROCAT and TREAT-NMD. The Czech Republic is also a partner country of the Severe Chronic Neutropenia International Registry (SCNIR), monitoring the clinical course, treatment, and disease outcomes in patients with severe chronic neutropenia.

The Czech Republic also participates in many international-level activities including ERNDIM (a consortium for quality assessment in biochemical genetics for rare diseases) and Europlan, developing guidelines for national rare disease plans.

2.2.2.6. DENMARK

Research activities

There are no specific programmes for rare disease research in Denmark or focussed calls/grants. Although there are no specific initiatives to support research into rare diseases in Denmark, Danish researchers are active in the field and there are resources in place (biobanks, registries, databases) for rare disease research.

E-Rare

Denmark is not currently an E-Rare partner.

Participation in European projects

Danish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPI, NEUROPED, Paediatric Hodgkin Lymphoma Network, PAAIR, EN-RBD and Care-NMD. Danish teams participate, or have participated, in a number of European research projects for rare diseases, including: ALPHA-MAN, CILMALVAC, EURHAVAC, E-IMD, EMSA-SG, EUROCRAN, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EMVDA, EUNEFRON, HDLOMICS, HUE-MAN, HUMALMAB, LEISHMED, MMR-RELATED CANCER, MYASTAID, NEUROKCNQPATHIES, NEUROPRION, NM4TB, PULMOTENSION, SPASTICMODELS, SIOPEN-R-NET, SERO-TB, TB TREATMENT MARKER and VACCINES4TB. Amongst others, Danish teams contribute to the following European registries: EUROCARE CF, EMHG and EUROCAT. Denmark contributes to the EUROPLAN project and EU Network of experts on newborn screening.

2.2.2.7. ESTONIA

Research activities

According to the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products, Eesti Teadusfond (Estonian Science Foundation) supports research on rare diseases at the national level on the basis of appropriate applications, but there is no distinction from other projects not related to rare diseases

(approximately 600-800 000 EEK available over four years)²⁸. Some projects that involve research on rare diseases are financed by Targeted Financing from the Estonian Government (congenital adrenal hyperplasia, phenylketonuria, Prader-Willi syndrome).

E-Rare

Estonia is not currently a partner of the E-Rare consortium.

Participation in European projects

Estonian teams participated in the following European Reference Network for rare diseases: PAAIR. Estonian teams participate, or participated, in European rare disease research projects, including: AAVEYE, EURAPS, MOLDIAG-PACA and RD PLATFORM. Estonian teams contribute to the following European registry: EUROCARE CF. Estonia contributes to the EUROPLAN project.

2.2.2.8. FINLAND

Research activities

Research in the field of rare diseases has been focused on diseases of so-called Finnish Disease Heritage; nearly 40 rare inherited diseases are over-represented in Finland in comparison to other populations. Most of the genes associated with these diseases have been mapped and cloned in Finland during the last 20 years. Also, rare forms amongst more common ones, like hereditary nonpolyposis colorectal cancer (HNPCC), hereditary connective tissue diseases, and long QT syndrome, have been studied.

Many different bodies fund medical research programmes in Finland. There are no specific programmes for research of rare diseases, which compete with more common diseases for the funds. Part of this funding for research goes towards research on orphan medicinal products. Five universities with medical faculties have programmes of their own, which are partly funded by a special State contribution (EVO). The Finnish Academy and private foundations provide substantial funding for medical research and some rare disease research programmes, among others.

E-Rare

Finland is not currently a partner of the E-Rare consortium.

Participation in European projects

Finnish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPNET and EPI. Finland participates, or has participated, in European rare disease research projects including: BNE, CLINIGENE, EUGINDAT, EUMITOCOMBAT, EURAPS, EUREGENE, EUROBONET, EUROAGENTEST, EUROPEAN LEUKEMIA NET, GEN2PHEN, LYMPHANGIOGENOMICS, NEUROPRION, PEROXISOMES, PROTHETS, PULMOTENSION, TREAT-NMD and RD PLATFORM. Finland contributes to the following European registries: TREAT-NMD and EUROCAT. Finnish experts also contributed to the EUROPLAN project.

2.2.2.9. FRANCE

Research activities

Public funding is available for rare disease projects from the National Funding Agency for Research (ANR) (basic research) and Health Care Department (PHRC) (clinical research). In addition, some charities and private foundations provide funding for research, such as the AFM's *Téléthon*. The links between these funding sources should be improved under the second RD plan to make it easier to apply for funding for rare diseases.

The *GIS Maladies Rares* (Institute for Rare Diseases) was created in 2002 to coordinate and support research into rare diseases and to initiate and implement research on rare diseases at the national and European levels. At the national level, the GIS was instrumental in implementing research programmes on rare diseases (in particular networks) in the early 2000s (through yearly calls for research projects). These research programmes were subsequently entrusted to the French Funding Agency for Research in the context of the First French National Plan for Rare Diseases (2004-2008). Several targeted strategic actions are carried out by the *GIS Maladies Rares* to facilitate (and fund) access to technology platforms (i.e. genetically-modified animal models, high throughput sequencing and drug screening, etc.) for the French community of researchers on rare diseases.

In 2009, different public bodies joined together to create the "*Plateforme Mutation*" that aims to identify unknown mutations in rare diseases by means of high throughput sequencing technology.

In 2010, the Ministry for Higher Education and Research gave the outlines of the Health and Biotechnology programme of the national 'grand emprunt' (loan): this scheme aims to invest € 8 billion in research, including national and European technological platforms, genotyping, the screening and production of stem cells, industrial production of cellular therapies, the creation of laboratories for the production of biomedicines, the running of clinical trials, the acquisition of phenotyping material, etc. All of these areas would be beneficial to the field of rare diseases.

In 2010, the AFM allocated a budget of € 73 million to research in the field of neuromuscular diseases and rare diseases.

In June 2010, Généthon announced²⁹ the opening of a production unit for vectors for genetic therapies (Généthon Bioprod) in 2011. The production of industrial-sized batches is a step towards clinical trials of genetic therapies for rare diseases.

OrphanDev launched its first newsletter in October 2010: the aim of this network is to increase the number of clinical trials for rare diseases in France and to improve their quality. The network was formed within the *Centre de Gestion des Essais des Produits de Santé – CeGEPS* (Centre for the Management of Health Product trials).

Other funding opportunities for rare disease research in 2010 included: the 2010 Actelion – SFPC fund for rare disease research; funding from the Line Pomaret Delalande Foundation for doctoral research in the field of rare diseases; the Courtin Foundation's 2010 call for research for chronic inflammatory rheumatism; and a call for projects funded by the French Rett Syndrome Association.

E-Rare

The GIS Maladies Rares is the coordinating partner of the E-Rare ERA-Net for Research Programmes on Rare Diseases, and organised the first joint transnational call in 2007³⁰ for research on rare diseases, with the participation of 6 countries and a total of 13 consortia (French teams participated in each of these projects/consortia). France took part in the 2nd E-Rare Joint Transnational Call and France is represented in 11 of the 16 consortia selected for funding in 2009, with funding totalling

around € 2 million. France also took part in the 3rd transnational call launched at the start of 2011 in the context of E-Rare2.

Participation in European projects

France participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, EPNET/ EPI (main partner), EUROHISTIONET (main partner), NEUROPED, Paediatric Hodgkin Lymphoma Network, EN-RBD, and TAG (main partner). France participates, or has participated, in European rare disease research projects including: ARISE, ANTEPRION, ANTIMAL, AUTOROME, BIOMALPAR, BIO-NMD, BRAINCAV, BNE, CARDIOGENET, CAV-4-MPS, CUREFXS, CLINIGENE, CONTICANET, CONTICABASE, CHEARTED, CRUMBS IN SIGHT, CUREHLH, CRANIRARE, ELAST-AGE, EPOKS, EMINA, ERMION, EVI-GENORET, EPINOSTICS, EUROBFNS, EuroGeBeta, ENRAH, ENS@T-ACC EUNEFRON, EMSA-SG, EUMITOCOMBAT, EURAMY, EUREGENE, EURO CARE-CF, EUROAGENTEST, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROWILSON, EUROAS, EURO IRON1, EURO-LAMINOPATHIES, EUORETT, EUROSCA, EURSPA, EUROTRAPS, ENCE-PLAN, EUSTAR, EPOKS, EURO-PADNET, EURIOFNET, FAD, GETHERTHAL, GENESKIN, GENOSTEM, HMA-IRON, HSCR, HAEIII, HUE-MAN, INHERITANCE, IMMUNOPRION, KINDLERNET, LEISHMED, LYMPHANGIOGENOMICS, MANASP, MILD-TB, MITOCIRCLE, MM-TB, MTMPATHIES, MPCM, MITOTARGET, MYASTAID, MYORES, MYELINET, NEUROBID, NEOTIM, NEUPROCF, NMD-CHIP, NOVSEC-TB, NM4TB, NEUROISIS, NEUROPRION, NOVELPID, NEMMYOP, NEUTRONET, NSEuroNet, OSTEOPEPTR, PODONET, PEMPHIGUS, RATSTREAM, RAPOSDI, RISCA, SKINTHERAPY, STEM-HD, SIOPEN-R-NET, RHORCOD, RDPLATFORM, TB CHINA, THERAPEUSKIN, WHIPPLE'S DISEASE and WHIMPath. France contributes to the following European registries: EUROCAT, EUROHISTIONET, EPI-EPNET, EURECHINOREG, European central hypoventilation syndrome registry, EUROTRAPS, CHS, EURO CARE CF, ECFS, INFEVERS, and TREAT-NMD. France contributes to the EUROPLAN project.

2.2.2.10. GERMANY

Research activities

In 2003, the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung, BMBF*) funded ten networks of national academic groups, clinical centres, specialised laboratories and patients organisations for basic and clinical research for an initial three years. After a successful interim evaluation, nine of the networks for rare diseases were funded for another two years. The budget of this rare disease research programme was € 31 million.

In 2007, the BMBF opened a new funding programme on rare disease research with a substantial increase in budget to € 24 million for the first 3-year period and a possible extension of the maximum funding duration of 3 renewable 3-year periods for new networks. As of October 2008, 16 networks were being funded. Six of these are extensions of previously funded networks, while the other 10 networks are new. In 2010, the networks were granted € 6 million in additional funds for investments in shared research equipment, most notably next generation sequencing. In September 2010, a new call for proposals for the possible extension of the 10 networks which started in 2008 and the creation of new networks was published.

Additional funding of rare disease research is ongoing in other funding initiatives of the BMBF such as the National Genome Research Network (NGFN), the Competence Networks for Medicine, Innovative Therapies, Clinical Trials and others with about € 20 million in 2010. All these activities are funded

within the framework programme “Health research”. In co-operation with the Federal Ministry of Health, the *BMBF* is responsible for the programme, which is financed with funds from the *BMBF*.

The *Eva Luise und Horst Köhler Stiftung für Menschen mit Seltenen Erkrankungen*, a foundation of the First Lady and the president of the Federal Republic of Germany, is dedicated to patients with rare diseases and supports research projects into rare diseases annually since 2006.

Regional sources of funding are also available.

E-Rare

Germany is a partner of the E-Rare project, represented by the *BMBF* and the Project Management Agency of the German Aerospace Centre (*PT-DLR*). Germany participated in the first E-Rare joint transnational call in 2007 and funds the participating German research groups of 10 transnational research projects with a total € 3.3 million funding. Germany also participated in the second transnational call in 2009 for which PT-DLR managed the joint call secretariat. The *BMBF* funds the participating German research groups of 14 transnational research projects with € 3.2 million. Germany is currently participating in the 3rd Joint Transnational Call.

Participation in European projects

German teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN-CF (main partner), ENERCA, EPI, EPNET, EUROHISTIONET, NEUROPED, Paediatric Hodgkin Lymphoma Network (main partner), PAAIR, EN-RBD and Treat-NMD (Main partner). German teams participate, or have participated, in European research projects for rare diseases including: AUTOROME, ANTEPRION, BIOMALPAR, BNE, CAV-4-MPS, CRANIRARE, CURE-FXS, CHD PLATFORM, CILMALVAC, CUREHLH, EMVDA, ENRAH, ENCE-PLAN, EURADRENAL, EUCILIA, EUNEFRON, EURIPFNET, EUROBONET, EUROBFNS, EUROSD, EURO-LAMINOPATHIES, EUROPEAN LEUKEMIA NET, EUROSCA, EUROTRAPS, EURORETT, EUROSPA, ERMION, EuPAPNet, EUBNFS, EURO-CGD, ELA2-CN, EMINA, EPINOSTICS, EUREGENE, EUROPEAN LEUKEMIA NET, EMSA-SG, ESDN, FASTEST-TB, GETHERHAL, HMA-IRON, HAE III, HDLOMICS, HUE-MAN, HMANASP, INTHER, KINDLERNET, LEISHDRUG, MANASP, MITOTARGET, MYORES, MIMOVAX, MOLDIAG-PACA, NEUROSIS, NSEuroNet, NEUTRONET, NEMMYOP, NEWTBDRUGS, PULMOTENSION, OVCAD, OSTEOPETR, PODONET, PEMPHIGUS, RD PLATFORM, RevertantEB, RHORCOD, RATSTREAM, RISCA, WHIPPLE’S DISEASE and TB-VIR. German teams contribute to the following European registries: EUROCANT, TREAT-NMD, EBAR, EHDN, EurIPFnet, EURIPEDES, European Alport registry, EUROSCA-R, EUTOS and RegiSCAR. Germany contributes to the EUROPLAN project.

2.2.2.11. GREECE

Research activities

The General Secretariat for Research and Technology (Ministry of Education, Life Long Learning and Religious Affairs) has been funding research projects related to all aspects of rare diseases (rare cancers included) in the framework of “biomedical research”. However, there are no specific programmes for rare disease research and thus, it is very difficult to determine the funding allocated to rare disease research only.

E-Rare

Greece, through the General Secretariat for Research and Technology (GSRT), participated in the 2nd Joint Call of E-Rare-1. In this context, one project coordinated by a Greek team (with total funding of around € 140 000) was approved following peer-review evaluation and is ongoing. Greece currently participates in E-Rare-2, and is represented by two institutions: GSRT and the Hellenic Center for Disease Control and Prevention (HDCP). GSRT has participated in the 3rd Joint Transnational Call in the context of E-Rare 2 launched in autumn 2010.

Participation in European projects

Greece participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, EUROHISTIONET, EN-RBD and TAG. Greece participates, or has participated, in European rare disease research projects including: BIOMALPAR, BNE, EPINOSTICS, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EVI-GENORET, GEN2PHEN, GETHERTHAL, HDLOMICS, ITHANET, MYASTAID and NEUROPRION. Greece contributes to the following European registry: EUROCARE CF registry. Greece contributes to the EUROPLAN project.

2.2.2.12. HUNGARY **Research activities**

Research funds for rare diseases are available from the Hungarian Scientific Research Fund for Rare Disease Research.

In Hungary, the Ministry of Health announces its health-related research grants through the Scientific Health Council (ETT), Department of Research Coordination every three years. In the last evaluated period (2004-2006) € 3 million went to support research grants. While rare diseases were previously not one of the priority areas, although many rare diseases related grants were financed (e.g. the authorities supported the project on the periconceptional folate status and on attitudes towards different supplement programs), rare diseases are now a priority for research. A multidisciplinary centre had been established in the Semmelweis University (Budapest) on rare neurological disorders. The centre organises its work according to the principles published in the Communication from the European Commission on Rare Diseases. The centre has a patient registry, a diagnostic department, a multidisciplinary care-providing network, research projects, and a teaching program³¹. To ensure the scientific expertise for the NRDRCC, the general director of the National Centre for Healthcare Audit and Improvement, the rector of Pécs University, and the head of the Department of Medical Genetics signed the detailed agreement which established the National Rare Disease Research Coordinating Centre on the 21 April 2009. This Centre is still a part of the Department of Medical Genetics. The Medical Faculty, Faculty of Health Sciences and the Faculty of Special Pedagogy are involved in this cooperative project. The experts employed by these faculties come from the fields of medicine, paramedicine, social services and education. The new working environment is expected to improve the Hungarian teams' ability to contribute to the work of European organisations.

All Hungarian Medical Faculties are expected to establish their own coordinating centres to harmonise their rare disease-related activities, including research.

The IT centre of the NRDC elaborated the on-line registration system for health care providers, laboratories, research programs and patient groups related to rare diseases. This data collection is in line with the Orphanet data collection standards. The system has been launched and the primary database will be used to contribute to the Orphanet database.

E-Rare

Hungary is a full partner of E-Rare-2 via the National Rare Disease Research Coordinating Centre at University of Pécs.

Participation in European projects

Hungary participates, or has participated, in the following European Reference Networks for rare diseases: EPNET/EPI and Care-NMD. Hungary participates, or has participated, in European rare disease research projects including: BNE, EUROBONET, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, GENESKIN, NMD-CHIP, TREAT-NMD, SCRIN-SILICO, BBMRI and SIOPEN-R-NET. Hungary contributes to the following European registries: EUROCAT and TREAT-NMD. Hungary contributes to the EUROPLAN project.

2.2.2.13. IRELAND **Research activities**

The Medical Research Charities Group (MRCG) was formed in 1998 to inform and support charities in Ireland in the development of their medical research. As an alliance promoting medical research, the MRCG works to raise the profile of medical research, increase funding, and ultimately alleviate suffering and mortality caused by illness. Since 2006 the MRCG charities have been co-funding research projects with the Health Research Board (HRB). This is made possible by an allocation to the HRB from the Department of Health and Children. While the scheme does not focus solely on rare diseases a number of research projects in the area have been funded. Since the Scheme was put into action in 2006, 44 projects (covering rare and non rare conditions/diseases) have been supported. In this joint funding scheme, the Department of Health and Children provides an ongoing annual allocation of € 1 million to the HRB which is matched by the research charities. Total investment for the three years 2006, 2007, 2008 was € 6 million of which € 3 million was provided by the Department of Health.

In addition to the joint funding scheme activities, the MRCG also has a working group on rare diseases and has prepared a policy paper on rare diseases entitled "It's not rare to have a rare disease"³².

E-Rare

Ireland is not currently a partner of the E-Rare project.

Participation in European projects

Ireland participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, EPNET, EPI, Care-NMD, EN-RBD and the Paediatric Hodgkin Lymphoma Network. Ireland contributes, or has contributed, to European rare disease research projects including: AUTOROME, EPOKS, EURAPS, EUROPEAN LEUKEMIA NET, EVI-GENORET, GENESKIN, MANASP, MOLDIAG-PACA, NEUROPRION and NOVSEC-TB. Ireland contributes to the following European registries: EUROCAT and EUROCAT CF. Ireland contributes to the EUROPLAN project.

2.2.2.14. ITALY

Research activities

In Italy, there are efforts to coordinate research between the Regions, Italian Drug Agency (AIFA)³³, Ministry of Health and ISS. Funds for rare disease research are provided by the Ministry of Health, ISS, AIFA and Ministry of Education, University and Research, Telethon, patient organisations and a few charities. The last Health Ministry call for projects for rare diseases³⁴ had a total budget of € 8 million. The call for projects was published in 2008 and 13 projects were granted funding in 2010.

AIFA issued calls to fund independent research on the development of orphan drugs. In particular, AIFA financed a three-year initiative, launched in 2005, to support clinical research on drugs of interest to the NHS where commercial support is inadequate: one of the concerned areas was the field of rare diseases and orphan drugs. Three topics were included in the clinical research area concerning rare diseases: the benefit-risk profile of orphan drugs designated by EMA; the benefit-risk profile of off-label drug use (and in particular generics); the benefit-risk profile of drugs for non-responders to standard treatments. Projects in these topic areas were funded for up to a maximum of € 300 000, with the therapy costs funded separately. From 2008 onwards, rare diseases and orphan drug research was funded by the Ministry of Health, within the general health research call, with a specific budget reserved for rare diseases research. A specific call to fund research projects on rare diseases was issued by the Ministry of Welfare in 2009.

The annual Telethon was able to fund 36 out of the 48 selected research projects on genetic diseases thanks to fundraising activities in 2009.

Foundations and associations promote campaigns funding genetic research or research on specific diseases. Voluntary funds can be collected through general taxation.

E-Rare

Italy, represented by the ISS, is a partner of the E-Rare project and took part in all three Joint Transnational Calls. Italy participated in 12 of the 13 consortia selected for funding by the first call. In the second E-Rare transnational call, Italy participated in 8 of the 16 consortia/projects selected for funding with a budget of about € 1 million. Italy will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

Italy participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ENERCA, EPNET, EPI, EUROHISTIONET, NEUROPED, PAAIR, EN-RBD (main partner) and TAG.

Italy participates, or has participated, in European rare disease research projects including: AAVEYE, ADIT, ANTIMAL, BIG HEART, BIOMALPAR, BIO-NMD, CARDIOGENET, CUREHLH, CUREFXS, CLINIGENE, CONTICANET, CSI-LTB, ENRAH, EURADRENAL, EUCILIA, EUCLYD, EMSA-SG, EUROBONET, EUROGROW, EURO-LAMINOPATHIES, EUROPAPNET, EUROBNFS, EURO-CGD, EUROTRAPS, EURPIFNET, EURODS, EPINOSTICS, ERMION, EUROGEBETA, EURORETT, EUROPSPA, EUMITOCOMBAT, EURAMY, EURAPS, EUREGENE, EUROCARE-CF, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, GENESKIN, INHERITANCE, HAE III, HMA-IRON, HSCR, KINDLERNET, MTMPATHIES, LEISHMED, LIGHTS, MALARIA AGE EXPOSURE, MANASP, MITOCIRCLE, MOLDIAG-PACA, MCSCS, MILD-TB, MM-TB, MYELINET, MYORES, NANOMYC, NEUROKCNQPATHIES, NEUROPRION, NEUROPROMISE, NEUROSIS, NMD-CHIP, NSEURONET, OSTEOPESTR, PEROXISOMES, PNSEURONET, PROTHETS, PODONET, PEMPHIGUS, RD

PLATFORM, RISCA, READ-UP, SIOPEN-R-NET, SPASTICMODELS, SME MALARIA, STEM-HD, TAMAHUD, TARGETHERPES, VITAL, WHIPPLE'S DISEASE and WHIMPATH.

Italy contributes to the following European registries: EUROCAT, TREAT-NMD, HAE-registry, RBDD, AIR and EUROCARE CF. NCRD (National Centre for Rare Diseases) coordinates the EUROPLAN project and a service project for the Evaluation of Neonatal Screening practices in EU Member States.

2.2.2.15. LATVIA

Research activities

Funding is available for rare disease projects (through state budget, charities and pharmaceutical companies) although funds are not specifically earmarked for rare disease research.

E-Rare

Latvia is not currently a partner of the E-Rare project.

Participation in European projects

Latvian teams participate/ participated in the following European Reference Networks for rare diseases: Dyscerne and PAAIR. Latvian teams contribute to the following European registry: EUROCARE CF. Latvia contributes to the EUROPLAN project.

2.2.2.16. LITHUANIA

Research activities

In recent years, funding has been available for fundamental research and research concerning medicinal products: this second area of research is in particular targeted by the European Union Structural Assistance Operational Programme 2007-2017 for Economical Growth, and research projects for rare diseases may receive financial support by taking part in tendering processes. Additionally, in 2007 the Government of the Republic of Lithuania adopted the Lithuanian Research and Development Priorities for 2007-2010 (Governmental Decree No. 166, 7 February 2007) which also includes as a priority the development of medicinal products, including those targeting rare diseases.

An academic research project in Lithuania entitled "National hereditary childhood cancer research platform" which focuses on six genetic diseases (von Hippel-Lindau syndrome, Li-Fraumeni syndrome, multiple endocrine neoplasia syndromes - MEN1 and MEN2, Familial adenomatous polyposis and Type 2 Neurofibromatosis), molecular epidemiology and establishing a molecular diagnostic facility, as well as information dissemination concerning rare diseases, is on-going.

E-Rare

Lithuania is not currently part of the E-Rare consortium.

Participation in European projects

Lithuanian teams participate, or have participated, in the following European Reference Networks for rare diseases: ECORN CF and PAAIR. Lithuanian teams participate, or have participated, in the EUROPEAN LEUKEMIA NET research project. Lithuania contributes to the following European registry: EUROCARE CF. Lithuania has contributed to the EUROPLAN project.

2.2.2.17. LUXEMBOURG **Research activities**

An annual rare disease telethon, organised by the Lions Club, raises money and pools this with that of the AFM (*Association française contre les myopathies*) which then redistributes these funds to research projects, including some in Luxembourg.

E-Rare

Luxembourg is not currently a partner of the E-Rare project.

Participation in European projects

Luxembourg does not currently participate, or has not participated, in any European Reference Networks for rare diseases. Luxembourg contributes to the following European registry: EURO CARE CF. Luxembourg contributes to the EUROPLAN project.

2.2.2.18. MALTA **Research activities**

Funding for research into haemoglobinopathies and other rare genetic disorders is available through various sources (including the European Structural Funds, Ithamet and the University of Malta). According to the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products, *“measures [...] are being taken to promote research and development in Malta. Enterprises carrying out research and development are entitled to various tax credits according to the nature of the specific investments. These tax credits are in addition to the standard 100 % deductions allowed under the Income Tax Act (Cap. 123). These credits are granted under a general framework, which applies to all Research and development initiatives and not exclusively to the pharmaceutical sector³⁵”*.

E-Rare

Malta is not currently a partner for the E-Rare project.

Participation in European projects

Teams from Malta do not currently participate in a European Reference Network for rare diseases. Malta contributes to the following European registry: EUROCAT. Malta also contributes to the EUROPLAN project.

2.2.2.19. THE NETHERLANDS **Research activities**

The preparations for executing the ZonMw programme on priority medicines for rare disorders and orphan drugs started in 2011. The main objective of this is to stimulate translational research in rare diseases with the aim of developing therapies. € 13.6 million is available for the programme. The first call will be launched in early 2011.

ZonMw has also provided and continues to provide funding through several research programmes for research on rare diseases (e.g. the Innovative Research Incentives Scheme, the Gene Therapy

subsidy scheme and the additional research programme on efficiency of Expensive and Orphan Medicines). The Steering Committee on Orphan Drugs funds some rare disease projects (max. € 50 000 per year).

Another programme specific to orphan drugs (STIGON-Weesgeneesmiddelen) ended in 2010 and involved two projects with a total budget of € 500 000: the appointment of an orphan product developer (see below) and of a PhD student. The PhD student defended a thesis entitled “From research on rare diseases to new orphan drug development” on 3 February 2010. His research (e.g. analysis of factors in the success or failure of orphan drug development) resulted in several papers in international peer-reviewed journals.

There are tax reductions for R&D in high-tech start-ups (named the “WBSO measure”) from which orphan drug companies can benefit. There are also several programmes from the Ministry of Economic Affairs to facilitate start-ups (Innovation Subsidy Collaboration projects (IS), Subsidy programme on exploiting knowledge and Technostarters) that orphan drug companies can benefit from.

The Netherlands Organisation for Scientific Research provided € 22.5 million to a consortium of 8 Dutch university medical centres and other research institutes and universities in order to establish a national biobanking infrastructure, the Biobanking and Biomolecular Resources Research Infrastructure Netherlands (BBMRI-NL), which will integrate clinical materials and data gathered over many years with the goal of improving access to human samples. Such samples are important to rare disease and orphan medicinal product research.

E-Rare

The Dutch Organisation for Health Research and Development (ZonMw) and the Dutch Steering Committee on Orphan Drugs participated in E-Rare 1 (2006-2010) and is participating in E-Rare 2 (2010-2014), and in the 2nd Joint Transnational Call in 2009 (€ 1.7 million was granted in funds for 14 Dutch research groups, involved in 9 of the 16 funded projects/consortia). The Netherlands will not participate in the 3rd E-Rare Joint Transnational Call (2011).

Participation in European projects

The Netherlands participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA EPI, EPNET, EUROHISTIONET, NEUROPED, Care-NMD and PAAIR (main partner). The Netherlands participates, or has participated, in European rare disease research projects including: ANTEPRION, ANTIMAL, BIGHEART, BIONMD, CARDIOGENET, CHEARTED, BIOMALPAR, BNE, CELL-PID, CONTICANET, CURE-FXS, CRUMBS IN SIGHT, ELA2-CN, DIALOK, EDAR, EMVDA, EMINA, EUCLYD, EuPAPNet, EURO-CGD, EUMITOCOMBAT, EUNEFRON, EUROBONET, EURAMY, EUROCARE-CF, EUROAGENTEST, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, EVI-GENORET, EUROSD, EUROPADNET, EUROSTEC, HSCR, GENESKIN, GEN2PHEN, GENTECH, HDLOMICS, IMMUNOPRION, MLC-TEAM, NEMMYOP, NSEuroNet, NEUROSIS, NMD-CHIP, NOVSEC-TB, MITOCIRCLE, MITOTARGET, MMR-RELATED CANCER, MYASTAID, NEUROPRION, OLIGOCOLOR, PEROXISOMES, PERSIST, PNSEURONET, PRIBOMAL, PWS, TB-DRUG, TREAT-NMD, VACCINES4TB, VITAL, RD PLATFORM and REVERTANT-EB. The Netherlands contributes to the following European registries: TREAT-NMD, AIR, EUROCARE CF, EPCOT and EUROCAT. The Netherlands contributes to the EUROPLAN project.

2.2.2.20. POLAND **Research activities**

There are no research programmes specifically aimed at rare diseases in Poland. Research on rare diseases is financed within different programmes for state-funded research but there are no specifically allocated funds. Around 10% of projects approved for funding are related to the field of rare diseases.

E-Rare

Poland is not currently a partner of the E-Rare project.

Participation in European projects

Polish teams participated/participate in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, EPI/EPNET, EUROHISTIONET, PAAIR, European Network of Paediatric Hodgkin's Lymphoma, Care-NMD and TB PAN-NET. Polish teams also participate/participated in European rare disease research projects including: EUROGLYCANET, ERNDIM, EUROCARE-CF, EUROAGENTEST, EUROPEAN LEUKEMIA NET, EUROWILSON, EUROSCA, EURADRENAL, EURO-GENE-SCAN, MYELINET, NEURO.GSK3, NEUPROCF, RD PLATFORM and SIOPEN-R-NET. Polish teams contribute to the following European registries: ERCUSYN, RARECARE, SCNIR, TREAT-NMD, EUROCARE CF and EUROCAT. Poland contributed to the EUROPLAN project.

2.2.2.21. PORTUGAL **Research activities**

The public funding agency, Foundation for Science and Technology (FCT), runs several programmes to fund research on rare diseases, as along with the Ministry of Health itself and the private sector.

E-Rare

Portugal, represented by FCT and the Directorate General of Health, joined the E-Rare project in 2009, for the 2nd Joint Transnational Call: Portugal is represented by a team in one of the projects/consortia selected for funding, with funding of around € 200 000. Portugal did not join the 3rd Joint Transnational Call in 2011.

Participation in European projects

Portugal participates, or has participated, in the following European Reference Networks for rare diseases: Dyscerne, ENERCA NEUROPED and TAG. Portugal participates, or has participated, in European rare disease research projects including: CLINIGENE, EPOKS, EHDN (European Huntington Disease Network), Euro-WILSON, SPATAX, EURAMY, EUROCARE CF, EuroGentest, EVI-GENORET, LEISHMED, MMR-RELATED CANCER, NEUPROCF, PEROXISOMES, POLYALA, RHORCOD, SAFE, PHGEN and SIOPEN-R-NET.

Portugal contributes to the following European registries: TREAT-NMD, EUROCARE CF and EUROCAT. Portugal contributes to the EUROPLAN project.

2.2.2.22. ROMANIA **Research activities**

Funding is currently available from some sources in Romania, although there are no specific programmes for rare disease research in Romania. Research projects dedicated to rare diseases are included in the same category with other research projects. Funding of research projects was markedly reduced in 2010 and no new calls were launched. There were no rare disease-related calls for projects in 2010. There are currently no fundraising initiatives for rare disease research in Romania.

E-Rare

Romania is not currently a partner of the E-Rare consortium.

Participation in European projects

Romanian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA, TAG and Care-NMD. A Romanian team contribute/contributed to the EUROPEAN LEUKEMIA NET European research project. Romanian teams contribute to the following European registries: EUROCARE CF and European Registry for CML (EUTOS). Romania contributes to the EUROPLAN project.

2.2.2.23. SLOVAK REPUBLIC **Research activities**

Currently there are no specific programmes for rare disease research in the Slovak Republic.

E-Rare

Slovak Republic is not currently a partner of the E-Rare Project.

Participation in European projects

Teams from the Slovak Republic participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne and Care-NMD. Teams from the Slovak Republic participate, or have participated, in European rare disease research projects including: ANTEPRION and NM4TB. Slovak Republic contributes to the following European registry: EUROCARE CF.

2.2.2.24. SLOVENIA **Research activities**

The Slovenian Research Agency is a government body which awards grants for research. Although not specifically aimed at rare diseases, in the past rare disease topics have been given research grants.

E-Rare

Slovenia is not currently a partner of the E-Rare project.

Participation in European projects

Slovenian teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, NEUROPED, TAG, Care-NMD and EN-RBD. Slovenian teams participate, or have participated, in European rare disease research projects including: CONTICANET, EMSA-SG, MYELINET, PNSEURONET and SARS/FLU VACCINE. Slovenia contributes to the following European registry: EUROCARE CF. Slovenia contributes to the EUROPLAN project.

2.2.2.25. SPAIN

Research activities

In Spain, research related to rare diseases is included in the “*Plan Nacional de Investigación Científica*” (National Plan for Scientific Research), “*Desarrollo e Innovación Tecnológica*” (Development and Technological Innovation) (2008 – 2011), and specifically within the “*Acción Estratégica en Salud*” (Strategic Action on Health [Research]), in which rare diseases constitute one of the most important research subjects. In September 2007, the outlines of the National R&D&I Plan were presented. According to the Ministry of Education and Science, the Public Central Administration will increase its investment at a rate of 16% per year starting in 2008 and up to a total expenditure of 2.2% of GDP in 2011, in line with European Union recommendations. This estimate includes the business sector, which will finance 55% of the total investment.

The most relevant government initiative for research on rare diseases was the creation by ISCIII, of the Biomedical Research Network on Rare Diseases (CIBERER) in order to act as a research-performing body on rare diseases in Spain. CIBERER is a centre orientated towards the development and implementation of cooperative research in the field of rare diseases, performing basic, clinical and epidemiological biomedical research, placing special emphasis on transferring the research from the laboratory to the patient’s bedside and scientifically responding to the questions that arise from the interaction between physician and patient. This network acts as a public consortium of 29 institutions; the network has more than 700 professionals integrating 60 research groups and is mainly funded by the Institute of Health Carlos III and is attached to it. The aims of CIBERER are: to improve the resources available for researching rare diseases and rare disease treatments, to promote the integration between basic and clinical biomedical research groups in order to aid collaboration between the laboratory and the clinical setting, to develop cooperative investigational projects that allow for the exploration of new scientific hypotheses and technological developments, to demonstrate the value of rare disease research, and to establish collaborative efforts with the pharmaceutical and biotechnological industries.

The following institutions give support for academic / industrial research on rare diseases:

- Fund for Health Research (FIS) (which belongs to the Institute of Health Carlos III) has funded single and multi-centre research projects as well as technology assessment projects since 2001. Thus, for example 12 Cooperative Health Thematic Health Networks (RETICS) were created, which involved research groups and centres belonging to the National Health System with a budget amounting to € 20 million for three years. Two different calls for proposals of projects to study the potential of new orphan drugs have been funded by the Ministry of Health, Social Policies and Equality, and managed by the FIS (ISCIII).
- CIBERER (which is attached to the Institute of Health Carlos III) was given funding by ISCIII amounting to € 6.2 million in 2007, € 8 million in 2008, € 7.7 million in 2009 and € 5.8 million in 2010 for research activities (basic, clinical, epidemiological and translational) in the field of rare diseases.

- *Instituto de Investigación de Enfermedades Raras* – IIER (National Research Institute for Rare Diseases), within the Institute of Health Carlos III (ISCIII) was founded in November 2003 to promote basic, clinical and epidemiological research on rare diseases.
- *Federación Española de Enfermedades Raras* – FEDER (Spanish Federation of Rare Diseases) is a federation which includes most Spanish patient organisations for rare diseases. FEDER also provides funding for research on rare genetic diseases in the scope of the national R&D plan.

Since the National Strategy on Rare Diseases began, rare diseases have been considered as a priority research area of the Fund for Health Research (FIS) and the Strategic Action in Health (AES) for 2008-2009. Rare diseases are also taken into account in the area of "additional performances" contemplating the strengthening of both basic research and clinical trials or the development of orphan drugs.

In 2009, a € 12 million budget in R&D&I and more than 700 researchers were made available by ISCIII as resources for translational research into rare diseases. CIBERER was provided with funding amounting to € 5.8 million in 2010 for research activities (basic, clinical, epidemiological and translational) in the field of rare diseases. In 2010, *La Marató de TV3* raised almost € 9 million in donations destined to fund biomedical rare disease research projects. In late 2009, the Sant Joan de Déu hospital and the Hospital Clinic (both of Barcelona) became the first in Europe to establish a biobank specifically for paediatric tissue. The entity seeks to promote the donation of much needed paediatric tissue, such as tendons, bones, skin, cornea, and heart and lung valves. While organ donations for transplant in the paediatric population are more frequent, tissue donations are lacking. Such tissues can be vital to rare disease patients. Working with the Transplant Service Foundation³⁶, the new bank will network with other banks and institutions in Spain and in other parts of Europe. According to a news report, the bank has already been authorised to send tissue to the UK's National Health Service.

ISCIII has created CAIBER (Plataforma Española de Ensayos Clínicos (Spanish Clinical Trial Platform) with the participation of 40 CROs (entities promoting research) and legal personality and attached to it as a platform for clinical trials (including rare diseases) with a sustainable core funding of € 10 million per year, that will be the Spanish arm of ECRIN (the European clinical trials infrastructure in process of constitution as a European Research Infrastructure Consortium). ISCIII has created RetBioH (a network of biobanks including biobanks for rare diseases with a sustainable funding of € 6 million per year, which will be the Spanish arm of BBMRI (the European biobanking infrastructure in process of constitution as an ERIC).

E-Rare

Spain, represented by the Institute of Health Carlos III (ISCIII), is a partner of E-Rare. Spain has participated in the two calls for proposals managed by the Fund for Health Research (FIS), the Public Health Agency for Health Research, which is part of the ISCIII. Spain participated in the 2007 and 2009 E-Rare transnational calls with a total of € 3.25 million of initial funding committed to the project Spain. Spanish teams participate in 6 of the 13 funded projects/consortia selected following the 1st Joint Transnational Call, and in 6 of the 16 consortia/projects selected for funding in the 2nd Joint Transnational Call, with a total funding of around € 580 000. Spain will participate in the 3rd Joint Transnational Call in 2011.

Participation in European projects

Spanish teams participate, or have participated, in the following European Reference Networks for rare diseases: Dyscerne, EPI, EPNET, ENERCA (main partner), EUROHISTIONET, NEUROPED, Paediatric Hodgkin Lymphoma Network and PAAIR. Spanish teams participate, or have participated, in European rare disease research projects including: ANTEPRION, ANTIMAL, BNE, CLINIGENE, CHD-PLATFORM, CONTICANGET, CAV-4-MPS, CureFXS, EMSA-SG EUGINDAT, EuroRETT, ENRAH, EUGINDAT, EUMITOCOMBAT, EUROBONET, EUROGENTEST, EUROEAN LEUKEMIA NET, EVI-GENORET, EUROSCA, EPINOSTICS, EUROBFNS, EuroGeBeta, GEN2PHEN, GENESKIN, HSCR, HMA-IRON, LEISHMED, LEISHDRUG, MALARIA AGE EXPOSURE, MCSCS, MOLDIAG-PACA, NANOTRYP, NEUROKCNQPATHIES, MLC-TEAM, PNSEURONET, TRYPOBASE, RISCA, RAPSODI, RD PLATFORM, RevertantEB, SIOPEN-R-NET, SERO-TB, TAMAHUD, TREAT-NMD, and WHIMPath. Spanish teams contribute to the following European registries: EUROCAT, ERCUSYN, EUGINDAT-PIADATABASE, MOLDIAG-PACA, AIR, EURO CARE CF and TREAT-NMD. Spain also participates in the EUROPLAN project.

2.2.2.26. SWEDEN

Research activities

The Swedish Research Council (SRC) is a government agency under the Ministry of Education and Science. The agency evaluates and prioritises research in medicine, pharmacy, odontology and dental care sciences and decides on project grants in these fields. Project funding is based on quality criteria (bottom-up procedure) and not subject to prioritisation based on research area, with a few exceptions. SRC also makes decisions on financing for principal investigators in areas of research where directed support is of strategic value.³⁷ Rare diseases are thus funded through a yearly call for proposals for project grants. However, there is no dedicated budget for rare diseases. Instead, applications dealing with rare diseases compete with other applications on the basis of the quality of the proposal and not subject to prioritisation of research areas, with some exceptions. Approximately 80 research projects on rare diseases have been funded by SRC.

A number of private foundations also support medical research on rare diseases but these grants are not specifically designated to rare diseases.

Research on rare diseases is performed at many universities and university hospitals. This research is supported by grants from the government as well as from non-governmental foundations. Clinical research concerning rare diseases is partly supported by county councils/regions and clinical trials are partly sponsored by orphan drug companies. Some 50 national hospital units and 30 university departments involved in research activities are registered in the Orphanet database.

The Swedish Cancer Society and the Childhood Cancer Foundation are examples of a non-profit organisation which contributes to the funding of cancer research (including rare cancer), information-sharing and supporting activities which aim to improve cancer treatment and care. Research projects are funded following the same policy as that of the SRC.

It is impossible to separate support for rare disease research from support for orphan drug development, as these research efforts are often mixed. In all likelihood, however, probably very little money directly supports orphan drug development.

An example of a centre performing research on rare disorders is the Mun-H-Centre. Their activities focus on oral health and orofacial functions such as eating, speech, facial expression and saliva control in rare diseases. During 2010, a number of scientific papers and investigations were

published. Since 1996, data on oral health and orofacial function have been collected through structured parental and clinical observations and registered in a database. Selected data from the database is presented at the Mun-H-Centre website³⁸ and the information is updated regularly.

The Family programme and Respite service at *Ågrenska* provides the opportunity to meet a large number of children with rare diseases. During family stays using an assessment form (validated by University of Gothenburg, Institute of Psychology), *Ågrenska* performs systematic observations of the children in their school, pre-school and leisure activities, and the results are put together in a database.

E-Rare

Sweden is not currently a partner of the E-Rare project.

National participation in European projects

Swedish teams participate or have participated in the following European Reference Networks for rare diseases: Dyscerne, ECORN CF, ENERCA EPI, EPNET, EUROHISTIONET, Paediatric Hodgkin Lymphoma Network and PAAIR.

Swedish teams participate or have participated in the following European research projects for rare diseases: ANTEPRION, BIOMALPAR, BNE, CHD PLATFORM, CUREHLH, CLINIGENE, EMVDA, EUMITOCOMBAT, EURAPS, EUCLYD, EURODSO, EUROBONET, EUROGENTEST, EUROPEAN LEUKEMIA NET, EVI-GENORET, EMSA-SG, EUROCRAN, EURADRENAL, EURAMY, EURO-GENE-SCAN, GENESKIN, HDLMOICS, INHERITANCE, NMD-CHIP, LYMPHANGIOGENOMICS, MANASP, MOLDIAG-PACA, NEUPROCF, NEOTIM NEUROPRION, NEWTBDRUGS, PRIBOMAL, PWS, TRYPOBASE, TB-DRUG OLIGOCOLOR, TREAT-NMD, RD PLATFORM and VITAL.

Swedish teams contribute to the following European registries: AIR, EUROCARE CF. Sweden is a partner of the EUROPLAN project.

2.2.2.27. UNITED KINGDOM

Research activities

Rare diseases research has been supported in the UK up till now although no special funding mechanism is as of yet in place. Government funding is mostly available through the Research Councils (i.e. the Medical Research Council) and the National Institute for Health Research (NIHR). There are several major funding charities, particularly for cancer and heart diseases, and a number of rare disease charities fund research (such as the Muscular Dystrophy Campaign, the Cystic Fibrosis Trust, the Dystrophic Epidermolysis Association, etc). Many products for rare diseases have been put through trials in the UK by major pharmaceutical companies (i.e. enzyme replacement therapies, drugs for pulmonary hypertension, etc).

The Biomedical Research Centres, funded by the National Institute for Health Research (NIHR), also fund some research on rare diseases. The Manchester Biomedical Research Centre specialises in genetics and developmental medicine and is a leader in engaging and involving patients/publics in the research process. The patient involvement and public engagement programme for Manchester Biomedical Research Centre is led by Nowgen. Nowgen has undertaken a detailed mapping exercise with researchers and identified excellent practices. A comprehensive strategy for engagement and involvement has been developed by Nowgen and is being implemented through training courses and resources to support researchers. Examples of Nowgen's current work include: investigating young

peoples' information needs when taking part in clinical research and developing a DVD in partnership with teenagers about gene therapy for Cystic Fibrosis. The London-based Biomedical Research Centre of the National Institute for Health Research (NIHR) developed in 2010 a guide intended to aid researchers to involve patients, carers, families and patient groups in the various stages of research³⁹. These include the development of grant applications, the design/management of research, the undertaking of research, the analysis of the research data, and the dissemination of research findings. The guide outlines ways in which patients and other users can be involved in each of these stages and how researchers can facilitate this involvement. In a press release, Dr David King, Director, NIHR Central Commissioning Facility is quoted as saying that "Patient and Public Involvement (PPI) will increase in importance in the work of all NIHR Biomedical Research Centres and Units as it is increasingly recognised that PPI is a win/win for both patients and researchers. This new guide for research staff will greatly enhance PPI across the NIHR, especially in the area of experimental medicine." Experimental medicine is an important area in the field of rare diseases.

In an open access article⁴⁰ published in PLoS Medicine, researchers from Scotland depict how the "ever-increasing bureaucracy" attached to academic research has imposed a significant obstacle. The situation is critical to research for rare diseases, often shunned by the biopharmaceutical industry due to the inherent lack of profits treatments for low-prevalence diseases afford. Specifically, the authors cite the incorporation of the European Directive 2001/20/EC on clinical trials into UK Good Clinical Practice (GCP) law. Whether or not the components of this directive are intended for academic clinical trials is not clear, but the number of non-commercial trials has decreased since the UK implemented the new GCP regulations. A survey of eight cancer clinical trial centres reveals that the cost of non-commercial trials has doubled, and that trials have been delayed since the EU regulation came into play. Furthermore, industry has sought to avoid the costs engendered by the increased regulation by moving trials out of Europe. Thus, by the end of 2005, "it was estimated that the number of European trials submitted for grants or ethical review had fallen by 30% to 50% and that the proportion of non-commercial trials was reduced from 40% to 14%". The authors observe that the desired European harmonisation of laws has not materialised and that "the ability...to compete with the better funded US non-commercial trials has been damaged, perhaps irreversibly". In particular, emergency medicine has been impeded, along with non-commercial paediatric trials. Although EU Regulation 1901/2006, which came into force in 2007, was created specifically for the development of medicinal products for children, it insists on full compliance with the Clinical Trial Directive. Citing the phenomenon of "regulatory creep" in which regulations are over-interpreted, the authors instead call for some "regulatory retreat" where "academics try to ensure that the interpretation of any rules and procedures, that are not mandated by law, are the most favourable for academic research whilst ensuring patient safety". They invite other areas of the world to learn "from the misguided trial regulations that have been created in Europe".

E-Rare

The UK is not currently a partner of the E-Rare project.

Participation in European projects

British teams participate or have participated in the following European Reference Networks for rare diseases: Dyscerne (main partner), ECORN CF, EPI/EPNET, ENERCA, EUROHISTIONET, NEUROPED, Paediatric Hodgkin Lymphoma network, PAAIR, Care-NMD and EN-RBD. British teams participate or have participated in European rare disease research projects including: AAVEYE, ANTEPRION,

ANTIMAL, BIG HEART, BIOMALPAR, BNE, CARDIOGENET, CHD PLATFORM, CHEARTED, CRUMBS IN SIGHT, CILMALVAC, CLINIGENE, CONTICANET, CSI-LTB, EMSA-SG, EUROCRAN, EMVDA, EURADRENAL, ENRAH, EPOKS, EUMITOCOMBAT, EURAMY, EUREGENE, EUROBONET, EUROCARE CF, EUROAGENTEST, EUROGLYCANET, EURO IRON1, EUROSICA, EUROTRAPS, EUCILIA, EURO-LAMINOPATHIES, EUNEFRON, EUROPADNET, EUROWILSON, ENCE-PLAN, EVI-GENORET, ESDN, GEN2PHEN, GENESKIN, INHERITANCE, HUMALMAB, LEISHDNAVAX, PWS, MITOTARGET, MPCM, MALARIA AGE EXPOSURE, MITOCIRCLE, MM-TB, MOLDIAG-PACA, MPCM, MYELINET, MYORES, NEOTIM, NEUPROCF, NEUROKCNQPATHIES, NEUROPRION, NEUROSIS, PSYCHCNVS, NEWTBDRUGS, PNSEURONET, PULMOTNESION, PWS, RATSTREAM, SPASTICMODELS, RD PLATFORM, STEM-HD, TAMAHUD, TREAT-NMD, VITAL and THERAPEUSKIN, Biology of cilia formation and intraflagellar transport project, and Relationship of BBS proteins in Wnt pathways project. British teams contribute to the following European registries: EUROCAT, TREAT-NMD, AIR, EUROCARE-CF, EUHASS, EUROPAC, the European Prader-Willi database and EUROWILSON. The United Kingdom contributes to the EUROPLAN project.

2.2.3. Initiatives and Incentives in other European countries

2.2.3.1. CROATIA

Research activities

There are around 40 projects funded by the Ministry of Science, Education and Sports for the investigation of genetic diseases and various other groups of rare diseases. Some pharmaceutical companies involved in the management of rare diseases support investigations of specific rare diseases. There is a database of clinical studies in Croatia (<http://www.regpok.hr/>) in the Croatian language.

E-Rare

Croatia is currently not an E-Rare partner and has not yet participated in these calls.

Participation in European projects

Croatian teams participate, or have participated, in the following European Reference Networks for rare diseases: TAG and Care-NMD. Croatian teams participate, or have participated, in European research projects on rare diseases, including: EUROGLYCANET and EUROPEAN LEUKEMIA NET. Croatia contributes to the following European registries: EUROCARE CF and EUROCAT. Croatia contributes to the EUROPLAN project.

2.2.3.2. NORWAY

Research activities

National centres of expertise are involved in a number of research projects concerning rare disorders.

E-Rare

Norway is not currently a partner of the E-Rare project.

Participation in European projects

Norwegian teams participate/participated, in the following European Reference Networks for rare diseases: Dyscerne, Paediatric Hodgkin Lymphoma Network, EPNET and Care-NMD. Norwegian teams participate/participated in European rare disease research projects including: CHEARTED, ECFR, EUROCRAN, EURAPS, EURADRENAL, EUROBONET, HUE-MAN, MYELINET, NEUROXSYS, NEUROKCNQPATHIES, SIOPEN-R-NET and VITAL. Norwegian teams participate/participated in the following European registries: EURADRENAL, EUROCAT and EUROCARE-CF.

2.2.3.3. SWITZERLAND

Research activities

Although there is no specific national budget for rare disease research, the Telethon Suisse raises funds specifically for rare diseases, and research into rare diseases. Moreover, many projects on rare diseases are supported by the Swiss National Science Foundation and a few public foundations (i.e. the Gebert Rűf Foundation).

Gebert Rűf Foundation⁴¹, a Swiss grant programme specifically for rare diseases, announced its second call for projects in 2010. The independent foundation is committing CHF 2 million (€ 1.3 million) per year to researchers based at Swiss universities, university hospitals, federal institutes of technology and universities of applied sciences. The Rare Diseases – New Approaches grant programme, which was launched last year, was established as a five-year area of activity. The first two calls in 2009 and 2010 selected ten finalists from 106 applications. In 2009, the chosen topics were: Preventing Nodule Formation in Hyaline Fibromatosis Patients; Genetic Screening for Disease-Causing Mutations in Familial Polycythemia Using Next Generation DNA Sequencing; Gene Hunting for Recessive Hereditary Peripheral Neuropathies by Recent and Highly-Parallel Technologies; Hereditary Sensory Neuropathy Type 1 - Pathomechanism and Therapy; and Identification of New Factors Implicated in Genetic Gonadal Disorders. In 2010, the chosen topics were: Towards a better mechanistic understanding of Friedreich's Ataxia; Role of macroautophagy in CGD and correction of the defect; Consanguinity and rare recessive disorders; Rescue of dysfunctional RNA processing in spinal muscular atrophy through PGC-1-alpha; and Novel mechanisms causing Lafora disease.

E-Rare

Switzerland is not currently a member of the E-Rare project.

Participation in European projects

Switzerland has participated and participates in the following European Reference Networks for rare diseases: Dyscerne, ENERCA, EPI/EPNET and PAAIR. Switzerland participates or has participated in European rare disease research projects including: AAVEYE, ANTIMAL, AUTOROME, BIOMALPAR, CLINIGENE, CSI-LTB, CSI-LTB, EMVDA, EURADRENAL, EURO-LAMINOPATHIES, EUGINDAT, EURAPS, EUREGENE, EUROBONET, EUROAGENTEST, EUROGLYCANET, EUROPEAN LEUKEMIA NET, EVI-GENORET, GENESKIN, GEN2PHEN, HDLOMICS, HUMALAB, IMMUNOPRION, LEISHMED, LYMPHANGIOGENOMICS, MYELINET, MILD-TB, MPCM, MYORES, NEUROPRION, NANOTRYP, NOVSEC-TB, NM4TB, PEMPHIGUS, PULMOTENSION, TRYPOBASE, THERAPEUSKIN, and SIOPEN-R-NET. Switzerland contributes to the following European registries: AIR, TREAT-NMD, EUROCARE-CF and EUROCAT.

2.2.3.4. TURKEY

Research activities

TÜBİTAK (The Scientific and Technological Research Council of Turkey) has in the past supported research on rare diseases in Turkey.

E-Rare

Turkey, represented by TÜBİTAK, was a member of the E-Rare and E-Rare-2 projects. TÜBİTAK participated in the first two Joint Transnational Calls (JTC) of the E-Rare-1 project and the first JTC of E-Rare-2. In the 1st Joint Transnational Call, Turkey was represented in 2 of the 13 consortia/projects selected for funding of € 700 000. In the 2nd Joint Transnational Call E-Rare, Turkey was represented in 4 of the 16 consortia/projects selected for funding, with a total of around € 400 000 funding. Turkey also participated in the 2011 3rd Joint Transnational Call.

Participation in European projects

Turkish teams participate/participated, in the following European Reference Networks for rare diseases: Dyscerne, TAG and EN-RBD. Turkish teams participate/participated, in European rare disease research projects including: CELL-PID, CRANIRARE, ELA2-CN, EMINA, EURO-CGD, NEUTRONET and PodoNet. Turkish teams contribute to the following European registries: TREAT-NMD and EURO CARE CF. Turkey contributes to the EUROPLAN project.

2.3. Initiatives and incentives in the USA

A comprehensive study, entitled *Rare Diseases and Orphan Products: Accelerating Research and Development*⁴² has been produced by the independent, non-profit Institute of Medicine of the National Academies at the request of the US National Institutes of Health. Offering a detailed overview of the rare disease and orphan drug situation in the United States, with frequent comparisons to Europe and other countries, the document encompasses epidemiology, cause, prevention, diagnostics, treatment, and the impact of rare diseases. The regulatory framework for orphan drugs is delineated, with comparisons between the US approach and other countries. In the field of research, the report evaluates target discovery, therapeutics discovery, the infrastructure for basic research and drug discovery for rare diseases, and innovation platforms for target and drug discovery. The authors – comprising a committee of experts from diverse institutions and organisations – consider the development of new therapeutic drugs and biologics, medical devices, and explore issues relating to coverage, reimbursement and various incentives and disincentives for rare disease product development.

For each section of the report, recommendations are put forward. Central to these is the call for a national task force of stakeholders, to be structured similarly to the European model that has been operating since 2004 (now the European Union Committee of Experts on Rare Diseases – EUCERD⁴³). In the report brief, seven key elements are defined for an integrated national strategy, components of which already exist, but need to be reinforced or elaborated. These elements include: Active involvement and collaboration by a wide range of public and private interests; Timely application of advances in science and technology; Appropriate use and further development of trial design and analytic methods; Creative strategies for sharing research resources and infrastructure to make good and efficient use of scarce funding, expertise, data, biological specimens, and participation in

research; Reasonable rewards and incentives for private-sector innovation and prudent use of public resources for product development; Adequate organisation and resources, including staff with expertise on rare diseases research and product development for public funding agencies; and Mechanisms for weighing priorities for rare diseases research and product development, establishing collaborative as well as organisation-specific goals.

The hefty exposé comes just in time to brief participants on the state-of-the-art in rare disease and orphan drug research and policies in the USA at the time when the European Commission and the National Institute of Health launch a joint International initiative.

Following the release of the report, a *Wall Street Journal* health blog article⁴⁴ queries whether the time has now come for a full-scaled “war” on rare diseases, similar to the “war on cancer” that was launched in the USA in the 1970s. If it is indeed the time for such a war, the development of recent events leads to the conclusion that Europe and America will be fighting shoulder to shoulder on behalf of rare disease patients.

A comment by members of the US Food and Drug Administration’s Office of Orphan Products Development and Office of New Drugs, appearing in *Nature Reviews Drug Discovery*, highlights new policy initiatives that aim to enhance progress in the developmental process of medicinal products for rare diseases in the USA. *Accelerating Orphan Drug Development* details the achievements of the Orphan Drug Act (1983) in the USA: over 2 250 orphan drug designations, of which 361 have received marketing approval. Furthermore, “in 2009, orphan drugs constituted 38% of the 29 new therapies that the US Food and Drug Administration (FDA) approved for marketing”. Of particular interest are initiatives to speed up the process of bringing products to market for rare conditions, which include the recently founded Rare Diseases Program within the Office of New Drugs of the FDA’s Centre for Drug Evaluation and Research; the recently published report by the Institute of Medicine on accelerating rare disease drug development; and the FDA’s internal Rare Disease Review Committee (mandated by the Section 740 Amendment), which is “currently performing a comprehensive analysis of current and projected practices for rare disease review and regulation at the FDA. The report describing the findings and recommendations of the review group is due to be presented to the US Congress in March 2011”. The article sums up by stating that the “FDA is committed to accelerating orphan drug development through a regulatory system built on integrity, consistency and transparency; a system that has delivered benefits to people who desperately need them and promises to deliver much more”.

3. STATE OF THE ART OF RESEARCH AND OF R&D IN 2011

3.1. State of the art of Research in Europe according to Orphanet data

Currently, the Orphanet database contains 4 212 ongoing research projects for about 2 131 different rare diseases. These research projects are conducted in 27 countries. Among these projects, 232 do not concern a particular stage of research and correspond to an activity of coordination of research projects. A hundred research projects in the Orphanet database belong to the socio-economic category of research projects (Public health, health economy and health sociology). These projects usually cover a large scope and do not consider a particular disease or group of diseases.

We could therefore give a more accurate estimate of the Orphanet database content which could be 3 880 research projects for 2 100 rare diseases in 27 countries. These projects have been classified and counted (see Figure 4):

Stage of research	Number of Projects
Basic research	2 750
Pre-clinical research	331
Clinical research	487
Diagnostic & Biomarkers	312

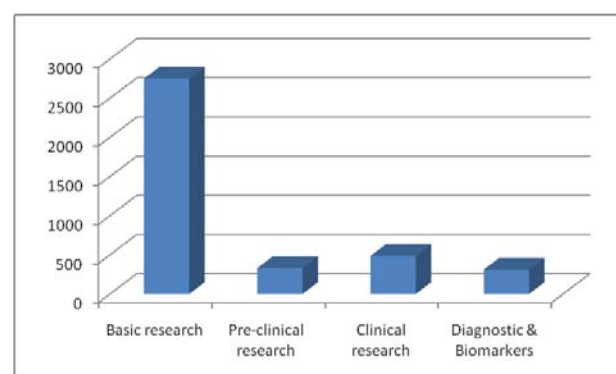


Figure 4: Number of research projects by stage of research

The “Basic research” category gathers research projects such as gene search, mutation search, gene expression profile, genotype-phenotype correlation, in vitro functional study, animal model and human pathophysiological study.

Pre-clinical research covers areas of drug development, gene therapy, cell therapy and medical devices development. These steps are often performed by Industry and are then not fully accessible, which may explain the low score presented in Figure 4.

Clinical research includes non-therapeutic clinical research, epidemiological research and excludes clinical trials that will be discussed later.

Diagnostic & biomarkers concerns studies that are conducted with the goal of identifying biomarkers and/or developing a diagnostic test that is not already available in clinical laboratories.

The category represented the most is “Basic research”. Up to now, 2 369 genes have been linked to 2 306 rare diseases (2 228 genes linked to 2 203 rare diseases with exclusion of rare tumors except cancer-predisposing syndromes – 2 147 genes linked to 2 134 rare diseases with exclusion of rare tumors and cancer-predisposing syndromes) and identification of pathophysiological mechanisms supporting the onset or progression of a disease remains a high-value challenge for all the stakeholders, including Industry. “Basic research” is an active field and the challenge is particularly important since the results may concern both rare and common diseases, rare diseases being used as models for more common disorders.

Focus on collaborative research in Europe

Among the research projects registered in the Orphanet database, some belong to collaborative European research projects. As mentioned earlier, collaborative research in Europe has two main sources of funding: the Framework Programme of DG Research and E-Rare.

A complete list of European projects funded in the past few years, in the area of RDs, is available as an Orphanet Report Series⁴⁵.

The analysis of this list shows that some disease areas were far more frequently covered than others, as shown in the following table (see Figure 5):

Medical domain	Number of European projects
Infectiology	61
Neurology	37
Inborn errors of metabolism	12
Oncology	11
Immunology	9
Respiratory diseases	8
Cardiology	6
Ophthalmology	6
Dermatology	5
Ciliopathies	3
Hematology	3
Nephrology	3
Systemic & rheumatological diseases	3
Bone diseases	2
Endocrinology	2
Gastroenterology	2
Hepatology	2
Malformative diseases	2

Figure 5: Medical areas concerned by European projects funded by FP5, FP6, FP7 or E-Rare

It is not possible to examine what is justified or not based on the available data.

3.2. State of the art of testing for rare diseases

Research aims at improving the knowledge on a disease or a group of diseases. One of its goals that deserves particular attention is improving diagnosis in order to reduce diagnostic variability, which is a classical feature of rare diseases.

Currently available testing in Europe is summarized in Figure 6. The number of genes tested and number of laboratories differs considerably among European countries.

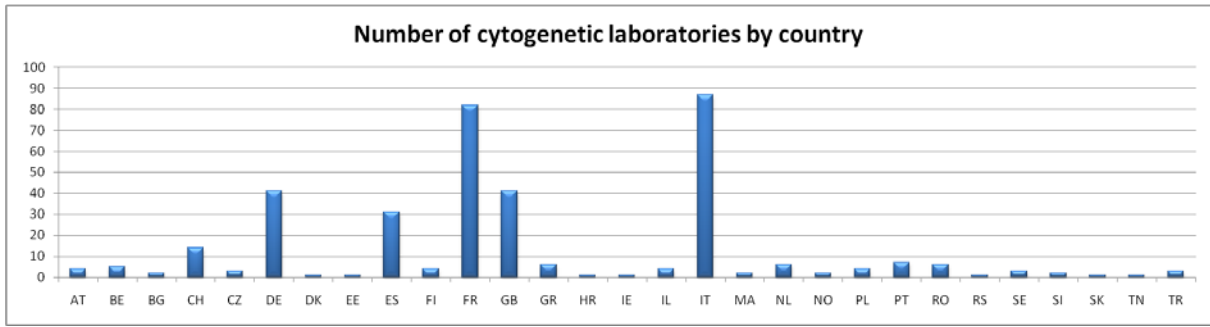
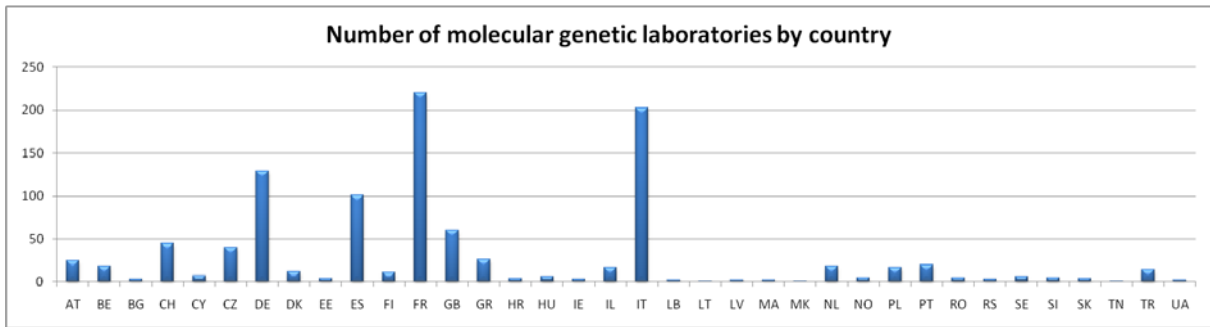
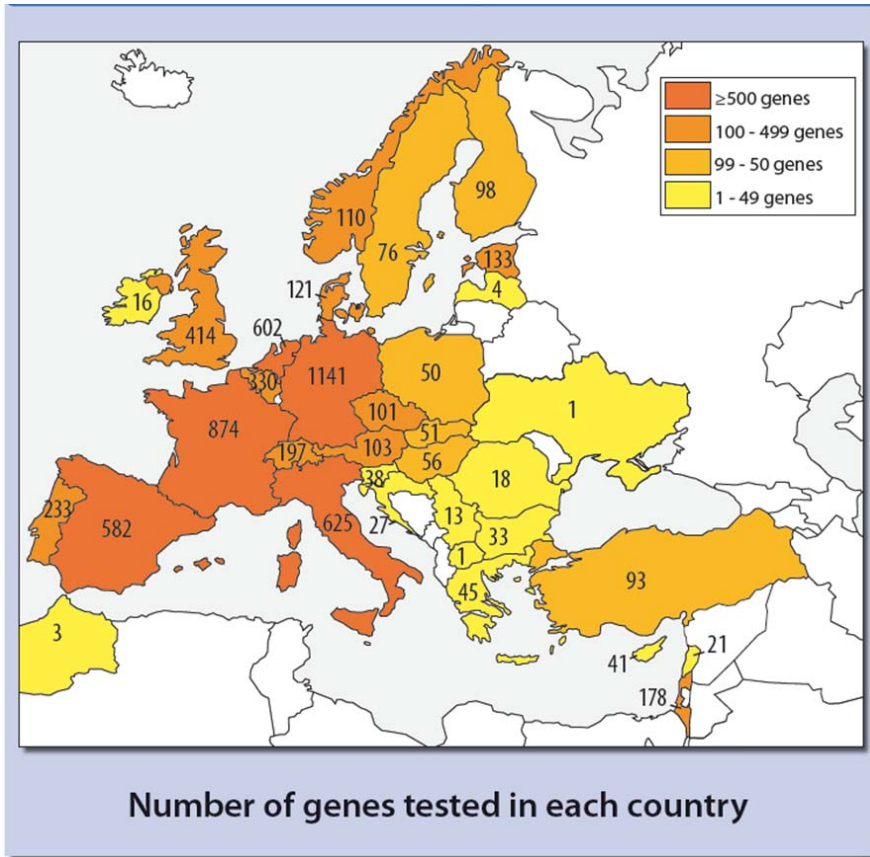


Figure 6: Available testing in Europe

In addition, the Top 25 diseases tested in the highest number of countries is provided in Figure 7.

Disease	Number of countries
Cystic fibrosis	32
Hemochromatosis	27
Duchenne and Becker muscular dystrophy	26
Fragile X syndrome	26
Nonsyndromic genetic deafness	25
Angelman syndrome	24
Familial breast cancer	24
Chromosome Y deletion	24
Huntington disease	24
Prader-Willi syndrome	24
Familial nonpolyposis colon cancer	23
Congenital factor II deficiency	23
Friedreich ataxia	23
Phenylketonuria	23
Homocystinuria due to methylenetetrahydrofolate reductase deficiency	22
Steinert myotonic dystrophy	22
Congenital factor V deficiency	21
Proximal spinal muscular atrophy	21
Achondroplasia	20
Beta-thalassemia	20
Chronic myeloid leukemia	20
Monosomy 22q11	20
Multiple endocrine neoplasia, type 2	20
Rett syndrome	20
Williams syndrome	20

Figure 7: Top 25 diseases tested in the highest number of European countries

3.3. State of the art of therapeutic development

3.3.1. Current landscape of R&D/Therapy development

A recently published study indicates that the orphan regulation has stimulated research into rare diseases in the US⁴⁶. The EMA shares this view⁴⁷.

3.3.1.1. Pipeline of products in Europe

There are three main indicators to monitor R&D activity in the field:

- The annual number of designations which reflect the activity at an early stage of development, usually the pre-clinical stage. This information is available on the EMA website.
- The number of clinical trials performed annually. This information was very difficult to retrieve until recently as it was not released by the EMA. It is now available online on the following website: <https://www.clinicaltrialsregister.eu/>. So far, Orphanet has collected the information from multiple sources and releases it on its website, but the data cannot be considered comprehensive.
- The annual number of marketing authorisations. This information is available on the EMA website.

3.3.1.2. Orphan designations for orphan medicines⁴⁸

Currently the status of orphan-designation applications is the following:

- 1113 applications have been submitted to date for the designation of orphan medicines.
- 760 positive opinions on orphan designation have been adopted by the COMP.
- 269 applications have been withdrawn and 16 have received a negative COMP opinion.
- 724 medicines have been granted orphan status by the European Commission.

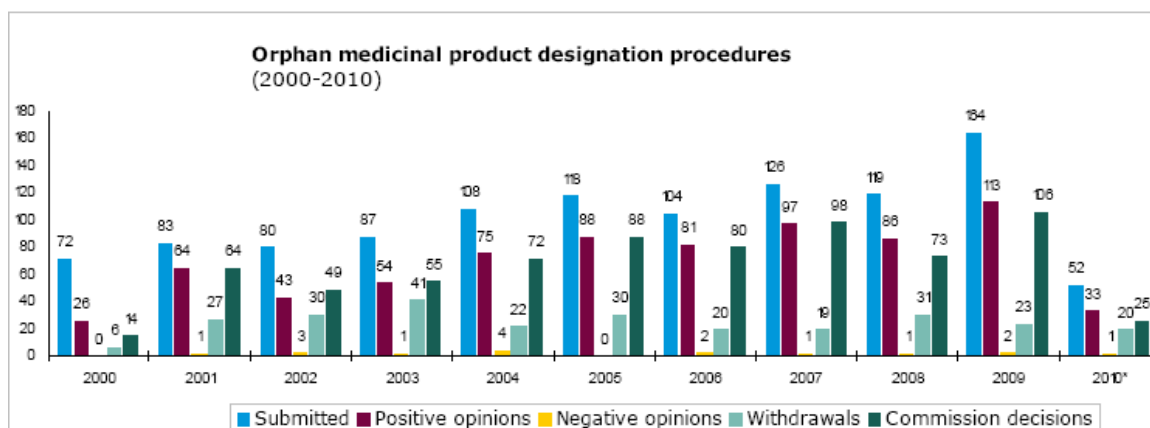


Figure 8: Orphan medicinal product designation procedures (2000-2010) – Source: EMA
* Figures for 2010 as of 30 April 2010.

Currently, 704 designations are active, intended to treat 322 different RDs and representing 578 different products.

3.3.1.3. Marketing authorisations for orphan medicines⁴⁹

A total of 114 marketing authorisation applications for orphan-designated medicines have been submitted to the European Medicines Agency since 2000. 62 orphan-designated medicines have received a marketing authorisation valid across the EU.

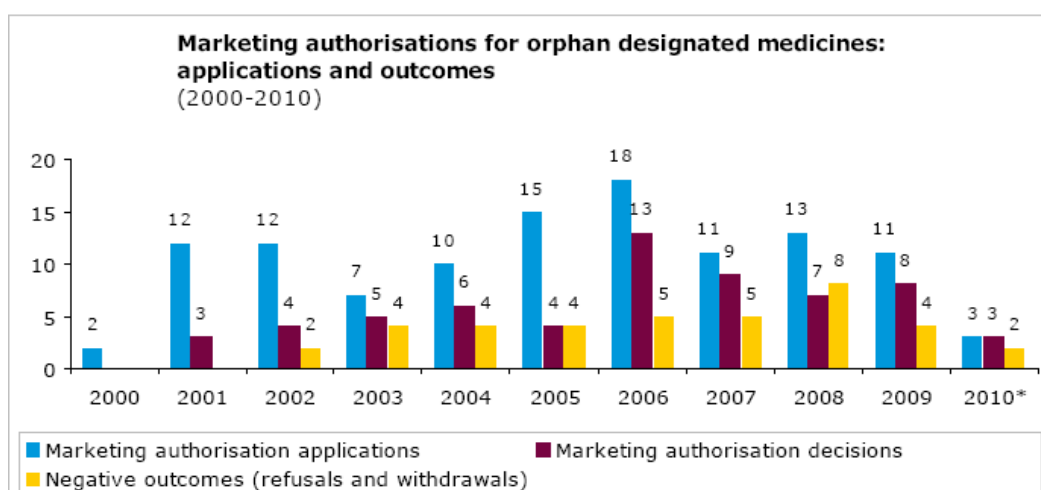


Figure 9: Marketing authorisations for orphan-designated medicines: applications and outcomes (2000-2010) – Source: EMA / * Figures for 2010 as of 30 April 2010.

These marketing authorisations concern indications for the treatment of 66 different RDs and represent 61 different products.

These figures demonstrate that R&D is flourishing in the field of RDs but also that therapeutic developments are far too limited compared to needs.

3.3.2. Determinants of R&D

3.3.2.1. Prevalence of RDs as a determinant

One question we can ask is whether the degree of rarity influences efforts or even the success of research in rare diseases, as it has been suggested that prevalence directly affects the likelihood of obtaining an orphan designation⁵⁰.

When looking at the figures of the COMP (Committee for Orphan Medicinal Products) regarding COMP opinions by prevalence of condition, the majority of conditions for which products have been given orphan designation affect between one and three in 10 000 people in the EU (see Figure 10).

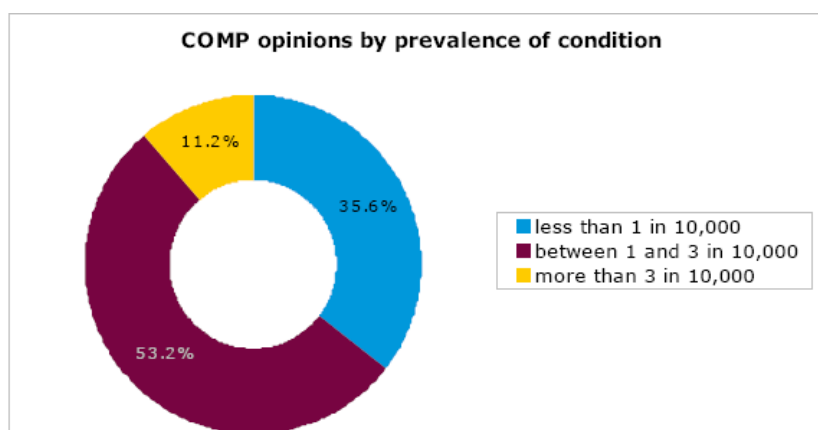


Figure 10: COMP opinions by prevalence of condition⁵¹

Therefore, although a “higher” prevalence could lead to an increased awareness of a disease and could facilitate some aspects of research such as clinical research, there is no clear correlation between the level of prevalence and the submission of an orphan designation, which means that Industry is willing to develop products for diseases with a very low prevalence, providing that there is a real medical need and a good potential product.

3.3.2.2. Medical area as a determinant in Europe

While low prevalence is a characteristic feature of RDs, this field is actually very heterogeneous and considering RDs as a single group may sometimes obscure the analysis. This is why it may be interesting to consider RDs by medical field in order to establish some specific trends.

Harald E. Heemstra⁵² highlighted the fact that disease-specific factors or disease classes are of high interest when examining the translation of rare disease research into orphan drug development. For example, rare cancers could be considered, on the one hand, because they often benefit from the global research momentum in the oncology field⁵³. Indeed, rare cancers, such as acute myeloid leukaemia for instance, are in the top 20 indications for which drugs that have been granted an orphan designation by the COMP (see Figure 11).

Designated Orphan Indication	Number of Designation
Treatment of acute myeloid leukaemia	31
Treatment of glioma	24
Treatment of cystic fibrosis	22
Treatment of pancreatic cancer	19
Treatment of renal cell carcinoma	18
Treatment of acute lymphoblastic leukaemia	17
Treatment of multiple myeloma	15
Treatment of ovarian cancer	14
Treatment of chronic lymphocytic leukaemia	11
Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	11
Treatment of hepatocellular carcinoma	11
Treatment of Duchenne muscular dystrophy	10
Treatment of chronic myeloid leukaemia	8
Treatment of cutaneous T-cell lymphoma	8
Treatment of Hodgkin's lymphoma	8
Treatment of idiopathic pulmonary fibrosis	8
Treatment of soft tissue sarcoma	8
Treatment of amyotrophic lateral sclerosis	7
Treatment of acute lung injury	6
Treatment of myelodysplastic syndromes	6
Treatment of tuberculosis	6

Figure 11: Top 20 indications for drugs that have been granted an orphan designation by the COMP (Rare cancers are highlighted in blue)

The observed differences may also be explained by the differences in the feasibility of identifying a suitable target and drug lead. Thus, a metabolic disease which results from the defect of one specific enzyme may be treated by the replacement of the lacking protein. On the other hand, for developmental anomalies leading to congenital malformations, most of the time there are no therapeutic possibilities because of the intrinsic nature of these disorders.

Another determinant of the likelihood for a product being developed in a specific area is the number of publications per disease, by disease class and time period. The number of publications for each rare disease included in the study published by Heemstra⁵⁴ was determined using a PubMed⁵⁵ search. For each disease, a PubMed search string was developed consisting of the disease name and synonyms of the disease mentioned in the Orphanet database⁵⁶. The possibility of including a publication erroneously because the disease name corresponds to an author (e.g. Wilson disease) or a geographic region (e.g. Japanese encephalitis, West syndrome) was addressed by including Boolean NOT statements and PubMed search field tags for these terms, in a way comparable to that of Mendis and McLean⁵⁷. All searches were limited to English language articles and original research or case reports only. Reviews, comments and letters were excluded. (see Figure 12)

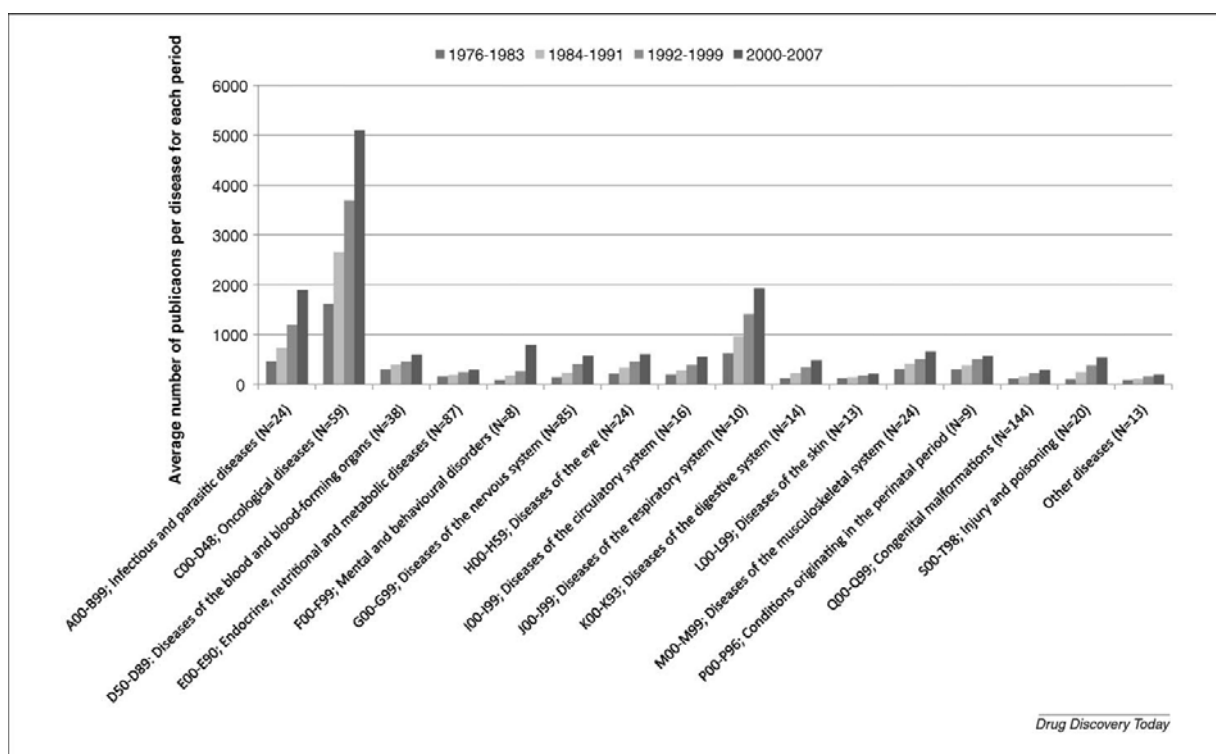


Figure 12: Average number of publications per disease, by disease class and time period⁵⁸.

These data clearly show that research is a long-term process which builds on previous results. Therefore, R&D activities are only launched if there have already been several decades of basic, preclinical and clinical research in the field. This is why it is unsurprising to see that the products on the market, both in Europe and in the US, cover areas where there is a long tradition of research.

As shown in the two figures from the EMA (see Figures 13&14), for potential drugs that have been granted an orphan designation by the COMP and for drugs that have been granted a marketing authorisation by the CHMP (through a centralised procedure at the EMA), the main therapeutic area concerned is oncology: this illustrates the preceding discussion and highlights the fact that there is actually a similar proportion of potential drugs in the pipeline to those on the market with an indication in oncology. In terms of numbers, we can consider that there are about 10-12 times more products with an orphan designation than those on the market (62 orphan drugs to date), which gives an idea of the number of drugs currently in development in the area of oncology.

A list of orphan drugs in Europe is available in the Orphanet Report Series “Lists of Orphan Drugs in Europe”⁵⁹.

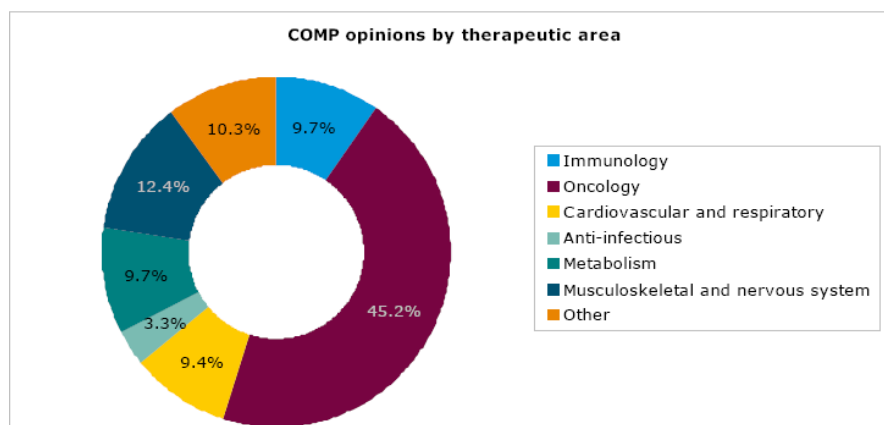


Figure 13: COMP opinions by therapeutic area⁶⁰

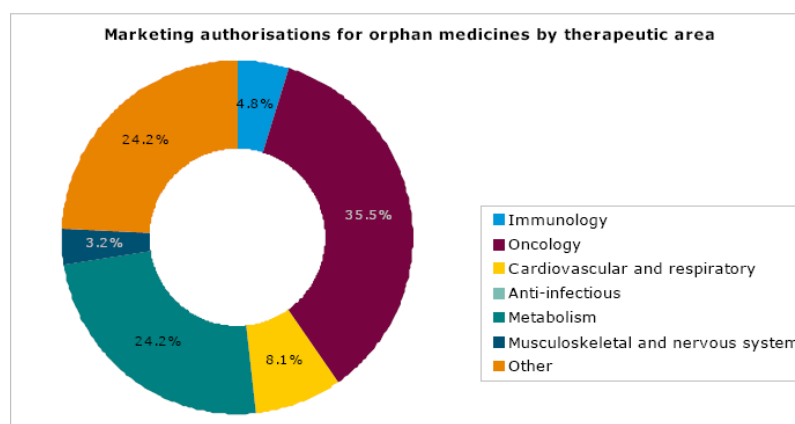


Figure 14: Marketing authorisations for orphan medicines by therapeutic area⁶¹

The development of products in the field of inborn errors of metabolism has also been very successful, but we can see that the percentage is higher for marketing authorisations than for orphan designations, perhaps showing a loss of momentum related to the lack of new therapeutic targets and the difficulties the manufacturer encounters with recombinant proteins.

On the contrary, the number of products with a therapeutic indication in a disease affecting the musculoskeletal and nervous system is quite low, whilst there are many products in development that have been granted an orphan designation. This probably reflects specific difficulties in the R&D process for neuromuscular and neurological diseases, amongst them the difficulty of defining outcome measures.

Beyond the usual process of basic research leading to therapeutic development (either drugs or biological products) that will then benefit from the regulation on orphan drugs, we must also consider other fields of research.

When looking at the products in development at the disease level, rather than at the medical area level, it appears that a small number of diseases have obtained several orphan designations, indicating that these diseases are in mature fields where innovation occurs rapidly. Figure 15 provides the list of diseases with three or more orphan designations. The diseases in blue are from the oncology field.

Designated Orphan Indication	Number of Designation
Treatment of acute myeloid leukaemia	31
Treatment of glioma	24
Treatment of cystic fibrosis	22
Treatment of pancreatic cancer	19
Treatment of renal cell carcinoma	18
Treatment of acute lymphoblastic leukaemia	17
Treatment of multiple myeloma	15
Treatment of ovarian cancer	14
Treatment of chronic lymphocytic leukaemia	11
Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	11
Treatment of hepatocellular carcinoma	11
Treatment of Duchenne muscular dystrophy	10
Treatment of chronic myeloid leukaemia	8
Treatment of cutaneous T-cell lymphoma	8
Treatment of Hodgkin's lymphoma	8
Treatment of idiopathic pulmonary fibrosis	8
Treatment of soft tissue sarcoma	8
Treatment of amyotrophic lateral sclerosis	7
Treatment of acute lung injury	6
Treatment of myelodysplastic syndromes	6
Treatment of tuberculosis	6
Treatment of Gaucher Disease	5
Treatment of Graft-versus-Host disease	5
Treatment of haemophilia A	5
Treatment of Huntington's disease	5
Treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis	5
Treatment of systemic sclerosis	5
Treatment of Familial Adenomatous Polyposis	4
Treatment of follicular lymphoma	4
Treatment of gastric cancer	4
Treatment of haemophilia B	4
Treatment of malaria	4
Treatment of mantle cell lymphoma	4
Treatment of retinitis pigmentosa	4
Treatment of spinal cord injury	4
Treatment of traumatic spinal cord injury	4
Conditioning treatment prior to haematopoietic progenitor cell transplantation	3
Prevention of the ischaemia/reperfusion injury associated with solid organ transplantation	3
Treatment of acromegaly	3
Treatment of adrenal insufficiency	3
Treatment of Fabry disease	3
Treatment of Friedreich's ataxia	3
Treatment of gastro-entero-pancreatic neuroendocrine tumours	3
Treatment of hyperphenylalaninaemia	3
Treatment of idiopathic thrombocytopenic purpura	3
Treatment of malignant gastrointestinal stromal tumours	3
Treatment of metachromatic leukodystrophy	3
Treatment of neuroblastoma	3
Treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated)	3
Treatment of post-essential thrombocythaemia myelofibrosis	3
Treatment of post-polycythaemia vera myelofibrosis	3
Treatment of primary myelofibrosis	3
Treatment of progressive supranuclear palsy	3
Treatment of sickle cell disease	3
Treatment of small cell lung cancer	3
Treatment of visceral leishmaniasis	3
Treatment of Wilson's disease	3

Figure 15: Designated Orphan indications with 3 or more designations

This table shows that oncology is the most successful area. Cystic fibrosis is the top-ranking non-cancer RD with a high number of products in development, a disease which does not yet have a product on the market.

When looking at the 62 drugs on the European market with an indication for an RD, which do not have an orphan status because they did not ask for an orphan designation or because they were marketed before the orphan regulation, their distribution by medical area is very similar to the distribution for orphan drugs, as shown on Figure 16:

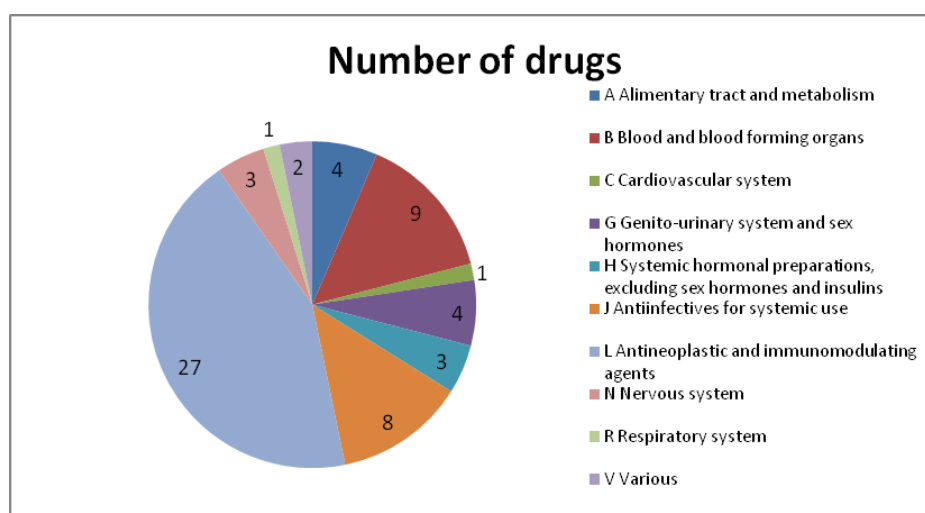


Figure 16: Number of drugs with at least one indication for a rare disease but without orphan status by ATC category

3.3.2.3. Medical area as a determinant in the USA

Currently⁶², 2 002 products have obtained orphan drug designation with 352 drugs obtaining FDA approval. Approximately 33% of orphan drugs are oncology products. On average, products obtain 1.7 orphan designations with approximately 70% obtaining a single designation. At least 9% of orphan drugs have reached blockbuster status with two-thirds having two or more designations. An additional 25 orphan drugs reached sales exceeding US\$ 100 million in 2008 alone. Since 1983, at least 14 previously discontinued products have been recycled as orphan drugs.

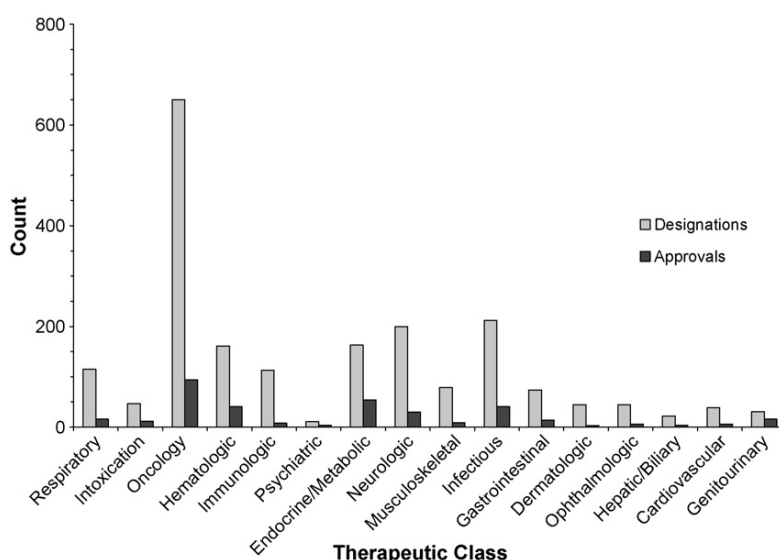


Figure 17: Classification according to therapeutic class of orphan drug designations (grey bars) and orphan drug approvals (black bars) granted in the United States during the period of 1983–2009⁶³.

The distribution by medical area is very similar to the distribution in Europe.

3.3.2.4. Contribution of European countries to the R&D process

An analysis of the contribution of the European countries to the R&D process for RDs has been published⁶⁴, based on the first 300 orphan designations. The country of origin of a designated orphan medicinal product was defined as the country in which the company or institution was located that led the step from preclinical work to initial clinical development of the particular product for the designated indication (typically Phase I or Phase I/IIa clinical trials or proof-of-concept). For products not yet in clinical development, the country of origin was determined as the country in which the company or institution was located that led the latest preclinical development program for the designated indication. For multinational companies, the country of origin was defined as the country of the headquarters of the company. Publicly available sources (e.g. PubMed, company websites, patent databases, press releases) were used to determine the country of origin. Data in (b) were standardised per million of population (2000–2007). (See Figure 18)

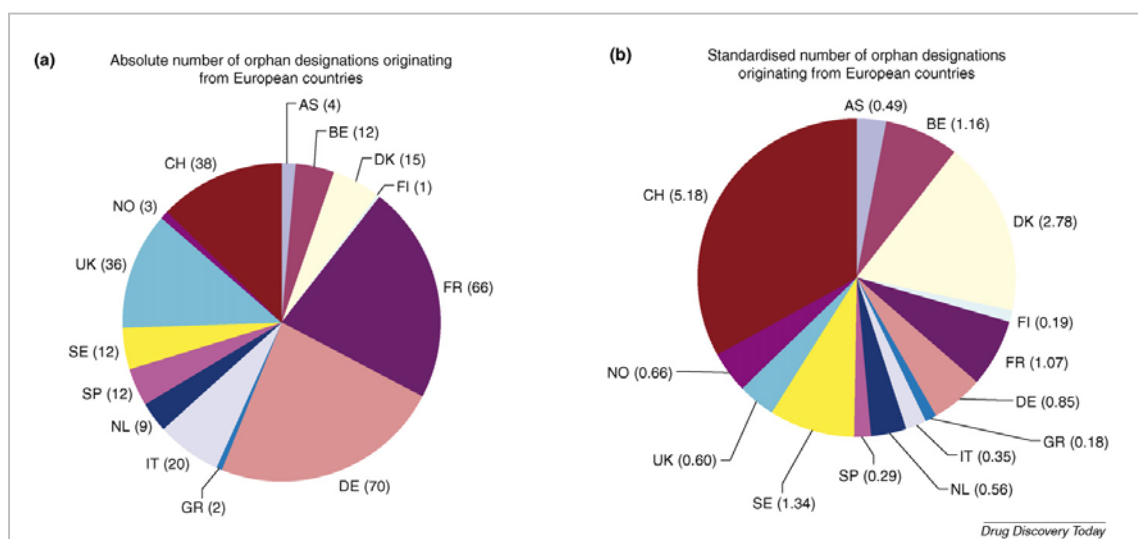


Figure 18: Absolute and standardised number of orphan designations originating from European countries⁶⁵ (AS, Austria; BE, Belgium; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; IT, Italy; NL, the Netherlands; SP, Spain; SE, Sweden; UK, United Kingdom; NO, Norway; CH, Switzerland.)

Another part of the analysis concerns biomedical scientific output, innovation in pharmaceutical development and orphan designations in Europe⁶⁶. Rankings of pharmaceutical innovation performance are calculated from the integer of the combined ranking of expenditures on pharmaceutical R&D, pharmaceutical patents and pharmaceutical SMEs. Rankings for biomedical scientific output are based on the number of citations in biomedical sciences. Only countries for which data were available for all indicators have been included in the graph. ‘Bubble’ size corresponds to the standardised number of orphan designations for each country (in brackets). Countries corresponding with the ‘bubbles’ in the top right-hand corner of the graph (Switzerland, Denmark, Sweden) rank highest in pharmaceutical development and scientific output. The number of orphan designations from Sweden is lower than expected based on its position in the graph. The group of countries corresponding to the ‘bubbles’ in the middle of the graph develop average numbers of orphan designations. The two ‘bubbles’ above this group represent countries (Finland and the Netherlands) that have a lower ranking for innovation in pharmaceutical development than for scientific output.

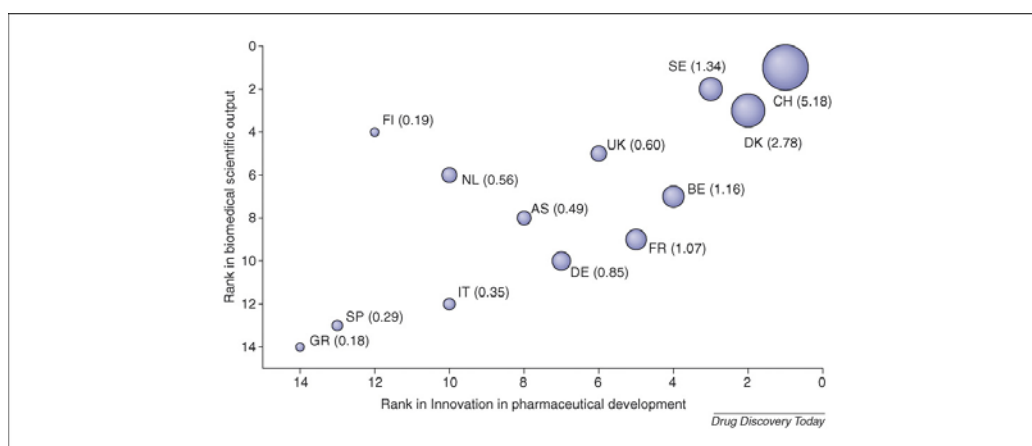


Figure 19: Biomedical scientific output, innovation in pharmaceutical development and orphan designations in Europe⁶⁷. (AS, Austria; BE, Belgium; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; IT, Italy; NL, the Netherlands; SP, Spain; SE, Sweden; UK, United Kingdom; NO, Norway; CH, Switzerland.)

This data shows that there are large differences between European countries in terms of contribution to the R&D process, which are neither fully explained by the ranking of the country as regards innovation in pharmaceutical development, nor by the ranking in biomedical scientific output.

3.3.2.5. The case of medical devices

Some of the diseases that would not be candidates for the development of drugs or biological products, gene or cell therapies, could also benefit from the development of medical devices. While a regulation on orphan drugs does exist both in the Europe and the US, medical devices for rare diseases are not considered in any special way in European countries. However, the US regulation pays attention to this issue with the regulation of 1990 on Humanitarian Use Devices and the establishment of the Humanitarian Device Exemption⁶⁸. Medical devices are then eligible to orphan products grants at the same level as drugs in development in the US. This concern is coming into the foreground in Europe with debates about whether or not to revise the current regulation on medical devices to be used by small populations.

3.3.3. Other considerations regarding the field of R&D

Research may also be dedicated to the improvement of knowledge on a particular disease or a group of disease in a broader way, in order to better diagnose the patient suffering from a rare disorder, to complete the natural history of a disease, to identify the state of the art and finally to improve the global care of patients. Because the understanding of a disease forms the necessary foundation for any successful discovery and development program⁶⁹, the more a disease is identified, the more knowledge will be produced, the more scientific publications will be published, and therefore the more the disease will be highlighted...

This is the point of view of patient organisations, a view which cannot be ignored when considering research in the field of rare diseases. Patient organisations have been a huge motor in the development of research programs: the diseases or medical fields that have benefited the most from their involvement are cystic fibrosis and neuromuscular disorders. Patients were therefore

implicated in the beginning of the development of enzyme replacement therapies⁷⁰. A study conducted by EURORDIS in 2009 showed that funding from patient organisations is mainly focused on basic research, while they consider public funding for clinical, diagnostic and therapeutic research to be a high priority⁷¹.

Therefore, one of the most important issues is to identify the neglected sectors of research and the specific needs in terms of unmet medical needs, unmet device needs, etc.

The identification of unmet medical needs seems to be a main driver of R&D in the field of rare diseases as this is the major reason for patient organisations to collaborate with researchers and Industry; academic researchers are already highly motivated by this topic and it is also a very attractive feature for Industry.

There is a large gap between the current basic scientific knowledge and clinical development for RDs, more so than in other areas in medicine, due to the limited knowledge concerning these diseases by the scientific community and Industry, and due to the limited knowledge in general concerning each disease.

This has led to the creation of the “Critical Path Research” consortia as the interface between industry members and the US Food and Drug Administration (FDA). One part of this, the Predictive Safety Testing Consortium, is dedicated to biomarkers in order to establish the “fit-for-purpose evidentiary process of linking a biomarker with biological processes and clinical endpoints”. In addition, the EMA and the FDA have concluded the first joint qualification process for biomarkers, following the submission of scientific data by the Predictive Toxicology Consortium (C-Path PSTC). Under the C-Path PSTC, the pharmaceutical industry has for the first time pooled together data from different companies in order to achieve the critical mass of scientific information that allowed the Agency and FDA to qualify the use of seven biomarkers of drug-induced renal toxicity in the context of non-clinical drug development. Data were submitted to both regulatory agencies and jointly evaluated using state-of-the-art standards⁷².

Another issue is that earlier orphan drug research and development activities were usually conducted by academics and/or smaller start-up biotechnology companies. While academics are quite familiar with FP7 application procedures, SMEs are not usually well prepared for this⁷³. In fact, there are some hurdles in the process that make it difficult for SMEs. In such programmes, research topics are predefined and funding is related to long cycles, two features that do not fit with SME requirements. In the field of biomedical engineering and medical technology (that can sometimes overlap with the field of rare diseases), the European Commission has funded the SM BIO POWER project which aims at assisting SMEs with their participation in EU research⁷⁴.

Finally, during the R&D process the problem of rarity is the most crucial at the stage of clinical evaluation due to the difficulty in designing and monitoring clinical research in small populations. In the context of clinical trials, rarity means a small number of patients and therefore necessitates multiple, geographically distinct sites: this practice is associated with high costs⁷⁵. For example, Replagal® and Fabrazyme®, the two first orphan drugs indicated for the treatment of Fabry disease, have been approved with reference to pivotal clinical trials on 41 and 56 patients, respectively⁷⁶. Clinical trials in the field of rare diseases suffer from some weaknesses: because of the small number of participants, a statistically significant benefit may be difficult to reach; clinical trials are often too

short regarding the natural history of a disease; they lack surrogate end-points with strong evidence of validity; they are often placebo-controlled (instead of controlled with an active comparator); and it has been stated that only 57% of approved orphan drugs have been tested in a randomised clinical trial before approval⁷⁷.

Moreover, the significant benefit is always questionable as is the possible acceptable benefice/risk ratio as we are dealing with chronic and life-threatening diseases: "Doing no harm or doing nothing which is a fatal risk?"⁷⁸. How to define benefit in a progressive disorder where some endpoints may vary with age of patients and progression of diseases is another question raised. This issue is increasingly complicated when considering advanced therapies or paediatric population.

Some regulatory assistance has been proposed⁷⁹. In 2006, the EMA issued guidelines for small clinical trials giving a hierarchy of evidence from placebo-controlled studies to case reports. The FDA organises training for investigators. Both agencies are working on relationships between agencies and with developers including protocol assistance, scientific advice, joint advice program, guidelines for annual reporting.

Furthermore, since 2003, NIH has established the Rare Diseases Clinical Research Network to ensure better recruitment of patients. We can draw a parallel with the European network ECRIN⁸⁰. A new application has been submitted to pursue this project and to establish a European hub for clinical research in order to provide help for designing and monitoring clinical trials, especially to academics and SMEs. One specificity of Europe is the fact that clinical trials have to be multicentric and also multinational: this raises issues regarding the different laws of each Member State, different ethic committees requiring different protocols, different rules regarding compassionate use, etc.

There are already several different European initiatives, such as the European Centre for Clinical Trials in Rare Diseases⁸¹, one of a European Network of Centres of Excellence, whose objective is to facilitate the conduct of clinical trials in rare diseases at the National University of Ireland, Cork. This network focuses on one technical aspect of the research in rare diseases, i.e. the clinical part; other types of Networks of Excellence are also used as instruments for strengthening excellence by tackling the fragmentation of European research, but these may be focused on a group of diseases, such as Treat-NMD⁸² which offers a translational view of each step of research in neuromuscular diseases.

In addition to the difficulty of conducting clinical trials in a rather effective manner to obtain a marketing authorisation, there is a possible lack of knowledge concerning the safety profile of the tested therapeutic agent which could lead to safety issues in clinical practice. These findings seem to be even more accurate when the marketing authorisation is obtained following accelerated circumstances, such as approval under exceptional circumstances or conditional approval⁸³. Thus, emphasis has been put on risk management strategies and pharmacovigilance, through post-marketing plans, phase 4 studies after approval and/or follow-up studies using cohorts of patients or registries⁸⁴.

Because of the small number of patients affected by a specific rare disease, it is often impossible to reach a critical mass of patient data at national level to allow efficient basic and clinical research. To ensure this critical mass it is essential to establish international collaborations to share patient datasets. It is essential to define the mandatory dataset which will be shared between national registries or sources of data. When defining the mandatory dataset of a patient registry, it is important to bear in mind the end use of the registry data. Indeed, patient registries are tools to

collect genetic and clinical data necessary for clinical trial recruitment and post marketing surveillance, but they also have many other uses: epidemiological studies, gene/mutation search, genotype/phenotype correlations, natural history studies, comparison of care standards, marketing feasibility, data collection for cost effectiveness of treatments, etc. Maintaining the anonymity of participants is a particular challenge for rare disease clinical research because of the small number of patients, so access to and utilisation of the information collected should include ethical and privacy considerations⁸⁵.

In conclusion, we can see that rarity in the R&D area in the field rare diseases is a challenge in terms of identifying patients with unmet medical needs, identifying existing skills and already available tools, designing and monitoring accurate clinical research and managing in the meantime technical, methodological and regulatory issues. Some indicators have been identified which have been associated with failure of clinical development programmes. Failure is often due to type/size of the developer (i.e. SMEs have higher negative outcomes), to an inadequate demonstration of efficacy and/or safety, to a failed development strategy or an immature application to regulatory authorities, some of these findings may be resolved or at least improved by compliance with scientific advice or protocol assistance guidance⁸⁶.

3.4. Research infrastructures

3.4.1. Disease registries

Patient registries (PRs) and databases constitute key instruments to develop clinical research in the field of rare diseases (RDs), to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients.

According to the Orphanet database accessed in December 2010, there are 514 Disease Registries in Europe (50 European, 29 International, 373 national, 61 Regional, 1 undefined). The complete list is provided in the Orphanet Report Series “Disease Registries in Europe”⁸⁷. The European registries cover the medical areas presented in Figure 20:

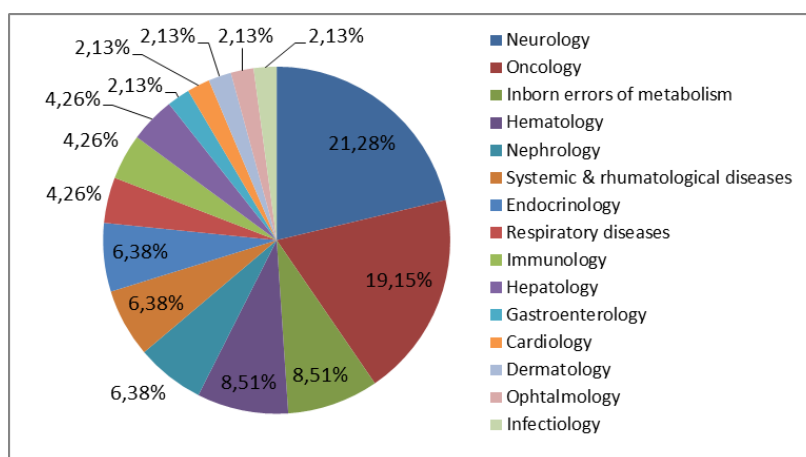


Figure 20: Medical areas with patient registries

Almost all of them are for diseases or for groups of diseases where there is an innovative treatment, either in development or already on the market. This is not surprising as registries of patients treated with orphan drugs are particularly relevant: they enable evidence to be collected on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorisation is usually granted at a time when evidence is still limited although already somewhat convincing.

Most of the registries are established in academic institutions. A minority of them are managed by pharma or biotech companies, others being run by patient organisations. (See Figure 21)

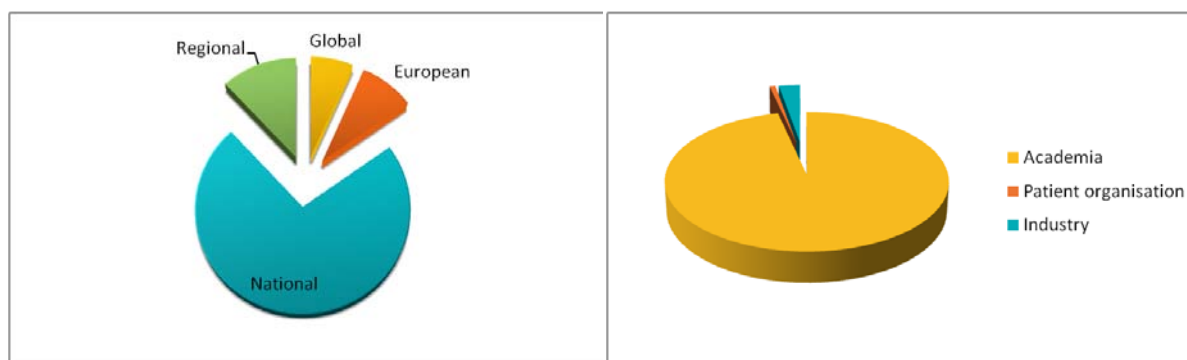


Figure 21: Characteristics of patient registries

When established, databases should be maintained and their use optimised through exchange of data between interested parties. However, the status of such databases is not well defined and most institutions have no written policies or agreements regarding this activity.

Regulations concerning registries are in early stages in most European countries and, with the multiplicity of actors and of rules at MS level, the situation is difficult to comprehend. No guidelines are available yet on best practices for exchanging and sharing data. The notion of return of benefits to research subjects or communities is fairly recent.

Databases are expensive to establish and maintain. They require the cooperation of many healthcare providers and require careful management. PRs should only be established when financial resources and expertise are present to support them. Furthermore, PR systems tend to have added value if the disease in question has a good prospect for intervention, control, prevention and for research that can lead to these ends.

They are of high interest to researchers, industrial partners, healthcare professionals and ultimately to the community. It is difficult to separate public and private research, as researchers from both sectors are often involved in the same projects. Whilst this enables effective technology transfer, it also gives rise to concerns about conflicts of interest. There is a need to promote confidence in research based on data collections.

Patient registries have been in place for several decades in sectors such as cancer, birth defects and cardiovascular diseases. This long and broad history of data collection is the basis on which to build guidelines for registration of patients with an RD, although RD patient registries have some additional features which make them specific:

- Most RDs are genetic in origin and a large proportion of them are familial, which implies that family related cases have to be traceable;

- The scarcity of cases imposes a large geographical coverage of data collection which implies multiple collaborations and exchanges of data, usually transnationally;
- The cost of establishing and maintaining a PR is nearly equal for a prevalent disease as it is for an RD, although budgets are more difficult to obtain for the latter.

Collaborative efforts to establish and maintain data collection should be supported, providing that these resources are accessible through agreed upon rules. Many research and public health networks financially supported by DG RTD and by DG SANCO have put in place such shared infrastructures, which have been proven to be very efficient tools in improving knowledge and organising clinical trials.

Areas to be supported by the MS and the European Commission include: quality standards, development of strategies and tools for periodic monitoring of the quality of databases and for database upkeep; a minimum common set of data to be collected for epidemiological and public health purposes; attention to user-friendliness, transparency and connectivity of databases; intellectual property; and communication between databases/registries (genetic, more generically diagnostic, clinical, surveillance-driven, etc). Importance should be given to linking international (European) databases to national and/or regional databases, when they exist. Finally it is vital to promote the establishment of disease registries and to ban product registries, in order to have unified sources of data on patient outcomes, for diseases for which there are several therapeutic options.

3.4.2. Ontologies and Bioinformatics for Rare Disease Research

3.4.2.1. Ontologies for RDs

The field of rare diseases stands to profit from bioinformatics like no other field in medicine. Amongst the most important uses of bioinformatics for research and diagnostics in rare diseases are ontologies of phenotypic features (signs, symptoms, and findings of diseases), and ontologies (nosologies) of diseases and disease groups. Ontologies are structured, automated representations of the knowledge within a certain domain⁸⁸. Ontologies provide a classification of the entities within a domain, and their relationships to one another, and are increasingly being used to define a standard, controlled vocabulary for different fields in science and medicine.

Ontologies have been developed for a large number of domains in biomedical research. The most widely used ontology is the Gene Ontology (GO), which provides structured, controlled vocabularies and classifications for several domains of molecular and cellular biology and is structured into three domains, molecular function, biological process and cellular component⁸⁹. Other biomedical ontologies of broad interest include the Mammalian Phenotype Ontology⁹⁰, the Foundational Model of Anatomy (FMA) ontology⁹¹, the Sequence Ontology⁹², the Cell-Type ontology⁹³, the Chemical Entities of Biological Interest (ChEBI) ontology⁹⁴, and the mouse pathology (MPATH) ontology⁹⁵, amongst many others⁹⁶. GO has been extensively adopted by the molecular biology community as a kind of lingua franca for describing the biological function of gene products in humans and model organisms using a consistent and computable language. Although GO was originally developed to primarily provide a means for integration, retrieval, and computation of data, it is now commonly used to help understand the results of high-throughput expression profiling experiments, network modelling, analysis of semantic similarity, and many other applications⁹⁷.

Clinical medicine and research have not yet embraced ontologies and information technology to the same extent. Clearly, improving knowledge transfer between researchers and practicing physicians, as well as improving the exchange of information amongst clinicians themselves, are essential measures for streamlining research, improving clinical decision making based on current research findings, and making optimal use of available information to improve the quality of patient care.

The Human Phenotype Ontology (HPO) has been developed as a tool for the analysis and annotation of human phenotypic abnormalities, especially those typically found in rare diseases⁹⁸. The HPO allows the use of ontological search algorithms to improve the performance of computer algorithms designed to support the differential diagnostic process in medical genetics⁹⁹.

At the same time, the development of the ontology of traits and qualities PATO and advances in ontology algorithms have begun to enable cross-species phenotypic analysis^{100&101}, and the integration of multiple ontologies into a semantic network allows terms from one ontology to be defined using other ontologies. To give a simple example, it is possible to define the GO term Nitrate reductase activity as an oxidoreductase activity (GO:0016491) that reduces nitrate (CHEBI:17632). A collaborative project between the Berkeley Ontology group that includes founding members of the GO consortium and the OBO Foundry, the University of Cambridge, and the HPO team, has been initiated to provide logical definitions of human phenotypic abnormalities by providing all HPO terms with computer readable logical links to ontologies for anatomy, biochemistry, cell types, pathology, proteins, and to GO itself (n.b. a preliminary report has been published¹⁰²). This will allow computational comparisons of all 5 000 diseases currently annotated with HPO terms to model organism (mouse, zebrafish) phenotypes, will allow the structure of the HPO to be aligned to current knowledge in anatomy, physiology, and molecular genetics, and will provide a platform for computationally linking phenotypic abnormalities to many other fields of biomedical research via the linked ontologies.

3.4.2.2. Next-generation sequencing (NGS) technologies

Next-generation sequencing (NGS) technologies are poised to revolutionise diagnostics in the field of genetic diseases. It is now possible to determine the DNA sequence of the protein-coding exons of nearly all genes in the human genome for a few thousand Euros (the price is likely to fall under a thousand Euros in the near future).

A number of groups in the United States and Europe have begun to harness this technology to discover new disease genes¹⁰³. It is widely expected that next-generation technologies will considerably accelerate the pace of discovery of new disease genes in the next several years. The molecular basis of approximately 3 000 Mendelian traits has been clarified since the discovery of the first gene mutations in the cystic fibrosis gene nearly three decades ago. There are almost 4 000 rare diseases with a known or suspected Mendelian basis for which the disease gene has not yet been identified, and it appears likely that the basis of most of these diseases will be clarified in the next ten years. Additionally, the molecular aetiologies of rare diseases such as congenital heart defects with a suspected oligogenic basis – whereby mutations in two or in a few genes are responsible for the disease phenotype – are amenable to investigation with NGS technologies.

Although animal models are of great value, using the wealth of existing human variation (incl. rare genetic traits) should be quite simple, effective, relatively cheap and of even greater value. Unfortunately, this resource is not used to its full potential. Applying existing (next-generation sequencing) and soon to be available technology (stem cell/iPS directed differentiation), we could learn a great deal. Samples to be analysed include cases from all rare diseases, typical examples (peculiar pathogenic variants) of more common diseases and any (larger) Structural Variants (from diseased and healthy subjects). The latter for instance, especially when including deletions / duplications, gives unique opportunities to study dosage-driven gene regulation networks.

One of the main difficulties with NGS technologies for medical diagnostics is the sheer number of changes found in any one individual. Even healthy individuals have been found to carry tens or hundreds of sequence variations – such as nonsense mutations or missense mutations previously associated with disease – so that the mere finding of a sequence variation that “looks deleterious” is not in itself enough to make a diagnosis.

Standards and databases for exchange of genetic and phenotypic data will be required to bring the promise of NGS technologies to the clinics and to benefit patients with rare diseases. What is needed is data on the probability that mutations in a given gene will be associated with a disease entity, as well as the probability that specific mutations are associated with a phenotypic feature that is a component of the disease entity. Similar efforts have been a part of the fields of cytogenetics and array CGH research for some time, and it has become commonplace to submit appropriately de-identified data to central public databases such as DECIPHER, and the more recent ISCA consortium (whose data will be hosted by the NCBI). This has been extremely valuable to clinical and research communities to rapidly identify pathogenic vs. benign copy-number variants (CNV). At present, there is no similar database for Mendelian disorders (which are most often caused not by CNVs but by point mutations such as nonsense or missense mutations).

The approach would be to collect samples and perform standardised "molecular phenotyping" on patient-derived samples. First would be to generate an exome sequence (in due time a full genome sequence). Second, a gene expression profile after culturing the cells and isolating and preparing the RNA under standardised conditions (this should minimise the noise that is introduced when many different groups generate these data). Third, depending on the phenotype and tissue affected, using stem cell/iPS technology, cells can be driven in a direction (tissue) of interest and again expression profiles can be generated. This approach would facilitate the study of the early effects of the genetic defect which might be quite different from those observed in a patient tissue sample where one sees the overall effect of a tissue experiencing and trying to resolve a basic problem for decades after the problem emerged. Other analyses that might be performed include of course proteomics, metabolomics, DNA methylation, small RNA, etc. Collection of samples could be promoted by giving everybody the possibility to contribute. When an adequate phenotype description is available, a sample from the patient (fibroblast, maybe blood) can be sent to the repository. Any data generated will be made available to the sender of the sample and, perhaps after a short delay, to a central public database. Over time the value of the resource will grow extensively and it will allow selection of candidate samples for more specific analysis to test new hypotheses.

3.4.2.3. Computational standards and central databases

The field of rare disease research needs computational standards and central databases to achieve its full potential for patients. These needs are particularly pressing in the following areas:

- The creation of international computational standards for the human disease phenotype to cross reference and harmonise Orphanet's classification of diseases, the Human Phenotype Ontology, the terminology of the Elements of Morphology consortium, the data and classifications in the Online Mendelian Inheritance in Man (OMIM) knowledge base, and others.
- The cross-referencing of these terminologies with ICD10 then 11, with SNOMED-CT and more generally with UMLS.
- The production of a complete set of computational definitions of the human phenotypes and of phenotypes of model organisms, especially mouse and zebrafish. These definitions will link the phenotypes to anatomy, physiology, biochemistry, behaviour, cells, pathology, genes and proteins, and molecular functions by means of interlinking bio-ontologies representing these areas to the phenotype terms.
- The development of algorithms and software for interspecies phenotype comparisons. This will allow for the use of phenotypic data from model organisms for diagnostics and research in human diseases.
- The creation of a genotype-phenotype database for rare diseases. The database will for the first time enable genotype and phenotype information on arbitrary genetic diseases to be entered using standard vocabularies and ontologies for mutation nomenclature, phenotypes, and diseases. The database would enable the information to be used for diagnostics in the setting of traditional dysmorphological and syndromological diagnosis as well as for NGS-based diagnostics, in which the relation of arbitrary sequence variants to phenotypes needs to be evaluated.
- The provision of annotations for diseases. That is, which phenotypic abnormalities occur in which diseases? What proportion of patients is affected? What is the typical age of onset? Are there known modifiers? Much of this information has been published in medical articles, but currently very little of it has been included in databases, except partially in Orphanet where the information on age of onset, age at death, prevalence, mode of inheritance is already provided. There is no standard format for recording phenotype information using standard fields. It is necessary to develop such a standard and use it to revise and extend current annotations at Orphanet and OMIM for these databases to be uniform and comprehensive. This information is invaluable for computational algorithms designed to help physicians with the differential diagnosis in patients with rare diseases, and is also essential for biomedical research that aims to unravel the connections between individual phenotypic features and perturbations of cellular networks.

3.4.2.4. New knowledge management environment

The techniques and tools for a major step forward in combining knowledge representation and software development are available but remain to be brought together in an industrial strength package. What is needed is the following environment:

- Requirements-driven rather than technology/logic-driven.
- Robust, extensible, and comprehensive, using the strength of ontologies and logic-based systems as a skeleton and supporting context sensitivity but easily extensible to hybrid reasoning for defaults and exceptions, rules, uncertainty, probabilities, etc.
- Integrated with standard software engineering methodologies with clear schemas, APIs, links to Model-Driven and Service-Oriented Architectures, UML etc. The goal is support

ultra-adaptable software and support ultra-agile development within a logically sound environment.

- Supported by a high level, user-oriented environment that can be mastered, at least to the first level, in hours or days.
- Linked to text mining and natural language processing and generation.
- Supportive of quality assurance, unit testing, modularity, collaborative development, well defined software interfaces, etc., so as to fit naturally with best software development processes.

Most of what is needed involves existing technologies brought together in new ways with new user interfaces and views. In this perspective, OWL, RDF, XML, various Query and Rule languages, etc. are the low level means analogous to assembly languages.

Robust, high level environments that integrate software, ontologies, and knowledge representations are to be developed. In a few cases there are gaps, but even these have been explored in theory. What is required is an engineering effort to bring existing methods together in novel ways.

The benefit would be a major reduction in the effort to build, maintain, localise and evolve systems and improvement in the re-use, interoperability and standards of both knowledge resources and software.

3.5. Conclusions and recommendations in the field of data repositories

Development of repositories of data is a major aspect of current changes in the field of rare diseases; the range of applications is wide from exome studies to diseases registries. Attention has to be paid to the harmonisation and homogenisation of practices.

First of all, we need to think about initiatives and incentives to bring clinicians to actively participate to the collection of data. Then guidelines and templates have to be established to allow gathering of data issued from different sources.

Several aspects have to be explored such as repository of the questionnaires, data format, governance rules, agreement, quality assessment by EUCERD for example; in other words, the full package of the registry toolkit.

4. WHAT COULD BE PROPOSED – ISSUES TO HIGHLIGHT FOR THE FUTURE AND SUGGESTIONS

4.1. Funding of European collaboration and continuity in action

Networks are essential tools in the field of rare diseases for knowledge and data-sharing. Establishing European or global networks of all stakeholders involved in the care, treatment and research of rare diseases is the only way to address healthcare issues. These networks are the only way to achieve the critical mass which is necessary, in terms of resources and expertise, to successfully treat rare diseases. Most EC-funded research projects and networks on rare diseases include as one of their objectives the establishment of international patient registries. Consistent budgets are dedicated to the creation of these databases, whereas no specific instrument is available to maintain them as research tools for future use.

The main issue brought up during the discussions is related to the sustainability of the structures which have already been created thanks to the funding of research projects and networks, such as patient registries, but also biobanks, and technological platforms. Participants at the RDPlatform expert workshop of experts (3 December 2009) proposed potential solutions for the sustainability of these kind of structures once EC funding is over. The budget for maintaining the infrastructure is relatively small in comparison to the budget which is necessary for the initial construction of the network so the EC could be involved in the financing of the coordination and maintenance of these structures through a specific call for proposals. Two possibilities were proposed: 1) The E-RARE instrument could take care of including these kinds of calls in their programme, and it was proposed that lobbying should be carried out so that developing national plans for rare diseases include national participation in the E-Rare project as an efficient means to fund RD research; 2) A new instrument could be created at DG Research to allow for the transposition of a project from a research project to a tool for public health. One other proposal was that some databases could be allocated to learned societies.

4.2. Incentives for clinical trials in the US which do not exist in Europe¹⁰⁴

The aim of the orphan product development (OPD) grant program is to assist sponsors in defraying the costs of clinical trials incurred in the development of drugs, medical devices, and medical foods for rare diseases and conditions. The program has an annual budget of approximately \$ 14 million. Domestic or foreign, public or private, non-profit or for-profit entities (excluding those engaging in lobbying activities), state and local units of government, and non-HHS federal agencies may apply. To be eligible, the clinical investigation of the drug or the device must be conducted under an active investigational new drug application or investigational device exemption, respectively. Applicants may apply for OPD grants electronically via <http://www.grants.gov/>. Beginning in the 2009 fiscal year, funding levels for these grants will be up to \$ 200 000 per year for up to three years for Phase 1 clinical investigation and up to \$ 400 000 per year for up to four years for Phase 2 or 3 clinical investigation. Between 2000 and 2006, OOPD received an average of 69 grant applications annually. Of these, about 17 were funded each year. The majority of grantees (76%) were affiliated with

universities and medical centres. Approximately 19% of grants were awarded to pharmaceutical companies. A quarter (24%) of grants was for oncologic drugs, 14% for metabolic disorders, and less than 10% for each of a number of other disease categories. To date, OPD grants have supported clinical development of 41 approved orphan drugs and medical devices.

4.3. Expanding knowledge and databases

There is a lot of data that still need to be collected, about prevalence, natural history, biological mechanisms, etc., in order to improve the R&D area. But apart from the generation and collection of new data, some existing data may be compiled and used. For example, the FDA recently proposed the “rare disease repurposing database”: the aim is repurpose previously approved products which have already followed the R&D process¹⁰⁵. The same approach may be used in Europe with data concerning off-label use.

The most accurate tool for data collection would be international registries, but there is often some heterogeneity in the quality of the different sources of data and sometimes one has to face different types of regulations. New approaches would allow for optimal use of heterogeneous sources of data. In this vein, Concept Web Alliance¹⁰⁶ is addressing the challenge associated with the production of an ever increasing amount of data from different types of sources. The main features of this challenge include storage, interoperability and analysis of such massive and disparate data sets.

Such an approach includes the comparison of nomenclatures, ontologisation of concepts, mechanistic approaches, and data mining of patient data from hospitals or from health insurance records.

Some ideas of application have been provided¹⁰⁷:

- Improving phenotyping: Devise an intelligent web-based tool, the PhenoTyper, that helps people make an adequate, and for others useful, description of the phenotype of the patient. A phenotype description is often a weak part of data available from a patient. Although this is partly the fault of the person creating the description, it certainly is also caused by the fact that proper tools to help this person are not available. Related to this it is often difficult to determine whether some aspects of a phenotype were not present or not checked. The PhenoTyper tool should help to use proper terminology (ontology) during phenotyping, registering any aspect that was checked (or not checked) and automated reporting. Pictures could be shown as examples and to clarify choices available. Example: Question 1-date of visit; Question 2-gender of the patient; Question 3-age of the patient; Question 4- complaints (age at onset). At this point the intelligent software comes in suggesting things to check/questions to ask based on the observations given up to that point. A very simple example; when the complaints include "difficulty climbing stairs", check Gower's sign, ..., measure CK-level.
- Repository for standardised molecular phenotyping

4.4. International initiative to be launched

Europe is not the appropriate level for collaboration. An international initiative is required as increasing the number of therapeutic and care options for RD patients requires a better knowledge of pathophysiology and natural history of the RD, so as to help identify potential therapeutic targets, validate biomarkers and define appropriate surrogate end-points to adequately evaluate treatments and therapies. In order to translate research results into the marketing of orphan drugs, it is important that meaningful, validated data are collected and shared internationally. Furthermore, it is essential to strengthen the links between academia and industry, so that industry better capitalises on strong academic research results to translate these into new diagnostic tools and therapies. Patients have an important role to play in this process.

For rare disease research, coordination of efforts is the key to success in order to maximise scarce resources. Worldwide sharing of information, data and samples to boost research is currently hampered by the absence of an exhaustive RD classification, standard terms of reference and common ontologies, as well as harmonised regulatory requirements. Duplication of research efforts must also be avoided, and links between teams working on similar issues must be created.

An International Rare Diseases Research Consortium was recently announced by the EU and by the US. It will stimulate and coordinate basic and clinical research, by promoting the links between existing resources, fostering the molecular and clinical characterisation of RD and encouraging translational/preclinical and clinical research. Priorities for such an international endeavour are: the elaboration of standard terminologies and common ontologies with a view to an adequate classification of diseases; the development of predictive, validated *in vitro* and *in vivo* animal models; the identification and validation of biomarkers and surrogate end-points; and the development of new diagnostics and therapies.

4.5. Points for action

4.5.1. On funding processes

- Although there are well-identified sources of funding, both at the EU and national levels, and a clear determination of the European Commission as well as of some countries to support rare disease research, the various initiatives are still not coordinated. The relationships and dialogue between the different Funding Agencies at EC and national level is strongly encouraged, in order to provide a coherent view of the funding opportunities to potential applicants.
- The conclusions from the discussion among experts were that national funding should better aim at supporting emerging projects. E-rare funding (national funding for teams participating in a joint European project) is appropriate to start collaboration at EU level, when EC funding is more for mature projects between partners already involved in joint activities.
- EC support is crucial for networking between experts, organization of consensus meetings, sustainable infrastructures and common tools such as disease registries.
- Extension of funding for already funded projects and avoidance of fractionated funding also have to be taken into consideration.

- National plans have to be designed keeping in mind the field of research and allowing the reporting of funded medical domains at the national level.
- In the process of grant attribution, to be labelled as a project for “rare diseases” may have quite a negative impact compared to projects on common diseases. But the field of rare diseases is a pioneer field in terms of research and deserves to be allowed to live its own life without been systematically assessed in the same way as the other fields. This is why the International Research Initiative is so welcome.
- An International initiative has to be encouraged to allow for a more global collaboration.

4.5.2. To address the specificities of research in the field of rare diseases

- All stakeholders agree that it is crucial to avoid duplicating efforts: therefore it is important to share resources and data, and to establish as much as possible open-access precompetitive platforms, such as databases, knowledge bases, biobanks or collections of animal models.
- Emphasis has to be put on funding projects aimed at elucidating the pathophysiological mechanisms of rare diseases, in terms of genes, gene-environment interactions and cell signalling.
- This field remains of high interest for Industry and interest will increase with the implementation of new technologies such as next generation sequencing. One of the main bottlenecks to resolve for now is to allocate resources to epidemiological research in order to establish prevalence of these diseases in a more accurate manner.

4.5.3. To make the most of data repositories and information technologies

- Development of repositories of data is a major aspect of current changes in the field of rare diseases; the range of applications is wide from exome studies to diseases registries. Attention has to be paid to the harmonisation and homogenisation of practices.
- Initiatives and incentives have to bring clinicians to actively participate in the collection of data. Then guidelines and templates have to be established to enable data collection from different sources.
- Several aspects have to be explored such as repository of the questionnaires, data format, governance rules, agreement, quality assessment by EUCERD for example; in other words, the full package of the registry toolkit.

4.5.4. To ensure that patients and families will benefit from research outcomes

- We recommend that the international efforts be directed toward the identification of clear, specific genotypic and phenotypic criteria for the diagnosis of all diseases, disorders or conditions, whatever their cause, and that these criteria should be available to clinicians across clinical specialties and national healthcare systems, together with the associated resources necessary to operationalise these in everyday clinical practice to secure their application, and that systems be in place to enable the data generated to lead to improvement in the quality and quantity of life of patients and families with rare diseases.
- We recommend that the necessary collaboration between stakeholders across countries and across disciplines be made possible so as to ensure optimal development of new therapies where and when possible. Cross-border regulatory hurdles should be addressed and public-private partnerships for precompetitive resources should be encouraged.

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