EURORDIS
Rare Diseases Europe

P O S I T I O N P A P E R

WHY
Research on Rare Diseases?

October 2010

"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"

William Harvey, English physician (1578-1657)

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WHY RESEARCH ON RARE DISEASES?

This paper aims to review ethical, social, economic and scientific needs for research into Rare Diseases (RDs). It highlights where the most urgent attention is needed and makes specific recommendations to EU Member States. EURORDIS feels urged to take this initiative following the call of the rare diseases community, supported by the analysis carried out in recent years, on the need for enhanced efforts in the fields of fundamental, translational, epidemiological, clinical and health/social services research; the respective responsibilities of the public and the private sectors; and the impact on patients affected by RDs, their families and the rest of society.

The Orphan Drugs Regulation has stimulated research and development for Orphan Drugs and has enabled approximately 60[1] new treatments for RDs to be authorised across the EU. Market exclusivity and other incentives have been crucial to close the loop between information and interest in RDs, to research commitment and funding, through bringing research outcomes from the bench to the bedside. Such initiatives demonstrate the impact that policy decisions can have in driving forward innovative research.

EU initiatives have also been important elements in stimulating research into RDs and they show the successful outcomes that public policy intervention can achieve. However, much more attention is needed by governments in addressing the perceived lack of attractiveness in researching RDs. RDs patients deserve greater emphasis in both national and European research programmes. A number of important shortcomings are still to be overcome, in particular:

- There are currently 4,770 ongoing research projects, excluding clinical trials, covering 2,121 diseases[2]. However, some 30 million Europeans and their families are affected by one of the 6,000 to 7,000 RDs identified so far[3]. Further investment and support for research is urgently needed for patients who currently have no treatment on the market.

- Research projects on RD run for a short duration and often suffer from neglect at the end of the provision of public funds. Governments must be committed to implement sustainable policies that incentivise the actual development of therapies.

- Due to the perceived lack of commercial interest related to research in RDs, scientists may be reluctant to pursue a career in this field. They may also be less aware of the opportunities offered by research into RDs.

- Despite the urgent need for research, it can be particularly difficult to increase research on RDs because researchers are often scattered within a country, across the EU or even internationally; diseases may require a multidisciplinary research approach in order to

[1] Until May 2010.
[2] Ségolène Aymé's presentation at the European Workshop "Bridging Patients and Researchers to Build the Future Agenda for Rare Disease Research in Europe", Brussels 1st March 2010
[3] From Orphanet: "There are thousands of rare diseases. To date, six to seven thousand rare diseases have been found and approximately five new diseases are described every week in the medical literature. This number also depends upon the accuracy of the definition. Whether a single pattern is considered unique depends on the state of our knowledge, on the accuracy of clinical and investigative analysis and on the way we choose to classify diseases in general. Certain related diseases can be considered as a unique entity (they are lumped together) or subdivided and classified as separate disorders (they are split). This complexity is reflected in the various classifications of rare diseases which are provided by Orphanet".

find innovative solutions; many diseases lack a "research community" altogether, which is needed in order to gather the expertise into centres of expertise.

- Resources needed to conduct research may be similarly scattered or altogether lacking, e.g., databases, biological resource centres, registries, diagnostic testing and international epidemiological and pharmacovigilance systems.

- Conducting research into RDs may be more costly and time-consuming than in other areas as researchers may need to build *ex novo* their links with researchers in other disciplines, gather scarce data and deal with the uncertainty of unsustainable funding.

- Trying to keep a realistic stance, it is probable that hundreds, or even thousands, of rare diseases will never benefit from a specific therapy. Therefore, there is a need for alternative research lines to be pursued, at both national and European levels, in the fields of socio-psychological and health economical research for the rare diseases patients that will remain outside the traditional medico-therapeutic sphere. Unfortunately, these fields of research are often not recognised as "hard " science and are often neglected, especially by funders, both private and public.

Because of all of the above, RD patients need greater emphasis in policy-making on research and greater attention in supporting specific research into their conditions. Member States should place higher priority into incentivising and supporting research policy on RDs, including robust policies and programmes, substantial budget investments and incentives for the research community.

This call fits in the broader request for higher prioritisation and more significant budget allocations to health research in general, which will enhance both EU competitiveness in a knowledge-based society and improve social justice. Research into RDs should not be seen in isolation: innovative research into RDs has led to advancements in more frequent diseases and new research avenues being opened up. The paper sets out a number of issues demonstrating why support for research in RDs is needed and suggests some ways forward for generating more research in this field.

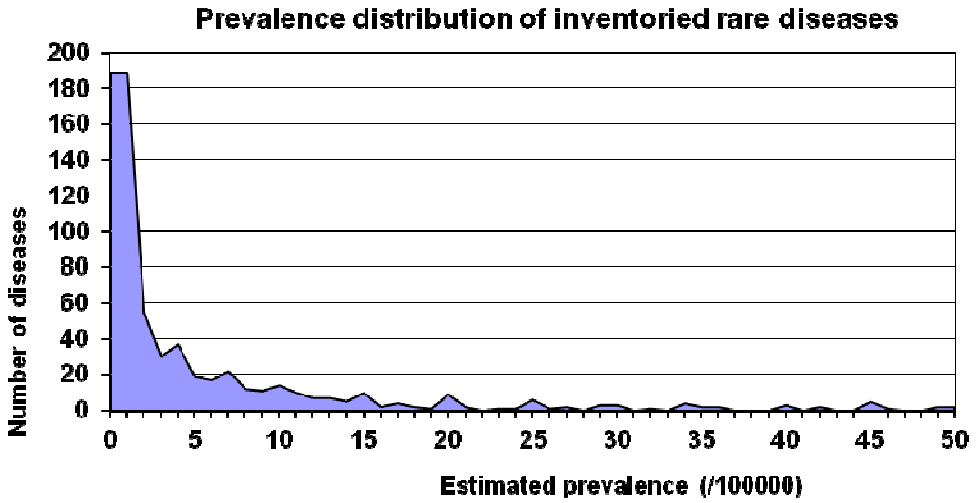
1. THE ETHICAL AND SOCIAL JUSTICE IMPERATIVE: "EXTRA" VULNERABILITY DEMANDS "EXTRA" ORDINARY MEASURES

1.1. Introduction: specific features of Rare Diseases

RDs comprise thousands of different pathologies sharing specific characteristics that increase patient vulnerability and demand concerted actions. These **common features** are the following ones:

- **Their very rarity:** RDs are defined in the EU as affecting no more than 5 per 10 000 people[4]. This low prevalence results into small or very small numbers of patients who therefore feel particularly isolated. The isolation felt by RDs patients is not only geographical but also means marginalisation within society at large and within healthcare systems designed for common diseases.

[4] Council Recommendation of 8 June 2009 on "An action in the field of Rare Diseases".



The above chart from ORPHANET (www.orpha.net) illustrates that most of the inventoried RDs have a very low prevalence (a few patients/100 000 people).

- **Rare Diseases are a complex mix of heterogeneous diseases,** currently numbering 5,000 to 7,000 in total. Up to 2009, one or more responsible genes were identified for only 2105 of the over 6,000 rare diseases listed on the Orphanet website. For the vast majority of these diseases, no research is being conducted. There are only 395 patient registries across Europe and less than 150 rare diseases do have a marketed drug. Their heterogeneity means that research and therapeutic responses should be diverse and elaborated in each disease or group of RDs. In addition, for the same disease, symptoms can affect different organs or systems. This complicates the diagnosis significantly and requires specialists from different medical areas.

- **Expertise on Rare Diseases is limited**. Because of their rarity and complexity, scientific knowledge on RDs is scarce overall; when it does exist, it is fragmented and scattered across national or EU territory. For most RDs the causes, pathogenesis/pathophysiological mechanisms and epidemiology are still unknown, which makes diagnostic methodologies and therapies difficult to develop. These features result in aggravated patients' vulnerability and disadvantage them relative to the rest of society and to other patients affected by more common diseases.

- Other characteristics aggravating the vulnerability of RDs patients can be named: there is often substantial delay, sometimes for many years, in reaching the correct **diagnosis**; RDs often result in a reduced **life expectancy**; they are usually life-long conditions, testing the resources of health services and challenging models of care (eg. **Patients' transition from paediatric to adult healthcare services**); RDs are frequently diagnosed and managed in childhood, thus representing a real challenge for clinical trials, since trial approval for research in children, especially in some countries, can prove problematic and/or very slow.

1.2. The rationale of a specific EU response to research on Rare Diseases

The **principle of equality** is reaffirmed by several EU declarations and documents:

- In **Regulation 141/2000/EC on Orphan Medicinal Products**: "Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients". "Patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients". In order to achieve this goal, the Regulation provides for specific enhancing measures, notably incentives to sustain development and market approval of orphan drugs: free protocol assistance, fee reductions and ten-year market exclusivity. This policy is a model of how to encourage innovation in disadvantaged areas, thus promoting equality for all citizens.

- In the constitutions of all European countries, as a fundamental principle in structuring the functioning of public authorities and relations between persons5.

- In the **Council Conclusions on common values and principles in European Union Health Systems,** Member States share a common commitment to ensure universal access to high quality healthcare on the basis of equity and solidarity[6].

- In the **Council Recommendation on RDs[7]:** "the principles and overarching values of universality, access to good quality care, equity and solidarity, as endorsed in the Council Conclusions on common values and principles in EU health systems of 2 June 2006, are of paramount importance for patients with RDs".

- In the **Communication on RDs[8]:** "Member States share a common commitment to ensuring universal access to high quality healthcare on the basis of equity and solidarity".

This sense of **social justice** and **solidarity** expressed by any responsive society does call for accrued action in favour of more vulnerable groups, like patients with RDs who need particular measures to be undertaken by their governments and healthcare system in order to experience the same level of treatment as other patients. To help improving the implementation of equality, a more favourable treatment of persons who are at a disadvantage, is necessary. In other words, RDs patients do need "**positive action**".

In this context, the European Commission - and DG Research in particular - have a strong role to play to push forward research into RDs, especially through the 8th Framework Programme of Research and Development.

It is worth-noticing that there are good examples of European Research Networks, initiated by Patient Organisations, which coordinate research activities into rare diseases and would certainly benefit from a wider coordination beyond European boundaries, in order to pool together sufficient resources and a critical mass of patients to enter into clinical trials.

1.3. The specific features of RDs demand specific research initiatives

Because of their rarity and diversity, RDs particularly require the following elements to ensure success:

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[5] This principle is also laid down in the Lisbon Treaty of the EU, which added to the previous Treaty of the EU the positive obligation to observe equality and equal treatment in all European Union action. In all its activities, the Union shall observe the principle of equality of its citizens, who shall receive equal attention from its institutions, bodies, offices and agencies.

[6] Council Conclusions on Common values and principles in European Union Health Systems, OJ 2006/C, 146/01.

[7] See footnote n°1.

[8] COM (2008) 679 Communication from the Commission to the European Parliament, the Council the Economic and Social Committee and the Committee of the Regions on RDs: Europe's challenges.

- **A multi-disciplinary and coordinated approach**. The only way to improve scientific and medical knowledge on any RD is to combine the complementary expertise of various specialists within and between countries, including alternative avenues in the fields of health economics and psycho-social research need to be further investigated. In order to achieve this coordinated approach, Member States must urgently create European structures of excellence through programmes supporting networking and cooperation between centres of expertise,

  Coping with the specific features of RDs involves a global rethinking of health and social care within a wider complex system. This would therefore require a new deal of training and information, from the university stage to the daily care. This innovative participatory approach and continuous training would improve dissemination of scientific advanced knowledge but also co-production of knowledge from patients and carers themselves.

- **A supranational response,** across Europe and beyond. Research on RDs cannot be developed in isolation: centres of excellence, whether actual or virtual, should serve to make the best use of both experts and patient panels, and minimise duplication and isolation within single laboratories. A true European and international approach is needed.

- **Optimised resources**, such as databases, BRCs (biological resources centres), registries, international epidemiological surveillance, and pharmacovigilance systems. Governments should pool together scarce resources in order to optimise their use. Only through tight cooperation, efficiency can be improved and duplication of efforts avoided. Disease-specific projects, based on excellence, can be used as models for more rare or common diseases. Supranational common infrastructures, long-lasting investments and a sustained approach are necessary to develop and maintain complex and often multi-national infrastructures needed to advance research on RDs.

In this context, the role of the Centres of Expertise at national level, and their networking activities at EU level, through European Reference Networks, are instrumental to provide excellence of care, as well as to perform and link high level research on RDs with a better use of resources.

2. THE ECONOMIC ARGUMENT: PUBLIC INTERVENTION TO OVERCOME PERCEIVED LACK OF ATTRACTIVENESS

2.1. Inherent lack of economic and career attractiveness

The perceived lack of attractiveness of researching into RDs does have a negative impact on clinical research and translational research aimed at developing industrial products. This lack of attractiveness is not equally perceived in the area of basic, fundamental research where RDs are being investigated in order to answer questions about mechanisms in biology and they do serve as models of dysfunctioning to advance scientific knowledge.

Even though RDs can be considered as attractive topics for basic research, the situation is much more difficult concerning the development of new therapies. Drug development is already complex, long-term and expensive for common diseases and much worse for RDs. For most of them, it is premature to suggest new treatment options because so little is known about the causes, pathogenesis/ pathophysiology and natural history of the disease. Since animal models are rarely available, preclinical studies are difficult to perform. In addition,

there are often no well-defined and validated markers/ surrogates for monitoring disease progression and treatment responses. This overall lack of understanding - due to the scarcity of funds invested and of human resources devoted to investigating RDs - partially explains the difficulty faced by pharmaceutical companies to invest in this area as often they would have to start research from the very fundamental stages[9]. Furthermore, clinical trials need to be multinational because of the limited existing experience[10] at national level as well as the small number of patients affected by the same rare disease. Additional difficulties come from the fact that national clinical trial registration authorities are not familiar with clinical trials in small populations.

All these hurdles, combined with the estimated low return on investment due to very small markets, can prove discouraging for the pharmaceutical industry and prevent it from developing drugs for RDs, despite the huge unmet medical need. Nevertheless, the Orphan Drug Regulation has shown that mainly SMEs are interested in the early stage of orphan drugs development based on knowledge that has been obtained via academic, publicly funded, research, while big pharmaceutical companies become interested in taking orphan drugs at a later development stage.

This perceived economic unattractiveness also deters scientists from pursuing careers in research on RDs. They may either be unaware of most RDs or inhibited by the short-term limited funding available. In fact, when PhD students are interested in RDs research, they do not get funding opportunities to pursue their research or build their own research group after their thesis. To overcome this serious short-fall in young RD researchers, improved medical and scientific training is needed as well as a research climate favourable to collaborate productively in the long-term. Furthermore, one specificity of the basic research field in Europe is that many fundamental advances are being made, but then the gap between the research world and the industry sector is so wide in Europe, that most clinical trials "emigrate" elsewhere. This serious shortage in translational research has to be rebalanced if Europe wants to keep up with the rest of the world.

All these factors explain why the development of therapies for RDs has been hampered until today and why the RD patients' community calls for urgent targeted measures.

2.2. The case for public support

Given the inherent characteristics of RDs which lead to scarce commercial interest for private sponsors, **research on RDs does not happen spontaneously.** Also, there is not enough competition between potential private investors, and therefore not enough impetus for innovative research. Some RD patient organisations have made valuable attempts to fill this gap by funding research activities (see survey) but there are still huge needs in research funding. As a result, **only public research funds can bridge the critical gap in research on RDs**. This is especially important for some new Member States and developing countries, where the necessary resources to research into RDs are missing. Public financial intervention is needed for social justice and equal treatment for all patients. The accomplishment of the universally accepted "right to health"[11] is a public good that must be pursued by national authorities, assuming the role of investors in research when private funders do not do it.

[9] See WHO Report Priority Medicines for Europe and the World "A Public Health Approach to Innovation", Background Paper "Orphan Diseases", by S. van Weely, Ph.D. and Prof. H.G.M. Leufkens, page 21.

[11] A Right to Health is stated in the Universal Declaration of Human Rights (1948), Article 25.

The call for public support

The need for public funding had already been identified in the 2004 *WHO Report "Priority Medicines for Europe and the World, A Public Health Approach to Innovation", Background Paper "Orphan Diseases"*[12]: **"To fill the gaps in our knowledge of RDs more public funding is needed, both at national and at international level. For many RDs, the first gap for pharmacological interventions that has to be filled is performing fundamental research to find the therapeutic targets. Due to the rarity of the patients with a specific disease it is recommended to fund research with public money."**

The recently adopted ***Council Recommendation on RDs***[13] states that **"the development of research and healthcare infrastructures in the field of RDs requires long-lasting projects and therefore an appropriate financial effort to ensure their sustainability in the long term."** It invites Member States to **"include in their plans or strategies provisions aimed at fostering research in the field of RDs".**

This requires a strong commitment by the EU and the Member States to ensure long-term sustainable projects and common infrastructures, such as biobanks, databases and registries. The EU R&D Framework Programmes have been very good instruments for funding this research. Nevertheless, important shortcomings persist, notably the short duration of research projects.

One important advance is the "***Therapeutics for Rare and Neglected Diseases Program***" or ***TRND*** (May 2009), recently adopted by the NIH (National Institute of Health). As NIH Acting Director Raynard S. Kington explained that "the federal government may be the only institution that can take the financial risks needed to jumpstart the development of treatments for these diseases". The Director of the NIH Office for RDs Research (ORDR), Stephen Groft, adds "this is the first time NIH is providing support for specific, preclinical research and product development known to be major barriers preventing potential therapies from entering into clinical trials for rare or neglected disorders."

Clearly, it is critical that the **budget for research on RDs be substantially increased over the next years**. Complementary contributions from the private and public sectors are especially crucial in the field of RDs. In particular, public private partnerships should be encouraged, "private" referring to funds not only from industry but also patient organisations or other interested parties. This spirit of partnership between public sector, private sector and patient organisations is a decisive element of success. The current European Commissioner for Research, Innovation and Science, Ms Geoghegan-Quinn, stated during her hearing in the European Parliament in January 2010, that "the targeted participation of SMEs (in the EU Research Framework Programmes) remains an issue of concern requiring determined efforts into the future. My first priority would be addressing the simplification of EU FP financial and administrative procedures. For our vital Public Private Partnerships, this means more innovation friendly operating rules and conditions". In her concluding remarks, Ms Georghegan-Quinn insisted on cooperation to achieve results, including cooperation with the private sector to mobilise investment in innovative markets and international research cooperation.

Investing for research on RDs

1. EU level: European Commission's Framework Programme for R&D (FP) – estimated

[12] See footnote n°6 for the full reference.
[13] See footnote n°3 for the full reference.

budget allocated directly to RDs or for projects potentially useful for them (fundamental research on genetic or cell therapies):

- 6th Framework Programme (FP6) – years from 2002 to 2007 (entire programme duration) = 230 million EUR
- 7th Framework Programme (FP7) – years from 2008 to 2009 – approx. 80 million EUR (FP7 is still ongoing, it will end in 2013)

Hence, in both EC Programmes, the average yearly spending for direct or indirect research on RDs is approximately of 40 million EUR.

2. EU Member States: an indication of the national spending on research on RDs could be provided by the two Calls launched under the E-Rare project[14] and contribution of national funding agencies that participated in the two E-Rare Joint Translational Calls of the project (JTC 2007 and JTC 2009). These figures of course do not intend to cover all national spending on RD research:

	JTC 2007	JTC 2009
France	**2 500130**	**1 988 273**
Germany	**3 360000**	**2 824 680**
Italy	**2 000000**	**1 000 000**
Spain	**1 502973**	**585 500**
Turkey	**505 010**	**316 150**
Netherlands		**1 661 968**
Austria		**582 645**
Greece		**252 000**
Portugal		**197 280**
TOTAL	**10 040 743**	**9 545 796**

Furthermore, the figures of the total research funding for RDs are available for three EU Member States:

France: the INSERM/GIS and then, from 2005, the ANR (French National Funding Agency for Research), entrusted as funding body of rare disease research by the 1st National Plan on Rare Diseases (2004-2008), have been instrumental in funding the research on rare diseases by organizing calls for research proposals: for disease-oriented networks (2002-2005) and for multidisciplinary projects (2005-2009). Since 2002, 277 research projects on rare diseases have been funded for more than 66 Mio €.

Germany: the BMBF and PT-DLR are responsible for the funding and implementation of the national rare disease research programme (2008-2017; ~7.5 Mio € p.a.), which is the expansion of the previous rare disease programme (2003-2009, 31 Mio €). In the programme, currently 16 consortia for rare disease research are funded. Additionally, the BMBF has funded / is funding research on rare diseases in several other funding initiatives with approximately 10 Mio € per year.

[14] E-Rare (ERA-Net for research programs on RDs) is a network of ten partners – public bodies, ministries and research management organisations – from European countries, responsible for the development and management of national/regional research programs on RDs.

Spain: the ISCIII manages the national programme for rare disease research. Rare diseases are one of the research priorities of the new Strategic Action for Health Research within the National Plan of Spain for Research, Technological Development and Innovation (2008–2011) within the Strategic Action for Health Research. Funding of Research on rare diseases follows several approaches: (1) the general extramural research funding on Biomedical and other Health Sciences Research based on yearly competitive calls for proposals. These calls are not specific for rare diseases, but rare diseases are included as a call priority. (2). A "Network Centre for Research in Biomedicine for Rare Diseases" (CIBERER) with legal personality, attached to ISCIII, and specialized in rare diseases was launched in 2006 with a 4 year grant. The centre encompasses 61 Spanish research groups with an annual budget of 6 to 7 Mio €. (3) Furthermore there is intramural funding for a branch of ISCIII called Institute for Research on Rare Diseases (IIER).

3. United States:

- Intramural awards (NIH "Bench to Bedside" programme) – year 2010 = forecast 1 620 000 $ (270.000 $ x 6 projects)
- Therapeutics for Rare and Neglected Diseases (TRND, programme creating a drug development pipeline), a NIH initiative = $24 million in 2009, plus $26 million planned in 2011

2.3. Counterbalancing the perceived unattractiveness of research on RDs while promoting real innovation

In Europe, research on RDs has had almost no impact on Gross Domestic Products, despite incentive-based orphan drug regulations. In the US, by contrast, the blossoming of the biotech industry has been directly attributed[15] to the stimulation created by Orphan Drugs legislation in 1983. That resulted in the establishment of more than 50% of the world's leading biotech companies[16], stimulating sustainable jobs and investment in innovation. Similarly, the implementation of the EC Regulation on Orphan Drugs adopted in 1999 led to a dramatic (30%) increase in the number of new biotech companies and to many existing companies making a new start on RD research. Jobs related to orphan drugs also increased by 43% on average – which is faster than in industry generally[17]. These data show that political/legislative decisions can both stimulate the industrial high technology sector and directly benefit patients.

Moreover, it follows that investment in high profile research can have a positive impact on overall growth in our knowledge-based society. Because of their diversity, RDs offer abundant opportunities for the kind of innovation envisaged by the Lisbon Strategy: "to make the EU the most dynamic and competitive knowledge-based economy in the world".

[15] Reaves N.D. "A model of effective health policy: the 1983 Orphan Drug Act". Journal of Health & Social Policy, Volume 17, Issue 4 February 2004, pages 61 - 71.

[16] Including Amgen (Forbes listed world's largest biotech company, whose revenue in 2008 was worth 15 billion US$), Genzyme, Genentech.

[17] SEC(2006) 832, Commission Working Staff Document of 20 June 2006, on the experience acquired as a result of Reg. 141/2000/EC on orphan medicinal products and account of the public health benefits obtained.

2.4. The cost of non-research

Too many health professionals are still unaware of too many RDs. Consequent delays or errors in diagnosis are stressful for patients and their families, affect their quality of life, can be costly or even dangerous by delaying access to accurate treatments. Misdiagnosis/delayed diagnosis translate into an increase of expenses and a waste of resources for the healthcare and social systems, as well as into increased financial burden - and consequent pauperisation - for families. This is particularly unacceptable considering that some RDs may be compatible with a normal life if diagnosed on time and properly managed, which keeps patients into an active life and work system.

Any research that could improve diagnosis, understanding or treatments of just some of the estimated 6,000 to 7,000 different RDs, would substantially reduce costs for healthcare systems. A RD patient, when properly treated, stops being a consumer of irrelevant tests or ineffective treatments or superfluous hospital admissions. Years of recurring diagnostic failures are very expensive and still much too frequent. **Ignorance can be more expensive than the research aimed at improving knowledge.**

There is a regrettable scarcity of data to quantify the costs of non-research. This scarcity results more from a lack of political will to expose these costs than from the resources needed to shed light on neglected medical domains. Studies on the costs of non-research, and research in the field of health economics at large, are needed to break this vicious circle.

3. SCIENTIFIC TRENDS: RESEARCH ON RARE DISEASES BRINGS WIDER BENEFITS

3.1. Research on RDs advances medical research in general

"Research on RDs has proven to be very useful to better understand the mechanism of common conditions such as obesity and diabetes, as they often represent a model of dysfunction of a single biological pathway"[18]. Research on specific RDs has given much insight in pathophysiology of more prevalent diseases, like migraine for example[19]. Furthermore, when SMEs develop a technology for the treatment of a RD, this may be used for developing treatments for other rare or more prevalent diseases.

In general, history shows that a substantial part of the universal medical knowledge did start with a model of a RD and helped understanding more common diseases. Genetic mapping of some RDs has identified previously unknown or under-appreciated normal biological processes, e.g. in immunological self-tolerance (AIRE) or in primary cilia (defective in polycystic kidney disease)[20].

Pioneering multidisciplinary approaches and new methods or treatments in RD research can often benefit the much wider public affected by common diseases. When RDs are very serious or life-threatening and with no available therapies, any unknown risks of new treatments must be outweighed by the potential benefits to patients and/or science. For example, there is much research on gene therapy for RDs such as severe combined immunodeficiencies (SCID and ADA-SCID), Adrenoleucodystrophy, Duchenne Muscular Dystrophy (DMD), Spinal Muscular Atrophy (SMA), Wiskott Aldrich syndrome and Leber's

[18] COM (2008) 679 Communication from the Commission to the European Parliament, the Council the Economic and Social Committee and the Committee of the Regions on RDs: Europe's challenges.
[19] De Vries B, et al. (2009) Molecular genetics of migraine. Hum. Genet. 2009 Jul ;126(1) :115-32
[20] D Mathis and C Benoist 2007; A decade of AIRE. Nat Revs Immunol.7, 645-50

congenital amaurosis. Moreover, that has prompted researchers to devise new methodologies for clinical trials on small patient series; these could equally be applied in common diseases with consequent savings in patients, materials and costs.

In addition, RDs are at the forefront in personalised medicine, which applies genetic information about each patient to tailor treatments medical care to individual needs. Today, certain drugs are increasingly being targeted specifically to the best responder patient subgroups, to improve patient outcomes, minimise side-effects and reduce costs. Indeed, some diseases are so rare that their proper diagnosis and groundbreaking treatment has to be personalised, e.g. for extremely rare tumours[21].

In the last decade, we have witnessed huge progress in medical research, especially in pharmacology, gene and cell therapies, tissue engineering, high-tech medical devices, gene testing and other sophisticated diagnostic tools, including medical imaging. However, bringing these high-value innovations to patients, to optimise medical solutions (as well as use of economic resources), requires both centres of excellence and increased collaboration across the EU.

3.2. Rare Diseases as a laboratory for new health care policies

Because RDs are so overlooked, the EU Commission and some national health systems are developing specific solutions and innovative approaches to the challenges they pose in addressing patients needs. It is important to remember that - in application of the subsidiarity principle[22] - Health Policies fall within the competences of the national authorities.

As clearly stated in the Commission Communication and in the Council Recommendation, Centres of Expertise should be identified at national and regional levels and resources allocated for diagnosis, care, clinical trials, epidemiology etc. The added value of Centres of Expertise for the national health care system is that of **providing a rating scheme** that helps patients to access the Centres most appropriate to their particular case, and also healthcare managers to **identify where to target funding[23]**.

Patient registries are necessary to perform clinical research. Centres of Expertise have an important role to play as they can improve knowledge on where RD patients are located. Centres of Expertise are also expected to coordinate most of their activities at the European level by organising themselves in European Reference Networks for specific diseases or groups of RDs, so to combine multidisciplinary expertise in pursuing new research avenues, develop social care guidelines and improved standards of diagnosis and care.

We believe that such a **new public health model could be a prototype for innovative approaches to more common diseases**. Today, the national health care systems of EU countries are increasingly criticised and in financial deficit. By encouraging existing voluntary European collaborations to improve all partner centres, the emerging RD healthcare model could pioneer new optimised use of existing healthcare resources to the benefit of all citizens.

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[21] Examples of this are the findings for chronic myeloid leukaemia (CML), seminoma, gastrointestinal stromal tumour (GIST). From the paper "Importance of Research on RDs and Orphan Drugs", Dr. Patrick Corley, Avril Daly, June 2009.

[22] The principle of subsidiarity is defined in Article 5 of the Treaty establishing the European Community. It is intended to ensure that decisions are taken as closely as possible to the citizen and that constant checks are made as to whether action at Community level is justified in the light of the possibilities available at national, regional or local level. Specifically, it is the principle whereby the Union does not take action (except in the areas which fall within its exclusive competence) unless it is more effective than action taken at national, regional or local level. It is closely bound up with the principles of proportionality and necessity, which require that any action by the Union should not go beyond what is necessary to achieve the objectives of the Treaty.

[23] RD Task Force (RDTF) Report 2008 on Centres of Expertise and European Reference Networks.

3.3. Trends in social research

Many rare diseases will not benefit from a medical treatment for a very long time to come. It is therefore important to invest in the field of social research. The positive outcomes of this type of research are horizontal and will benefit patients affected by all rare diseases. Quality of life studies and development of innovative treatments.

Rare Diseases do represent a "laboratory" with implications in different areas: not only is medical research on RDs valuable for more common diseases; not only the "RDs case study" can be used as a test field to develop new healthcare policies; but it is also expected - and already shown through different initiatives – that RDs may open innovative avenues in the field of social care, which will indeed benefit society at large. In fact, by developing a social response targeted to the specific needs of the concerned patients and their families, the costs are maybe higher in the first place, but the resulting improvement in the conditions of the patients does – in the medium term – end up reducing the hospitalisation costs and potential non-adapted therapies and treatments. Costs of social care are mainly manpower costs, which are proportionate to the national GDP and to the actual level of salaries in the different countries, contrary to the costs of orphan drugs and other medicinal products at large which vary much less from poor to rich countries.

Furthermore, quality of life and social research on rare diseases is useful to generate important data needed by HTA Agencies, in view of assessing the added value of treatments for rare diseases and in view of launching clinical trials.

4. IN CONCLUSION

The above arguments should help to overcome the shortcomings in research policy-making. The EU Regulation on Orphan Drugs and its ongoing implementation has partially addressed the perceived unattractiveness of developing therapeutics for RDs. It has also highlighted institutional and political attitudes to this socio-medical problem, especially the lack of political will for the fundamental and translational research demanded by patients' organisations. Times are mature for scientists to open new research avenues using RDs as "models", as emphasised throughout this paper. To pursue these opportunities optimally, it is essential that the EU Member States apply the principles of equity and solidarity on which their health and social care systems are founded.

The RDs community at large, comprising of patients, researchers, health professionals, and industry, expects that public authorities take appropriate political steps in order to improve research efforts in the field of rare diseases. In this context, EURORDIS believes that priority actions should be taken alongside three main axes:

1. Within **Research programmes**, RDs should be given a higher priority at both national and European (or even beyond) levels;

2. Budgets to fund the creation, functioning and maintaining of **research infrastructures** should be increased and ensured in the long-term, in a sustainable manner;

3. Within the **calls for proposals in the field of therapeutics**, favourable political decisions should be taken and followed by suitable funding, in order to boost research projects in this area.