



EUROPEAN CONFERENCE ON RARE DISEASES



Luxembourg 21-22 June **2005**



EUROPEAN CONFERENCE ON RARE DISEASES



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For more information: www.eurordis.org
Webcast of the conference and abstracts: www.rare-luxembourg2005.org

ACKNOWLEDGEMENTS AND CREDITS

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the following persons/organisations/companies
for their role :

HER ROYAL HIGHNESS THE GRAND DUCHESS OF LUXEMBOURG

•

THE EUROPEAN COMMISSION

•

THE GOVERNEMENT OF LUXEMBOURG

•

THE CHAMBER OF COMMERCE OF LUXEMBOURG

George Peters, Carine Radoux

•

ASSOCIATION FRANCAISE CONTRE LES MYOPATHIES AFM/TELETHON

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OUR PARTNERS

ALAN in Luxembourg, Alliance Maladies Rares, Agrenska,
Federacion Espanola de Enfermedades Raras, Rare Diseases Denmark,
Czech Agency for Drug Control, Orphanet and Eurocat

AFM, Prader Willi France, Psico Ballet, Een Häerz fir Kriibskrank Kanner

•

THE MEMBERS OF THE PROGRAMME COMMITTEE

•

AND ALL ECRD2005 PARTICIPANTS

•

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PARTNERS

Organisers / Partners



EURORDIS (European Organisation for Rare Diseases). The European Organisation for Rare Diseases brings together 217 rare disease patients' organisations from 23 countries including fifteen EU member states. It is one of the largest patients' organisations in Europe. Eurordis' objectives are to build a strong pan-European community of people affected by rare diseases, to be their voice at the European level, and to fight against the impact of rare diseases.

www.eurordis.org



ÅGRENSKA CENTRE is a Swedish national competence centre for rare disorders. It provides programmes for children and young people with disabilities, their families and for professionals concerned. Ågrenskas' family program is directed towards families who have children with rare disabilities, and arranges about twenty family stays with different diagnosis each year.

www.agrenska.se



ALAN asbl Luxembourg was founded in April 1998 as an association that wished to support people living with neuromuscular diseases and since January 2005, also people living with a rare disease.



ALLIANCE MALADIES RARES (French Alliance for Rare Diseases) is a national alliance of 141 patient organisations. It covers approximately 1000 rare diseases and represents more than one million patients in France.

www.alliance-maladies-rares.org



EUROCAT (European Surveillance of Congenital Anomalies) is a European network of population-based registries for

the epidemiologic surveillance of congenital anomalies. Currently, forty registries in nineteen European countries survey more than one million births per year. EUROCAT is currently funded under the Public Health Programme of the EC General Directorate for Health. The Central Registry is based at the University of Ulster, UK.

www.eurocat.ulster.ac.uk



FEDER, Federación Española de Enfermedades Raras, is a charity organisation which represents more than 90 rare diseases support groups in Spain. Since 1999 Feder has carried out activities to raise awareness on this health and social public problem, to support these families and improve their quality of life.

www.enfermedades-raras.org



ORPHANET is a European database that deals with rare diseases and orphan drugs. ORPHANET aims to improve the diagnosis, care and treatment of patients. ORPHANET includes an encyclopaedia and a directory of services: specialised outpatient clinics, clinical laboratories, research activities and support groups.

www.orpha.net



RDD is an alliance of more than thirty national rare disease organisations. Rare Disorders Denmark works to improve the living conditions for people suffering from rare disorders and create a space for the mutual exchange of ideas and experiences.

www.raredisorders.dk



SUKL (State Agency for Drug Control, Czech Republic) is the regulatory body in the Czech Republic responsible for the regulation and surveillance of human medicinal products. It is also involved in the regulation and surveillance of medical devices.

www.sukl.cz

Official Support



EUROPEAN COMMISSION, Public Health Programme, DG Health and Consumer

Protection

Programme of Community action in the field of public health (2003-2008)

The programme, meant to complement national policies, aims to protect human health and improve public health. On 23 September 2002, the European Parliament and the Council adopted a new six-year Community action programme for public health. This programme runs from the 1st of January 2003 to the 31st of December 2008.

The new programme is based on three general objectives: information, rapid reaction to health threats and health promotion through addressing health determinants. Activities such as networks, co-ordinated responses, sharing of experience, training and dissemination of information and knowledge will be inter-linked and mutually reinforcing.

<http://europa.eu.int/comm/health>



MINISTRY OF HEALTH, Luxembourg



AFM (Association Française contre les Myopathies). Created in 1958, the French Muscular Dystrophy Association (AFM) is a non-profit association whose members include patients and families affected by neuromuscular diseases. Its mission is to find a cure for these diseases, most of which are of genetic origin, and assist people affected by them. Supported by the generosity of millions of donors, AFM supports more than 400 research programs each year and has contributed to the emergence of policies and structures dealing with rare diseases in France and Europe.

www.afm-france.org



LIONS INTERNATIONAL

PROGRAMME COMMITTEE

Members of the Programme Committee

The programme committee was co-chaired by Ségolène Aymé and Christel Nourissier, with the following members:

- Ségolène Aymé, Task Force on Rare Diseases and Orphanet, [France](#)
- Violetta Anastasiadou, Archbishop Makarios III Medical Centre, [Cyprus](#)
- Terkel Andersen, Hemophilia Association, KMS, [Denmark](#)
- Stéphane Buron, Alliance Maladies Rares, [France](#)
- Elisabeth Dequeker, Departement of Human Genetics, [Belgium](#)
- Helen Dolk, Faculty of Life and Health Sciences, [United Kingdom](#)
- Liz Gondoin, ALAN, [Luxembourg](#)
- Katarina Kubackova, University Hospital of Motol, [Czech Republic](#)
- Yann Le Cam, Eurordis, [France](#)
- Christel Nourissier, Prader Willi, Alliance Maladies Rares, [France](#)
- Anders Olauson, Agrenska, [Sweden](#)
- Hans-Hilgers Ropers, Max Planck Institute for molecular genetics, [Germany](#)
- Rosa Sanchez De Vega, Aniridia Spanish Association, FEDER, [Spain](#)
- Hélène Tack-Lambert, AFM, [France](#)
- Domenica Taruscio, Centro Nazionale Malattie Rare, Istituto Superiore di Sanità, [Italy](#)
- Josep Torrent-Farnell, Committee for Orphan Medicinal Products, EMEA, [European Union](#)



Participants at the conference

Conference Programme

FROM DIFFICULTIES TO SOLUTIONS FOR THE RARE DISEASE COMMUNITY

TUESDAY JUNE 21ST 2005

Session 1

OPENING CEREMONY

Under the patronage of Her Royal Highness
The Grand Duchess Maria Teresa of Luxembourg

- Mr Terkel Andersen, Eurordis
 - Mr. Fernand Sauer, Director for Public Health, DG Health and Consumer Protection, EC
 - Mr Mars di Bartolomeo, Minister of Health of Luxembourg
- “Living with a rare disease” : a documentary by Josée Blanc Lapierre

Session 2

DELAYS IN DIAGNOSIS, DISCRIMINATION AND INSUFFICIENT COMPENSATION

Chair: Yann Le Cam, Eurordis

- Diagnosis and public health: diagnostic delays – EurordisCare2 survey
 - Dr. Madelon Kroneman, Nivel, The Netherlands
- A patient’s testimony
 - Marianna Lambrou, Tuberos Sclerosis Association, Greece
- A health professional’s testimony
 - Prof. Helena Kääriäinen, Turku University Hospital, Finland
- Disability: are financial compensations adequated?
 - Rosa Sanchez de Vega, FEDER, Federación Española de Enfermedades Raras, Spain

Discussion

Dr. Yolande Wagener, Ministry of Health, Luxembourg
 Sarah McFee, Cystic Fibrosis Association, France
 Prof. Reinhold Schmidt, Clinical Immunology, Germany

- Press conference
- Poster session

Session 3**BENCHMARKING INITIATIVES TO IMPROVE CARE**

- co-chair : Dr. Milan Cabrnach MEP
 - co-chair : Dr. Edmund Jessop, Office for National Statistics, United Kingdom

- Comparison of national plans and practices
 - Dr. Domenica Taruscio, National Centre for Rare Diseases, Italy
- Trans-border access to care
 - Prof. Dr. Piet van Nuffel, European Court of Justice.

Reference Centres

The Danish model, Torben Gronnebaeck, KMS, Denmark
 The Belgian model, Dr. Annick Vogels, University Hospital Leuven, Belgium
 The French model, Dr. Alexandra Fourcade, Ministry of Health, France

Discussion**Session 4****BUILDING COOPERATION BETWEEN STAKEHOLDERS TO IMPROVE RESEARCH****TARGETING RESEARCH TO IMPROVE QUALITY OF LIFE**

- Chair : Prof. Hans Hilger Ropers, Germany

Building cooperation between stakeholders to improve research

- A multi-disciplinary approach
 - Prof. Anthony Holland, Department of Psychiatry, University of Cambridge, United Kingdom
- Transfer from academic research to industrial development
 - Prof. Pascal Schneider, University of Lausanne, Switzerland
- Strengthening co-operation between academia and industry
 - Dr. Valérie Thibaudeau, Orphanet, France

Targeting research to improve quality of life

- New therapeutic avenues
 - Prof. Stanislas Lyonnet, Necker Hospital, France
- European Clinical Research Infrastructures Network:
 - a response to the needs of the clinical trial community
 - Prof. Christian Ohmann, ECRIN, Germany

Discussion**END OF THE DAY 1****WEDNESDAY JUNE 22nd 2005****Session 5**
**ACCESSING APPROPRIATE CARE
 ORGANISATION OF CARE
 BEST PRACTICES GUIDELINES
 FOR CARE MANAGEMENT**

- Co-chair : John Ryan, EC
 - Co-chair : Prof. Anders Fasth, Sweden

- survey results from illustrating
 - difficulties in access to care in Europe
 - Elisabeth Wallenius, Sällsynta Diagnoser, Sweden
- Clinical networks as a response
 - to scarcity of databases
 - and guidelines for best practices
 - Dr. Cornelia Zeidler, Rare Severe Chronic Neutropenia network, Germany

Discussion**Session 6**
**FIGHTING THE FRAGMENTATION
 OF RESEARCH**

- Co-chair : Prof. Manuel Palacin, Spain
 - Co-chair : Dr. Eva Steliarova-Foucher

Sharing data

- Collecting and sharing tissue
 - and DNA
 - Dr Veronica Karcagi, EuroBioBank network, Hungary
- Patient registries : a platform
 - for exchange between professionals
 - Prof. Odile Boespflug-Tanguy, European Leucodystrophy Association, France
- Collecting and sharing registry data
 - Prof. José Luis Oliveira, InfoGenMed, Portugal

Discussion

<ul style="list-style-type: none"> • Specific difficulties in access to : <ul style="list-style-type: none"> • Access and availability of molecular genetic tests : uncovering the rationales for transborder testing <ul style="list-style-type: none"> - Dr Elettra Ronchi OECD • Medical devices and equipment <ul style="list-style-type: none"> - Liz Gondoin Goedert, ALAN, Luxembourg • Education: educational implications of rare diseases <ul style="list-style-type: none"> - Anders Olauon, Agrenska, Sweden <p>Discussion</p>	<p>Building technology platforms</p> <ul style="list-style-type: none"> • Building a technology platform <ul style="list-style-type: none"> - Dr. Judith Fischer, National Centre for Genotyping, France <p>Building strategies for prevention</p> <ul style="list-style-type: none"> • Strategies based on the assesment of epidemiological evidence <ul style="list-style-type: none"> - Prof. Helen Dolk, Eurocat, United Kingdom <p>Discussion</p>
<p>Session 7</p> <p>BENCHMARKING INITIATIVES TO IMPROVE CARE: BEST PRACTICES GUIDELINES FOR CARE MANAGEMENT (continued)</p> <ul style="list-style-type: none"> - Co-chair : Lesley Greene, United Kingdom - Co-chair : Dr. Manuel Posada, Spain <p>Information and training</p> <ul style="list-style-type: none"> • Help phonelines and written information <ul style="list-style-type: none"> - Lesley Greene, Children Living with Inherited Metabolic Disorders, United Kingdom • Internet resources <ul style="list-style-type: none"> - Prof. Jörg Schmidtke, Medizinische Hochschule Hannover, Germany • Training families and carers <ul style="list-style-type: none"> - Britta Nilson, Frambu, Norway and Anders Olauon, Agrenska, Sweden <p>Discussion</p>	<p>Session 8</p> <p>FIGHTING THE FRAGMENTATION OF RESEARCH (continued)</p> <ul style="list-style-type: none"> - Co-chair: Alan Vanvossel, DG RES - Co-chair: Jose Luis Valverde <p>Building a community of patients and professionals</p> <ul style="list-style-type: none"> • Patient representatives : examples of patients' organisations that successfully brought together researchers' networks <ul style="list-style-type: none"> - Dr. Tsveta Schyns, Alternate Hemiplegia network, Austria • Establishing larger networks <ul style="list-style-type: none"> - Dr. Serge Braun, Association Française contre les Myopathies AFM, France

<p>Data collection and management</p> <ul style="list-style-type: none"> • Diseases with no code : the perspective of patients <ul style="list-style-type: none"> - Annet van Betuw, The Rare Chromosome Disorders network, The Netherlands • Why and how to code and classify rare diseases <ul style="list-style-type: none"> - Dr. Ségolène Aymé, Orphanet, France <p>Discussion</p> <p>Dr. Ilse Feenstra, ECARUCA, The Netherlands Prof. Joan Lluís Vives Corron, ENERCA, Spain Dr. Yllka Kodra, NEPHIRD, Istituto Superiore di Sanità, Italy Severine Rastoul, Maladies Rares Info Service, France</p>	<p>Co-ordinating funding initiatives</p> <ul style="list-style-type: none"> • Rare funding initiatives for rare diseases <ul style="list-style-type: none"> - Prof. Hans Hilger Ropers, Max Planck Institute for Molecular genetics, Germany • DG Research : lessons learned from FP5 and FP6, plans for FP7 <ul style="list-style-type: none"> - Prof. Ketty Schwartz, Inserm, France <p>Discussion</p>
<p>Session 9</p> <p>TREATING WITH ORPHAN DRUGS</p> <p>JOINT MEETING OF ALL INTERESTED PARTIES: THE EUROPEAN ENVIRONMENT FOR ORPHAN MEDICINAL PRODUCTS</p> <ul style="list-style-type: none"> - Co-chair : Prof. Henri Metz, Luxembourg - Co-chair : Thomas Lönngren, EMEA <ul style="list-style-type: none"> • Status report and health benefits after five years of Orphan drug legislation <ul style="list-style-type: none"> - Dr. Melanie Carr, EMEA, Scientific Advice and Orphan Drugs • Panellist views 1 : Experience gained by stakeholders <ul style="list-style-type: none"> - Views of an academic representative : Dr Bruce Morland, Birmingham Children's Hospital, United Kingdom - Views of a patient representative : Yann Le Cam, Eurordis, France - Views of a representative from industry : Catarina Edfjall, Orphan Drug Working Group, Actelion, Switzerland • Availability of orphan medicinal products in Europe <ul style="list-style-type: none"> - François Houjé, Eurordis, France • Panellist views 2 : Access to drugs and responsibilities of Member States <ul style="list-style-type: none"> - Views of the health care systems, Prof. Peter Littlejohns, The National Institute for Clinical Excellence, United Kingdom - Views of a national competent authority, Dr. Domenica Taruscio on behalf of Dr. Nello Martini - Views of the European Commission, Agnès Saint Raymond, Head of Sector-Scientific Advice and Orphan Drugs on behalf of DG Enterprise 	

Session 10

MOVING FORWARD IN EUROPE

- Chair: Mars di Bartolomeo, Health Minister, Luxembourg

- Proposals from the Task Force on Rare Diseases
 - Dr. Ségolène Aymé, Orphanet
- A society where rarity does not affect opportunity
 - Christel Nourissier, Eurordis
- A word by the European Commission
 - John Ryan, Head of Health Information Unit, Public Health and Risk Assessment Directorate, DG Health and Consumer Protection, EC

CONFERENCE CLOSES

Key features of the conference

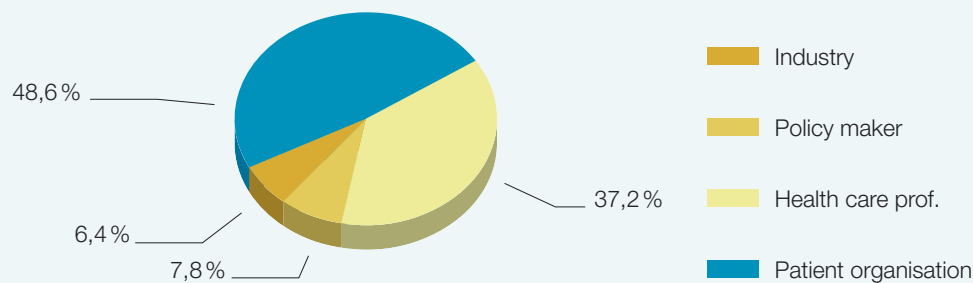
Participants

As shown on figure 1 below, the objective to gather all stakeholders acting against rare diseases was successfully reached, with a fair balance between health care professionals, patient representatives, national and European policy makers, and representatives from the health industry. Among 300 attendees, 40% were males, 60% females.

Health care professionals included treating physicians, clinical researchers, fundamental researchers, paramedical professions, epidemiologists etc.

Among patient representatives, many different diseases were represented. The list of attendees and their respective organisation/institution is available on the web site of the conference (www.rare-luxembourg2005.org).

PARTICIPANTS AT ECRD 2005: OCCUPATION (Figure 1)



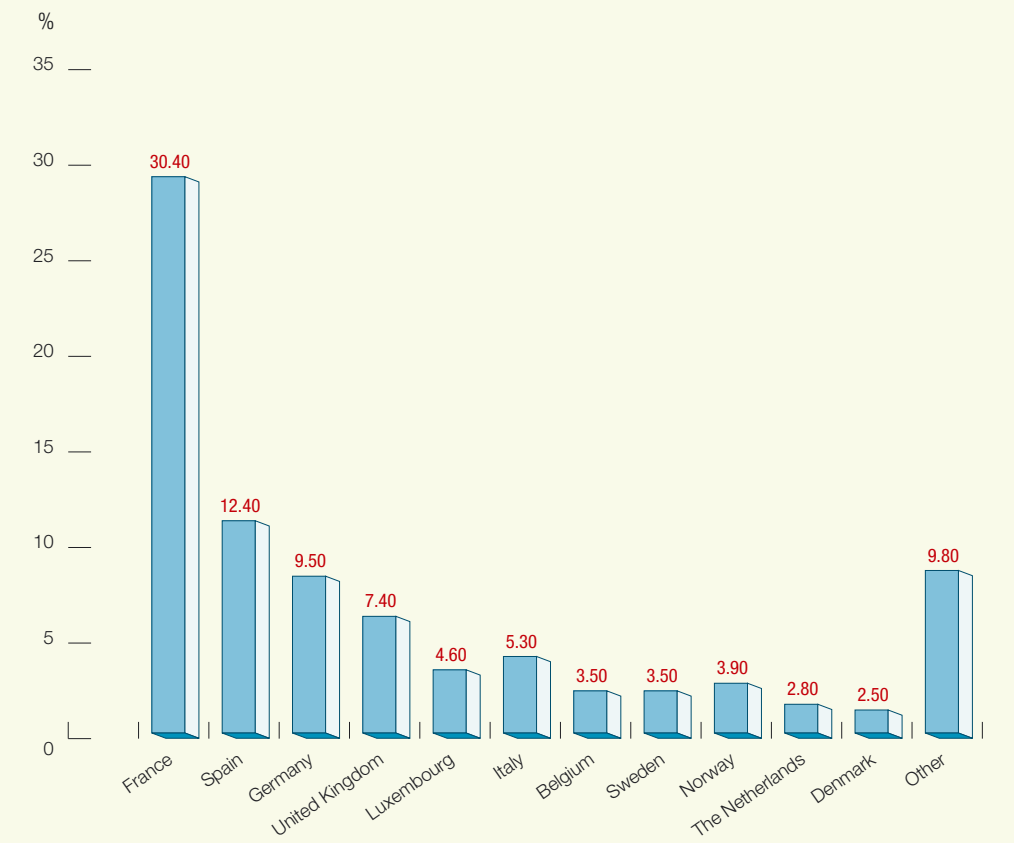
The geographic origin of attendees reflected also a truly European event, with participants from 21 European countries (EU and EEA), and even beyond from Canada, Vietnam, Northern Africa, and Argentina...

A larger delegation came from France, probably due to the geographic proximity, the support by Association Française contre les Myopathies AFM-Téléthon and a well developed network of actors against rare diseases in this country.

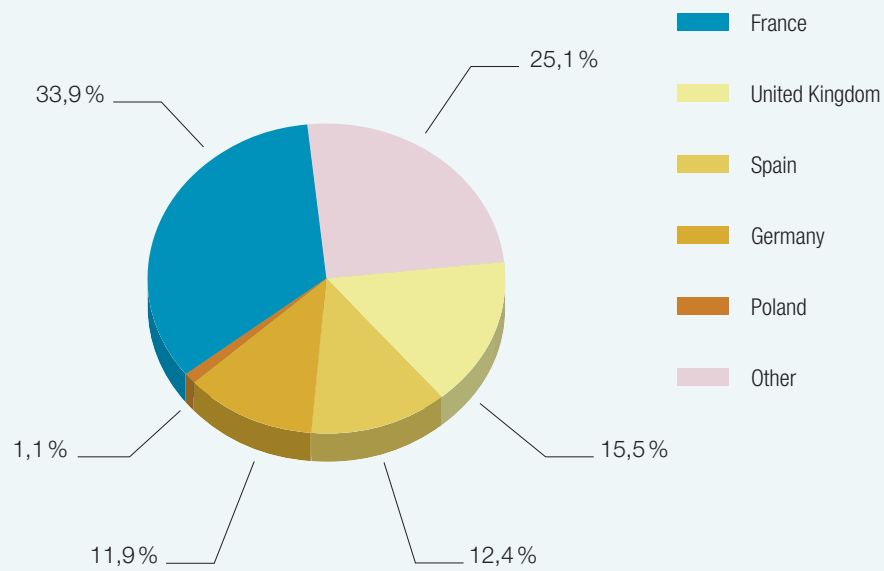
Efforts to facilitate the participation of persons who were not English-native speakers were fruitful, with direct interpretation from English to German, Spanish, Polish and French. Except for Polish with very few attendees from this country, interpretation certainly helped attendees to register the conference.

Figure 2 below shows the first language spoken by participants. It illustrates well the impact of offering direct interpretation during the sessions.

PARTICIPANTS AT ECRD 2005: STATE OF RESIDENCE (Figure 2)



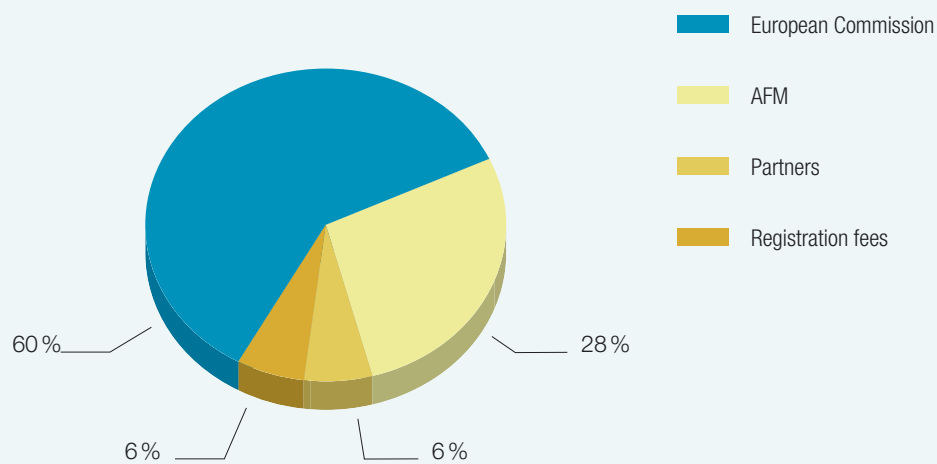
LANGUAGES OF THE CONFERENCE AND ATTENDANCE (Figure 3)



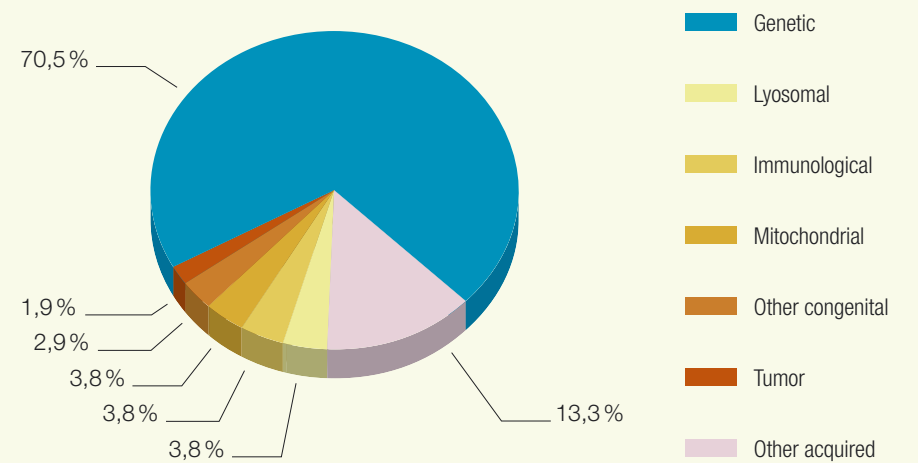
Funding of the conference

The European Conference on Rare Diseases ECRD2005 was mainly funded by the European Commission and patient organisations (see details figure 4) for a total cost of 416 640 €. In kind contributions were also offered by the ministry of health of Luxembourg.

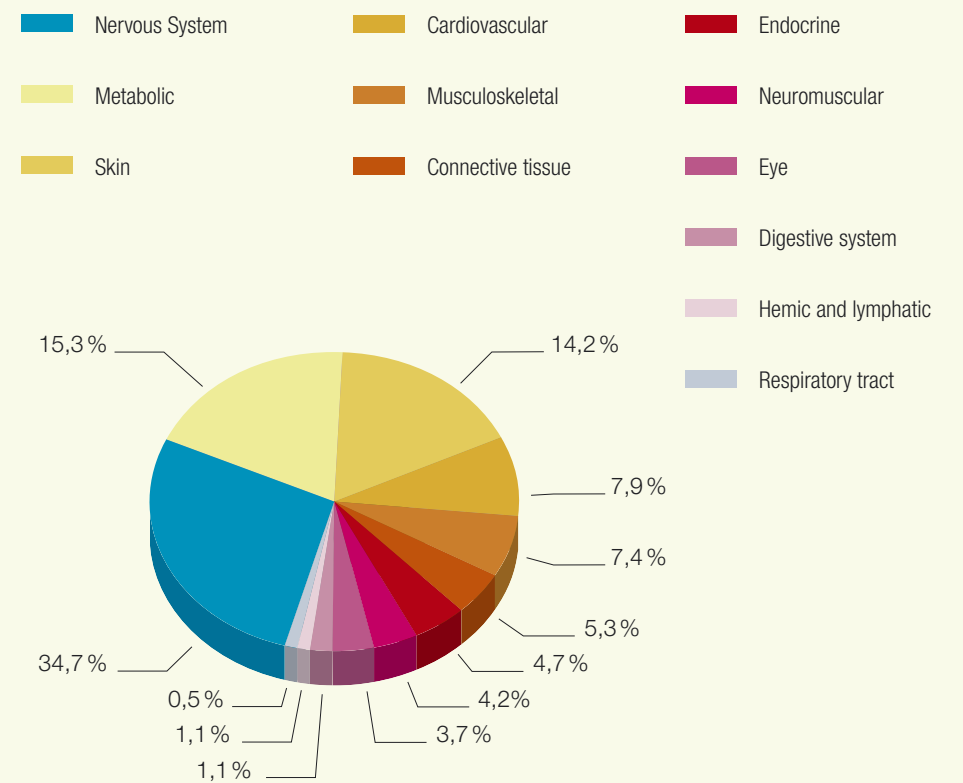
ECRD 2005 FUNDING (Figure 4)



PATIENT ORGANISATIONS BY FAMILY OF DISEASE REPRESENTED (Figure 5)



PATIENT ORGANISATIONS BY CLINICAL MANIFESTATION OF THE DISEASE REPRESENTED (Figure 6)



SPEAKERS

- **Mr Terkel Andersen**, Chair of the Board of Directors, Eurordis. terkel.andersen@newmail.dk
- **Dr. Ségolène Aymé**, Director of Orphanet, France, and Leader of the Task Force on Rare Diseases. ayme@orpha.net
- **Mr Mars di Bartolomeo**, Minister of Health of Luxembourg. ministere-sante@ms.etat.lu
- **Annet van Betuw**, President of the European Chromosome 11q Network, The Netherlands. avbetuw@wxs.nl
- **Prof. Odile Boespflug-Tanguy**, European Leucodystrophy Association and Child Surgery Department, Clermont Ferrand hospital, France. odile.boespflug@inserm.u-clermont1.fr
- **Dr. Serge Braun**, Director of Research and Therapeutic Development, Association Française contre les Myopathies AFM, France. sbraun@afm.genethon.fr
- **Dr. Milan Cabrnach**, Member of the European Parliament, Czech Republic. cabrnach@cabrnach.cz
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- **Prof. Anders Fasth**, Prof. of Pediatric Immunology, The Queen Silvia Children's Hospital, and Member of the Task Force on Rare Diseases, Sweden. anders.fasth@pediat.gu.se
- **Dr. Ilse Feenstra**, MD, Clinical Database Manager European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations ECARUCA, The Netherlands. i.feenstra@antrg.umcn.nl
- **Dr. Judith Fischer**, National Centre for Genotyping, Inserm U429, France. judith.fischer@cng.fr
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- **Liz Gondoin Goedert**, President of the Association for Neuro-muscular Diseases of Luxembourg, Luxembourg. alanasbl@pt.lu
- **Lesley Greene**, Children Living with Inherited Metabolic Disorders, United Kingdom and former Project Leader PARDIII, Eurordis. Lesley@climb.org.uk
- **Torben Gronnebaeck**, President of Rare Disorders Denmark, Denmark. tog@newmail.dk
- **Prof. Anthony Holland**, Senior Lecturer, Department of Psychiatry, University of Cambridge, United Kingdom. ajh1008@cam.ac.uk
- **François Houÿez**, Health Policy Officer, Eurordis. francois.houyez@eurordis.org
- **Dr. Edmund Jessop**, Department of Health, Office for National Statistics, United Kingdom and member of the Task Force on Rare Diseases. edmund.jessop@doh.gsi.gov.uk
- **Prof. Helena Kääriäinen**, Professor, Department of Medical Genetics, Turku University Hospital, Finland. helena.kaariainen@utu.fi
- **Dr. Veronica Karcagi**, Head of Department Molecular Genetics and Diagnostics "Fodor Jozsef" National Centre for Public Health, Hungary, and EuroBioBank network. karcagiv@okk.antsz.hu
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- **Yann Le Cam**, Chief Executive Officer, Eurordis. yann.lecam@eurordis.org
- **Prof. Peter Littlejohns**, Clinical and Public Health Director, National Institute for Health and Clinical Excellence (NICE), United Kingdom. peter.littlejohns@nice.org.uk
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ECRD 2005 REPORT

INTRODUCTION

Figures of rarity

A rare disease is a disease that occurs infrequently or rarely in the general population. In order to be considered as rare, each specific disease can not affect more than a limited number of people out of the whole population, defined in EU as less than 1 in 2000 citizens (EC Regulation on Orphan Medicinal Products) While one out of 2.000 seems very few, in a total population of 459 million EU citizens this could mean as many as 230.000 individuals for each rare disease. It is important to underline that the number of rare disease patients varies considerably from disease to disease and that most of the people represented by the statistics in this field suffer from even rarer diseases, affecting only one in 100.000 people or less. Most rare diseases do only affect some thousands, hundreds or even twenty or so patients. These “very rare diseases” make patients and their families particularly isolated and vulnerable. It is worth noting that most cancers, as well as all cancers affecting children, are rare diseases.

Despite the rarity of each rare disease, it is always a surprise for the public to discover that according to a well-accepted estimation, “about 30 million people have a rare disease in the 25 EU countries” (Background Paper on Orphan Diseases for the “WHO Report on Priority Medicines for Europe and the World” – 7 October 2004), which means that 6% to 8% of the total EU population are rare disease patients. This figure is equivalent to the combined populations of the Netherlands, Belgium and Luxembourg.

“Unfortunately, the epidemiological data that are available are inadequate for most rare diseases to give firm details on the number of patients with a specific rare disease. In general people with a rare disease are not registered in databases. Many rare diseases are summed up as “other endocrine and metabolic disorders” and as a consequence, it is difficult to register people with a rare disease on a national or international basis, and in a reliable, harmonised way” (Background Paper on Orphan Diseases for the “WHO Report on Priority Medicines for Europe and the World” – 7 October 2004).

It is worth noticing that each and every one of us is a carrier of 6 to 8 genetic abnormalities, normally recessive ones. This generally has no consequences, but if two persons with the same genetic abnormality have children, these may be affected.

Paradox of rarity

The above-mentioned figures mean that even though the “diseases are rare, rare diseases patients are many”. It is therefore “not that unusual to have a rare disease”.

It is also not unusual to “be affected by” a rare disease, as the whole family of a patient is indeed affected in one way or another: in this sense it is “rare” to find a family where nobody is - or no ancestor has been - affected by a rare (or “unknown”, “unexplained”, “strange”) disease.

A mother tells:

“At the age of 6, Samuel was diagnosed with a rare metabolic disease. Almost three years after Samuel’s death, we are still a family with a rare disease: I have discovered that I have symptoms linked to the fact that I am a carrier, my marriage broke down due to the stress of loosing a child and my daughter was unable to sit her A level exams due to the grief of loosing her little brother and her father leaving”.

Diversity and heterogeneity of rare diseases

Rare diseases are also characterised by a high number and the broad diversity of disorders and symptoms that vary not only from disease to disease, but also within the same disease. For many diagnoses, there is a broad diversity of subtypes of the same disease. It is estimated that between 5.000 and 7.000 distinct rare diseases exist today, affecting patients in their physical aptitudes, their mental abilities, in their behaviour and sensorial capacities. Rare diseases also differ widely in terms of seriousness: most are life threatening, while others are compatible with a normal life if diagnosed in time and properly managed.

80% of rare diseases have identified genetic origins, involving one or several genes. They can be inherited or derived from de novo gene mutation. They concern between 3% and 4% of births. Other rare diseases are caused by infections (bacterial or viral), or allergies, or are

For a member state like France, occurrence from 3 to 4% at birth represents 22 950 to 30 600 new children born each year with a rare disease (764 700 live births in 2004, Institut National d’Etudes Démographiques INED). At the scale of the European Union, 3% to 4% of births represents 141 900 to 189 200 children born with a rare disease each year (Eurostat 2003).

due to degenerative proliferate or teratogenic (chemicals, radiations, etc) causes.

There is also great diversity in the age at which the first symptoms occur. Symptoms of some rare diseases may appear at birth or in childhood, including infantile spinal muscular atrophy, neurofibromatosis, osteogenesis imperfecta, lysosomal storage disorders, chondrodysplasia and Rett syndrome.

Many other rare diseases, such as Huntington disease, Crohn disease, Charcot-Marie-Tooth disease, amyotrophic lateral sclerosis, Kaposi’s sarcoma and thyroid cancer, only manifest themselves in adulthood.

It is also to be underlined that relatively common conditions can hide underlying rare diseases, e.g. autism (in Rett syndrome, Usher syndrome type II, Sotos cerebral gigantism, fragile X, Angelman, adult phenylketonuria, Sanfilippo,...) or epilepsy (Shokeir syndrome, Feigenbaum Bergeron Richardson syndrome, Kohlschutter Tonz syndrome, Dravet syndrome...). For many conditions described in the past as clinical entities such as mental deficiency, cerebral palsy, autism or psychosis, a genetic origin is now suspected or has already been described. In fact, these conditions are underlying rare diseases.

Common characteristics of rare diseases

Despite this great diversity, rare diseases have some major common traits and can almost always be characterised as:

- Severe to very severe, chronic, degenerative and usually life-threatening;
- Mostly affect children, but also adults;
- Disabling: the quality of life of rare diseases patients is seriously compromised due to lack or loss of autonomy;
- Highly painful: the suffering of rare disease patients and their families is aggravated by psychological despair and the lack of therapeutic hope;
- Incurable diseases, mostly without effective treatment. In some cases, symptoms can be treated to improve quality of life and life expectancy.

Clarification of some related concepts

It is not infrequent to read documents and publications where the concepts of rare diseases, neglected diseases and orphan drugs are not clearly defined and where they are used as interchangeable concepts. This situation has led to misperception and confusion as to precisely what each of these concepts refers to and as to what reality each of them covers.

Rare diseases

Rare diseases are firstly characterised by their low prevalence (less than 1/2000) and their heterogeneity. They affect both children and adults, anywhere in the world. Because rare disease patients are minorities, lacking public awareness and not representing public health priorities, little research is performed. Because the market is so narrow for each disease, the pharmaceutical industry is reticent to invest in research and to develop treatments for rare diseases. There is therefore a need for economic regulation in this field.

Neglected diseases

Neglected diseases are common, communicable diseases that mainly affect patients living in the poor developing countries. Because they do not represent public health priorities in the industrialised countries, little research is performed on these diseases. They are neglected by the pharmaceutical industry because the market is usually seen as unprofitable. There is a need for economic regulation and alternative approaches in this field in order to create incentives aimed at stimulating research and developing treatments to fight neglected diseases, which are prevalent in developing countries. Neglected diseases are therefore not rare diseases.

Fight for recognition

Rare diseases as a reality

It is fundamental to realise that rare diseases can affect any family at any moment. It is not just “something terrible that happens to other people”. It is a very cruel reality that can happen to anyone, either when having a child or in the course of one’s own life.

In fact, the terminology “rare diseases” only highlights the characteristic of rarity of the complex and heterogeneous mosaic of an estimated

7.000 life-threatening and heavily debilitating conditions. This terminology, which only underlines rarity, immediately puts a reassuring distance between the “poor people to whom something so terrible has happened” and the vast majority of citizens who feel protected by the low prevalence of rare conditions. If these diseases were officially called “terrible diseases that slowly kill your child - or yourself - and nobody cares”, which is the truth, then the existence of about 30 million people directly affected would strike public opinion more realistically.

Fortunately and mainly thanks to the relentless work of patient and parent organisations, things are slowly changing. Until recently, public health authorities and policy makers have largely ignored rare diseases. Today, and even though the number of specific rare diseases which are known is still very limited, we can witness an awakening of some parts of public opinion and, as a consequence, some actions are being taken by public authorities. The rare diseases for which a simple and effective preventive treatment is available are even being screened for, as part of public health policy. But this is not enough, and it is time for public authorities to consider rare diseases as a Public Health priority and take action to concretely support patients and families affected by rare diseases. As we know, most of these diseases involve sensory, motor, mental and physical impairments. These difficulties can effectively be reduced by the implementation of appropriate public policy.

As underlined in the Background Paper on Orphan Diseases for the WHO Report on Priority Medicines for Europe and the World, “despite the growing public awareness of rare diseases in the last one or two decades, there are still many gaps in knowledge related to the development of treatment for rare diseases. Policymakers have to realise that rare diseases are a crucial health issue for about 30 million people in the EU”.

1 OVERTURE

1.1 The word of the President of Eurordis

→ WELCOME

It gives me great pleasure to welcome you to the opening of the European Conference on Rare Diseases during the Luxembourg Presidency. In front of us we have two days of challenging and stimulating presentations on ways to improve survival, care and quality of care for people living with rare diseases across Europe.

Our hope for this conference is that it will take us forward to find better solutions for patients and families affected by rare diseases.

Rare diseases are a very heterogeneous range of conditions from metabolic diseases to rare cancers.

Rare diseases are a new concept but not a new phenomenon. Only 3 decades ago, rare diseases would hardly be understood as an issue for public authorities. Even many members of the medical community would most likely associate rare diseases to something which would serve as a “test case” for their knowledge of the bizarreness of nature. The complexity, firstly because of the names given to the diseases does not help to change this.

But today, this has changed. Rare diseases are now generating general awareness.

Generally, rare diseases patients when they are children are placed in institutions. Parents are advised to forget their child and to have another one. That is what happened in the past.

5000 to 7000 rare diseases are now known (more than 1000 diseases clinically described, and more than 4000 where only a few cases are described).

Rare diseases are rare but patients are many. But as a lack of data, it is hard to estimate the number of people affected. There is a lack of WHO codes, inadequate or non existing epidemiological data.

According to Orphanet studies, in 2003, 7.5 million European citizens are concerned with the most common rare diseases. This is a huge health and social issue (1, 7% of the European population). This number can be multiplied by 3 or 4 when adding the families and the other rare diseases.

The most severe rare diseases affect life of patients as a burden: severe, chronic, disabling and very often life threatening diseases, mental disabilities, autism, cerebral palsy, psychosis, respiratory and health problems. These diseases are usually incurable.



Terker Andersen
President of Eurordis

S P E A K E R

Orphanet studies show that of the 230 rare diseases studied, 65% appear at birth or in childhood, and 80% are genetic.

Rare diseases have a huge impact on the living conditions of the patient and the family, on society and have a lot of social consequences:

- The pre diagnostic maze is the period between emerging symptoms and correct diagnosis. This delay is much too long, leading to inappropriate treatments.
- Even with a diagnosis, people can be faced with too little information and help. This includes the lack of referral to qualified professionals.
- Little scientific knowledge basis, which causes shortage of therapeutic products, both medicinal products and appropriate medical devices.
- Rare diseases have huge social consequences; stigmatisation, isolation from school, and professional opportunities. Health care systems are not adapted to ensure early diagnosis (insufficient scientific knowledge, therapeutic treatments, and devices) and there is also a lack of good guidelines and multidisciplinary cares.
- People can live for several years in a precarious situation even after diagnosis. Frequently, the cost of care and treatments is high, thus leading to the impoverishment of families. Social security is no efficient enough.

Chances are different amongst diagnostic delays, depending on the rare diseases. Patients with rare diseases are given very different opportunities even within their own country. Their life depends to a large extent on chance or what could be called a postal code lottery.

Still we have come a long way over the past ten years. We have marked progress with 270 new drugs for rare diseases that have been designated as orphan drugs by EC and also the development of regulation on orphan drugs (OD) and draft paediatric drugs regulation, the creation of a European network of specialists, framework programmes for DG Research, Public Health Action for DG Health and Consumer Protection, particularly the Working Party on Morbidity and Mortality with academic representatives, and organisations for patients. We have most recently seen the European Parliament supporting a new EU policy on patient mobility. Last but not least we are building a European community with a very active participation of patient’s groups.

But there is still a long way to go before creating real improved quality of life as perceived by the majority of patients themselves and real improvement of their opportunities.

And unfortunately we are still mainly talking about diagnosis, survival and access to clinical trials and in some cases to treatment, but very

rarely about how to address the need and legitimate right of these patients and their families for psychosocial support, how to cope, the economic impact, how to create equal opportunities also at school and in participation in all aspects of life in general.

The perspectives so far are to create a better synergy between scientific progress, genetic research, internet, involvement of patient's organisations, society concern and more public policies at a national level and to create cohesion between Members of the EU Parliament, associations, scientific community health care professionals and industry.

1.2 The European Commission

On behalf of Marcos Kyprianou, EU Commissioner for Health, I would like to thank Mars di Bartolomeo, Ministry of Health of Luxembourg and also the organising committee.

Lack of information on rare diseases often means that patients suffering from a rare disease (more than 7% of the EU population) do not always benefit from the health services they need. It is not yet possible to develop a European public health policy specifically for each rare disease but a global approach to rare diseases can be established in the areas of scientific and biomedical research, drug research, training, information, social benefits, hospitalisation, and outpatient treatment.

Rare diseases were considered as a priority in the precursory EU health programme until 2002. They are still a priority in the current programme (2003-2007), and will continue to be a priority in the next programme if the proposal by the EU Commission is adopted by EU Parliament and Council. The work plan of DG Health and Consumer Protection focuses on information exchange through existing European networks, development of mechanisms for information exchange and coordination at EU level to encourage trans-national cooperation.

Regarding Orphan Drugs, the EMEA celebrated last March its 10th anniversary, as it was created in London in 1995. On the same occasion, it celebrated 5 years of orphan drug policy. The EMEA has provided Europe and its citizens with the best scientific assessment of the quality, safety and efficacy for approximately 300 medicinal products.



Fernand Sauer
Director for Public Health, DG Health and Consumer Protection, European Commission

S P E A K E R

Five years of Orphan drug policy led the EMEA to decide so far on the designation of approximately 300 products for rare diseases. Of those, 20 products were granted marketing authorisation at EU level.

I personally had the privilege to participate in the launch of the COMP (Committee of Orphan Medicinal Products) established at the EMEA and launched in 2000 with Prof. Torrent Farnel, Yann Le Cam and Alistair Kent. It was the first European committee ever where patient organisations were directly and permanently represented.

Turning to the main outputs of the precursor community action programme on rare diseases 1999-2002, there were 24 projects for a total of 6.5 million €.

Some of these projects became international references in the field:

- The Orphanet database, the most important database in the EU for rare diseases and Orphan drugs.
- The successive projects of Eurordis for building a public policy on rare diseases, improving quality information on rare diseases and orphan drugs.
- The Eurocat network (Surveillance of Congenital Anomalies in Europe), which surveys more than 1 million persons per year in 19 countries, providing essential epidemiological information.
- Enerca (Rare Congenital Anemias) is an information tool including a list of specialised centres, definitions, and information about standardisation of diagnostic services.
- The last is a database on rare forms of dementia which is being updated.

In the new public health programme 2002-2004, the first priority of the programme when it came into effect was the continuation of some major projects from the previous period.

For example the organisation of this conference, and as a result, the European Rare Disease White Book providing best practices and recommendations to all MS to develop and strengthen EU cooperation.

Also the establishment of the scientific secretariat for the Rare Diseases Task Force under the chairmanship of Segolène Aymé: this Task Force provides a forum for discussion and exchange of views, experience, information and knowledge and it participated very actively in the organisation of this conference.

Research is also a priority: the 6th Research Framework Programme and thematic priorities under which actions to tackle rare diseases are conducted.

Just a word about the EU cooperation through the High Level Group on Patient Mobility & Health Services: in 2003, the Commission invited all health ministers and representatives from 6 NGOs including patient groups to engage in a High Level reflection process on the mobility of patients which was seen by certain as a threat, but by others as an opportunity also.

The Commission has drawn a report from the responses in April 2004, making proposals to enable a better use of resources at EU level, better information for patients and professionals, and responding to investments in health and health infrastructures.

One of the working groups under the High Level Group addresses centres of reference. This working group is led by France and exchanges have already taken place with the Task Force on Rare Diseases.

In conclusion, the Commission proposed on the April 6th a new health strategy for Europe together with an ambitious funding plan, under the new financial perspectives.

1.3 The Ministry of health of Luxembourg

→ LADIES AND GENTLEMAN,

The construction of Europe needs conferences like this to demonstrate the added value of working together against issues like rare diseases and to carry out very strong messages.

In the last months during the European Presidency by the government of Luxembourg, we had the opportunity, together with our partners, to make European health progress dramatically. Even though public health is a national competence and not a priority in European treaties, there are possibilities to make advances, not as a compulsory domain but based on the good will of all member states.

Indeed, public health has no frontiers.

During the Presidency by Luxembourg, we also had the opportunity to disseminate strong messages. First we insisted on a certain number of principles: free access to care, high quality of care, and affordability of care, with no difference with regard of income. Based on such principles, we decided to consider health services as different from any



“ Mars di
Bartolomeo
The ministry of health
of Luxembourg

SPEAKER

other kind of services, and to address them in a different directive than the directive on services.

Please allow me to mention briefly some recent steps forward and successes with the WHO, Commissioned and Non Governmental Organisations working together :

- WHO European Ministerial Conference on Mental Health, Facing the Challenges, Building Solutions, Helsinki, Finland, 12–15 January 2005
 - Conference on Patient Safety: Making it happen! Luxembourg, 4-5 April 2005, insisting on good offers for care and good diagnosis first
 - The European Union 2005 e-health conference in Tromsø Norway, 23-24 May 2005, progressing in a collaborative
- manner to implement solutions to improve health care services and to support more responsive health services, greater awareness through better health information,
- The initiative of the Luxembourg Presidency on quality of life, promoting health protection in addition to treating diseases.

Other examples illustrating the necessity to work together :

HIV/AIDS: during the last months, Aids has become a priority at the Council level. Difficulties are present; a collaborative strategy shows the interest for a common approach in the EU.

It is a great pleasure to welcome you in Luxembourg.

It shows again that alone we are very weak, but together we can act stronger. The French say “L’union fait la force”, “union gives us the strength”. In this field it is truer than in any other domain. Rare diseases taken separately are not a priority, but all together they certainly are a high priority. Thank you for having chosen Luxembourg for this conference, for having made this conference possible.

I wish you all the success it deserves, I wish you to be successful in your efforts to make Europe progress in its fight against rare diseases.

2 EPIDEMIOLOGY

2.1 Rare diseases in numbers

Preliminary report from an on going bibliographic study¹

→ STUDY RATIONALE

- Very little documented information on the epidemiology of rare diseases
- Important to estimate the total number of affected people and the prevalence per disease
- Need to assess the natural history of rare diseases to adapt care and monitor improvements

→ STUDY OBJECTIVES

- To assess the prevalence in Europe of each rare disease
- To document the age of onset, the life expectancy and the mode of inheritance

→ METHOD 1 : selection of rare disease (for the purposes of the current report)

- A selection of rare diseases focussing on the more common ones according to the literature review to date
- The most frequently requested pages on the Orphanet website

→ METHOD 2 : search strategy, several data sources

- Websites: Orphanet, e-medicine, geneclinics and OMIM
- Medical books, grey literature and reports from experts were also some important sources of available data.
- Medline was consulted using the search algorithm: "Disease name" AND (Epidemiology [mh] OR Incidence [ti/ab] OR Prevalence [ti/ab] OR Epidemiology [ti/ab])

→ METHOD 3 : limitations of the study

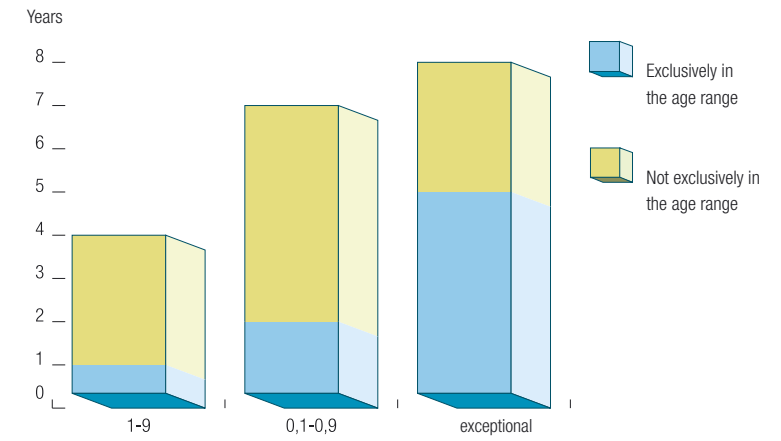
- Exact prevalence rate is difficult to obtain from the available data sources
- Confusion between incidence and prevalence
- Low level of consistency between studies
- Confusion between incidence at birth and life long incidence.
- Poor documentation of methods used

¹. (This study was initiated by Eurordis in partnership with Orphanet)

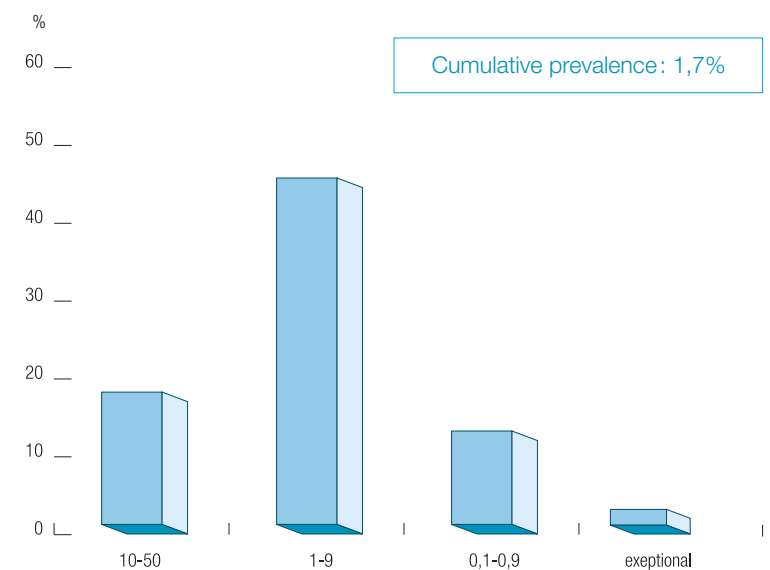
→ RESULTS

Preliminary results from the analysis of 359 rare diseases. Not all data were available for every disease. More results will be available in a few months time.

 **AGE OF ONSET OF 353 RARE DISEASES (YEARS), (figure 7)**



 **PREVALENCE RANGE OF 230 RARE DISEASES (/100 000), (figure 8)**



→ **MODE OF INHERITANCE OF 359 RARE DISEASES**

- 26.5% autosomal dominant inheritance
- 28.1% autosomal recessive inheritance
- 7% X-linked inheritance
- 10% several modes of inheritance
- 13.4% multigenic / multifactorial diseases
- 8.1% sporadic diseases
- 5.8% unknown aetiology

→ **LIFE EXPECTANCY OF 323 RARE DISEASES**

- 37.5% normal lifespan
 - 25.7% potentially lethal at birth or before 5 years of age
 - 36.8% reduced lifespan,
- depending on the severity, penetrance or type (child, juvenile or adult types for example) of the disease

**DISEASES WITH PREVALENCE DATA AVAILABLE**

DISEASE NAME	Estimated prevalence (/100,000)
Brugada syndrome	50
Protoporphyrin, erythropoietic	50
Gelineau disease	49
Guillain-Barre syndrome	47,5
Melanoma, familial	46,8
Autism, genetic types	45
Tetralogy of Fallot	45
Scleroderma	42
Great vessels transposition	32,5
Focal dystonia	30
Marfan syndrome	30
Non-Hodgkin malignant lymphoma	30
Retinitis pigmentosa	27,5
Alpha-1 antitrypsin deficiency	25
Polycythemia vera	25
Diaphragmatic hernia, congenital	25
Juvenile arthritis, idiopathic	25
Neurofibromatosis type 1	25
Oesophageal atresia	25
Charcot-Marie-Tooth disease	24
VATER association	23
Coffin-Lowry syndrome	22,5

Rendu-Osler-Weber disease	21,25
Dermatitis herpetiformis	20,2
Atresia of small intestine	20
Duodenal atresia	20
Ehlers-Danlos syndrome, classic type	20
Hirschsprung disease	20
Microdeletion 22q11	20
Spherocytosis hereditary	20
Turner syndrome	20
Cardiomyopathy, familial dilated	17,5
Breast cancer, familial	17
MELAS syndrome	16
Leucinosi	15,6
Acyl-CoA dehydrogenase, medium chain, deficiency of	15
Lennox-Gastaut syndrome	15
Fragile X syndrome	14,25
Myeloma, multiple	14,25
Primary biliary cirrhosis	13,5
Stickler syndrome	13,5
Williams syndrome	13,3
Willebrand disease	12,5
Gastroschisis	12
Microphthalmia	12
Omphalocele	12

DISEASE NAME	Estimated prevalence (/100,000)
Sarcoidosis	12
Cystic fibrosis	12
MURCS association	11,25
Stargardt disease	11,25
Glioblastoma	11
Sickle cell anemia	11
Multiple endocrine neoplasia type 1	11
Prader-Willi syndrome	10,7
Alopecia totalis	10,5
Nephroblastoma	10,1
Pheochromocytoma	10
Duane syndrome	10
Neuroblastoma	10
Hodgkin disease	9,4
Dermatomyositis	9,25
Polymyositis	9,25
Tuberous sclerosis	8,8
Myasthenia gravis	8,5
Congenital adrenal hyperplasia	8,5
Rett syndrome	8,2
Huntington disease	8
Angelman syndrome	8
Cataract, total congenital	7,9
Hyperlipidemia type 3	7,8
Hemophilia	7,7
Trisomy 18	7,7
Behcet disease	7,5
Immunodeficiency, common variable	7,5
Microscopic polyangiitis	7,5
Idiopathic torsion dystonia	7,25
Oculocutaneous albinism	7,15
Facioscapulohumeral muscular dystrophy	7
Holoprosencephaly	7
Sclerosing cholangitis	7
Sotos syndrome	7
Galactosemia	6,6
Optic atrophy, Leber type	6,5
Osteogenesis imperfecta	6,5
Smith-Lemli-Opitz syndrome	6,5

Amyotrophic lateral sclerosis	6
Treacher-Collins syndrome	6
Tay-Sachs disease	5,75
Retinoblastoma	5,4
Rubinstein-Taybi syndrome	5,4
Alzheimer disease, familial	5,3
Zollinger-Ellison syndrome	5,3
Cornelia de Lange syndrome	5,25
Familial adenomatous polyposis	5,25
Acromegaly	5
Fructose intolerance	5
Primary ciliary dyskinesia	5
Supranuclear palsy, progressive	5
Porphyria, acute intermittent	5
Deletion 5p	4,6
Achondroplasia	4,5
Steinert myotonic dystrophy	4,5
Ceroid lipofuscinosis, neuronal	4
Phenylketonuria	4
Smith-Magenis syndrome	4
Wilson disease	4
Muscular dystrophy limb girdle type 2A, Erb type	3,8
CDG syndrome	3,75
Niemann-Pick A disease	3,75
Propionic acidemia	3,75
Waardenburg syndrome type 1, type2 and type 3	3,75
Beckwith-Wiedemann syndrome	3,65
Adrenoleukodystrophy, X-linked	3,5
Goldenhar syndrome	3,5
Usher syndrome	3,5
Muscular dystrophy, Duchenne and Becker type	3,4
Multiple endocrine neoplasia, type 2	3,3
Systemic mastocytosis	3,3
Von Hippel-Lindau disease	3,25
Polyarteritis nodosa	3,07
Friedreich ataxia	3
Poland anomaly	3
Proximal spinal muscular atrophy	3
Saethre-Chatzen syndrome	3
Wegener granulomatosis	3
Kennedy disease	2,8
Cystinosis	2,75

DISEASE NAME	Estimated prevalence (/100,000)
Amaurosis congenita of Leber	2,5
BOR syndrome	2,5
Bullous pemphigoid	2,5
Kartagener syndrome	2,5
Niemann-Pick B disease	2,5
Pseudoxanthoma elasticum	2,5
Leigh disease	2,25
Peutz-Jeghers syndrome	2,2
Autosomal dominant spinocerebellar ataxia	2,15
Albinism ocular	2
Alport syndrome	2
Crouzon disease	2
Deletion 4p	2
Klippel feil syndrome	2
Langerhans cell histiocytosis	2
Nail-patella syndrome	2
Persistent hyperinsulinemic hypoglycemia of infancy	2
Aniridia, sporadic	1,75
Fabry disease	1,75
Variegata porphyria	1,7
Budd-Chiari syndrome	1,5
Darier disease	1,5
X-linked severe combined immunodeficiency, T- B+	1,5
Bile ducts paucity, syndromic form	1,4
Cat-eye syndrome	1,35
Apert syndrome	1,25
Spastic paraplegia, familial	1,25
Adult Onset Still's disease	1,23
Polycystic kidney disease, recessive type	1,2
Pierre Robin syndrome	1,2
Glycogen storage disease type 2	1,1
Mucopolysaccharidosis type 3	1,1
Zellweger syndrome	1,1
Nephronophthisis	1,05
3-hydroxyacyl-CoA dehydrogenase, long chain, deficiency of	1
Albers-Schonberg disease	1

Angioneurotic edema	1
Ataxia telangiectasia	1
Chondrodysplasia punctata, rhizomelic type	1
Coloboma, ocular	1
Emery-Dreifuss muscular dystrophy, X-linked	1
Fanconi anemia	1
Gaucher disease	1
Gorlin syndrome	1
Holt-Oram syndrome	1
Hypokaliemic periodic paralysis	1
Isovaleric acidemia	1
Mucopolysaccharidosis type 1	1
Nemaline myopathy	1
Neuroendocrine tumor	1
Thomsen and Becker disease	1
Churg-Strauss syndrome	0,9
Ellis Van Creveld syndrome	0,9
Joubert-Boltshauser syndrome	0,85
Bardet-Biedl syndrome	0,8
Ebstein anomaly	0,75
Hyperkaliemic periodic paralysis	0,75
Krabbe disease	0,75
Mucopolidosis type 2	0,75
Albright hereditary osteodystrophy	0,72
Menkes syndrome	0,7
Niemann-Pick C disease	0,7
Glycogen storage disease type 4	0,6
Alpha-sarcoglycanopathy	0,57
Beta-sarcoglycanopathy	0,57
Delta-sarcoglycanopathy	0,57
Gamma-sarcoglycanopathy	0,57
Tetrasomy 18p	0,55
Neurofibromatosis type 2	0,5
Xeroderma pigmentosum	0,5
Agammaglobulinemia X-linked	0,45
Cowden syndrome	0,45
Werner syndrome	0,45
Christ-Siemens-Touraine syndrome	0,45
Glutaryl-CoA dehydrogenase deficiency	0,4
Homocystinuria due to cystathionine beta-synthase deficiency	0,4
Mucopolysaccharidosis type 4	0,4

DISEASE NAME	Estimated prevalence (/100,000)
Lesch-Nyhan syndrome	0,38
Pfeiffer syndrome	0,38
Severe combined immunodeficiency T- B	0,35
Anemia congenital hypoplastic, Blackfan-Diamond type	0,32
Alkaptonuria	0,3
Lissencephaly, type 1, due to LIS 1 anomalies	0,3
Dopa-responsive dystonia	0,3
Lipodystrophy, Berardinelli type	0,25
Progeria	0,25
Granulomatous disease, chronic	0,2
Jeune syndrome	0,2
Nanism due to growth hormone resistance	0,2
Neurodegeneration with brain iron accumulation (NBIA)	0,2

Creutzfeldt-Jakob disease	0,19
Lowe syndrome	0,19
Mucopolysaccharidosis type 6	0,16
CHARGE association	0,14
Metachromatic leukodystrophy	0,13
Barter syndrome	0,12
Muscular dystrophy fukuyama type Walker-warburg syndrome Muscle eye brain disease	0,12
Ewing sarcoma	0,1
Hypercholesterolemia, familial (homozygous form)	0,1
Fibrodysplasia ossificans progressiva	0,08
Tyrosinemia type 1	0,05
Factor XIII deficiency, congenital	0,04
Factor XIII deficiency, congenital	0,04
Perinatal hypophosphatasia	0,03



DISEASES WITHOUT PREVALENCE DATA AVAILABLE BUT WITH PUBLISHED CASES

DISEASE NAME	Number of published cases
Klippel trenauay weber syndrome	1000
Whipple disease	1000
Incontinentia pigmenti	750
Aicardi syndrome	500
CADASIL	500
Li-Fraumeni syndrome	400
Silver-Russell, syndrome de	400
Castleman disease	400
Cutis marmorata telangiectatica congenita	300
Möbius syndrome	300
Alström syndrome	300
Kabuki syndrome	300
Ondine syndrome	300
Job syndrome	250
Kearns-Sayre syndrome	223
Xanthomatosis cerebrotendinosa	200
Cockayne syndrome	200

Gunther disease	200
Cogan syndrome	200
Kimura disease	200
Alpha thalassemia-mental retardation, X linked	164
McCune-Albright syndrome	158
Denys-Drash syndrome	150
Cohen syndrome	100
Seckel syndrome	100
CINCA syndrome	100
Larsen syndrome	100
Macrophagic myofasciitis	100
Capillary leak syndrome	57
Waardenburg-Shah syndrome	50
Peters-plus syndrome	50
Coffin-Siris syndrome	40
Acrocallosal syndrome, Schinzel type	34
Pallister-Killian, syndrome de	30
Aicardi-Goutieres syndrome	30
CHILD syndrome	30
Schinzel-Giedion midface retraction syndrome	30

2.2 Rare cancers among rare diseases

Incidence of rare cancers in Granada (1998-2001)

→ INTRODUCTION

Scarce information on prevalence, incidence and survival is available for rare cancers. Definitions of rare diseases are based on prevalence, but for tumours they have been based on incidence, although there is not a standard accepted definition.

The aim of the study was to provide a list of Rare Cancers in the Province of Granada (south of Spain) from 1998 to 2001.

→ MATERIAL AND METHODS

A population-based study was carried out. All incident cancer cases diagnosed in the province of Granada during 1998-2001 were included. Data were provided by the Granada Cancer Registry. Rare Cancers were defined as those with an incidence lower than 3 cases per 100 000 inhabitant /year.


→ RESULTS

A total of 14 538 cases were registered in this Province from 1998 to 2001, with an average annual crude incidence rate of 450.9 per 100 000 inhabitants, for overall cancer.

Rare cancers represent 7.2% of overall cancers, excluding non-melanoma skin cancer.

Classifying the cancers according to anatomical site (using the ICD-10) and sex, 33 cancers in men and 34 cancers in women were classified as rare cancers.

Results are shown in tables below.

 **INCIDENCE OF RARE CANCERS IN GRANADA, 1998-2001. MALES**
Number of cases, crude and standardised world population (asr-w) incidence rates per 100 000 men

ICD-10	ICD-10	Cases	Crude rate	ASR-W
C33	Trachea	1	0,1	0,1
C37	Thymus	1	0,1	0,1
C30	Nasal cavity and middle ear	3	0,2	0,2
C72	Spinal cord, cranial nerves & other parts of CNS	3	0,2	0,2
C88	Immuno-proliferative malignant diseases	3	0,2	0,1
C08	Other and unspecified major salivary glands	4	0,3	0,2

Poster 87

“ MJ Sanchez-Perez²,
C Martinez Garcia², JD
Martin-Ortiz², M. Posada
de la Paz³

2. Granada Cancer Registry, Andalusian School of Public Health

3. Scientific coordinator of REPIER Network

ICD-10	ICD-10	Cases	Crude rate	ASR-W
C70	Meninges	5	0,3	0,2
C31	Accessory sinuses	6	0,4	0,3
C93	Monocytic leukaemia	6	0,4	0,2
C38	Heart, mediastinum and pleura	7	0,4	0,5
C46	Kaposi Sarcoma	7	0,4	0,3
C75	Other endocrine glands and related structures	7	0,1	0,5
C74	Adrenal glands	9	0,6	0,6
C07	Parotid glands	11	0,7	0,5
C13	Hypopharynx	12	0,8	0,6
C48	Retroperitoneum and peritoneum	13	0,8	0,7
C21	Anus and canal anal	14	0,9	0,6
C50	Breast	14	0,9	0,6
C69	Eye	14	0,9	0,8
C40-41	Bone	15	1	0,8
C09	Tonsil	17	1,1	0,8
C17	Small intestine	18	1,1	0,7
C45	Mesothelioma	18	1,1	0,7
C73	Thyroid gland	19	1,2	0,9
C10	Oropharynx	20	1,3	1,0
C60	Penis	22	1,4	1,0
C11	Nasopharynx	23	1,5	1,1
C66	Ureter	23	1,5	0,8
C23	Gallblader	24	1,5	0,8
C12	Pyriform sinus	28	1,8	1,4
C24	Extra hepatic biliary tract	33	2,1	1,1
C81	Hodgkin disease	37	2,3	2,1
C62	Testis	43	2,7	2,4



INCIDENCE OF RARE CANCERS IN GRANADA, 1998-2001. FEMALES
Number of cases, crude and standardised world population (ASR-W) incidence rates per 100 000 women

ICD-10	ICD-10	Cases	Crude rate	ASR-W
C10	Oropharynx	1	0,1	0,0
C33	Trachea	1	0,1	0,0
C37	Thymus	1	0,1	0,0
C38	Heart, mediastinum and pleura	1	0,1	0,2
C58	Placenta	1	0,1	0,1
C66	Ureter	1	0,1	0,0

ICD-10	ICD-10	Cases	Crude rate	ASR-W
C93	Monocytic leukaemia	1	0,1	0,0
C09	Tonsil	2	0,1	0,1
C30	Accessory sinuses	2	0,1	0,1
C72	Spinal cord, cranial nerves & other parts of CNS	2	0,1	0,1
C69	Eye	3	0,2	0,1
C74	Adrenal glands	3	0,2	0,2
C45	Mesothelioma	4	0,2	0,1
C46	Kaposi sarcoma	4	0,2	0,1
C88	Immuno-proliferative malignant diseases	4	0,2	0,2
C07	Parotid gland	5	0,3	0,2
C32	Larynx	5	0,3	0,2
C70	Meninges	5	0,3	0,2
C75	Other endocrine glands and related structures	5	0,3	0,3
C11	Nasopharynx	6	0,4	0,3
C52	Vagina	7	0,4	0,3
C48	Retroperitoneum and peritoneum	8	0,5	0,4
C40-41	Bone	9	0,5	0,3
C65	Renal pelvis	9	0,5	0,2
C17	Small intestine	11	0,7	0,5
C21	Anus and canal anal	13	0,8	0,3
C15	Oesophagus	17	1,0	0,4
C03-06	Mouth	20	1,2	0,8
C01-02	Tongue	22	1,3	0,7
C81	Hodgkin disease	27	1,6	1,6
C00	Lip	32	1,9	0,9
C51	Vulva	39	2,4	1,0
C24	Extrahepatic biliary tract	42	2,5	1,1

For the overall rare cancers, 58% and 80% show an annual average incidence rate lower than 1 per 100 000 males and females, respectively. Results from Granada are similar to those obtained in a previous study on rare cancers carried out in 11 population-based cancer registries in Spain from 1993 to 1997⁴.

4. This study has been partially funded by ISCIII: PIO20686, REPIER Network (GO3/123) and RCESP Network (C03/09).



Dr. Madelon Kroneman, Researcher, Netherlands Institute for Health Services Research Nivel, The Netherlands.

The rare disease dilemma: EU health care systems unable to diagnose what patients are suffering from.

3 DIAGNOSING RARE DISEASES: health care systems always challenged

3.1 EurordisCare2: patients loose confidence in health care systems

EurordisCare2, a survey on delay in diagnosis in Europe for 8 rare diseases⁵.

Late diagnosis of rare diseases: a remaining issue resulting in individual and familial consequences

Rare diseases are poorly taken into consideration the general public and also health care professionals. As a result, even their diagnosis is an issue.

This survey was launched to document, through patient experience, the extent, causes and consequences of late diagnosis in 8 rare diseases in Europe. 69 patient organisations from 17 countries sent questionnaires in 12 languages to 18 000 patients. Patients returned 5980 to Eurordis, (5300 analysed).

This study was the first approach on this matter

→ METHODS



Table below shows the main characteristics of the diseases:

	Genetic	Prevalence /10 000	Main clinical aspects
Crohn	No	2-15	digestive
Cystic fibrosis	inheritable	3	digestive, respiratory
Duchenne	inheritable	1,2	neuromuscular
Ehlers Danlos	inheritable	-	dermatologic, joints
Fragile X	inheritable	1,5	cognitive
Marfan	inheritable	2	cardiovascular, osteoart, OPH
Prader Willi	Sporadic	0,5	metabolic, cognitive
Tub, sclerosis	Sporadic Anher	1	neurologic, cognitive

For a given disease, the number of returned questionnaires varied from 485 (Ehlers Danlos Syndrome) to 1079 (cystic fibrosis) and the number of participating countries from 5 for Crohn's disease and Ehlers Danlos syndrome to 14 for Prader Willi syndrome.

5. [This article has been submitted to a peer-reviewed scientific magazine for publication. Therefore only a preliminary report can be published in this report]

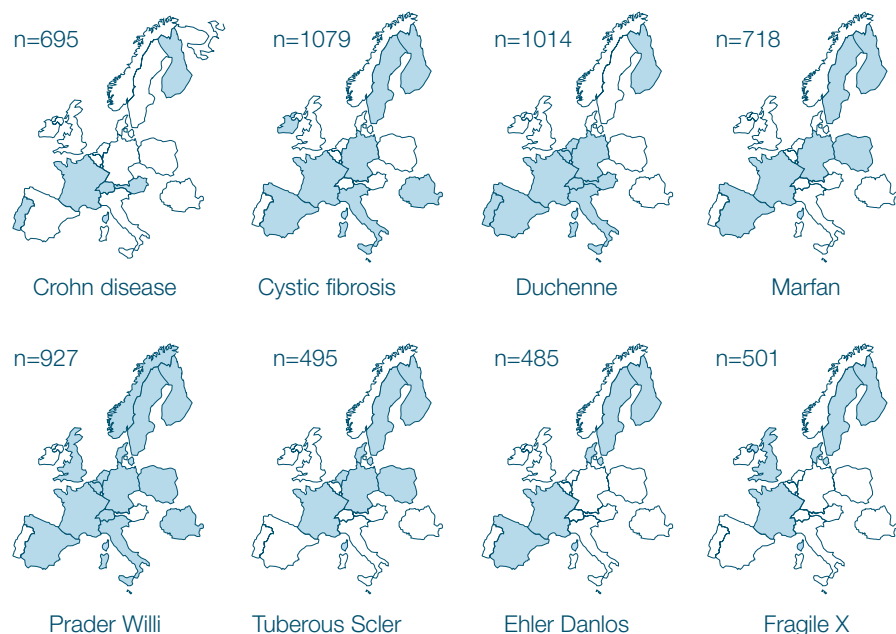


Figure 9 displays, by disease, the countries in which the questionnaire was sent to patients.

→ STUDY POPULATION

The study population (respondents) was well distributed geographically, a third living in a country village, a third in small and medium-size cities, and a third in larger cities.

Respondents were from all professional categories, with a slight overrepresentation of the management and teacher sectors, and underrepresentation of manual workers and retired persons.

→ RESULTS: DELAYS FROM FIRST SYMPTOMS TO CONFIRMATORY DIAGNOSIS

For a given disease, there was a wide variability in delays. For most diseases, a diagnostic was obtained without delay for one quarter or half of the patients. Unfortunately, a consistent number of patients had to wait for a long time before diagnosis.

Waiting for diagnosis was not a calm period but a continuous quest. Patients had to consult numerous doctors. One quarter of patients consulted at least 4 doctors in Fragile X syndrome, 6 doctors in Prader Willi syndrome and Marfan syndrome and 16 in Ehlers Danlos syndrome.

The final 25% of diagnosis required at least 1.5 years in cystic fibrosis, 3 to 6 years in Duchenne muscular dystrophy, Prader Willi syndrome, Fragile X syndrome and Crohn's disease, 11 years in Marfan syndrome and 28 years in Ehlers Danlos syndrome!

The loss of confidence in medicine was observed in all diseases with frequencies varying from 11 to 17 % of patients.

Before receiving a confirmatory diagnosis, 40% of patients received first an erroneous diagnosis, while 60% received none.

The trend to misdiagnosis depended both on the disease (1/4 in Marfan syndrome versus $\frac{1}{3}$ in Ehlers Danlos syndrome), and on the country (1/3 in Finland, Spain, United Kingdom and Ireland versus $\frac{1}{4}$ in Austria, Denmark, Germany, Romania, Sweden and Poland).

Frequently, misdiagnosis resulted in various medical interventions: medical treatments in 1 out of 3 patients, surgery in 1 out of 6 patients, and psychological care in 1 out of 10 patients.

Delay in diagnosis had personal consequences: physical, psychological and intellectual consequences. Physical consequences were reported in more than $\frac{1}{3}$ patients in the case of Marfan syndrome and Ehlers Danlos syndrome; psychological and deterioration in cognitive development mainly in Prader Willi syndrome, Fragile X syndrome and tuberous sclerosis. More dramatically, diagnosis delay was considered to be responsible for the death of the patient in 6 % of cases in the case of Marfan syndrome.

Besides individual consequences, familial consequences represent a hidden but dramatic issue: the birth of an affected sibling affected more than 8% of patients in cases of Marfan syndrome and Ehlers Danlos syndrome. Unacceptable behaviour of relatives was reported in 1 out of 10 to 1 out of 4 patients in cases of 7 diseases.

The conditions of the announcement of the diagnosis were far from satisfying: the diagnosis was announced in unsatisfactory terms or conditions in 33% of cases, and in unacceptable ones in 12.5% of cases. The genetic nature of the disease was not communicated to the patient or family in 25% of cases. This was paradoxical, given the genetic origin of 80% of rare diseases.

→ CONCLUSIONS

- Diagnostic delays exist and may have serious consequences.
- Obtaining the exact diagnosis is only the beginning of the hurdle that patients and their parents have to go through when suffering from a rare disease.
- Disclosure of the diagnosis needs improvement: a point of attention for the medical community.
- There are differences between the countries. It is not clear whether they are cultural or structural.

EurordisCare® is a research programme initiated by Eurordis in 2002, involving rare disease patient organisations, to survey and compare access to care between European countries and between different rare diseases.

3.2 Primary immune-deficiency: a clear illustration of diagnosis delays

The Impact of Diagnosis Delays in Primary Immune-deficiencies (PIDs):

Primary Immune-deficiencies are a group of more than 100 diseases of the immune system. They are genetic conditions that range in severity and bare the clinical hallmarks of persistent, recurring infections. Delayed diagnosis and insufficient treatment leads to increased morbidity, mortality, and inflated medical costs - not to mention a life of chronic illness, permanent organ damage, PIDs can appear at any age and know no racial or ethnic boundaries. Symptoms are often overlooked because they appear to be common childhood illnesses - sinus and ear infections, pneumonia, fever and bronchitis. Physicians often treat ailments without addressing the underlying cause.

A poster jointly submitted by the key organisations representing the EU and international PID nurse, patient and physician community

10 WARNING SIGNS OF PRIMARY IMMUNODEFICIENCY (figure 10)

Primary Immunodeficiency (PI) causes children and young adults to have infections that come back frequently or are unusually hard to cure. In America alone, up to 1/2 million suffer from one of the 100 known Primary Immunodeficiency diseases. If you or someone you know are affected by two or more of the following warning signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1	eight or more new ear infections within one year.	Recurrent, deep skin, or organ abscesses.	6
2	Two or more serious sinus infections within one year.	Persistent thrush in mouth or elsewhere in skin, after age 1.	7
3	Two or more months on antibiotics with little effect.T	Need for intravenous antibiotics to clear infections.	8
4	Two or more pneumonias within one year.	Two or more deep-seated infections	9
5	Failing of an infant to gain weight or grow normally.	A family history of Primary Immunodeficiency.	10

Poster 40,
Bianca Pizzera
Piantanida
IPOPI - International
Patients Organisation
for Primary Immune-
deficiencies, IPOPI

Primary immune-
deficiency

presented an awareness campaign to inform members of the European Parliament: The European Society for Immune-deficiencies (ESID), The International Nurses Group for Immune-deficiencies (INGID), The International Patient Organisation for Primary Immune-deficiencies (IPOPI), the European Federation of Immunological Societies (EFIS) and The Jeffrey Modell Foundation (JMF). “We call upon the European Commission DG Consumer Health & Protection, to urgently take action to ensure that PIDs are named as a priority for action in rare diseases within the EU’s Public Health Programme”.

3.3 A patient’s testimony



Marianna Lambrou,
Tuberous Sclerosis
Association, Greece

SPEAKER

Marianna Lambrou is sharing her experience with her daughter Katerina, who suffers from Tuberous Sclerosis. She was initially diagnosed with a congenital cardiopathy. She underwent open-heart surgery in the USA, with great success. However, at the age of 3, Katerina had her first light epileptic seizure and then a doctor at the Children’s Hospital of Athens mentioned Tuberous Sclerosis, a disease almost unknown at the time in Greece. He said “we” were unlucky and lucky at the same time, because she didn’t suffer from the regular serious symptoms of the disease (mental retardation, severe epilepsy, autism, and severe skin problems). She had treatment for epilepsy and grew up normally.

At the age of 10, and on the occasion of a trip in England, Katerina had her first CT scan, which confirmed Tuberous Sclerosis and showed typical tumours in her brain. She started suffering from severe headaches and was diagnosed with hydrocephalus. She was placed in a shunt system to drain the liquid. This results in a change for life because this is a complex system and it also meant of lot of trips to England where her neurosurgeon was. Katerina was 12.

She was operated for appendicitis, but the shunt system was disconnected and so another trip to England was necessary.

She had been then hospitalized several times in private and state hospitals because of pain and infection of the urinary tract, but with no diagnosis. She suffered from kidney problems. She was nevertheless trying to have a “normal” life.

Unfortunately, Tuberous Sclerosis invaded the child’s and the mother’s lives aggressively with severe pains due to haemorrhage and kidney rupture. The interventional surgery through embolism helped to save Katerina’s sole kidney five times up to now.

There was a need to create the Greek Association of Tuberous Sclerosis,

Tuberous sclerosis

in 1992 with a small group of doctors and parents, aimed to inform and support parents and their families.

Tuberous Sclerosis Association of Greece is a member of Tuberous Sclerosis International, Tuberous Sclerosis Europe and since 2000, a member of Eurordis that encouraged establishing the Greek Alliance of Rare Diseases in 2003.

Updating is most important for the correct confrontation of any disease, not only for Tuberous Sclerosis. Katerina has been operated on 15 times and at least half of them could have been avoided if doctors had been aware of the latest discoveries and research on the disease.

It's very important that European countries work together as diseases and their cure have no frontiers.

3.4 A health care professional testimony

The confirmation of the diagnosis is crucial, not only to treat the patient accordingly, which, after all, is the most important activity of ours (prognosis, treatment, care, risk of re-occurrence for genetic counselling), but also to give an identity to the patient and his family, and to promote research.

With a wrong diagnosis, or if the diagnosis is missing, then already today patients are losing treatment opportunities and can not be referred to the adequate treatment centre.

Still, the establishment of the diagnosis of a rare disease relies on corner stones that are not different from frequently occurring diseases:

- Careful physical examination
- Family history
- History of the disease

More refined techniques like genetic tests can only be prescribed if there are clinical clues: not all tests can be performed; they must be guided by a preliminary medical examination.

Genetic information can be related to phenotype and clinical presentation by searching in databases for published literature on similar cases. Clinical geneticists are used to seeking advice from experts who may even be abroad.

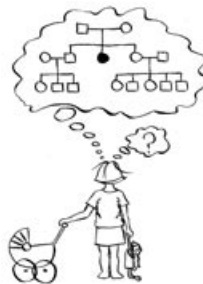
But the prerequisite is a well conducted examination of the patient by the treating physician.

In some cases, the diagnosis can be extremely rapid: one hour after birth and this can even be emotionally too rapid for the family. The possibilities for correct etiologic diagnosis have really changed during the last



S P E A K E R

“ Prof. Helena Kääräinen, Department of Medical Genetics, Turku University Hospital, Finland



twenty years, with very potent tools (gene tests and databases). In rare dysmorphic syndromes and malformation syndromes diagnosis may be reached, as the databases (LMD and POSSUM⁶) are very helpful.

However, many rare diseases are difficult to diagnose when their symptoms are common:

- Rare causes of high blood pressure
- Rare causes of primary immune-deficiency (see page x): probably 70-90% remain undiagnosed.
- Rare causes of diabetes.
- Rare causes of non-syndromic mental retardation: probably more than 50% remain undiagnosed).
- Rare causes of deafness, retinal dystrophy.

There are objective difficulties when the patients live far away from the medical centre (geographic barrier) or when he/she speaks a different language (cultural barrier).

→ DIAGNOSIS DELAYS IN EUROPE AND IN THE US

Confirming EurordisCare2 survey findings, a US based study on diagnosis delays lead to a conclusion on very similar results. The U.S. National Commission on Orphan Diseases in a detailed study some ten years ago on the problems of people with rare diseases noticed that

- it took 1-5 years for 30% of the patients to receive proper diagnosis
- 15% went undiagnosed for 6 or more years

→ DISCRIMINATION

Patients with rare diseases almost always suffer from discrimination by fellow citizens, employers, insurance companies and banks, etc. The health care system can also discriminate against patients with rare diseases: lack of knowledge, difficulties to diagnose and then to treat, and too few success stories make health care workers insecure.

→ COMPENSATION

Even with all possible financial compensation available, care remains expensive and personal expenses to face all aspects of the diseases are high. The European Society of Human Genetics has published policy recommendations on Genetic information and testing in insurance and employment: technical, social and ethical issues⁷ (www.eshg.org). It states that social rights and health insurance are an essential element of social structure, and even though they are supplied differently from one country to the other, they should not be conditioned by the genetic make up.

6. POSSUM is a computer-based system that helps clinicians to diagnose syndromes in their patients. www.possu.net.au

7. Recommendations of the European Society of Human Genetics
European Journal of Human Genetics (2003)
11, Suppl 2, S11-S12.

Among the solutions envisaged, Prof. Kääriäinen declared that the creation of specialised care centres is not the definitive response, but education and training at all levels and for all professions is a key strategy. The main follow-up should be ensured where people live and with the language they speak. Specialised centres or reference centres can help doctors to manage patients; however they are not the response for everyday care.

***Inheritance is not fair!
Some of us inherit good health, good qualities
to manage in life, even good looks!
This is not to say that everything, in a
fatalistic way, depends on genes.
On the other hand, some of us have
inherited lifelong diseases.***

3. 5 How to improve diagnosis?

A network to better diagnose X-Linked Mental Deficiency

X-Linked Mental Retardation (XLMR) is a heterogeneous group of more than 200 rare diseases characterized by mental deficiency of varied severity and a Mendelian X-linked inheritance, either dominant or recessive (for more information, see the XLMR Genes Update Web site: <http://xlmr.interfree.it/home.htm>). The prevalence of X-Linked mental retardation (XLMR) is approximately 1.8 males per 1000. Approximately two thirds of these patients have non-specific forms of XLMR in which the cognitive impairment is not associated with any recognizable physical features such as skeletal abnormalities or dysmorphic facial features.

During the last five years, more than fifteen new XLMR genes have been identified, and the pace of new gene discovery is dramatically increasing. Nearly one hundred genes are expected to be identified. Since a few families share a mutation in each of the new non-specific XLMR genes recently discovered, only little clinical data have been published and clinical diagnostic criteria are not available yet, especially for isolated mental retardation, without distinctive somatic, metabolic, radiological or neurological features.

To develop a clinical approach to improve the diagnosis of rare disease, such as non specific mental retardation, and for fine clinical phenotype, a multidisciplinary approach has been developed, including child neurologists, neuro-psychologists, and clinical geneticists in the frame of a national network that implemented a standardised clinical

Poster 118,
Vincent des Portes,
Neuro-paediatrician,
Hôpital Debrousse, Lyon.

X-linked mental
deficiency

Poster 75,
Agnes Bloch-Zupan,
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Dental anomalies

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Grenoble University
and Hospital, France

and psychological assessment of several MRX families. This research is being conducted in the framework of the European collaborative consortium (EuroMRX).

Moreover, for optimisation of multisite studies we created a secured platform available through the Internet (Medical Data bases, HC Forum, Grenoble), especially developed for mental retardation.

A database to better diagnose Oro-Dental anomalies⁷

Dental anomalies of number-shape-size, structure-colour, and eruption exist in isolation or associated with other traits in syndromes and reflect an altered odontogenesis.

A biomedical database accessible through an interactive web site phenodent.org will permit integration of data within the medical and genetic context enhancing multidisciplinary patient management approaches. It will facilitate understanding of dental and oral biology and associated disorders and diseases implementing science based evidence diagnosis and therapeutic options. It will stimulate patient recruitment and install a basis for molecular analysis and anatomopathological investigations. It will allow the creation of larger cohorts of patients with rare oro-dental defects that could be involved in research projects like:

- Identification of mutations in known genes involved in dental development and diseases
- Gene expression during odontogenesis
- Phenotype/genotype correlation
- Mouse/Human correlations
- Population genetics, new gene identification

This tool will offer links to other genetic databases like Orphanet, OMIM, and LDDB. It will constitute a link between participating clinical diagnosis centres and research laboratories thus representing a powerful tool for national (INSERM, GIS maladies rares – rare illnesses Odontogenetics network) and international (European COST B23 Oro-facial development and regeneration) networks. It will facilitate understanding of dental and oral biology and associated diseases implementing scientific based evidence diagnosis and therapeutic options.

This work is funded partially via INSERM “Réseau de Recherche Clinique ET Réseau de Recherche en Santé des populations 2003”

(Clinical Research Network and Health Research Network for Populations 2003) and COST-STSM-B23-00900.

A specialised clinic for Rare Diseases : the RD Outpatients' Clinic (RDOC) in Italy⁹

RDOC opened in 2003, bringing together a multidisciplinary team of 13 specialists in genetics, neurology, neuromuscular disorders, endocrinology, metabolism, psychology, immuno-hematology, dermatology, orthopaedics, and nephrology. This multidisciplinary approach has revealed itself to be a real advance in the care of patients with rare disorders as it offers an extensive response to the complex problems common to these diseases and reduces logistic problems for the family.

First contact is via the dedicated call centre or hospital portal (www.rarimanonsoli.it). The RDOC Coordinator then verifies whether the disease in question is suitable for the multidisciplinary approach.

The first appointment is preceded by a meeting with a psychologist, who listens to the patient's and family's needs and expectations. A "case manager" then conducts the clinical examination before presenting the case to the full team of specialists for thorough discussion. Finally, there is a meeting with the family to explain the diagnostic and therapeutic proposals.

The RDOC has been contacted by 815 families and has examined 118 patients. On arrival 34% of patients had no diagnosis or only a generic diagnosis. The Dept. confirmed the initial diagnosis in 34% of cases, formulated an alternative diagnosis in 19% and proposed a new diagnosis in 47%.

Most patients (92%) had symptoms requiring the expertise of more than one specialist.

Patients came to the RDOC from all over Italy (North 11%, Centre 55% South 34%). Family feedback via a questionnaire judged the RDOC to be VERY USEFUL; 66% and USEFUL; 32%.

“Poster 03,
Andrea Bartuli; Bambino
Gesù Children's Hospital,
Italy.

9. Bartuli A, Bertini E, Cappa M, Caviglia S, D'Argenio P, De Benedetti F, Digilio C, Dionisi-Vici C, El Hachem M, Emma F, Pagnotta G, Raponi M, Vignati, E Callea F. Bambino Gesù Children's Hospital in Rome, Italy.



THE PRINCIPAL OBSERVED SYMPTOMS WERE:

Skin/connective tissue disorders	16,9 %
Endocrine/metabolic disorders	16,1 %
Development impairments with genetic/malformation syndromes	14,6 %
Skeletal abnormalities	13 %
Immuno-hematology abnormalities	11%
Malformations and diseases of the nervous system	10 %
Muscular/neuromuscular disorders	6,1 %
Neural-motor development delay	5,3 %
Renal diseases	3 %
Genetic/malformation syndromes without development impairments	1,5 %
Neuro-cutaneous syndromes	1,5 %
Cardiovascular disorders	1 %

4 RARE, BUT EXISTING

4.1 No code, no name, no existence

Most of rare diseases do not have a WHO code.



SPEAKER

“**Annet van Betuw**,
European
Chromosome 11q
Network, Chromosome
Help-Station

11q terminal deletion disorder is a chromosome disorder that consists in the loss of the end of the long arm of the chromosome 11. It is a very rare condition, affecting 1/50 000 to 1/100 000 people.

Its clinical manifestations include heart diseases, renal insufficiency, bleeding disorders, undescended testicles, infections, short stature, “Droopy” eyes, learning and behavioural difficulties...

Parents often feel disoriented as articles on the disorder are rare, no code exists for the condition, and a feeling of loneliness often emerges. A network was created in the USA in 1996 and in 1997 in Europe. This is a larger network for conditions that are caused by partial trisomies, terminal deletions, interstitial deletions or unbalanced translocations. Thanks to this network, people with a very rare chromosome disorder can contact each other, laying down a solid basis to undergo research and concerted actions.

To stimulate research, a first conference took place in Europe in 1998, gathering 17 families from 7 countries. Half of the participants were related to the 11q terminal deletion / Jacobsen Syndrome. This con-

ference was supported by the Public Health Programme of the European Union.

Later, universities, policy makers, families, public health insurance companies, and health industries were approached to enlarge the network.

Through coordination and active communication, good companionship between parents and researchers, a high level cooperation was instituted.

Researchers themselves joined their efforts, creating an international cooperative network.

As a result, publications in scientific magazines analysing more than 110 persons with 11q terminal deletion were possible.

It is important to code diseases, as it provides them with a well known name, thus improving recognition of the condition, and boosting co-operation.



4.2 Why do we need to code rare diseases?

Dr. Ségolène Aymé explained why it would be important to code diseases more precisely.

As medical information is now recorded in almost all member states to optimise data collection and its use, and as the development of databases is becoming more and more a reality, registries for research and care, cohorts of patients for epidemiological surveillance etc., it is absolutely necessary to define specific codes for all diseases.

The exchange of data to establish evidence based medicine is also another reason to adopt universal codes.

Last of all, health indicators impose the standardisation of disease names and codes, for the purpose of evaluation and health policy, decision-making and bench marking.

Coding and classifying rare diseases are essential to achieve the following:

- Indexing medical diagnoses for
 - Epidemiology / surveillance
 - Planning / decision support
 - Audit of health care services
 - Development of expert knowledge systems



SPEAKER

“ Dr. Ségolène Aymé, Orphanet, Inserm SC11, France.

A universal coding/classification system requires compatibility for interoperability, non-ambiguous terms even for lay coders as classifications are not just used by experts. It also has to be upgradeable as knowledge is changing (3 new diseases published per week in scientific literature). It must accommodate all situations, undocumented diagnoses and complex medical contexts.

Until recently, rare diseases codes have been largely neglected:

- Most diseases have no specific code
 - There is no way to code unusual medical situations and
- specificities of rare diseases, like healthy heterozygotes, and pre-symptomatic cases

→ MAIN CODING/CLASSIFICATION SYSTEMS IN USE

- International classification of diseases (health data) established by the WHO
- And its specialised extensions (Paediatrics, neurology, oncology...)
- OMIM (genes and genetic phenotypes)
- MeSH (Medical Subject headings, used for Medline)
- Expert classifications (used in small circles)
- Orphanet (code but no classification)

→ HOW DOES IT WORK?

1. The International Classification of Diseases – WHO

This is the most widely used classification, undisputed, but maybe not quite as adequate for rare diseases, as many categories are too general and include too many possible medical entities. Only 300 rare diseases have a specific ICD code. For example the category:

Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)

Excludes: inborn errors of metabolism (E70-E90)

See figure 11 for other examples where ICD hardly applies to rare diseases.

2. The Online Mendelian Inheritance in Man

is often considered as the reference for coding genetic disorders, but in fact it is a catalogue of Human genetic phenotypes and related human genes more than a classification system: 12 000 entries in the catalogue, but not 12 000 diseases but rather 12 000 relations between phenotypes and genotypes.



figure 11

3. MeSH Tree Structure (Extract)

This is an interesting system as it is used by the National Library of Medicine in the US. A single disease can have different codes:

For example, the Kearns-Sayer syndrome appears in three different sections:

In the Musculoskeletal Diseases [C05] section:

- Muscular Diseases [C05.651]
 - Mitochondrial Myopathies [C05.651.460]
 - Ophthalmoplegia, Chronic Progressive External [C05.651.460.700]
 - Kearns-Sayer Syndrome [C05.651.460.700.500]

Then again in the Nervous System Diseases [C10] section:

- Cranial Nerve Diseases [C10.292]
 - Ocular Motility Disorders [C10.292.562]
 - Ophthalmoplegia, Chronic Progressive External [C10.292.562.775]
 - Kearns-Sayer Syndrome [C10.292.562.775.500]

And finally in the Eye Diseases [C11] section:

- Ocular Motility Disorders [C11.590]
 - Ophthalmoplegia, Chronic Progressive External [C11.590.641]
 - Kearns-Sayer Syndrome [C11.590.641.500]

This certainly helps to understand what are the organs/apparels involved in each disease, but it is not a unique code.

4. Classifications by expert groups

They are produced by expert groups, published in scientific and medical journals. Each of them serves a specific purpose and they follow different logics:

- By localisation (e.g.: peripheral nerve / mononevritis /polynevritis...)
- By aetiology (e.g.: Congenital malformations / genetic syndromes / Chromosomal I / teratogenic / unknown...)
- By mechanism (e.g.: metabolic disorders: Transporters /cell cycle/ repair defects....)
- By medical sub-specialty (e.g.: renal expression / neurological expression/ neonatal forms...)
- By severity (e.g.: cleft li and palate / limb defects....)

Therefore they are not universal.

5. Orphanet classification

Current situation: link between ICD-10 and OMIM classifications.

- Unique Identifier
- No hierarchy
- Indexation:
 - OMIM
 - ICD-10
 - List of signs/symptoms

New version in preparation (2006)

- Unique Identifier
- Indexation:
 - mode of inheritance
 - age at onset
 - Genes
- Poly-hierarchy
- MeSH
- ICD-10
- List of signs/symptoms
- Expert classifications

→ IN CONCLUSION :

- It is necessary to develop a specialised coding system and to collect expert classifications
- Collaborative efforts of all stakeholders are needed (Experts, WHO, National Library of Medicine)
- Dissemination of information (on all existing coding systems) to all potential end users to improve the interoperability of all codes
- This effort is part of the work plan of the Rare Disease Task Force

5 RESEARCH AND CARE

5.1 Research for Rare Diseases in the EU

Prof. H.H. Ropers described EU public funding for rare diseases in three European member states:

- Germany: 10 national networks (90 projects), 5 M€ / year for five years since 2003. Bundesministerium für Bildung und Forschung, Projektträger im DLR
- Spain: 13 networks, 6.6 M€ / year for three years since 2002. Instituto de Investigación de Enfermedades Raras (IIER) Instituto de Salud Carlos III, Madrid.
- France (for research only): 10 M€ for 2002-2004; 20 M€ for 2006-2008, plus contributions from AFM, GIS Institut des maladies rares; Ministère et Institut National pour l'Enseignement et la Recherche Medical INSERM)



Prof. Hans Hilger Ropers, Max Planck Institute, Berlin

SPEAKER

As a comparison, the support for research into common disorders in Germany is 135 M€ for National Genome Research Network (07/2004-06/2007), plus 225 M€ for 17 clinical Competence Networks until 2008 (Bundesministerium für Bildung und Forschung, Projektträger im DLR).

These overall efforts to discover genes that cause diseases are important: research on rare diseases has implications on common disorders, as shown in table. Some genes responsible for rare monogenic forms of common diseases were identified.

MONOGENIC FORM OF COMPLEX DISEASES

Clinical picture	Frequency of monogenic form	Identified gene
Colon carcinoma	3 – 6%	u.a MLH1, MSH2
Hypercholesterolemia	About 4%	LDLR, APOB, FH3
Non insulin dependent diabetes mellitus	> 5%	GCK, HFN4 alpha, HNF1 alpha, IPF1
Breast cancer	5 - 10%	BRCA1, BRCA2
Alzheimer disease	2%	APP, Presenilin1 u.2
Amyotrophic lateral sclerosis	10%	SOD1, Alsin
frontal - temporal dementia		

Table: adapted from *Campion 2001. Monogenic forms of complex diseases*

In other words, research into common diseases benefits significantly from research into rare disorders, which is an important argument for intensifying the efforts in this field. Other compelling arguments for scaling up research into rare disorders are:

- Main directions : finding the underlying defects, elucidating the patho-genetic mechanisms
- Availability of potent new techniques and concepts to elucidate rare diseases in a systematic fashion
- Some will require interaction with developing countries, and the EU should be prepared for that
- Improve structure of genetic services throughout Europe (EURORDIS study: practical consequences?)

The funding policy of the EU is characterised by:

- Limited funding for research into rare diseases, but massive funding of research into genetic risk factors for complex disorders
- « A priori » selection of disease groups qualifying for support (FP6)
- No overall strategy or coordination

5.2 Fighting the fragmentation of research

A multi-disciplinary approach

Prof. Anthony Holland's talk was based on his personal experience of trying both to engage in research in the field of rare diseases, as a psychiatrist working on learning disabilities/mental retardation, and also as a clinician seeing people with behaviour problems and learning disabilities. The key in helping people is having a sound understanding of the factors that contribute to such problems.



Prof. Anthony Holland, Department of Psychiatry, University of Cambridge, United Kingdom

SPEAKER

→ THE AIMS OF RESEARCH ON RARE DISEASES

- To inform on the development of new treatments or specific intervention strategies (medications, physical treatments, psychological interventions)
- To inform on clinical, educational or social care practices, particularly on the types of educational interventions that may best help the children
- (Good clinical practice like the Swedish guidelines on the use of growth hormone for Prader Willi syndrome, Quality of life, Educational strategies)
- Research should be tested as to whether it informs policy development to establish fundamental principles for the support of the people. It may guide the types of entitlements

and benefits that people need and it may be relevant when

then comes to issues like legal issues (Academic lawyer working in Prof. Holland's department).

→ WHY IS RESEARCH IN THE FIELD OF RARE DISEASES PARTICULARLY PROBLEMATIC?

1. Firstly the rarity itself

- Funding: the difficulty is to find funding for disorders that may affect only a few people in a context of competition with common diseases like heart diseases or cancer
- Interest of the research and clinical community for rare diseases which may be more interested in common diseases that affect more people
- Recruitment of participants: the involvement of patients because research cannot advance if patients suffering from the syndromes itself do not participate.
- Benefits seem to be only for the few persons concerned by the disease but the understanding of the disease often leads to general applications that benefit other diseases (e.g. understanding the eating disorder in patients with Prader Willi syndrome will help understand the problem in other syndromes with a similar symptom)
- The dissemination of the discoveries and to ensure that findings go out to the public domain.

One of the tensions that exist in research in rare disorders is that if we are able to obtain money for research it is inevitably going to be a relatively small amount of money. There is going to be a competition for that money. So how do we decide, and who decides, the research questions to be addressed. For example, the scientific scientist will say: "well, there's a logical approach to research of rare disorders". Once you have identified the disorder itself, say Prader Willis Syndrome, than there is usually a process of epidemiological research, basic science and so on, that characterizes that syndrome. But the families will say: "the problem that is affecting us most is, for example, problem behaviours". As a psychiatrist, that is of course my area and one of the greatest concerns for families are psychological, psychiatric and behaviour difficulties. And then of course there is the role of government in terms of policy and practice. I give you an example from the UK, where there was and has been over some years this great debate about the role of MMR vaccine as a possible cause of autism. And that has actually driven and taken resources away from what most of us would see as a rather different research agenda in the field of autism. And this is because of powerful lobby groups, politicians and others getting caught up in this issue on how you determine the research agenda.

2. Secondly, the complexity of the disease itself:

- Complex diseases affect different parts of the body (intellectual disability, heart, skin...), it complicates treatments: multi-system disorders.
- There is a need for different perspectives (biological, psychological and social), because we cannot treat a rare disease only with medicines.
- Complex diseases require a long term (often a lifetime) approach to treat and improve quality of life of the patients.
- There is also a need for specific ethical issues to allow people to consent.

3. Thirdly, the stakeholders in rare disease research and tension between them

To better understand the problems that occur for rare disease research, we have to understand the interests of each stakeholder.

- The patients themselves of course.
- But the family (and possibly other carers) is also very important
 - to provide information
 - to be part of the research themselves as participants especially when it turns to genetic disorders
- Researchers, clinicians and their respective organisations, who make the scientific progress
- Charitable organisations
- Organisation funding research (who have their own priorities and allow progress on specific areas)
- Industry
- Governments
- Ethic committees, research governance arrangements.

→ THE CONTENT OF RESEARCH

- The scientists after the initial identification follow a logical approach processing to epidemiologic studies, basic science that characterizes the disorder. The remaining problem is how to affect the fund in the research.
- The family will be more concerned with specific symptoms that affects their lives such as behaviour troubles
- The governments have also a very important role in practice and policy.

To summarise the problems of research in rare diseases:

- Those due to rarity of the disorder
- Potential for conflicting and contrasting views as to research priorities
- Complexity of the science and need for different academic perspectives
- Funding and organisation of research

→ SOLUTIONS

WHAT ARE THE SOLUTIONS?

- National and EU strategies for, and commitment to, “rare diseases” research
- Development of broad conceptual framework for what is required for a particular rare disorder (setting the research agenda)
- Shared resources within and between “syndrome groups and research groups - development of “networks”
- Partnerships and the development and maintenance of necessary resources over time

How do you get funding to start the process of research? Usually syndromes organisation plays an important role in the fundraising.

How then to secure longer term funding? How to sustain the expertise created after the research project has ended and until the results are in the public domain?

Dissemination of research

One can not underestimate the importance of syndrome organisations and patient groups. Web-based technology for immediate access exists, and there is no excuse for a practising doctor not being able to find out almost immediately about a particular syndrome.

→ PRACTICE AND POLICY

Partnerships between campaigners, clinicians, and researchers are an iterative ‘step by step’ process. The role of media must be outlined cautiously, as sometimes a media campaign can be counterproductive.

Illustration of the integration of disciplines for a single disease: Prader Willi syndrome

A population study drove to hypothesis on physical and psychiatric morbidities, and then genotype and phenotype studies produced more information on the subtypes of the disease.

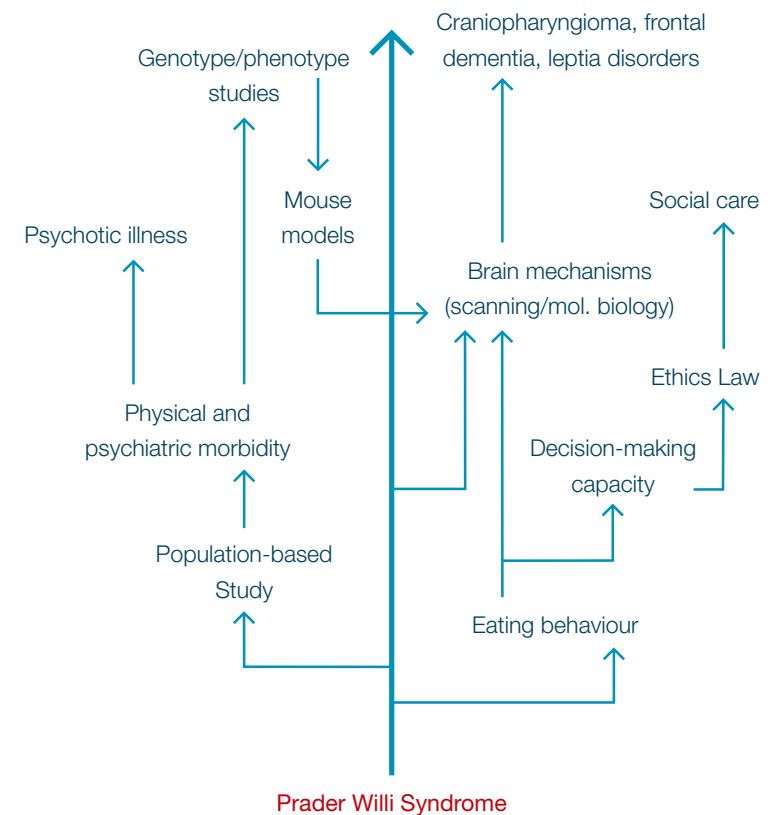
The results from humans were used in knock out mice (animal models). Eating behaviours were explored with other teams and radiologists and molecular analysis to understand the brain mechanisms, and this led to better explain other similar problems like cranio-pharyngioma or frontal dementia. It also led to legal and ethics

The multi-disciplinary approach in research on Prader Willi syndrome led to legal and ethics issues: what right do you have in stopping a patient with Prader Willi syndrome from eating and eating to the extent that they might die once they are an adult?

issues: what right do you have in stopping a patient with Prader Willi syndrome from eating and eating to the extent that they might die once they are an adult?

The organisation of the research project on this particular disease (Prader Willi syndrome) was as follows:

- It started as a small project locally funded
- One or two researchers
- PWSA (UK)
- Move to National projects (Funded through national research grants)
- Small research group (multidisciplinary)
- PWSA (UK)
- Ultimately as a European project (EU funded)
- 11 academic centres (basic and clinical sciences)
- French and UK PWSAs
- Other National Associations

INTEGRATION OF PWS RESEARCH (figure 12)

Transfer of academic research towards industrial development

Fc-EDA as a potential new drug for a rare disease (XLHED)

Prof. Pascal Schneider presented an inspiring example of collaboration between academic research and a private partner, for the development of a potential drug for patients suffering from X-linked hypo-hydrotic ectodermal dysplasia.



S P E A K E R

“Prof. Pascal Schneider, Department of Biochemistry, University of Lausanne, Switzerland

X-linked hypohydrotic ectodermal dysplasia (XLHED)

- Scientific prerequisites must be collected from animal studies or from a biological model. This is to validate the concept of the idea.
- With this dossier, discussions can be engaged with an industrial partner, under confidentiality.
- When an agreement is reached, a feasibility study can be planned, exploring the market, verifying intellectual property rights, a financing plan, regulatory issues and strategic collaborations.
- If the drug is for a rare disease, it can then be submitted for an orphan drug designation. If the company obtains this status, then Protocol Assistance can help the company on how to design the development programme.
- Preclinical development can then start
- Followed by clinical development (phase I, II and III).

→ FEATURES OF THE DISEASE

XLHED is a well known disease, first reported in 1875 by Charles Darwin (toothless men of Scinde). It is X-linked, affects mostly boys, and is recessive. The phenotype is characterised by the absence or dysfunction of hair, teeth, sweat glands ...

There are Mouse and dog models of the disease. Figure x shows a wild type mouse tail and a mutant mouse with the ectodysplasin A (EDA) deficiency.

→ PHYSIOPATHOLOGY

Teeth, sweat glands and hair originate from similar groups of cells, the placodes. Placodes are developmental intermediates giving rise to ectodermal appendages. EDA is involved in placode formation and its deficiency causes XLHED.

The figure x below shows the successive steps of such collaboration:

The principle of the treatment that Prof. Schneider is working on is to replace the genetically deficient EDA protein by a recombinant protein at the time when responsive cells express EDA Receptor (in utero or shortly after birth). The receptor is there, waiting for the sig-



nal to instruct cells to transform themselves into hair, teeth or sweat glands, but the signal itself is missing. By default, cells will differentiate into skin cells rather than sweat gland or hair cells.

This idea was tested in mutant pregnant mice: EDA was injected in the mother and transported, like an immunoglobulin to the embryo in the uterus. Results: figure x shows an untreated mouse, whereas figure x shows a treated mouse with a normal tail.

Other defects, such as those of sweat glands, were similarly improved.

→ THE PROCESS: A CONCEPT IDEA TRANSFORMED INTO A POTENTIAL TREATMENT

The gene was identified in 1998 (figure 13) and the complete sequenced was published. From this, the idea to use a recombinant protein emerged in March 2001. A patent was obtained in August 2002. Early studies were conducted and published in 2003. An agreement was then signed with Apoxis as an industrial partner, and the University of Pennsylvania joined the research team.

Shortly after, the team met with Eurordis on the possibilities to file for an Orphan Drug designation. An application was submitted to the COMP in June 2005 in order to obtain the Orphan Drug status. Apoxis S.A. is a privately held, Swiss based biopharmaceutical company developing innovative treatments, mainly for a variety of cancers and autoimmune disorders. The company is in close contact with representatives of ectodermal dysplasia patient organisations worldwide, including Olivia Niclas in France. In parallel, consultation took place with Orphanet and Eurordis.

→ CONCLUSIONS

- a therapeutic solution for XLHED is now considered for pre-clinical development, with the hope to enter into human phase trials
- To give this molecule a chance to serve the interest of patients, expertise in several areas is required: science, biotechnology, law, medicine ...

- Collaboration and mutual understanding of partners is required
- Innovations often result from interactions between distant fields. Innovations cannot be planned, but can be promoted in meetings like this one

From academic research to industrial development

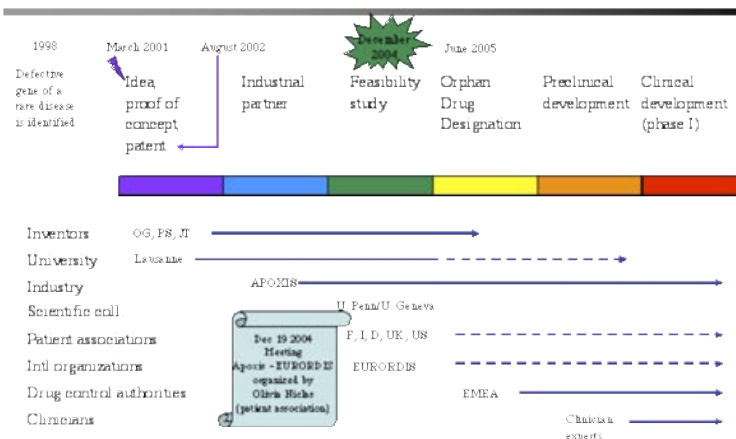


Figure 13

Strengthening cooperation between academia and industry

Actions that help improve cooperation between academia and industry exist and one of their aims is to overcome the bottlenecks in drug development.

Dr. Valérie Thibaudeau explained a few of these actions, under the supervision of Orphanet.

Orphanet, the European portal of rare diseases and orphan drugs, powers a set of services aimed at developing information tools to address, in a comprehensive and integrated manner, the factors affecting the coordination of research on rare diseases. Orphanet is a consortium of 20 countries supported by the European Commission.

To improve collaborations between research teams, Orphanet provides a directory of research projects. Over 2 000 ongoing National and European research projects are referenced in the database.

To provide information on clinical trials and to facilitate patient' recruitment for these trials, Orphanet contains a clinical trial directory (over 135 National and European clinical studies) along with an online service for voluntary patient registration; over 540 patients coming



S P E A K E R

« Valérie Thibaudeau, Orphanet, Inserm SC11

from 22 countries have registered with this service.

To foster partnerships between academia and industry, the European project orphanXchange has been developed.

→ FOCUS ON ORPHANXCHANGE

OrphanXchange is a tool for boosting the development of diagnostic tools and therapeutic products.

It is a market place for innovative research projects and potential orphan designations that are of interest for industry. Information on these projects is freely available to industry representatives; contact with project leaders can be made through the website.

The portfolio of promising innovative research projects is identified from the list of academic research projects referenced in Orphanet and through collaborations with departments of technology transfer.

OrphanXchange is also a catalogue of products initially marketed for other indications but which could also be of potential interest to treat rare diseases. Industry representatives can use the website to contact directly the research project leaders to find out more about their projects and to identify potential candidate drugs for their own portfolio.

Currently, OrphanXchange lists 125 innovative projects, involving 65 products initially marketed for other indications. Each month, the website is visited by 400 to 600 users, 153 of which have registered (50% from Pharma – Biotech - venture capital - consulting, 36% from Academia, 7% from patient organisations) and can get in contact with researchers. In total, 47 contact requests have been made between industry and academia.

To learn more about this project : www.orphanxchange.org.

→ OTHER EU PUBLIC / PRIVATE PARTNERSHIP

The ERDITI initiative is coordinated by the GIS-Institut des maladies rares, and sponsored by the European Science Foundation. It allows academic researchers to work with compounds that have been or are being developed by the pharmaceutical industry. Researchers can apply to this programme to carry out pre-clinical tests on rare diseases research models. The objective of the ERDITI initiative is to promote therapeutic research on rare diseases.

To learn more about this project: www.erditi.org.

EPPOSI, the European Platform of patients' organisations, Science and Industry has organised series of conferences: Brussels (2000), Paris (2001), Rome (2002), Den Hague (2003), Berlin (2004), and the next one in London in October 2005 entitled « People with rare disorders:

no longer alone in the world ». These conferences provide a meeting place for people in the trade and for patients' organisations. These workshops provide a boost for identifying bottlenecks, finding solutions and developing partnerships.

→ CONCLUSIONS

Orphanet offers powerful services for providing accurate information on on-going research activities, strengthening collaborations and developing partnerships. The Orphanet services are of interest to all users and their impacts will be assessed after a few years.

Strengthening cooperation between academia and industry is very challenging: it requires networking, partnership formation, and optimisation of existing resources.

Researchers' networks brought together by a patients' organisation

ENRAH: collaborative action against Alternating Hemiplegia

In spring 2003, a mother and a geneticist created the embryo for the European Network for Research on Alternating Hemiplegia, with the objective of accelerating research and development for a treatment for this rare but severe disease.

Alternating Hemiplegia of Childhood affects 1 in 2 million people (200 to 3000 cases world-wide), it is mostly sporadic, and the diagnosis may be delayed until 20 years of age. Pathophysiology is not well understood, there is no proper treatment or cure.

Not more than 2 years later, the ENRAH network (European Network for Research on Alternating Hemiplegia) has grown: patient organisations (Association ENRAH Austria, Association Française de l'Hémiplégie Alternante France, Associazione Italiana per la Sindrome dell'Emiplegia Alternante Onlus and Associazione la Nostra Famiglia MEDEA Italy), clinical centres (Landeskrankenhaus Klagenfurt Austria, Katholieke Universiteit Leuven Belgium, Charles University Prague Czech Republic, Fondazione Centro San Raffaele del Monte Tabor Italy, Leiden University Medical Centre The Netherlands, Hospital Sant Joan de Deu Spain, University College London United Kingdom, and University of Heidelberg Germany).

A research project supported by FP6 has started with 14 participants from 9 EU member states, representing 9 clinical centres and 2 patient organisations. It is a two-year project.

“ Dr. Tsveta Schyns,
Coordinator, European
Network for Research
on Alternating
Hemiplegia

“ Prof.
Ketty Schwartz,
Inserm, France

- Establishing an European patient Registry
- Creating a Multi lingual Web site for patients
- Identifying relevant Industry-Small and medium sized enterprises (SMEs)
- Integrating the SMEs into the Network (s)
- Promoting their participation in the FP 6 and 7

The importance of a collaborative network bringing together patients and scientists is large: for doctors and researchers, the objective of a patient registry is it to help understand the natural history of the disease. In addition, it facilitates clinical research and clinical trials. The immediate benefits for the patients are to receive an accurate diagnosis and appropriate counselling, as well as the possibility to meet with other people with the same disease.

5.3 Lessons learned from EU framework programmes for research

FP5 and FP6, and plans for FP7

This presentation is the report of a Workshop organised by the European Commission Health Directorate – Major Disease Unit in Brussels, 12-13 April 2005: Identifying the research needs for the Rare Diseases community.

Participants were invited to provide the European Commission with specific recommendations for optimising Rare Diseases research in the EU programmes. The participants represented all stakeholders:

- European Commission (DG SANCO, DG ENTR, DG RTD)
- Patients' representatives
- Coordinators and participants at FP5 and FP6 projects
- European Medicines Agency (EMA)
- Biopharmaceutical industry representatives

→ HISTORY

The former framework programme, FP5, aimed at promoting cooperation, collaboration and knowledge building. It funded 47 RD projects for a total of 64M€.

FP6 aimed at developing scientific and technical excellence to make a reality of the “European Research Area”.

The thematic Priority 1 was to translate genome data into practical applications to improve human health.

- 2 first calls funded 26 rare disease projects for a total of 93 M€
- 2 others calls (ongoing) are expected to fund a total of 150 M€

The thematic Priority 8 was to underpin the formulation and implementation of Community policies. It funded

- Germany: 10 networks, 5 M€/year for 5 years since 2003
- France: GIS Institut des Maladies Rares, 10 M€ for 2002-2004
- Spain: 13 networks, 6.6M€ / year for 3 years since 2002

In parallel, the Health & Consumer Protection Directorate - General conducted programmes for public health:

Action Programme 1999-2002: 24 RD projects 6.5M€ (60% of the budget)

Action Programme 2003 - 2008: 3 RD projects selected in 2004, establishment of a Task Force on Rare Diseases.

A consensus at the workshop was that the FP6 approach of defining strictly both focused topics and the instrument to be used per topic was not adapted to the major characteristics of RD, i.e. great number of RD, low prevalence and heterogeneity.

Key words that summarise the wishes of participants were:

- flexibility
- emerging projects
- long term support
- topics not focused on rare diseases
- infrastructures
- (pre) clinical studies
- industrial partners

→ RECOMMENDATIONS ON PRIORITIES :

- natural history of the diseases
- Mendelian phenotypes of common diseases
- Physiopathology of RD
- Pre-clinical and early clinical studies, including phase I and phase II clinical trials
- Therapeutic interventions with encouragement to putative industrial participants
- gene therapies

- cell therapies
- drugs including substitutive therapies
- devices
- Social sciences
- social perception
- daily experience
- impact of early diagnosis
- genetic counselling

→ RECOMMENDATIONS ON INFRASTRUCTURES

For infrastructures, the desire was to access to existing infrastructures with an extra budget and/or new infrastructures, as follows:

- Identification of genes and haplotyping
- Protein pathways (proteomics, 3D structure, metabolic profiling, molecular screening...)
- Animal models (Nematode, Xenopus, Zebra Fish, Mouse, Rat, Dog, NHP...)
- data management (hosting, analysis)
- Bio banks

For the type and size of the projects, the choice of the appropriate instrument (Network Of excellence, Integrated Projects, Specific targeted research projects, Specific Support Actions ...) is left to the consortium.

There should be support for emerging projects / teams and specific calls for small consortia (e.g. 3 partners, 1M) and also for Support for “Project building workshops”.

In some cases, long-term support should be possible.

5.4 Research networks

European integrated project on spino-cerebellar ataxias (EUROSCA)

Twenty two European groups from nine countries with expertise in clinical, clinical-genetic and basic research on spino-cerebellar ataxias (SCA) have jointly formed an “Integrated project” (2004-2008) to define the pathogenesis to develop and validate a Core Assessment Program for Interventional Therapies and to develop a treatment for patients suffering from this rare neurodegenerative diseases.

The European SCA Registry was created to ensure standardised data acquisition. This tool facilitates continuous recruitment of SCA patients (already 1400 in 2004) throughout Europe for linkage analysis, identification of novel ataxia genes and natural history studies. The

Poster 5
Holm Graessner, Peter Bauer, Michael Bonin, Nicole Hiringer, Olaf Riess, University Clinic Tübingen

potential to include all larger European SCA families into linkage analysis has been leading to the identification of new SCA loci and to the cloning of novel ataxia genes, respectively.

Subsequently, this combined effort offers a systematic large-scale search for genetic modifier factors for a better prognosis and to identify new potential targets.

EUROSCA can be considered as a prototype project which tackles a rare, genetically caused neurodegenerative disease spanning the entire bandwidth. Training programs complement research efforts and clinical work, e.g. distribute standardised diagnostic methods all over Europe.

Wilson Disease: Creating a European Clinical Database and designing randomised controlled clinical trials

→ AIMS OF THE PROJECT

To establish a European database of WD patients:

1. To determine the incidence
2. To determine the relative incidence of clinical subtypes (such as hepatic, neurological, pre-symptomatic)
3. To assess the feasibility of randomised clinical trials

→ WILSON DISEASE PRESENTS MULTIPLE CHALLENGES :

1. There is great phenotypic variability. It may present anywhere between 3 and 60+ years of age. Children tend to have liver disease, which may be fulminating needing emergency transplantation or resemble an acute hepatitis, or present with cirrhosis with portal hypertension. Adults tend to have extra-pyramidal-neurological disease, which varies in age of onset, rapidity of progression, and severity

2. Treatment is with copper chelators or zinc, BUT an evidence based treatment strategy is missing, as there are no randomised clinical trials comparing the different approaches.

- Starting treatment may cause initial neurological deterioration
- Different centres use different treatment regimens

Through this project, the quality of the assessment of WD should be improved. An electronic source of documents will help doctors when performing a neurological assessment.

This is a partnership with national bodies: GeneMove, the French Association for the Study of Wilson Disease, and the British Neurological Surveillance Unit.

Spino-cerebellar ataxia
Pathogenesis genetics,
Animal models
Treatment
Euroscsa

Poster 70
Stuart Tanner and
Samantha Parker,
University of Sheffield,
presented a network on
Wilson disease (WD) on
behalf of the EuroWilson
Consortium.

Wilson disease
EuroWilson project
6th FP



10. Eurowilson
is funded by the EU
sixth Framework
Programme priority 1
Life sciences, genomics
and biotechnology
for health proposal
no. :503430
It has UK MREC
approval reference
04/mre04/65

Poster 76,
Manuel Palacin,
University of Barcelona

Kidney diseases, renal
lithiasis, inherited amino-
aciduria.
EUGINDAT, 6th FP

Other goals consist in the establishment of a network of molecular diagnostic laboratories for DNA storage for future studies of modifier genes, in the creation of a patient and professional resource on the web, in the review of current treatments and their outcomes, the study of genotype-phenotype correlation and modifier genes.

EUGINDAT

Manuel Palacín, presented a poster on a large research network aimed at creating scientific knowledge on some specific inherited rare diseases (Amino-aciduria):

- cystinuria
- lysinuric protein intolerance
- Hartnup Disorder
- iminoglycinuria and dicarboxylic aminoaciduria

EUGINDAT is a large and specific targeted research project of the European Commission, VI Framework Programme, involving 19 groups, which include:

- clinic (4)
- genetics (4)
- physiology (3)
- molecular biology and biochemistry (4)
- bioinformatics (1)
- protein structure (1) groups
- two SMEs (Laboratorios Rubio, an orphan disease-devoted drug company, and Ingenium-Pharmaceuticals, providing ENU-mutated mouse models)

EUGINDAT has four activities: a clinic platform, aimed at generating a Primary Inherited Aminoaciduria Database (PIA-Database), an animal model platform for the generation of mouse models (knock out and ENU-mutated animals) of PIA and relevant amino acid and peptide transporters for renal re-absorption, a 3D protein structure platform for the resolution of amino acid and peptide transporters structures, and finally, a genetic platform for the identification of mutations causing PIA.

As a result, physio-pathology studies and development of new treatments in/for cystinuria and lysinuric protein intolerance should produce results by the end of March 2007.

5.5 Establishing networks in myology : Give more muscle to myology!

The Association Française contre les Myopathies has developed a large and pluri-disciplinary network for the eradication of neuro-muscular disease.

Specialists from very diverse origins are part of the network: basic research scientists, geneticists, clinicians, veterinarians, and industrials at the crossroads of anatomy, physiology, biochemistry, neurology, cardiology, paediatrics, and physiotherapy.

Still, neuro-muscular diseases are usually apprehended as part of Neurology by the Faculty of Medicine, whereas they could constitute a medical speciality: myology. In this regard, they are an orphan science. They represent 117 identified neuromuscular diseases, with a high level of heterogeneity in terms of prevalence, genetics, clinical presentation, and a wealth of organisations.

For single individual diseases, the critical mass that is required to gain public attention cannot be achieved at regional or national level; this is the reason why the development of networks is desirable.

Since its creation in 1958, AFM launched the annual TV fundraising event “Telethon”, that has raised 100 million on average per year.

→ OUTCOMES

In 2004, the following progresses and discoveries were reported out of the 815 genes that cause specific diseases:

- 185 were identified with the support of AFM/Telethon.
- contributions helped to increase genetic knowledge about 746 diseases (as of October 2001)
- 14 DNA banks are supported by AFM in France, Europe and Northern Africa
- 500 research projects are supported

Neuromuscular diseases of course are among diseases for which a causative gene has been identified with the help of AFM/Genethon, but this is also the case for other illnesses like prostate cancer, some types of diabetes, schizophrenia, Rett syndrome etc.

Moreover, the human genome is now decrypted, and as an outcome more than 30 clinical trials have been launched with the support of AFM, including the first gene transfer trial for Duchenne muscular



S P E A K E R

“ Dr. Serge Braun,
AFM (Association Française contre les Myopathies – French Muscular Dystrophy Association, Evry, France)



dystrophy. New therapies based on the knowledge of gene expression are now emerging. Other actions include advocacy for a better policy against rare diseases (participation to the working group for the National Plan for Rare Diseases, lobbying for the Disability Compensation act).

To respond to the need to develop myology as a medical speciality per se, the Institute for Myology was opened in 1997. The institute is an original partnership between a patient group (AFM), research institutions (INSERM, CEA, CNRS), University Paris VI, a hospital trust (Assistance-Publique - Paris) and the industry (clinical trials, protocols).

At this institute, genetic and diagnostic services are provided, a clinical unit for clinical evaluation, muscle pathology and genetic counselling is open as an ambulatory department (2 700 Consultations in myology, 2 200 consultations in genetics and 1 400 Day-hospitalisations). AFM/Telethon also supports the ENMC, based in Baarn, in The Netherlands. The goals of this new research network are ambitious: to contribute to the eradication of neuromuscular diseases, to improve efficiency in European neuromuscular research, and to facilitate and support research communication between European (and international) researchers and clinicians.

Together with AFM, ENMC is actively involved in European Framework Programmes.

In the previous EU 5th programme, a 3-year project Myocluster (2,4M€) for Emery Dreifuss muscular dystrophy, Congenital muscular dystrophies, and Bethlem myopathy.

During the EU 6th Framework programme, supported projects focused on rare disorders of mitochondria (Eumitocombat group, ENMC affiliated consortium), rational treatment strategies and MYORES, the first European Network of Excellence dedicated to study normal and aberrant muscle development function and repair.

For Serge Braun, the next challenges are to find solutions:

- for coordinating new technologies (gene-based therapies or stem-cell therapies)
- for homogenising outcome measurements, registries of patients
- for networking NMD centres for multi-centre clinical trials
- for securing trials funding

- for organising the participation of patients in the design and the conduct of clinical trials
- for establishing contact with physicians and myologists world-wide
- for networking with other international platforms for collaborative research world-wide

ENMC fully supports recent comments for the next call for proposals in FP6:

- New approaches to the treatment of NMDs such as gene therapy, cell therapy, gene repair, exon skipping and medicinal products
- Developing new non-invasive methods of efficacy assessment (i.e. imaging)
- Development of animal models for testing these therapies
- Mature networks of collaboration with ENMC, AFM, networks and between industrial partners, academics, patients and medical researchers
- Patient registries and bio-banks
- Agreeing on existing clinical outcome measures

5.6 Research and success stories

Clinical trials: research on specific domains/pathologies, the ESCAPE trial^{11, 12}

In children with chronic kidney disease, progression to end-stage renal failure is associated with high morbidity and poor quality of life. In adults, inhibition of the renin angiotensin system slows down the rate of renal failure progression. This concept is as yet unproven in children, in whom chronic renal failure (CRF) is more commonly due to hypo/dysplastic malformations than to acquired glomerulopathies as those typical for adult chronic kidney disease. The project aims at assessing the genetic and molecular mechanisms and cardiovascular consequences of progressive CRF and to develop a strategy of pharmacological reno-protection in children.

Almost 400 children with CRF from 33 European Pediatric Nephrology centres have been included in the trial. In the short term, ramipril treatment resulted in a substantial reduction in blood pressure and proteinuria irrespective of the underlying renal disease. Final results on Reno and cardio-protective effects of long-term ramipril treatment as well as the analyses on biochemical and genetic risk profiles for renal and cardiovascular disease progression will be available in summer 2006.

Poster 64,
Elke Wühl,
University Children's
Hospital, University of
Heidelberg, Germany.

Children with
chronic renal failure
Escape Trial
5th FP

11. Molecular Mechanisms of Disease Progression and Reno-protective Pharmacotherapy in Children with Chronic Renal Failure, The ESCAPE-Trial. Elke Wühl, Otto Mehls, Franz Schaefer and the ESCAPE Trial Group, University Children's Hospital Heidelberg

Poster 73,
Gerhard E. Feurle,
DRK Krankenhaus,
Germany

Whipple's disease
Infectious diseases.
5th FP

Rare Infectious Diseases that can be cured

European Project on Whipple's Disease

Whipple's disease (WD) is an infection induced by the actinomycete *Tropheryma whippelii* (T. whippelii). Although T. whippelii is widespread in the environment, WD is rare with an estimated incidence of 0.4 per million. As healthy carriers do occur, host factors are assumed to be important. Symptoms are arthropathy, weight loss and diarrhoea, but other organs notably the central nervous system may be affected. Untreated WD is fatal, whereas antibiotic therapy may eradicate the bacterium.

This 4-year project is funded by the European Community FP5 (QLG1-CT-2002-01049) and was started in November 2002. Ten centres from five European countries are cooperating with different research agendas:

- A central tissue bank is established in the coordinating centre at the Charité Campus Benjamin Franklin in Berlin.
- The occurrence of T. whippelii in sewage water and in healthy sewage plant workers is studied in Vienna.
- The immune system of infected persons is investigated in Berlin and in Pavia.
- Microarray technique is used to test for susceptibility for infection in Berlin.
- T. whippelii is cultured in vitro in Marseille.
- Pathology is studied in Leuven
- The first randomised treatment trial worldwide is organised in Neuwied: Study of the Initial treatment of Morbus Whipple (SIMW). This is a registered clinical trial comparing intravenous antibiotic therapy of Ceftriaxon with Meropenem/ Imipenem. This initial therapy is followed by 2 Co-trim forte for 1 year. 42 patients have been randomised; the follow-up period is 3 years. After termination of enrolment, a non randomised 3rd arm has been initiated.

Another goal is the dissemination of research data and general information: It is important that those dispersed persons afflicted with the disease in Europe and elsewhere are able to obtain information about diagnosis and current treatment recommendations. This facilitates also enrolment of patients for the treatment trial and provides tissue for laboratory investigation. A website, therefore, was launched that includes a public forum and a restricted area for the network partners: (www.whipplesdisease.info).

12. Funded by the European Commission 5th Framework Program Quality of Life and Management of Living Resources (QLG1-CT-2002-00908), Boehringer Ingelheim Stiftung and Aventis Pharma.

Collecting and sharing tissue and DNA: EuroBioBank

The European Network of DNA, Cell and Tissue Banks

Dr. Veronica Karcagi presented another European initiative, the creation and development of a database for DNA, cells and tissue.

→ **WHAT IS IT FOR AND WHY IS THIS USEFUL?**

Rare human samples are useful both for care and for research: to match with the sample of another patient whose diagnosis is already known or to test the sensitivity of a given tissue to a given drug candidate, or to investigate which genes are responsible for which phenotype, etc.

The 12 banks that are part of EuroBioBank contain a total of approximately 54 000 DNA samples and 39 000 tissue samples are available.

Figure 14 below show the activity of the network in 2004: total number of samples stored and distributed by EBB members.

→ **SERVICES INCLUDE :**

- Extraction of DNA from various cell lines
- Muscle biopsy for culture
- Good practices for cell culture techniques (aseptic and safety aspects of cell culture), heat inactivation and testing, freezing, cryo-preservation, storage and reactivation of cell lines, detection of contaminants...
- Fibroblast, lymphocyte cell culture...

→ **ACHIEVEMENTS**

- A public website for researchers and patients with a section exclusively reserved to communication and collaboration among partners of the network (EBB Intranet). The website is the central pivot of the network, displaying information on the available material and the network's activities. As of August 29th 2005, the content of 2 banks (ISC III in Spain and AFM in France) / 12 are on line (www.eurobiobank.org).



SPEAKER

“ Dr. Veronica Karcagi, Fodor Jozsef NCPH, Budapest, Hungary

- Information on the EBB network is spread through leaflets, patient magazines and posters and/or oral communications
- at international congresses. Several scientific papers have also acknowledged EBB.

SAMPLES STORED AND DISTRIBUTED BY EBB MEMBERS (figure 14)

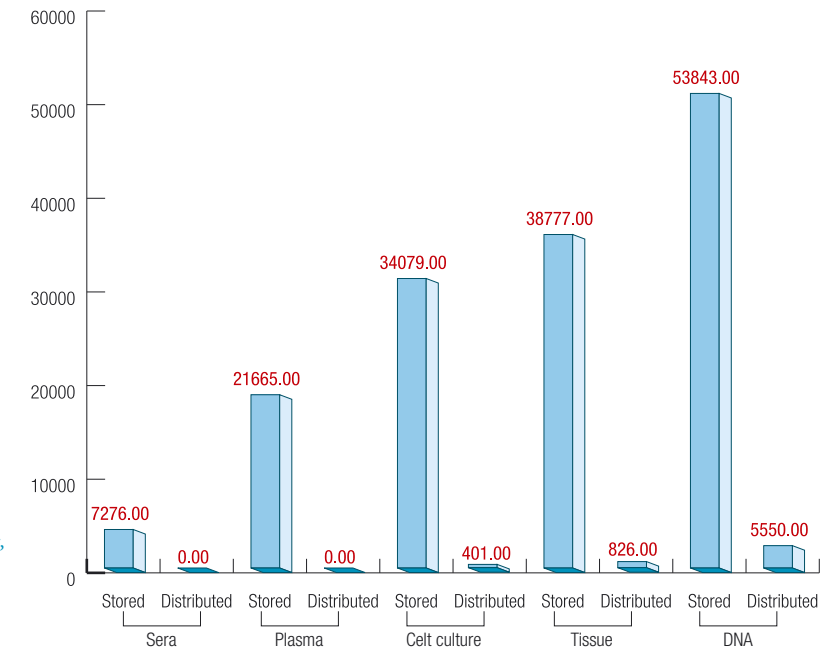


Figure 14: total number of samples stored and distributed by EBB members, 2004

EBB is funded by the EU Commission FP5 as a 3-year project for Research and Development, 2003-2005 (QLRI-CT-2002-02769).

The EBB network is a successful and operational model for supporting scientific exchange and cooperation. It was awarded the “Newropeans 2004 Grand Prix - Prize” for “Research and Technology”, in the framework of the closing event of the Newropeans Democracy Marathon 2003, for having significantly contributed to the democratisation of the European Union by closing the gap between European citizens and EU construction.

→ **EBB PARTNERS ARE :**

- EURORDIS (European Organisation for Rare Diseases)
- AFM (Association Française Centre les Myopathies) - Paris – France

CELLS	DNA	TISSUES
31 Collections	333 Collections	72 Collections
4277 Persons	31747 Persons	516 Persons

- INNCEB (Istituto Nazionale Neurologico Carlo Besta) - Milan - Italy
- Fundación CSAI Carlos III (Fundación para la Cooperación y Salud International Carlos III) - Madrid - Spain
- Généthon (Généthon III) – Evry - France
- UCL (Université Catholique Louvain, Centre de Génétique Humaine) - Brussels - Belgium
- University of Ljubljana (Medical Faculty) - Ljubljana - Slovenia
- UOM (University of Malta) - Malta
- MTCC (Muscle Tissue Culture Collection at the Friedrich-Baur-Institut of the Ludwig-Maximilians-Universität) - Munich - Germany
- NHMGB (Naples Human Mutation Gene Bank, Second Naples University) - Naples – Italy
- NCPH (Fodor József National Centre for Public Health) - Budapest – Hungary
- Ospedale Maggiore Policlinico - Main Poly-clinical Hospital IRCCS (University of Milan, Dept. of Neurological Sciences) – Milan -Italy
- NMTB (University of Padova, Dept. of Neurological and Psychiatric Sciences) - Padova – Italy
- B.E.T. (Bio Expertise Technologies) - Marseille – France
- UJF (Université Joseph Fourier) - Grenoble 1 - France
- TEAMLOG SA – Montbonnot - France

In comparison, one of the oldest and largest academic DNA banks in the US, the DNA Bank and Tissue Repository at the Centre for Human Genetics currently:

- contains samples for 127,500 individuals
- has established more than 65,000 cell lines
- has collected data (including family-history and clinical data) on more than 10,000 families

Data collection for the European Network on Brain Demyelinating Diseases ENBDD

Leukodystrophies are an example of a disease difficult to apprehend: its clinical and genetic heterogeneity makes the description and the recognition of symptoms difficult. It is a multi-organ disease, and a pluri-disciplinary approach is necessary to obtain the diagnosis.

To improve medical and scientific knowledge on these diseases, it is necessary to integrate the diversity of data: medical and clinical data, tissue samples, results from research, individual and familial information.



S P E A K E R

“Prof. Odile BOESPFLUG-TANGUY, INSERM UMR 384, Clermont-Ferrand, France

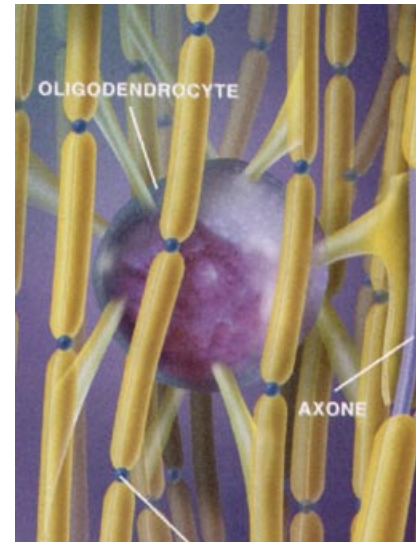


Figure 15: *dysmyelinating diseases, loss of continuity of the myelin sheath that impairs the conduction of the nerve impulse. This causes numerous diseases like leukodystrophies, a heterogeneous group of genetic disorders affecting the white substance in the brain.*

The collection of information must respect the patient's interests and consent; and the collected data must be protected.

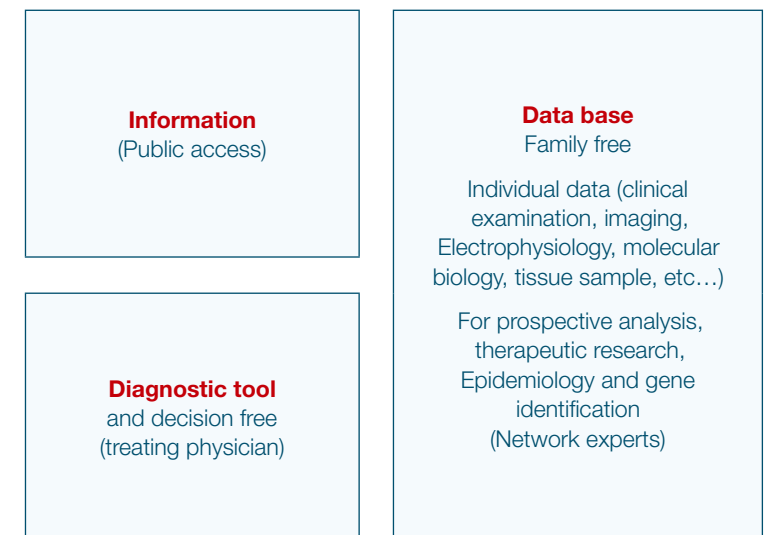
The network decided to create a database that would be accessible by patients, by the medical practitioner and medical experts. The data is used to follow-up patients at each visit, and also to generate research hypothesis, and scientific publications. The website is a platform for collection and exchange of data for human genetics: <https://hcforum.imag.fr/index.html>.

A family tree can be drawn online to report information on family members: clinical examination, pregnancy, neonatal development,

biochemistry, electrophysiology, tissue bank, gene tests, imaging, histophysiology, and treating doctors ... (see figure 15)

It is supported by Fondation pour la Recherche Médicale – Foundation for Medical Research, GIS Maladies Rares, Inserm and European Leukodystrophy Association.

THE LEUKODYSTROPHY PLATFORM. (figure 15)



5.7 Collecting and sharing registry data

José Luis Oliveira explored a similar avenue: how to integrate genetic data and medical information about rare diseases? Sources of information are various and numerous. The selection of the most relevant, updated and validated information is of key importance for researchers and treating doctors.

Among existing sources of information the following public databases were selected:

- Orphanet is a database dedicated to information on rare diseases and orphan drugs (www.orpha.net)
- clinicalTrials.gov, linking patients to medical research in the USA (www.clinicaltrials.gov)
- OMIM, Online Mendelian Inheritance in Man, a database of human genes and genetic disorders (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM)
- The National Centre for Biomedical Information in the USA (<http://www.ncbi.nlm.nih.gov/>)
- The European Molecular Biology Laboratory EMBL (www.embl-heidelberg.de)
- Entrez Gene (www.ncbi.nlm.nih.gov/entrez)
- Swiss-Prot (<http://ca.expasy.org/sprot/>)
- ProDom is a comprehensive set of protein domain families automatically generated from the SWISS-PROT and TrEMBL sequence databases (<http://protein.toulouse.inra.fr/prodom/current/html/home.php>)
- KEGG, Kyoto Encyclopaedia of Genes and Genomes (www.genome.ad.jp/kegg)
- GeneCards database of human genes, their products and their involvement in diseases (www.genecards.org/)
- PubMed is the U.S. National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature. (www.pubmedcentral.nih.gov/)
- PharmGKB, The PharmGKB is an integrated resource about how variation in human genes leads to variation in our response to drugs (www.pharmgkb.org/)
- HGNC, HUGO Gene Nomenclature Committee (www.gene.ucl.ac.uk/nomenclature/)
- EDDNAL, European Directory of DNA Diagnostic Laboratories (www.eddnal.com/)
- GO, Gene Ontology The Gene Ontology project provides a controlled vocabulary to describe gene and gene product attributes in any organism (www.geneontology.org/)



Prof. José Luis Oliveira, University of Aveiro, Portugal

SPEAKER

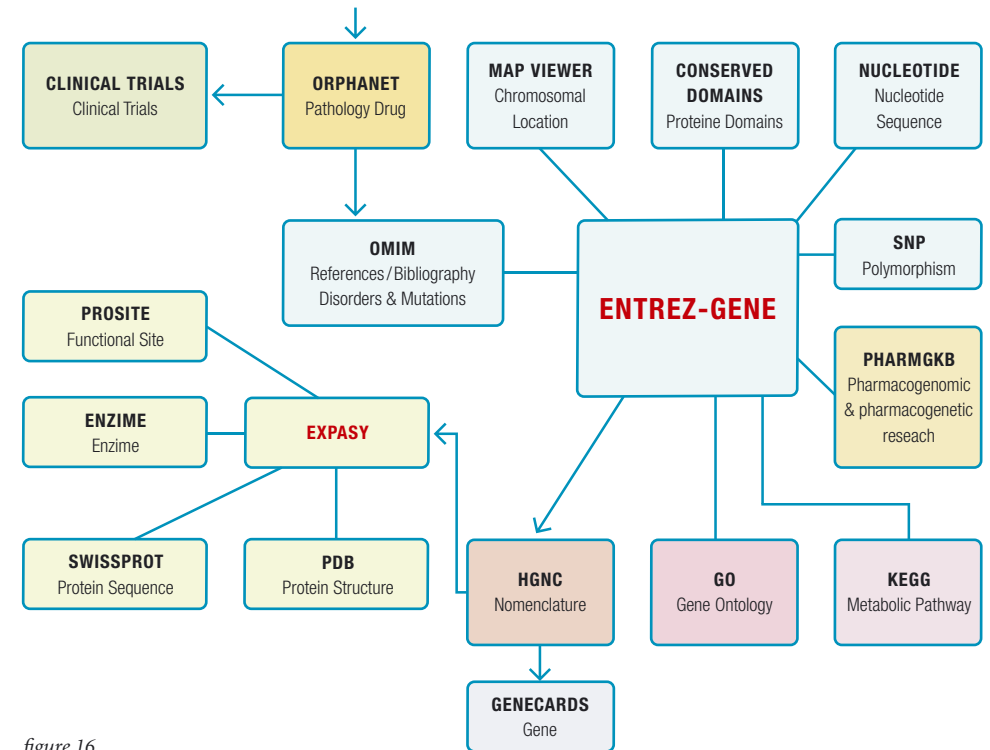


figure 16

From any entry (disease name), the principle is to guide automatically the information retrieval using the predefined protocol. Actions, like the following, can be taken like:

- To question OMIM for related genes;
- Consult the information (Entrez Gene) about protein domains, nucleotide sequence, polymorphism
- Or select other database depending on the kind of information the user is looking for (metabolic pathway, functional site etc.).

The main goal was to create automatically a card for each disease, integrating all the relevant information gathered from the distributed public databases defined in the navigation protocol. The navigation protocol can be changed easily to cope with new databases. This system relies completely on public validated sources, providing information from the phenotype to the genotype. It is available in the portal: <http://www.diseasecard.org>.

This work is supported by the University of Aveiro, InfoBioMed IST NoE, Instituto de Salud Carlos III, and the Institute of Electronics and Telematics Engineering of Aveiro (IEETA).

The use of various sources is organised in a navigation protocol that is summarised in figure 16 below.

5.8 Building a technology platform : Centre National de Génotypage

The CNG is a non-profit research organisation based at Genopole, Evry, near Paris. It provides technological infrastructure to the academic community for the identification of genetic causes of human diseases.

CNG was created in 1998 as a GIP (Public Interest Group) by the French Ministry of Research and New Technologies; it took over the genomic activities of Généthon, which pioneered genetic studies in France with the support of the French Muscular Dystrophy Association AFM.

→ PARTICIPATING RESEARCH INSTITUTIONS :

- INSERM (Institut National de la Santé et de la Recherche Médicale) National Institute for Health and Medical Research
- CNRS (Centre National de la Recherche Scientifique) National Centre for Scientific Research
- INRA (Institut National de la Recherche Agronomique) National Institute for Agronomical Research
- CEA (Commissariat à l'Energie Atomique) Atomic Energy Commission
- FIST (France Innovation Scientifique et Transfert, the technology transfer wing of the CNRS - National Centre for Scientific Research)

→ OBJECTIVES

The main objectives are firstly to develop and apply genotyping and related genomic technologies for the identification of genes associated with hereditary diseases, and secondly to facilitate and to strengthen research groups, laboratories and research centres in France and elsewhere (working on the identification of genes for each disease).

Resources include a fully automated genotyping platform and a sequencing platform. Currently, 76 rare diseases are being investigated.

For genodermatoses (e.g. ichthyosis), the Clinical Network Coordination obtained DNA from cohorts of patients. DNA and cells were stored. This network of cohorts involved numerous medical teams from the Mediterranean region (a total of 248 with 85 in Algeria, 81 in France, 25 in Turkey, 15 in Morocco, 11 in Tunisia, 11 in Italy, 7 in Portugal, 5 in Colombia, 3 in Sub-Saharan Africa, 2 in Syria, 2 in Spain, and 1 in Lebanon).

“ Dr. Judith Fischer MD,
PhD. (genotyping) (CNG),
Evry, France

DNA is then genotyped and sequenced, for the identification and localisation of the genes involved.

New genes were discovered, linked to rare ichthyosis (Table below): The projects on rare genodermatoses have performed in collaboration with Généthon (DNA extraction and storage of DNA and cells etc) and CNG (positional cloning, genotyping, sequencing etc). The projects have been supported by AFM/Généthon, CNG, Inserm and GIS/Maladies Rares).

	OMIM	Transmission	gene	Gene product	Name	Year of identification
Lamellar Ichthyosis, LI1	242300	AR	14q11.2	TGM1	Transglutaminase 1	1995
Nonbullous Congenital Ichthyosiform Erythroderma NCIE1	242100	AR	14q11.2	TGM1?	Transglutaminase 1	1997/1998
Lamellar Ichthyosis, LI5	606545	AR	17p13 17p13	ALOXE3 ALOX12B	Lipoxygenases	2002
Lamellar Ichthyosis, LI2	601277	AR	2q33-q35	ABCA12	ABC Transporter	2003
Lamellar Ichthyosis, LI3	604777	AR	19p12-q12			
Non-lamellar and Non-erythrodermic Congenital Ichthyosis NNCI	604781	AR	19p13.2-13.1			
LI/NCIE		AR	5q33	ichthyin	Receptor?	2004
Chanarin-Dorfman syndrome (Neutral lipid storage disease) NCIE2	275630 604780	AR	3p21	CGI-58	Esterase/lipase/thioesterase	2001

→ IN CONCLUSION :

- The infrastructure of the CNG offers state of the art technology to perform collaborative projects to study the genetics of diseases.
- The technological platforms developed at the CNG allow the scientific and clinical community to initiate large scale National and European or International programs.
- There is a large number of ongoing external collaboration, covering various disease areas.
- Their goal is to localise and to identify genes responsible for diseases, to discover polymorphisms in candidate genes or to perform high-throughput SNP genotyping.
- To submit a research project contact us by email at: project-manager@cng.fr

6 TREATMENT AND CARE

6.1 Targeting research to improve quality of life

Importance of making accurate, simpler and easier diagnostic

(Table, figure 17): for each of these rare diseases, the second column indicates prevalence, third column indicates the « old-time » diagnostic tool and the last column the availability of a DNA test to simplify and improve diagnosis. Old methods are usually invasive, and less sensitive.

Condition	Prevalence	Yesterday	Now: DNA test
Duchenne Muscular Distrophy	1/ 4 000	muscle biopsy	+
Cystic fibrosis	1/ 2 500	sweat test	+
Spinal Muscular Atrophy	1/ 6 000	muscle biopsy	+
Hemochromatosis	1/ 5 000	liver biopsy	+
Fragile X	1/ 5 000	caryotype	+
Myotonic dystrophy	1/ 5,000	muscle biopsy	+
Huntington	1/10,000	clinical presentation	+
Incontinentia Pigmenti	1/10,000	skin biopsy	+
Achondroplasia	1/10,000	X rays	+



S P E A K E R

Prof. Stanislas Lyonnet, Prof. Arnold Munnich. Département de Génétique et Unité de Recherches sur les Handicaps Génétiques de l'Enfant (INSERM U-393), Hôpital Necker-Enfants Malades, Paris, France

The genetic heterogeneity that causes disorders is such that it is not always possible to predict the onset of a disease when the person is carrying a genetic predisposition.

Testing is not a research activity, it is part of the patient management, or of the carrier management when the parent is carrying a gene without symptoms. Scientific knowledge serves to help patients or parents in making their decisions. It is part of the medical activity and should therefore be transferred and organised by clinical care settings, and not be confined in research ones only.

Therapeutic solutions that already exist for genetic diseases

Even though gene therapy has been emphasised in the recent years, and should still be regarded as a promising field, other solutions do

exist. They mostly derive from the knowledge of the genome, but they are not gene therapy per se:

- Dietary management
- Vitamin responsive metabolic diseases
- Organ transplantations / cell therapy
- Protein / drug engineering
- Enzyme therapies
- Gene therapy: the first steps ...
- Conventional pharmacology

→ DIETARY MANAGEMENT OF INBORN ERRORS OF METABOLISM

- Low protein diet : Phenylketonuria (PKU), hyperammonemias
- High cholesterol diet : Smith-Lemli-Opitz syndrome
- Mannose: CDG1b Congenital Disorders of Glycosylation (Phosphomanno isomerase deficiency)
Mannose, physiologically produced from fructose and glucose, can not be metabolised due to the absence of the Phosphomanno isomerase enzyme. Clinical manifestations include liver insufficiency, profuse diarrhea, hypoglycemia. Age at onset: 3 m-6 yrs. Oral mannose supplementation corrects the deficit as shown below :

MANNOSE DIET (0.2 g/kg/day in CDG1b PMI deficiency. (figure 18)

	T0	2-month	5-month
Mannose (µmol/l)	<10	100	200
ASAT	290	95	60
Factor XI	5%	46%	76%
Hypoglycemia	+++	0	0
Diarrhoea	+++	0	0
Vomiting	+++	0	0

→ VITAMIN/COFACTOR/SUBSTRATE RESPONSIVE METABOLIC DISEASES

- biotine (B8) responsive carboxylase deficiency
- pyridoxine (B6) responsive homocystinuria
- tocopherol (E) responsive pseudo-Friedreich ataxia
- carnitine responsive lipid myopathy / cardiomyopathy

- creatine responsive mental retardation. Arginine no longer metabolised into creatine, thus provoking muscle and brain abnormalities. Treatment based on creatine monohydrate (1mg/kg/j), arginine-controlled diet and high ornithine diet successfully improve the condition (no extra-pyramidal syndrome, improvement of epilepsy, cognitive impairment improvement)

→ ORGAN TRANSPLANTATION / NEO-ORGANES / CELL THERAPY

- Kidney Polycystic kidney disease (PKD), nephronoptosis, Alport
- Liver α 1AntiTrypsine deficiency, biliary atresia, metabolic diseases
- Heart obstructive cardio-myopathy, energy deficiency
- Bone marrow Severe Combined Immune Deficiency syndrome, storage diseases
- CNS brain « pace-maker »*

* Torsion dystonia (DYT1) observed in Pentothenate kinase deficiency, Huntington disease or mitochondrial diseases was successfully treated by surgery (Prof. Coubes PhD, Neurosurgery, CHU de Montpellier), by implanting electrodes in postero-ventral nucleus of the Globus Pallidum (a. lenticularis) guided by NMR Stereotaxy (see figure x adjacent).

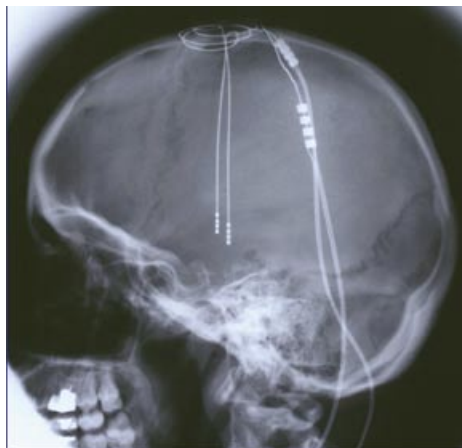


Figure 17: electrodes bilateral implantation to stimulate the nucleus using batteries that can last for five years.

→ PROTEIN/DRUG ENGINEERING

- Haemophilia : Factor VIII
- Diabetes mellitus : Insuline
- Growth retardation : Growth Hormone
- Congenital adrenal hyperplasia : Steroids

→ ENZYME THERAPY (GENZYME, TKT)

- Fabry disease
- Gaucher disease
- Hurler disease
- Pompe disease

→ GENE THERAPY, THE FIRST STEPS ...

- A gap between promises and results
- A number of unsolved technical problems
- A limited number of indications Immune deficiencies: selective advantage
..... Retinal dystrophies: tissue specificity
..... Inborn errors of metabolism
- A difficult approach : Toxicity (adenovirus, OTC, USA)
..... Insertional mutagenesis (retrovirus, SCID, Paris)

→ CONVENTIONAL PHARMACOLOGY

- To rectify splicing : Spinal Muscular Atrophy, Duchenne
..... Muscular Dystrophy: possibility to switch from a severe form (Duchenne dystrophy) to a less severe form (Becker dystrophy) using antisense oligotherapy
- To rectify translation : Gentamycine (in some cases of cystic fibrosis)
- To re-express a foetal gene : ... Hydroxyurea (Sickel Cell disease)
- To clear/chelate a toxic : Benzoate, cysteamine for Isovaleric Vcidemia
- To lock a pathway : NTBC (Type I Tyrosinemia)
- To activate a pathway : Fibrates, colchicine
- To inhibit a function : Bisphosphonates (Osteogenesis Imperfecta)
- To replace a function : Melatonin (Smith Magenis Syndrome): deletion on chromosome.17p11.2, with mental retardation, speech delay, automutilations, temper tantrum, hyperactivity and major sleep disturbance. As shown in figure x below, circadian cycle of melatonin production is reversed in affected children.
..... Treatment with melatonin reverses this cycle to normal, decrease the child's anxiety and temper antrum symptoms.
- To protect a function : Idebenone (Friedreich Ataxia)

→ CONCLUSIONS

- Identifying the disease-causing gene/mutation is consistently mandatory neither for diagnosis, nor for treatment
- One does not suffer from a mutation, but rather from its functional consequences
- Identifying the disease-causing mechanism helps devising the most appropriate therapeutic strategies
- Identifying the disease-causing mechanism occasionally brings about elegant and efficient therapeutic tricks
- Yet, identifying the mutant genotype might soon become very helpful for devising « à la carte » molecular approaches (exon skipping, non-sense mutations ...)
- The challenge is to identify the diseases that are presently treatable
- Fundings are necessary but not sufficient: «One cannot order a discovery» Lavoisier
- Beware of promises, single thoughts and dogmatism; A partly efficient drug is better than nothing... and one should not disregard any approach.
- No disease is rare for the one who is affected

Melatonin cycle is impaired during Smith Magenis syndrome as shown in figure 18 below:

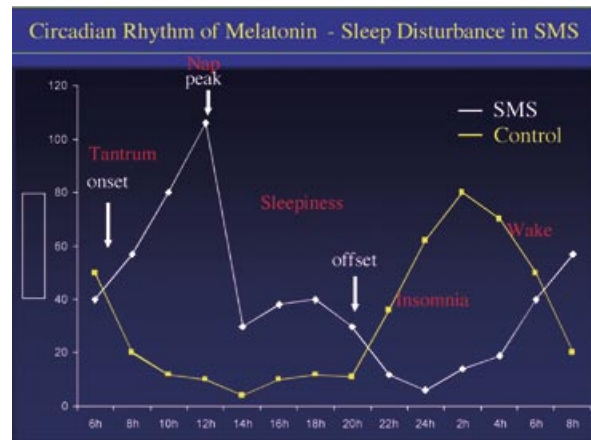


figure 18

Biphosphonates are useful to treat Osteogenesis Imperfecta (OI), as seen on figure 19 below.

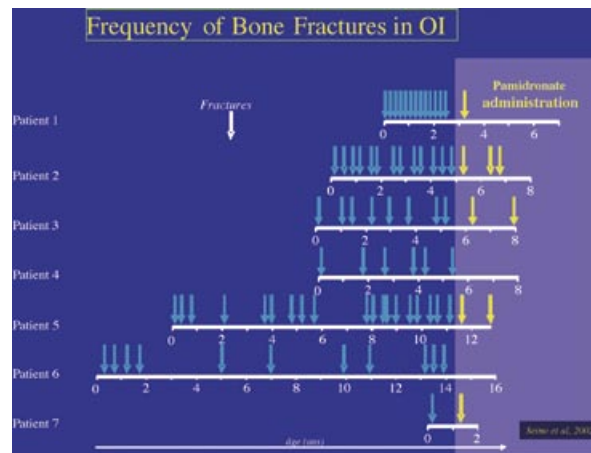


figure 19: prior to treatment, children born with OI may have 10 to 100 fractures a year (blue arrows. After treatment with biphosphonate that inhibit the bone destruction by osteoclast cells, fractures occur at a much lesser frequency (1 to 2 over 5 years).

6.2 A response to the needs of the clinical trial community

European Clinical Research Infrastructures Network (ECRIN)



Prof. Dr. C. Ohmann,
Coordination Centre for
Clinical Trials, Heinrich-
Heine-University Düsseldorf

S P E A K E R

Prof. Ohmann talked about the infrastructure which might be of enormous help for treating and diagnosing rare diseases. Other presentations focused on “cooperation, working together, and networking” and also on the need for more funding, for sharing resources and for optimisation. This is what ECRIN is about.

Ambitious goals, not specific to rare disease clinical research :

- To initiate and to support development of new diagnostic and therapeutic strategies
- To ensure adequate evaluation of efficacy and safety of medical products, devices, surgical techniques, etc.
- To improve quality and efficiency of clinical research

The main problems clinical research is facing are:

problem	description
transparency	limited transparency about ongoing and finished clinical trials
patient involvement and acceptance	deficits with respect to patient involvement in clinical trials still poor “trial culture” in the community poor patient recruitment in clinical trials
legal and regulatory conditions	harmonisation by EU Directives but divergent national implementations administrative burden for investigator initiated trials
sponsoring/ funding	industry sponsoring mainly for drug approval trials public sponsoring mainly for basic research missing clinical trial structures/ resources
quality	GCP but no harmonized practice and quality management deficient education of study personnel
specific problems for subpopulations	rare diseases – orphan drugs, paediatrics – off label/ off licence, incapacitated adults – informed consent, etc.

- move towards public registration of trials (Journal editors, WHO, Cochrane)
 - increased patient-orientation of clinical research (Patient organisations, outcome research)
 - improved EU-framework conditions for specific populations (E.g. orphan drugs, paediatrics)
 - some, but not enough initiatives for sponsoring/ funding of investigator initiated trials
 - successful disease- specific networks conducting multinational clinical trials in the EU (e.g. EORTC)
- But
- no systematic infrastructure to support multinational clinical trials in Europe

→ EXAMPLE : INSURANCE IN CLINICAL TRIALS

As a consequence of divergence in legislative systems :

- Major differences regarding insurance of clinical research (with respect to insurance coverage, type of sponsoring, drug approval status, type of trial, duration of insurance, etc.)
- extremely variable costs for insurance between countries

How ECRIN intends to solve some of the issues :

- bridge fragmented organisation of clinical research in Europe
- promote top harmonisation of support, training and practice for clinical research
- improve quality and efficiency of European clinical research

Network structure

national networks	characterisation	no. of centres
France Clinical Investigation Centres (CIC) Clinical Trial Units (ESPED)	core facilities core facilities	21 38
Italy Consorzio Italiano per la Ricerca in Medicina (CIRM) Mario Negri	departments subunits of departments	20 5
Germany Koordinierungszentren für Klinische Studien	core facilities	12
Denmark Clinical Research Centres (DCRIN)	mixed core facilities/ units of departments	8

national networks	characterisation	no. of centres
Spain Spanish Clinical Research Centres (SCReN)		8
Sweden Swedish Clinical Research Centres (SweCRIN)	mixed core facilities/ units of departments	10

Specific actions (EU FP-6 SSA 511963, 5/04 – 5/05)

Aim	identify traffic jams hampering trans-national studies define activities requiring top harmonisation
Work packages	website (www.ecrin.org) national workshops (9– 10/2004) with national reports comparative analysis closure meeting (14.-15.02.2005) final report

Target of proposed actions

European Clinical Research Infrastructures Network (ECRIN)

-planned services of proposed Concerted Action

information and consulting (free)

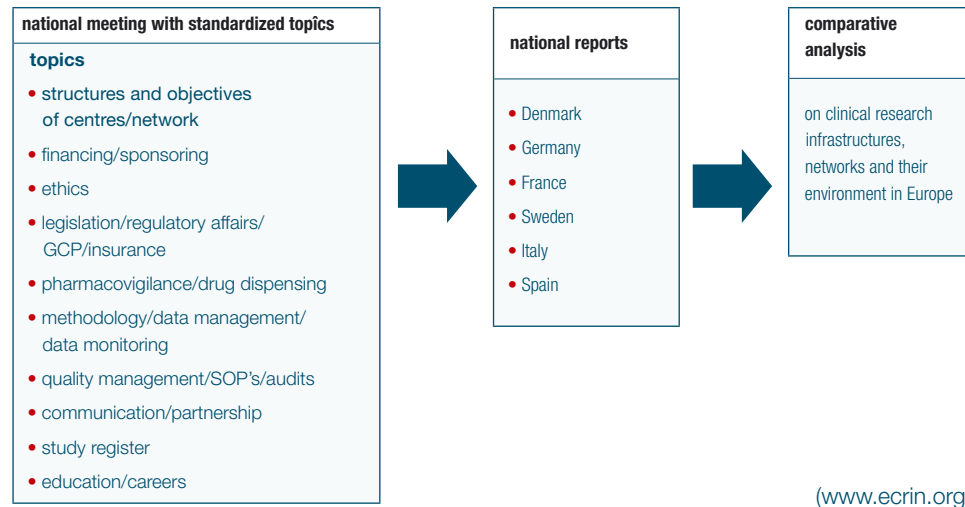
- methodology, protocol review, adaptation of study protocol to transnational constraints
- ethical review
- meta-analysis
- centre selection, stimulation of patients enrolment
- cost evaluation
- funding opportunities
- biostatistics
- data safety and monitoring committees
- insurance

flexible integrated services (charged to the sponsor)

- interaction with ethics committees
- interaction with regulatory authorities
- drug dispensing
- adverse event reporting
- data management
- data monitoring
- management of biological samples (“biobanks”)

European Clinical Research Infrastructures Network (ECRIN)

-Specific Support Action*-



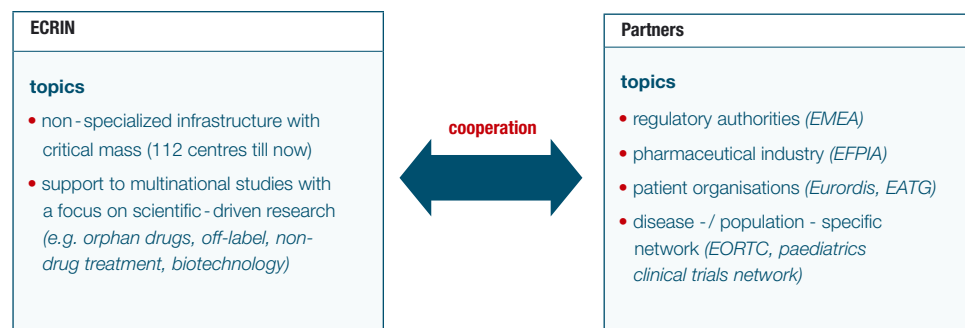
Target of proposed Concerted Actions

- Planned trans-national working groups to induce harmonisation and quality
- ethics, regulation, adverse, event reporting
- methodology, data management, monitoring
- quality management, SOPs, audits
- communication and partnership (*participants, patient's associations, investigators, sponsors, funding agencies, scientific associations*)
- coordination of integrated high-quality services

→ PARTNERS

European Clinical Research Infrastructures Network (ECRIN)

-Partners-



6.3 Treating with orphan drugs

Status Report and Health benefits after 5 years of Orphan Drug legislation



SPEAKER

“ Melanie Carr on behalf of Josep Torrent-Farnell, MD, PhD

In her presentation, Melanie Carr, on behalf of Prof. Josep Torrent Farnel, touched on the achievements of the orphan drug legislation, the protocol assistance, the marketing authorisations and the public health benefits to date.

The European orphan drug legislation consists of two regulations :

- Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products of 16 December 1999 that came into force
- with the Commission Regulation (EC) No 847/2000 of 27 April 2000

In April 2000, the EMEA received the first application for orphan medicinal product designation.

As provided for in the regulation, a review of the legislation is to take place after five years of orphan drug regulation. Therefore, the Committee for Orphan Medicinal Products COMP has prepared a report to the Commission, and this report will be posted on the EMEA web site.

The main recommendations that came out of this report are the basis of this presentation.

The aim of the orphan drug legislation is to address unmet medical needs of patients suffering from rare diseases within the Community, recognising that patients with a rare disease deserve the same access to treatment as all other patients. It is part of the Community policy to identify rare diseases as a priority area.

The legislation created incentives to attract the pharmaceutical industry and to develop interest on orphan drugs.

→ WHAT ARE THE EU INCENTIVES FOR ORPHAN DRUGS?

- Market Exclusivity for 10 years after granting of an EU marketing authorisation
- Centralised Procedure: direct access to EMEA
- centralised procedure for marketing authorisation
- Protocol Assistance: free scientific advice to optimise development

- Fee Reductions: reduction of centralised regulatory fees via a special fund from EU budgetary authority (to date this represents 12 million euros)
- EU-funded research grants from Community & Member State programmes

→ THE COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

EMA Committee: 31 members + Chairman

- 1 Member per Member State
- 3 members proposed by the EMA
- 3 representatives from patients groups

The COMP is responsible for:

- opinions on designation
- international co-operation
- advising on general EU policies

→ ACHIEVEMENTS: ORPHAN DESIGNATIONS

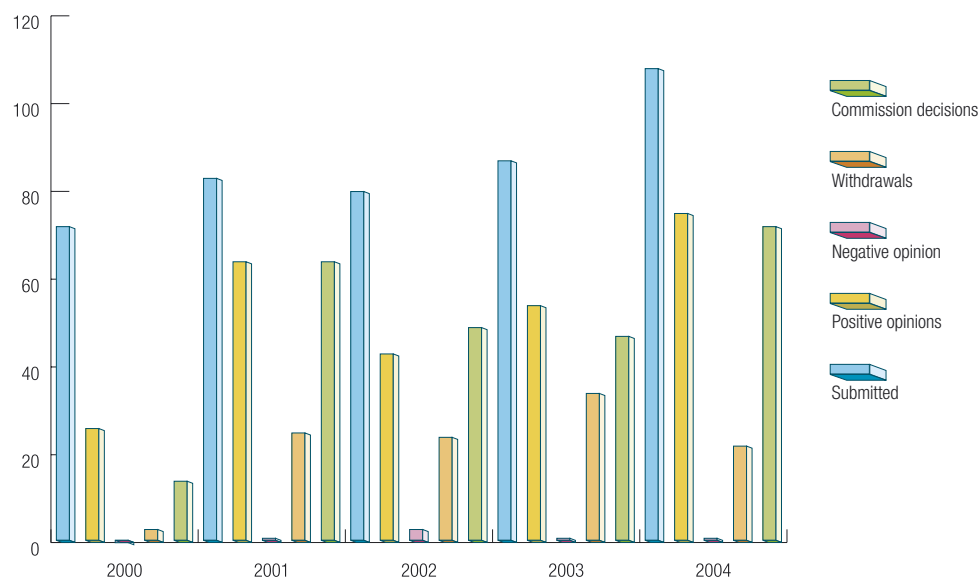
more than 480 submissions for designation (cumulated since 2000), of which 270 were designated.

The year 2004 was a record, with 108 submissions.

The year 2005 appears to be an active year as well, with 25 submissions in the last month (May 2005).

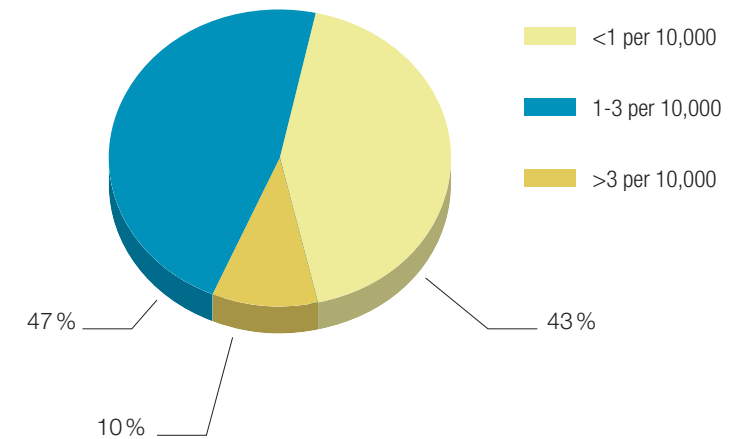
The Committee adopted its 300th opinion on designation during its meeting in May 2005.

COMP IMPRESSIVE ACTIVITY UNTIL END OF 2004 (figure 20)



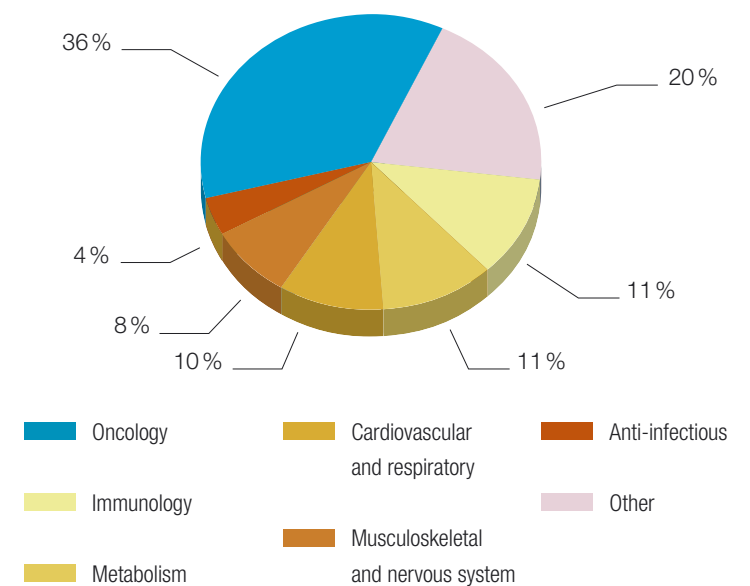
What kinds of products were designated? A majority were designated in oncology, and also for metabolic diseases, cardio-vascular and respiratory tract diseases to name but a few (see figure 21).

(figure 21)



In terms of prevalence, 90% of designations are for conditions that are affecting less than 3 / 10 000 patients (see figure 22) which is far below the 5/10 000 cut off for the epidemiological definition of rare diseases (or 230 000 persons).

(figure 22)



In terms of products, 21% of products submitted were biotech products. Innovativeness was also looked at, and the committee was pleased to note that 47% of products submitted were innovative ones; this includes novel chemicals, products for gene therapy and cell therapy.

→ PROTOCOL ASSISTANCE

Protocol Assistance is essentially Scientific Advice for companies developing Orphan Medicinal Products. It is particularly important for small and medium enterprises because it gives access to regulatory and scientific experts, thus a possibility for sponsors to discuss with them at an early stage.

In the majority of cases, protocol assistance gives the opportunity for oral explanation where additional and specific expertise (medical/patients) can participate. The COMP has recommended Protocol Assistance for more than 50 % of designated OMP. For orphan drugs, the fee reduction is important (currently 100% = free). This financial effort will need to be sustained in the years to come.

As of May 2005, 99 dossiers for protocol assistance had been received. In half of the cases (50%), assistance was asked for clinical aspects of the development, 34% for the non-clinical, 11% for biotechnologies and 5% for quality areas.

→ ORPHAN MARKETING AUTHORISATIONS

Up to April 2005, 20 centralised marketing authorisations had been granted to date:

- | | |
|---|---|
| • Fabrazyme for Fabry disease | • Ventavis for pulmonary arterial hypertension |
| • Replagal for Fabry disease | • Onsenal for Familial Adenomatous Polyposis |
| • Glivec for chronic myeloid leukaemia | • Litak for Hairy cell leukaemia |
| • Tracleer for pulmonary arterial hypertension | • Lysodren for adrenal cortical carcinoma |
| • Trisenox for acute promyelocytic leukaemia | • Pedeia for Patent Ductus Arteriosus |
| • Somavert for acromegaly | • Photobarr for Barret's oesophagus |
| • Zavesca for Gaucher disease | • Wilzin for Wilson's disease |
| • Carbaglu for hyperammonaemia | • Xagrid for Thrombocythaemia |
| • Aldurazyme for Mucopolysaccharidosis | • Orfadin for Hereditary tyrosinemia type 1 |
| • Busilvex for haematopoietic progenitor cell transplantation | • Prialt for chronic pain requiring intraspinal analgesia |

Three extensions of indication were authorised (Glivec for gastrointestinal stroma tumor GIST, for first line use in Chronic Myeloid Leukemia CML, for paediatric use in CML).

Fifteen centralised applications are currently in the review process, and two marketing authorisations were granted through Mutual Recognition.

So the total of authorisations is 22.

→ PUBLIC HEALTH BENEFITS

1. 22 orphan medicinal products have been authorised

The public health benefits of the EU orphan drug regulation are not easy to evaluate as they concern different areas. In terms of survival, life expectancy and quality of life it is too early to say what the impact has been on these parameters.

2. For the other designated products:

According to a recent EMEA survey of sponsors:

- 33% of orphan products are in final stage of clinical development (phase III)
- Up to 40% plan to file for marketing authorisation in the next 3 years

→ AMONG OBJECTIVE BENEFITS :

- Partnership with patient groups: the dialogue with patient groups had a positive impact on structuring network at EU level
- Increased level of scientific and public awareness
- Creation of expert network (350 experts registered)
- Impact on rare disease research
- International liaison with other Regulators, WHO, and NGOs on neglected diseases
- Transparency & pro-active dialogue with interested parties

→ FUTURE CHALLENGES STILL AHEAD

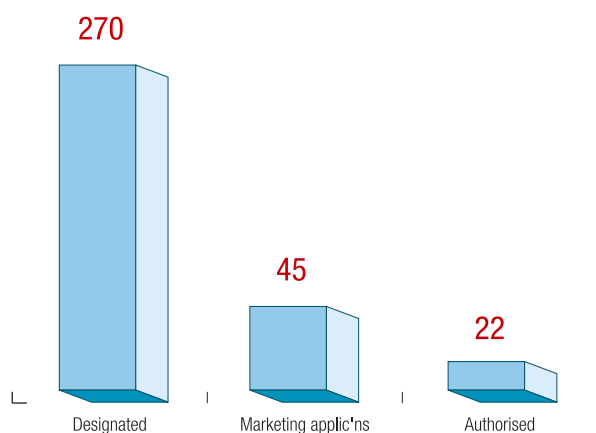
- Ensuring availability/access to OMP for all patients
- Strengthen early pharmacovigilance planning and risk management strategies
- Affordability and long-term sustainability of the orphan drug initiative
- Promote National Incentives
- Sustained public funding from EU/national institutions
- Better epidemiological knowledge of many rare conditions

→ CONCLUSION

As a final word, the true impact on public health has been in the figures: 270 designations, 45 applications for marketing authorisations, resulting into 22 marketing authorisations. From that, potentially more than 1 0430 00 patients stand to benefit.

Potentially more than 1 0430 00 patients stand to benefit

 (figure 23)



Treating with Orphan Drugs: an academic view

Dr. Bruce Morland is a treating oncologist in the UK, and he runs a cancer network developing new drugs for cancer. Dr. Morland also sits as an Academic member of a COMP sub-group, the Working Group of Interested Parties.

The starting point of Dr. Morland presentation was a question: Is there really anything in the Orphan Drug Regulation that is for interest for Academia?

For the pharmaceutical industry, the Regulation provides incentives, a centralised process for the designation and the evaluation of orphan products, and last but not least market exclusivity.

So, a comment that Dr. Morland often gets is “This is for industry not academia ».

But in fact the Regulation is very focused on patients, underlying the right for patients to receive the “...same quality of treatment”, setting the scheme for “...quality, safety, efficacy of products”, supporting “... research into diagnosis, prevention and treatment” etc.

After all, clinical academics treat patients too!



“ Dr Bruce Morland, Paediatric Oncologist, Birmingham Children's Hospital UK

SPEAKER

→ PROMOTE RESEARCH INTO RARE DISEASES

Academia has proven track record in “basic research”: it is able to move a concept hypothesis to the test tube, then to animal experimentation, but rarely to Human. Very few, if any, academic institutions in Europe can develop drugs. Academics can develop the science, the knowledge, but producing a drug is in the domain of the industry.

Therefore partnerships between Academia and industry are vital:

- Academic (for the collection of biological samples, volunteer patients etc)
- Industry (drug development/ manufacture)

Something the Regulation has perfectly done is not to force, but to put academic groups and industry in the same room at the same time, to allow these collaborations to take place.

The academic networks are very strong and developed. Collaborative links exist, although in the rare disease community there is a sense that research centres are sparse. When only one or two centres exist that are interested by the same rare diseases, how much collaboration is going on between them?

Fortunately or unfortunately, academia is extremely competitive. “I want to be the first person identify that gene, not you!”. Dr. Morland would argue that that is very healthy but other may consider this competition as a potential barrier to progress.

Research is not all about research and drug development, but it is also on epidemiology, diagnosis, prevention etc., domains where academic centres are leading the efforts.

→ FUNDING

Funding is the lifeblood of academic research. Unfortunately there is a bias towards “major diseases” provoked by the political dimension of research that drives research funding to cardiovascular disease, the elderly, mental health and cancer mainly. Research on rare diseases can be seen as an “orphan”. This is now changing.

EU funding is available: the pre-FP6 funding for rare diseases could fund a few research projects but on an “ad hoc” basis. Then the FP6 has specifically identified the need for research into rare diseases and this has to be applauded and congratulated. But we do not yet know whether FP6 has delivered for rare diseases. There has been a huge investment, but it will be some years before we know the results of

that investment in terms of scientific questions or benefits for patients. This will happen, but for the moment it is too early to say.

→ FUTURE EU FUNDING, FP7

There are very encouraging signs for FP7, as the COMP was successful in influencing the programme. Eurordis also produced a position paper on the subject, highlighting the following priorities:

- Descriptive and analytical epidemiology
- Genetic/molecular characterisation
- Pathophysiology
- Improving diagnostics
- Therapeutic research
- Research in human and social science

EU funding is important, but it contributes to only 5% to the total of the research budget available in the Community. The role of member states should not be neglected, as in addition to national research policies, member states are allowed to decide on national incentives for orphan drugs. They can vary considerably from country to country. However the inventory of such incentives is not completed, it should be published and regularly updated, but data are difficult to collect. Again, partnership with industry is key to increase the research budgets. Some charities and patient organisations fund research too, but this is an exception, as in general they are small patient-driven.

→ PROMOTING CLINICAL TRIALS IN RARE DISEASES

How do you conduct effective clinical trials in rare diseases?

We are talking about small patient numbers; we cannot use conventional scientific methodologies to study rare diseases. Some of these new methodologies with twenty patients still need to be validated and accepted by a wider scientific community and also regulatory authorities. For clinical trials, networks are also essential. In the cancer area, the situation can be seen as “luxurious” as very well established trial networks can conduct numerous trials. The fact that so many designations were obtained for anti-cancer drugs was not by chance, but thanks to these networks.

Funding is again becomes an issue for conducting clinical trials. EU Framework Programme has been very dominated by basic research not clinical trials, still trials are a vital part of bringing new treatments to patients and they need funding.

Industry struggles with rare diseases, finding the right collaborators or the correct number of collaborators that you need. It is a challenge to initiate lots of centres. We are now working in a “harmonised” clinical trials arena, and the promotion of clinical trials in that arena is not necessarily happening.

There are numbers of hurdles that academics have to face, and they are all for the right reasons:

- Compliance with EU Directive on clinical trials
- Ethical submission
- Medicines “regulations”
- Local Investigational Review Board /R&D approval
- Human tissue act
- Data protection act

There are pressures on everyone’s time, and in rare diseases clinicians have to go through the same bureaucratic processing for one or two patients than they would have to for five hundred patients with a frequent disease. This is a real dilemma, because the burden on putting these clinical trials together has to be eased for rare diseases.

→ THE ORPHAN DRUG REGULATION

It is definitely a huge progress for clinicians and patients.

A large range of disorders now benefit from a treatment, even though a third are for cancer and two third for paediatric patients.

For the other diseases, Dr. Morland questioned how to promote the orphan “orphans”? The products where little research is being made?

→ CONCLUSIONS

The Orphan Drug Regulation is bringing orphan drugs to patients. Whether or not the pace is quick enough is an open question. Often, the difficulty is to ensure that new discoveries are translated to treatment. This is an area where research incentives can make the difference: co-ordinated funding, promotion of trial networks. Reducing the bureaucratic burden for clinical trials is also a key solution.

Finally, we must remember the Orphan Drug Regulation is not about academic prestige, it is not about profiting industry, it is about giving patients access to new, better, safer therapies.

Orphan Drug Regulation: Views of a patient representative

In his introduction, Yann Le Cam insisted on the necessity to continue and to consolidate the work achieved so far thanks to the Orphan Drug Regulation that does not need to be changed after five years of adoption: it is working as only minor adjustments are needed.

→ **FIVE YEARS OF SUCCESSES** : Main outcomes

- Increasing number and quality of orphan drug applications
- 22 marketing authorisations
- 300 positive opinions for orphan designation!
- Benefiting potentially 1million patients in Europe
- For low-prevalence diseases, with innovative medicines, significant benefit over existing treatments, increasingly based on European research

During these five years, the pioneering role of patient representatives in the regulatory system, and the innovative dialogue with all interested parties has had a considerable input.

A limit though, member states policies on orphan drugs are not as developed as expected and encouraged in the EU Orphan Drug legislation.

The participation of patient representatives as full COMP members and members of the COMP Working Group of Interested Parties is a major political step: patients are taking decisions as other experts, and the EMEA is the only drug agency where patients are playing this role. Other participation of patients in the regulatory process includes:

- Patient representatives as external experts for COMP or Protocol Assistance.
- Patient representatives to be consulted for the evaluation of Risk/Benefit ratio when assessing a marketing authorisation application, as well as on the patient information leaflet.
- Patient representatives as members of the EMEA/CHMP Working Group of Patient Organisations and of the EMEA Management Board.
- Patient representatives as future full members of the Committee for Paediatric Medicines and of the Committee for Advanced Therapies.



“Yann Le Cam,
Chief Executive
Officer, Eurordis, and
patient representative,
Vice Chair, COMP

S P E A K E R

But beyond success, we need to recognise the lack of European and national overall policies on orphan drugs and call all interested parties and policy makers to join forces to address this loophole.

FIVE KEY ISSUES FOR THE FUTURE

→ **1ST ISSUE** : to develop more orphan drugs for unmet medical needs.

Beyond the first 200 conditions that are now benefiting from an orphan drug, more diseases are left untreated.

Proposal:

- European & national policies for rare disease research (research priority, research agenda and funding)
- Progressive elaboration of an « Inventory of unmet medical needs » and regular « COMP Call for Interest » by therapeutic fields.

→ **2ND ISSUE** : to improve the clinical development success rate to transform more orphan designated products into authorised medicines.

So far, from the 300 orphan designations, 22 orphan drugs are marketed. Comparing with the same flow in the US, where a fourth of designated products reach the market, is too early but we need to invent ways to improve this success rate in Europe. We must turn more orphan drugs “hopes” into “real” medicines.

Proposal:

- To create an « EU Orphan Drug Clinical Research Grant Programme » managed by EMEA / COMP through annual funds allocated by DG Research FP7. The office for Orphan Drugs at the FDA has a budget of 15 million dollars each year to initiate pre-clinical studies or Phase I/II studies. Europe could adopt a similar approach.

→ **3RD ISSUE** : to promote patient access to orphan drugs in each Member State.

We cannot accept that some drugs are still not available in all member states two years after their marketing authorisation.

Proposals:

- To implement the Commission Communication July 2003 and make the information about approved orphan drugs widely available (availability of drugs in each member state, distribution channel in each country, i.e. hospital pharmacies or community pharmacies, number of patients treated)

- To create a Working Group on Orphan Drug Availability at DG Enterprise with some volunteering Member States, COMP representatives and patient organisation representatives, to assess the Therapeutic Added Value and set a European reference price (catalogue) with the company. This would be a pilot. The industry often advocates that a unique price policy would be more adequate for Europe, so we give it a try.

→ **4th ISSUE:** to settle the unfair debate on orphan drug pricing

Some pretend that orphan drugs are expensive, or even too expensive. What does “too expensive” mean exactly? Does this mean that not all patients deserve treatment? They are not worth it? What would a scientific assessment of the positive risk/benefit ratio mean if yet another stakeholder states that I am not worth the product as a patient? This debate is unfair and should be closed.

Prior to the centralised procedure, some 200 other orphan products were already authorised in the EU, imported from the USA, and price was never an issue. Now that some are produced, developed, evaluated and marketed in Europe, with a return of investment in Europe and not in the USA, then the price should become an issue, all of a sudden? Europe playing against itself!

Furthermore, orphan drugs authorised during the last five years are not more expensive than other innovative products marketed during the same period (cf. the Alcimed report to European Commission).

→ **5th ISSUE:** to adopt a more international approach to designation, protocol assistance, marketing authorisation assessment and drug availability to patients.

Clinical development of orphan drugs is global. However expert centres, patients, financial resources are scarce. Time is a life and death issue. Issues raised by regulators in the US and EU are or should be the same, both for clinical development and post marketing studies.

Proposal:

- To pro-actively propose parallel Protocol Assistance EMEA/FDA for orphan drugs when already designated on both sides
- To explore and implement possible parallel procedure for orphan medicinal product designation applications

Orphan Drug Regulation: Views of an industry representative



S P E A K E R

Dr. Catarina Edfjäll, PhD, Director, Global Regulatory Liaison, Actelion Pharmaceuticals Ltd.

As a representative of EuropaBio and Emerging BioPharmaceutical Enterprises EBE, association of drug manufacturers that are developing the vast majority of orphan products in Europe today, Catarina Edfjäll stressed that it is too soon to judge results of the Orphan Drug Regulation - but the outlook is promising and the pharmaceutical industry as a whole should support this Regulation. This position has been summarised in the Industry White Paper.

The industry analysis concludes that rare diseases are now identified as a priority area for community action within the framework of public health in Europe. However, it seems that member states need to better understand the spirit of the Regulation and adopt a more active policy on national incentives. Alcimed's study confirmed that the price for an OMP in the EU is related to disease rarity and health systems.

However, the Regulation does not concentrate on research programmes or on access. In the EU, only limited action has been taken so far to stimulate the development of Orphan Medicinal Products (OMPs).

The experience in the USA and Japan show that the strongest incentive for industry to invest in development and marketing of orphan drugs is where there is a prospect of obtaining market exclusivity.

To improve the Regulation, the industry is making 9 recommendations (see the Industry White Paper) :

1. Undertake an educational programme to build awareness about rare diseases in Europe, at the European level as well as the national level.
2. Establish an EU-wide network for diagnostic testing for rare diseases → timely intervention for patients.
3. Promote a Europe-wide compassionate use system for the provision of orphan medicines to patients.
4. Increase the understanding of the Regulation in MS and eliminate conflicts in national legislation.
5. Review the incentives for OMP development in the Member States (Article 9).
6. Eliminate the confusion around the 10-year market exclusivity (Article 8(2)) & correct translations.
7. Review disincentives to orphan drug development at the national level, e.g. additional requirements for clinical and cost-effectiveness data.
8. Facilitate clinical trials in the field of rare diseases, under the EU “Clinical Trials Directive,” & review cost implications of post-marketing commitments.

9. Coordinate and streamline EU rare disease research and therapy development within the Commission and with the EMEA and the FDA.

This should be worked on and implemented by the Commission in a spirit of collaboration with all stakeholders.

About the 6th recommendation, Catarina Edfjall explained that market exclusivity is the strongest EU Regulation incentive and that it should be protected.

According to her, the review of market exclusivity should only be based on the designation criteria.

The risk is that confusion about the application of market exclusivity could erode the incentive. To her opinion, market exclusivity does not lead to higher prices, but the rarity of the disease does.

As shown on figure x, market exclusivity provides no monopoly: for pulmonary arterial hypertension, many therapeutic options exist, some with an orphan drug status. Finally, market exclusivity provides partial exclusivity in respect of similar products: similar and competitor products need to be clinically superior.

Orphan Regulation has NOT created monopolies - example PAH

Approved products for treatment of PAH

- Ca-channel blockers oral
- epoprostenol proctacycline i.v.

Approved orphan products for treatment of PAH

- bosentan ERA oral
 - iloprost prostacycline inhaled
 - (sildenafil(US) PDE-5 oral)
 - (Treprostinil (F) prostacycline s.c.)
- } New MoA or route of administration

Designated orphan products for treatment of PAH

- sitaxentan ERA oral
 - ambrisentan ERA oral
 - tadalafil PDE-5 oral
 - vardenafil PDE-5 oral
- } Similar? Clinically superior?

ERA: endothelin receptor antagonist; PDE: phosphodiesterase type-5

An important question is whether market exclusivity protects the innovator doing pioneering research.

- Orphan Regulation should stimulate development of new medicines for patients without treatment
- First step: Research of a new therapeutic field requiring 'pioneering' work (new animal models, not

yet validated endpoints, unknown safety profile...)

- Requires high investment and risk-taking

• Needs to be stimulated and rewarded

- So, in this context, is Market Exclusivity a real incentive?

→ **CONCLUSIONS**

Regulation should be continued and not be changed at this time. Regulation should be more fully applied in member states, especially for Incentives and Access.

Avoid confusion about incentives, especially Market Exclusivity.

The field of rare diseases should be taken very seriously, it leads into personalised medicine.

Availability of orphan medicinal products in Europe

The review of real patient access to orphan drugs after their marketing authorisation has been granted by the Commission, is the objective of a regular survey conducted by Eurordis.

Only a part of a disease population has access to an orphan product, when existing: the disease population is represented by the prevalence, but in fact not all cases are diagnosed. And even among diagnosed cases, not all patients correspond to the treatment indication (for example children when only an adult formulation is marketed with no information on the dosage for children). Then another limitation resides in the contra-indications, e.g. liver function or renal function impairment.

Then, even for the patients who should be treated, an important obstacle is the delay in placing an authorised product on the market.

This delay can be explained (but in no way justified) by several factors :

- The delay for fixing the price (negotiations between marketing authorisation holder and member states' authorities). the COMP assesses if the significant benefit still holds. So the therapeutic added value should automatically lead to reimbursement in each member state/EEE).
- The delay for deciding the reimbursement (for designated orphan products, the potential significant benefit is assessed at the time of designation by the COMP, at the time of marketing authorisation based on the marketing applications, • The treating physicians' lack of experience concerning the real medical benefits of these medicines and thus their reluctance to prescribe them. This can be the case



François Houjé, Eurordis, Health Policy Officer

S P E A K E R

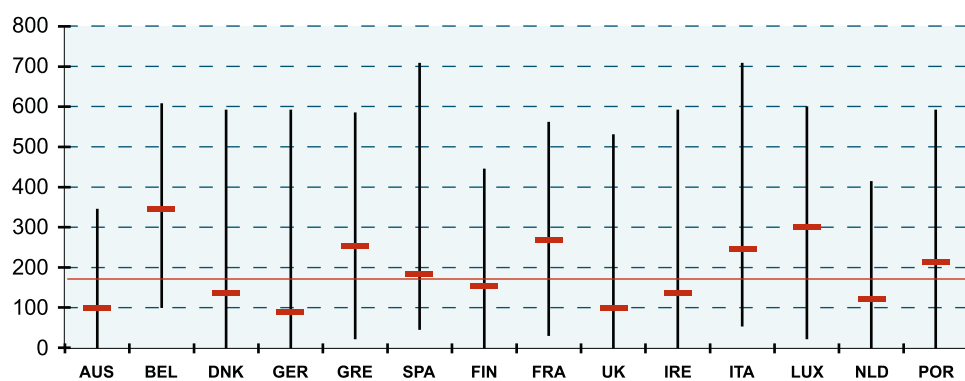
when a treating physician did not participate to the clinical trials as an investigator or when no clinical trials were run in his country.

- The absence of treatment consensus recommendations / guidelines.

These delays are well known: already in the audit performed in 1999 on the performance of the EMEA and the European Regulatory System and such delays were registered for the first 96 products authorised through the centralised procedure (1995-1999).

They are shown in figure 24. By that time, the average delay was 190 days, exceeding the 180 legal days, with maximum delays of up to 708 days. For the rare disease community, the objective was to explore to which extent this was also the case for orphan drugs: if rare diseases are a priority, then logically the placing on the market should be rapid. On the contrary, in the absence of a public health priority for rare diseases, similar delays would be observed.

AVERAGE DELAYS TO MARKET BY MS. (figure 24)



Participants at the conference

→ WHY MONITOR ORPHAN DRUG AVAILABILITY IN EU MEMBER STATES/EEE?

Eurordis is entitled to monitor the drug availability as this is in the interest of patients and as the Council Directive 89/105/EC sets the delays for member states to place the products on the market after their authorisation:

- COUNCIL DIRECTIVE of 21/12/1988 - transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (89/105/EC)
- Article 2 – 90 days legal delay to set a price which can be extended to 180 if questions arise
- Article 6 – Inclusion of medicinal product in the list of medicinal products covered by the health insurance systems within 90 days – the overall period of time taken by the two procedures does not exceed 180 days (possible extension if questions)

→ EURORDIS RESULTS

Table 25 below presents the 12 first OMPs authorised prior to December 31st 2003 (starting 2000 for the very first orphan drugs marketed).

Fabrazyme	Genzyme	Fabry Disease
Replagal	TKT Europe	Fabry Disease
Trisenox	Cell Therapeutics	Acute promyelocytic leukaemia
Tracleer	Actelion	Pulmonary arterial hypertension
Glivec	Novartis	<ul style="list-style-type: none"> • Chronic myeloid leukaemia • Gastrointestinal stromal tumors
Somavert	Pharmacia	Acromegaly
Zavesca	Oxford Glycosciences / Actelion	Gaucher disease
Carbaglu	Orphan Europe	N-acetylglutamate synthetase deficiency
Aldurazyme	Genzyme	Mucopolysaccharidosis type 1
Bulsivex	Pierre Fabre	Conditioning treatment prior to HPCT
Ventavis	Schering	Primary Pulmonary hypertension
Onsenal	Pharmacia Pfizer	Familial adenomatous polyposis

For these products, Eurordis asked several sources:

- IMS-Health, to detect sales in a sample of pharmacies in each member state (except Denmark)/EEE
- Patient organisations, to report on real availability of the products
- National Competent Authorities
- Marketing Authorisation Holders (MAH)

Data were collected until December 6th 2004; this was 341 days or 11 months and 6 days after December 31st 2003.

Figure 26 below shows the number of orphan products available in member states at the end of the data collection phase.

With the exception of Denmark, none of the member states had placed all 12 products on the market, one year or more after their marketing authorisation. The median number of products actually placed on the market is 5 out of the 12.

A first group of member states /EEE countries are doing better than average: Austria and France (11), Sweden (10), Finland, Germany and the Netherlands (9), then Italy, Spain and the United Kingdom (8).

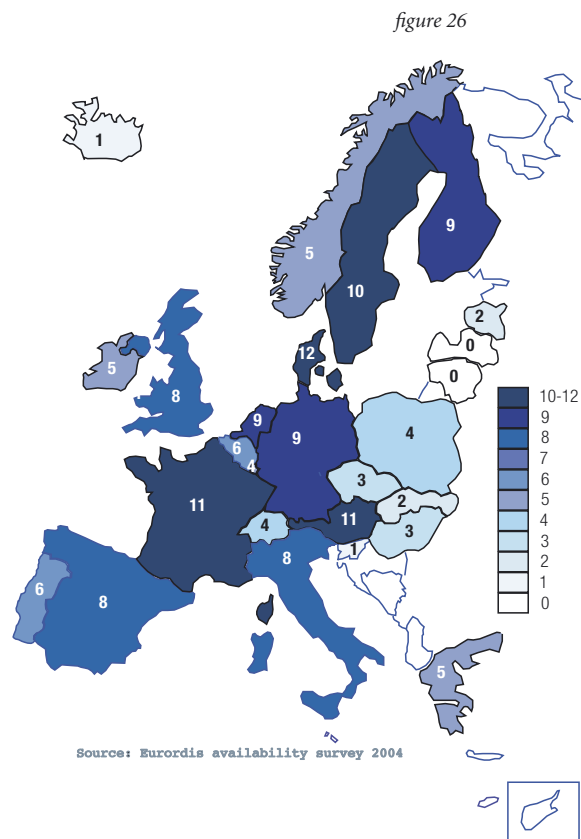
For a second group, only half or less of the authorised products are available: Ireland, Portugal, Norway, Belgium, Luxembourg, and Greece.

The last group, mostly represented by member states that entered the community in 2004, 0 to 4 products only are available.

→ DISCUSSION

A first comment is the difficulty in obtaining the information about drug availability. Even though all possible sources were solicited, some data may be missing as each source had its limitations:

- Pharmacies' sampling: the method may not be sensitive enough to capture orphan drug sales even when sample size is relatively large. For example only 3 hospitals are delivering Fabrazyme in France (total of 1200 hospital pharmacies, whereas the sample contains 300 pharmacies and was not likely to detect sales)
- Industry: of the 10 MAHs contacted, and despite their collective intention to participate, 6 provided part or all of the data requested (Actelion, Cell Thera-



peutics, Genzyme, Novartis, Orphan Europe, and Pfizer) for 9/12 products, 1 refused (TKT) and 2 never responded (Pierre Fabre, Shering Plough)

- Patient organisations: key contact persons do not always know where to find the information.
- Pharmacists (directly contacted by Eurodis)
- Hospital pharmacies that deliver all 12 OMPs considered are extremely rare.
- A survey among them should involve large numbers of pharmacists
- National Competent Authorities: they can inform on the achievement of negotiation phase on price and reimbursement, but have very little information on actual availability or use of the products.

→ THE POSSIBLE EXPLANATIONS OF INTER-COUNTRY DELAYS ARE NUMEROUS

1. Firstly, the pricing mechanisms as provided for in national regulation schemes differ from one country to the other. In some countries it is the average price from the prices already negotiated in other states (reference countries). In this case, as long as negotiations are still going on in the reference countries, no average can be calculated.

Country	Reference Countries	Basis of calculation	Prices re-calculated
Greece	Lowest price in Europe	Lowest price in Europe	No
Ireland	Denmark, France, Germany, Netherlands, UK	Lowest of average and UK price	No
The Netherlands	Belgium, France, Germany, UK	average	Yes
Portugal	France, Italy, Spain	Lowest	No

Panos Kanavos, LSE Health and Social Care 2001

Drugs are not all distributed through the same channel: complex named patient basis system, case by case reimbursement scheme, special fund for severe diseases, private or public purchasers etc. For each system, and several different systems can coexist in a same region, the decision is a complex process, often not transparent.

2. Secondly, rare diseases are not yet a public health priority in most of the 25 member states and 3 EEE countries, although regulation calls for specific national policies incentives.

3. Thirdly, not the price itself, but the accountability of pharmacies is source of extra-delays:

- Whether large or small sales volumes, hospital pharmacies have to budget the purchasing of new products for the following year: No "Open tap " budget

- When the decision of purchasing products depends on an annual budget, the head of the pharmacy has to select the patients he/she can afford to purchase drugs for:
- For an OMP that costs 150 000€ per patient per year, 600 000€ are needed to treat 4 patients
- With the same amount, 50 people with HIV infection can be treated each year.

→ PROPOSALS TO EASE THE PROCESS

- Establishing a new EU Committee or a subgroup of the EU Transparency Committee:
- To complete assessment of the Therapeutic Added Value (TAV) of each orphan drug
- To propose a reasonable European catalogue price based on discussion with the marketing authorisation holder
- A European procedure implemented by volunteering member states pooling their expertise on orphan drugs
- Advisory opinion: No compulsory single EU price. Only a “Reference TAV” and a “Reference Price” limited to Orphan Drugs that Members States can use for their own decisions. No need for a new legislation.

→ THE NEXT STEP: TO BETTER DOCUMENT

ON THE AVAILABILITY OF AUTHORISED PRODUCTS

Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use, and establishing a European Medicines Agency, confers to EMEA a role in documenting on real use of marketed products:

- Article 13: Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Community level, broken down by Member States, and any data in the holder’s possession relating to the volume of prescriptions.

→ CONCLUSIONS

The failure of most of member states to place on the market in due legal time most of orphan products approved through the centralised procedure is striking.

From our survey, it appeared that no single source or easily accessible sources are able to provide the information needed on drug availability. The channel to place orphan drugs on the market is complex, even Marketing Authorisations holders have difficulties in obtaining information on their own products (definition of availability, co-marketing, distributors, imports...)

A structured data collection system is needed and there is a possible collaboration with EuroMedStat on this matter.

Lastly, access to existing and authorised medicines is the patient first priority. National pricing and reimbursement negotiations are too often reducing the pace for accessing them.

Views of a health care system: The NICE approach to rare diseases

→ WHAT IS NICE?

The National Institute for Health and Clinical Excellence (NICE) is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

It was created 1st April 1999 to set national clinical standards and manage new interventions appropriately into the National Health-care System NHS. New expensive interventions were not coming in as equitably, fairly and rapidly as they should have.

It has three centres:

- Centre for Public Health Excellence: elaborates guidelines
 - public health interventions, for actions on individuals
 - public health programmes, for actions on populations
- Centre for Health Technology Evaluation: evaluates
 - cost effectiveness of drugs, their safety
 - technology appraisals
 - interventional procedures
- Centre for Clinical Practice
 - clinical guidelines on patient management

→ THE NICE APPROACH

- Evidence based (safety, effectiveness and cost effectiveness in particular). NICE is not evaluating the costs, as affordability is a governmental responsibility. NICE is assessing the relative benefits of an intervention over its adverse reactions, and the overall value to health services.
- Transparent (scientific and social values): as these decisions are important, all groups have the right to participate in the decision process.
- Inclusive (all stakeholders)

→ BACKGROUND TO NICE ASSESSING INTERVENTIONS IN RARE DISEASES

“The Department of Health and the Welsh Assembly Government have asked NICE what approach it would take if asked to appraise orphan drugs”.



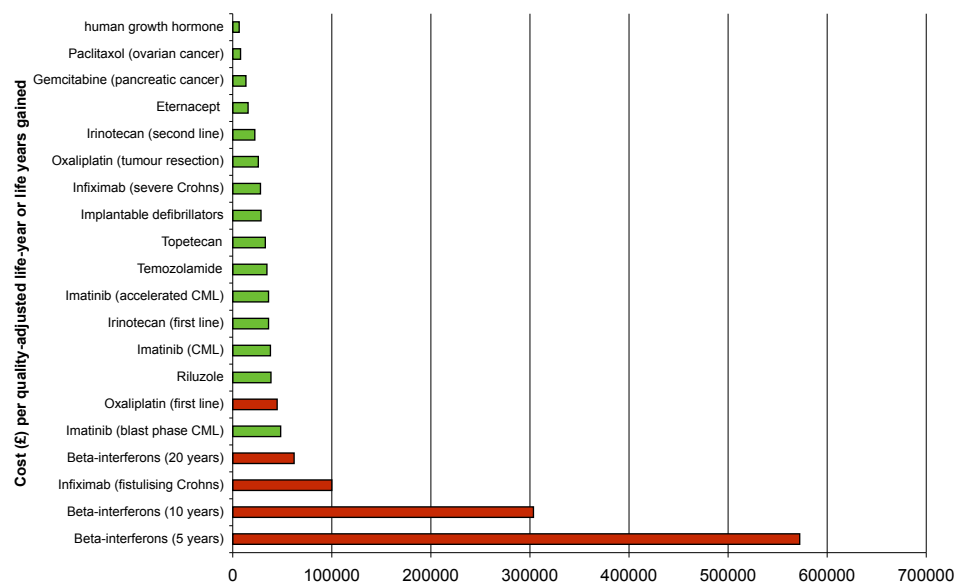
Prof. Peter Littlejohns, Clinical and Public Health Director, the National Institute for Clinical Excellence, UK.

SPEAKER

Country	Numbers of affected individuals	Prevalence (per 10,000 population)
United States of America	<200,000	7.5
Japan	<50,000	4.0
Australia	<2,000	1.1
European Union	<215,000	5.0

During the last six years, NICE assessed the value of marketed orphan products as shown in figure 27 below. Some of them were considered as non cost effective and were not supported by the centre (bars in red), others, though expensive, but highly cost effective, were supported (bars in green). Data shown represent the cost in £ per quality-adjusted life-year QALY or life years gained LYG.

COST (£) PER QUALITY-ADJUSTED LIFE-YEAR OR LIFE YEARS GAINED . (figure 27)



Are there interventions that are both very rare and very expensive? For the Ultra-orphan drugs, NICE took the decision to assess interventions responding to a more strict definition:

“Products for conditions with a prevalence of less than 1 in 50,000”, or put another way, “Products for conditions with less than 1000 cases in the UK”.

This was the case for the following orphan drugs:

Condition	Treatment	UK prevalent cases
Phenylketonuria	Dietary modification	500
Haemophilia B	Nonacog alfa	380
Gaucher’s disease (type 1)	Imiglucerase Miglustat	200
Fabry’s disease	Fabrazyme Miglustat	70-140
Mucopolysaccharidos (type 1)	Laronidase	500

Cost effectiveness appraisal consists in balancing the value of the product with quality of life. There is no automatic threshold, no cost above which a drug is declared non cost effective. There is a probability as the cost gets more and more that takes into account other factors than cost effectiveness: equity, fairness, which the drug has or not, if this is the only drug for the condition... These are not economical values, there are not produced by calculation. Instead, the process consists in a large and open discussion where all parties can express their views.

→ THE NICE METHOD

- Internal orphan drugs workshop at NICE to consider the above mentioned issues (Feb 2004) and see how NICE experts have been addressing the question during the last 6 years.
- Citizens Council (the public) debated orphan drugs (Nov 2004) to enlarge the consultation with tax payers.
- Patients–NICE meeting (Dec 2004)
- Royal College of Physicians-NICE conference (Oct 2004), with the participation of patients.
- Feasibility study, including Appraisal committee meeting (March 2005)

The consultation with citizens drew some useful conclusions: There is a public expectation that the NHS should be prepared to meet the reasonable treatment costs of expensive treatments for ultra-orphan conditions. Two caveats were listed:

- Commercial prices charged by manufacturers are reasonable.
- Opportunity costs are tolerable

A feasibility study was conducted with the industry to check whether these principles were realistic. The phases of the feasibility study were:

- To assess the evidence on clinical and cost effectiveness of the use of Enzyme Replacement Therapy for the treatment of type 1 Gaucher’s disease
- To organise an Appraisal Meeting which was separate from and additional to normal programme

- Manufacturers
- fully involved with development of the assessment report and the assessment process
- Took part in the Appraisal Committee meeting as both observers and external experts
- No guidance was issued by NICE as this was a pilot project
- Outcome of feasibility exercise will be reported by NICE to Department of Health

→ CONCLUSIONS

- There is no scientific or technical difficulty in appraising drugs with “orphan designation” (although they tend to have higher Incremental Cost Effectiveness Ratios ICERs and therefore will be scrutinised more closely)
- Normal NICE process for drugs for diseases greater than 1 in 50,000
- Need new process for “ultra-orphan” drugs (high acquisition costs, used solely in an ultra-orphan disease, severe life long disease)
- Proposal to be presented to Department of Health

Views of a National Competent Authority: The Italian Medicines Agency

The Italian Medicines Agency strategy for research and rare diseases is based on several specific actions:

- A specific fund is dedicated to rare diseases (subparagraph 19 of article 48 of the law establishing the Italian Medicines Agency).
- A percentage of this fund must be devoted to research on the use of drugs.
- 50% will be used to set up a national fund for orphan drugs and drugs not yet authorised and representing the hope of a treatment for severe diseases
- The remaining 50% will be used for:
 - implementing a National Centre of independent information on drugs
 - implementing a program of active pharmacovigilance aiming at advising and educating general practitioners and paediatricians
 - implementing research on the use of drugs and in particular head to head comparisons between drugs for the demonstration of the added therapeutic value, including for orphan drugs

Currently, 9 EU marketed orphan drugs are 100% reimbursed in Italy (Somavert (Pegvisomant), Zavesca (Miglustat), Aldurazyme (Laronidase), Carbaglu (carbaglumatic acid), Ventavis (iloprost), Fabrazyme (L-galactosidase A), Trisenox (Arsenic Trioxide), Tracleer (Bosentan), and Glivec (Imatinib).



“ Dr. Domenica Taruscio on behalf of Dr. Nello Martini.

SPEAKER

“ Poster 53, Bonet F(1), Salinas C(1), Alsina C(1), Bel E(1) and members of GITER and REPIER(2).

1. Departamento de Farmacia y Tecnología Farmacéutica. Universidad de Barcelona. España

2. Consejería de Sanidad y Consumo, Dirección General de Consumo y Salud Comunitaria, Servicio de Epidemiología de la Junta de Extremadura.

National incentives for the research and development of orphan products: Spain

Measures for availability of orphan drugs and research, information and support for rare disease.

The author exposed the measures taken in Spain that directly or indirectly favour research, availability and information of drugs aimed for treatment, prevention and diagnosis of rare diseases. The Spanish national laws had paid attention to the needs of “certain group of patients” but since the publication of Regulation EC 141/2000 the attention is paid specifically for rare diseases, with an increasing number of different measures.

In the field of rare diseases, national laws give the general rules and the Autonomous Communities have the power to develop these laws, but there is a diversity of measures according to different policies on rare diseases. Some Communities have enlarged the rights of patients. The difficulties to access this information, due to the regionalisation of health policy, and to the fact that some measures are not published, are major.

RESEARCH AND INFORMATION ON RARE DISEASES

National Rules	Measures
Ministerial Order 3158/2003 of 07/11/2003, BOE 14/11/2003	Creation of the Instituto de Investigación en Enfermedades Raras (Institute of Research on rare Diseases) Responsible for research in rare diseases and of an information system for patients and health professionals.
Resolution 24/07/2002, BOE 31/07/2002.	Program PROFARMA II, for the promotion of pharmaceutical research Priority to rare diseases
Ministerial Order 2446/2004 of 19/07/2004, BOE 22/07/2004	Financial support for highly important activities related to health care. When organising a conference, courses or other activities, one of the priorities are rare diseases
Ministerial Order 709/2002 of 22/03/2002, BOE 30/04/2002	Financial support for the development of research cooperative networks. Creation of REPIER (Epidemiological Network on Rare Diseases Research)
Regional Rules	
Galicia: Resolution 15/03/2002, DOGAL 04/04/2002	Regional plan on research, development and innovation (2002-2005) Priority to rare diseases
Extremadura: Order 14/05/2004, DOE 15/05/2004.	Creation of an Information System on rare Diseases. Epidemiological information and natural history of rare diseases.



AVAILABILITY OF TREATMENTS AND OTHER SOCIAL MEASURES

National Rules	Measures
Royal Decree 1348/2003 of 31/10/2003, BOE 04/11/2003	It adapts the classification of drugs to the ATC. It includes many drugs in the list of non reimbursable, but there can be exceptions in the case of orphan drugs. The law 25/1990 on medicinal products (art 94) and the Royal Decree 83/1993 on medicinal products reimbursement had previously contemplated the case for "certain groups of patients".
Ministerial Order 3461/2003 of 26/11/2003, BOE 12/12/2003	It incorporates in Spanish law Directive 2001/83 Including the marketing authorisation of orphan drugs.
Ministerial Order of 30/04/1997, BOE of 14/05/1997	It regulates dietician care and nutrition. It includes metabolic diseases in the list of diseases that can be reimbursed.
Ministerial Order of 03/03/1999	It regulates oxygen therapy at home. It includes treatment using aerosol for cystic fibrosis.
Ministerial Order of 02/06/1998, BOE of 11/06/1998	Regulation of enteral nutrition at home for patients with cystic fibrosis, multiple sclerosis, scleroderma and other rare diseases.
Resolution 17/09/2004, BOE 10/11/2004	Financial support for different NGO. It includes support for the activities of Federacion Espanola de Enfermedades Raras (Rare Diseases Spanish Federation). Support renewed every year.
Regional rules	
Galicia: Law 7/2003 of 09/12/2003, BOE 19/12/2003	Healthcare Law It establishes that rare diseases patients have the right to specific healthcare programs, carried out through public healthcare centres.
Cantabria: Law 7/2002 of 10/12/2003, BOCant 18/12/2003	Healthcare Law. It guarantees, through specific programs, the coordination of healthcare for rare diseases patients
Balearic Isles: Order 11/04/2002, BOIB 23/04/2002	It establishes support for the implementation of projects managed by the Instituto Balear de Asuntos Sociales. The regional government gives priority to rare diseases when deciding which projects are financed.
Catalonia: Order 10/12/2002, DOG 19/12/2002	Cystic fibrosis: it regulates oxygen therapy at home. It includes cystic fibrosis as a Social Security service
Valencia: Order 31/07/2001, DOGV 14/08/2001	Cystic fibrosis: it regulates the creation of special units for pharmaceutical products. Cystic fibrosis considered as a priority.
Catalonia: Order 16/10/2002, DOG 29/10/2002	Multiple Sclerosis: It merges advisory committees. Responsible for criteria about pharmaceutical treatment.
Galicia: Decree 13/2005 of 03/02/2005, DOGAL 07/02/2005	Alpha-1 Antitrypsin deficiency: creation of an advisory committee Responsible for criteria about pharmaceutical treatment.
Extremadura: Resolution de 17/02/2003, DOE of 08/03/2003	Multiple Sclerosis: social projects for persons with disability. It establishes a support project for patients.
Extremadura: Resolution 21/02/2005, DOE 08/03/2005	Autism: agreement on social volunteers training. Support for a specific project
Castilla- La Mancha: Decree 138/2002 of 08/10/2002, DOCLM 11/10/2002	Autism: special education. Creation of specific educational teams for those affected
Balears: Decree 54/2001 of 06/04/2001, BOIB 12/04/2001	Autism: regulation of admission in special education centres. It includes those affected of autism among the admissible in those centres.
Basque Country: Order 24/07/1998, BOPV 31/08/1998	Autism: educative curriculum in special education It establishes an special curriculum for those affected of autism

National Rules	Measures
Navarra: Order 10/02/2003, BON 11/04/2003	Metabolic diseases: reform of newborn congenital metabolic diseases screening.
Valencia: Resolution 01/03/2000, DOGV 27/04/2000	Metabolic diseases: it regulates dietician care and nutrition.
Catalonia: non-published circular letter from the Catalan government	Cystic Fibrosis: reimbursable treatments Treatments are free, when dispensed through public hospital pharmacies
Extremadura: non-published proceeding from the regional government	Compassionate use: protocol for dispensing It regulates the use of an investigational drug for a single patient

7 ACCESSING APPROPRIATE CARE: organisation of care

7.1 Disability: are financial compensations adapted to Rare Diseases?



Rosa Sánchez de Vega, Federación Española de Enfermedades Raras (FEDER)

SPEAKER

Rare diseases patient needs are not well taken into consideration and too often poorly reimbursed.

According to Rosa Sanchez de Vega, financial compensations are not adapted to rare diseases, as medical knowledge is too limited for most of them. Rare disease patients have special needs that should be covered by the Public Health System.

In most EU countries, financial compensations are granted on the basis of the evaluation of the disability degree. If the disability degree is not well evaluated, because the doctor in charge of this evaluation does not know the disease in depth: origin, prognosis, treatment, caused impairment, acute/chronic phases, the patient will not receive sufficient financial compensations or the invalidity benefit.

She listed some of the different types of care that patients with rare diseases may need at any given time during the course of their disease. This list immediately raises the issue of the coverage by health care and social systems in the EU.

→ INTRODUCTION

1. Direct medical needs

- Hospital and office visits in a centre of expertise or other medical settings
- Biological and genetic tests, complementary examinations
- Treatment
 - Surgical
 - Medicinal products (prescription drugs & OTC)
 - Bandages
 - Creams
 - Eye drops
 - Diet and special food
- Psychological care and occupational therapy
 - Physiotherapy
 - Speech therapy
 - Alternative and adjunctive therapies
- Inpatient stay
 - Short stay, medium stay, long stay
 - Daily hospital charge
- Home hospitalisation
- Residential and long-term care centre, custodial care facility, homes, educational centre

2. Indirect medical needs

- Transport
- Adapted devices
- Wheel-chair
- Child care
- The indirect costs:
 - loss of earnings
 - lost production due to premature retirement
- Equipment and Devices
- Volunteer carers

A qualitative survey was conducted in Spain for six rare diseases (Aniridia, Ataxia, Epidermolysis bullosa, Leukodystrophy, Giant congenital naevus and Wegener granulomatosis (systemic vasculitis))

→ RESULTS

1. Aniridia

Aniridia is a congenital eye disease which causes low vision. The clinical absence of the iris is associated to severe conditions, such as cataracts, opaque cornea, glaucoma, nystagmus, macular and optic nerve hypoplasia. There is no specific treatment for aniridia.

Type of care essential to patients	Reimbursement level	Comment
Support at school and at work	Reimbursed by the National Organisation for Blind Persons	
technical/visual aids	Reimbursed by National Blind Org.	
Therapeutic colour contact lenses, sun-glasses	0%	Not an esthetical need, but a physical one to prevent the eye deterioration due to the absence of the iris.
Specific eye surgery	0%	

2. Ataxia

Ataxia is the inability to coordinate voluntary muscle movements, thus provoking unsteady movements and staggering gait. Ataxia is a heterogeneous group of disorders characterized by a slowly progressive ataxia of gait, stance and limbs, dysarthria and/or ocular-motor disorder due to cerebellar degeneration in the absence of coexisting diseases. The degenerative process can be limited to the cerebellum or may additionally involve the retina, optic nerve, ponto-medullary systems, basal ganglia, cerebral cortex, spinal tracts or peripheral nerves.

Type of care essential to patients	Reimbursement level	Comment
Life-long Physiotherapy	0%	
Technical aids	Region and income dependant	
Home ergonomics	Region and income dependant	
School & work Support	Region dependant	

3. Epidermolysis bullosa

This is a group of skin fragilities in which blisters and erosions occur either spontaneously or after mild physical trauma. There are several forms of congenital and hereditary epidermolysis bullosa as well as acquired forms. Main characteristics include profuse skin and mucous lesions, the subsequent scarring of which can produce synechia and skin or even tendinous retractions. Growth retardation can be observed and in adults, fusion of all fingers and toes into mitten-like deformity, oesophageal and anal stenosis and eye disorders are common.

Type of care essential to patients	Reimbursement level	Comment
Dermatological creams	0%	
Physiotherapy	Region and income dependant	
Bandages	Region and income dependant	
Eye drops	60%	
Special surgery	0%	

4. Leukodystrophy

The symptoms are related to a progressive demyelination of the central nervous system (CNS) (brain and/or spinal cord) and peripheral adrenal insufficiency (Addison's disease).

The first manifestations are moderate cognitive deficits, followed by progressive demyelination of the central nervous system, with diminished visual acuity, central deafness, cerebellar ataxia, hemiplegia, convulsions and dementia leading to a neurovegetative state or death within several years.

Bone-marrow transplantation, when performed at an early stage of the disease, can stabilize and even reverse cerebral demyelination in boys with the cerebral form. No other therapy (Lorenzo’s oil, immune-suppressors, and interferon-beta) has proven to be effective.

5. Giant congenital naevus

Brown spots appear at birth. It is a congenital skin disorder that covers 10 % - 90% of a baby’s skin.

Surgery is needed and usually performed in a different region or even in another member state. Related and not reimbursed extra-costs include not only specific surgery and treatment, but also travel, care, post-surgery stay, and assistance.

6. Wegener granulomatosis (wg)– systemic vasculitis

WG is a necrotising inflammation of blood vessels. Its complete form is clinically characterised by ear, nose and throat manifestations, pulmonary involvement and renal involvement. The mean age of occurrence is 45 years. WG is a severe disease that is fatal if left untreated. However, currently available treatments can control its evolution and even cure most cases of the disease, although relapses remain frequent.

7. Critical periods

Difficulties to get a right disability degree or invalidity benefit

Type of issue	Comment
Pharmaceutical treatment	Can represent 80% of minimum family income
work absence	risk of losing job
Invalidity benefit or disability degree	As disease evolves by eruption or acute episodes, disability is inconstant and assessment of disability is difficult in between two episodes

→ CONCLUSION

It is obvious that needs that are essential to patients are not available due to poor reimbursement. In addition, different reimbursement levels based on the region of residence and/or family income introduce inequity in access to care.

It was interesting to compare provisions for care reimbursement between different EU member states. To do so, a qualitative questionnaire was sent to National Rare Disease Alliances in Denmark (Rare Disorders Denmark), Germany (B.A.G.H), France (Alliance Maladies Rares), The Netherlands (VSOP), Greece (Greek Rare Disease Alliance) and Spain (Federación Española de Enfermedades Raras).

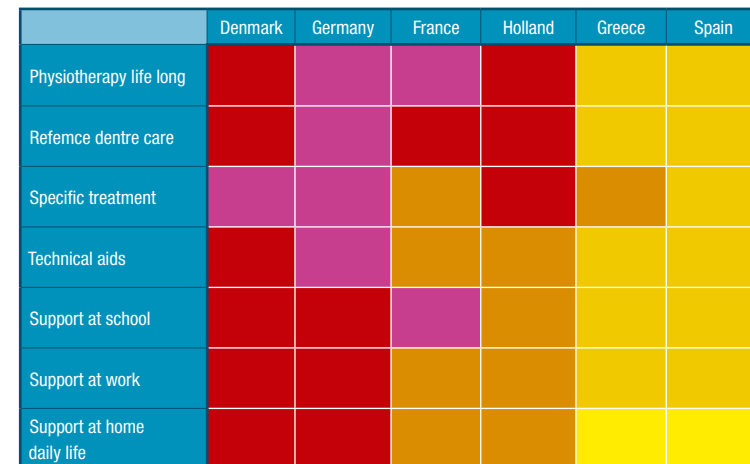
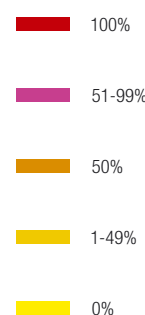


figure 28: Comparison of reimbursement for specific types of care in 5 EU member states. For each type of care, respondents indicated whether or not the type of care was reimbursed in the country, and at what level. Reimbursement levels were higher in Denmark and Germany, lower in France and in the Netherlands, and even lower in Greece and Spain.

As a general conclusion, Rosa Sanchez de Vega stated that financial compensations should neither depend on the subjective evaluation of the professional in charge of the disability report nor in the Region or EU country he/she lives.

Regionalisation of health care systems introduces a major drawback: reimbursement and thus access to care depend on where you live (in which EU member state and within member states, in which region). Family income is also a parameter that conditions access to care and equity of care.



S P E A K E R

Dr. Cornelia Zeidler, Severe Chronic Neutropenia International Registry, Medical School Hannover, Germany

7.2 Clinical networks as a response to scarcity of databases, and guidelines for best practices

To summarise what has been presented on the utility of clinical networks, Dr. Cornelia Zeidler presented the importance for patients with severe chronic neutropenia to benefit from a well organised network. The completeness of data collection is important, and sufficient patient numbers are needed for:

- Epidemiological and demographic analyses
- Increasing knowledge on the natural course of the disease
- Studying subgroups and new disorders
- Understanding pattern of inheritance index families' gene defects
- Monitoring late sequelae and concomitant symptoms
- Evaluating treatment response and outcome
- Measuring impact on quality of life

Overall, the goal remains to improve diagnosis, treatment and prognosis.

→ WHAT WAS KNOWN ABOUT SEVERE CHRONIC NEUTROPENIA IN 1980?

- Rolf Kostmann described an autosomal recessive trait with severe Neutropenia in Northern Sweden in 1956 "Morbus Kostmann"
- Absolute neutrophil counts (ANC) at diagnosis were below 500 per mm³ or even absent in the peripheral blood (normal is 1500 per mm³)
- Severe bacterial infections were frequent and might already occur during the first months of life
- Most patients died from bacterial infections during early childhood despite antibiotic treatment
- Cases of malignant transformation into leukaemia were reported in the literature
- Stem cell transplantation was the only treatment available

→ 1994: CREATION OF A REGISTRY

- First clinical trial with the haematopoietic growth factor G-CSF (granulocyte - colony stimulating factor) was initiated.
- 1994: the Severe Chronic Neutropenia International Registry (SCNIR) was established.
- 1994 – 2000: SCNIR was funded by Amgen Inc. for the collection of safety data on G-CSF (filgrastim) treatment annually reported to the FDA.
- 2000: continuing financial support was stopped after the final FDA safety report SCNIR became an independent US foundation
- Since 2000: data collection was expanded to include sub-diagnosis and to enrol untreated patients, but financial support of the European branch of Amgen was dramatically decreased.

→ THE SUPPORT OF THE EUROPEAN COMMISSION

To continue the registry, a project received support from the European Commission from 31 December 2001 to 31 December 2004 (Pro-

gramme on Community action on rare diseases Directorate - General Health & Consumer Protection).

The aims of the project were:

- To establish and expand a European network on SCN
- To improve diagnosis and therapy
- To promote the education of physicians and patients

→ EUROPEAN ENROLMENT

A total of 329 patients are now enrolled. Distribution by country as follows:

Country	Patients	Country	Patients	Country	Patients
Austria	12	Israel	11	Russia	1
Belgium	25	Italy	35	Serbia-Montenegro	2
Czech Republic	3	Luxembourg	2	Spain	19
France	6	Morocco	1	Sweden	26
Germany	128	The Netherlands	11	Switzerland	5
United Kingdom	62	Norway	13	Turkey	5
Greece	10	Poland	4		
Ireland	10	Portugal	1		

→ DATA COLLECTION: INTERNET ACCESSIBLE DATABASE PROMISE

1. Data collection on a yearly basis:

- Infectious and non-infectious events, physical assessment, treatment, pregnancy and death
- Examinations (bone marrow, cytogenetics, bone density)

2. Specific questionnaires for Leukaemia, Bone Marrow Transplantation, Pregnancy, Osteoporosis, Splenectomy, Vasculitis, Glomerulonephritis, Death

→ HOW DID ALL THIS INCREASE KNOWLEDGE ON THE DISEASE?

Through this registry, the scientific community learned that:

- Congenital neutropenia occurs in the population of all European MS
- The Incidence is approximately 2 cases per million people (0.2/100 000 inhabitants). Further epidemiological research is required.
- Different genetic disorders are summarized under the term CN:
 - recessive trait from Northern Sweden – M. Kostmann
 - consanguineous families in Southern European countries, recessive gene defect

- dominant inheritance in families from Northern European countries
- spontaneous occurrence in the majority of patients
- The genetic defects for some subgroups have been identified, but are still unknown in other subgroups of CN
- New subgroups can be identified by concomitant symptoms not known at the beginning of the registry, e. g. growth retardation, organ defects
- In the majority of patients daily G-CSF administration induces sufficient neutrophil counts, which prevent bacterial infections
- In subgroups of CN the risk for malignant transformation into leukaemia is increased by approximately 15%
- Osteopenia / osteoporosis is reported in about 30-50% of CN patients examined for bone mineral content

→ THE SUB-DIAGNOSIS THAT WAS ALSO FOLLOWED AND DOCUMENTED

1. Congenital Neutropenia

- Kostmann syndrome
- Shwachman-Diamond syndrome
- Glycogen storage disease type 1b
- Barth's syndrome
- Others

2. Cyclic Neutropenia

→ OUTCOMES: BEST PRACTICE GUIDELINES

Prerequisites :

- Knowledge on the natural course of a disease, late sequelae, treatment response and treatment related adverse events
- Sufficient patient numbers, which often cannot be achieved nationally

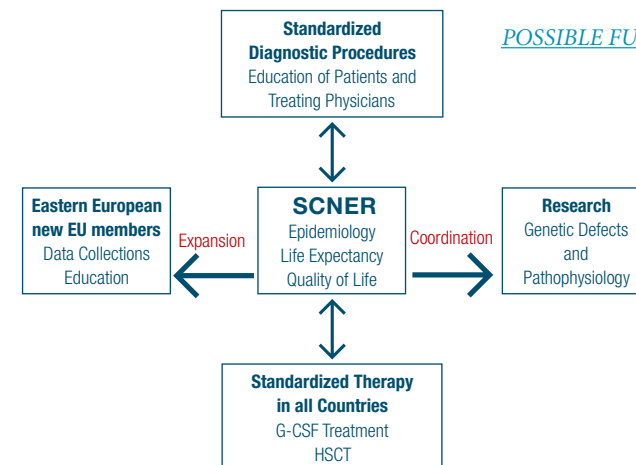
→ FOR SEVERE CONGENITAL NEUTROPENIA PATIENTS

- Different subtypes by heterogeneous patterns of inheritance and clinical phenotypes, and specific treatment recommendations
- Incidence of malignant transformation in congenital neutropenia subtypes : patients at risk are under close observation
- Outcome of treatment for leukaemia : Bone Marrow Transplantation (BMT), not chemotherapy, has become frontline therapy and a European BMT protocol was submitted to the EBMT.

13. Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Report of a Survey on 18 OECD Member Countries. www.oecdbookshop.org

→ LIMITATIONS OF A RARE DISEASE NETWORK

- Continuous financial support is required to keep up good quality of a registry:
 - Maintenance of a European database
 - Regular meetings with partners for exchange of information
 - Organisation of educational sessions and workshops
 - Publications and scientific presentations
- Rare diseases are not eligible for most of the national or international grants
- Rare disease foundations lack sufficient funds to support registries or networks continuously



POSSIBLE FUTURE ACTIVITIES (figure 29)

Future possible activities are shown below, from studies on quality of life and life expectancy, extension to other countries, to training and education programmes and research on genetic defects. Visit www.severe-chronic-neutropenia.org.

7.3 Access and availability of molecular genetic tests: uncovering the rationales for trans-border testing



Dr. Elettra Ronchi, OECD

S P E A K E R

Dr. Elettra Ronchi highlighted the difficulties and the challenges of molecular gene testing from an OECD survey published in 2005 and available on the OECD web site¹³. Although these data were collected by the OECD, the views presented at ECRD2005 represent Dr. Ronchi's interpretation of the data.

Data are available from 827 laboratories throughout 18 countries: Austria, Belgium, Canada, the Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, the United Kingdom and the United States.

→ A WORD ON THE OECD

The OECD was created in 1961 as a component of the Marshall Plan. Currently 30 countries are member countries, and 70 other, mainly from the developing world, are associates.

The OECD is a unique policy forum for economic and social policy issues on health, environment and education.

→ GENE TESTING AND RARE DISEASES

The majority of identified rare diseases are genetic conditions, genetic testing is an essential element of the diagnosis.

Table x below lists single gene conditions and gene targets for which in vitro diagnostic devices are commercially available in Europe¹⁴.

Table 30: Single gene conditions and gene targets for which in vitro diagnostic devices are commercially available in Europe .

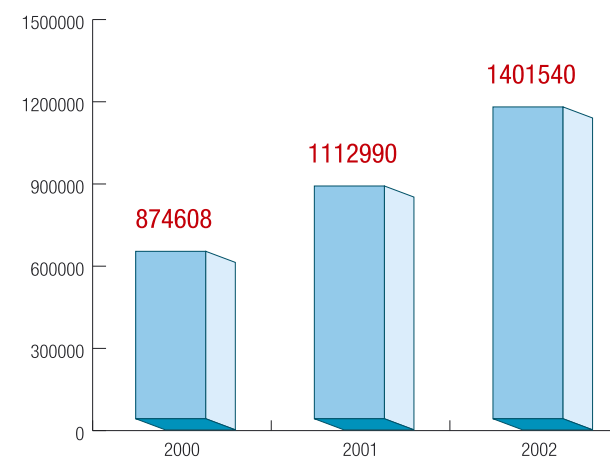
Alpha 1 antitrypsin	Multiple Endocrin Neoplasia 1
Apolipoprotein E	Methylene tetra hydro folate reductase
Blooms syndrome	Mucopolidosis IV
Breast cancer (hereditary)	Neiman-Pick disease
Canavan disease	Neurofibromatosis type 2
Charcot Marie Tooth disease	Ornithine carbamyltransferase
Colon cancer (hereditary)	Pelizaeus Merzbacher
Connexin 26	Predisposition to colorectal cancer
Cystic fibrosis	Predisposition to thrombosis
Digeorge syndrome	Protein C
Duchenne Muscular Dystrophy	Prothrombin mutation
Factor V Leiden	Retinoblastoma
Familial Dysautonomia	Rett syndrome
Fanconi Anaemia	SHOX
Fragile X	SOTOS syndrome
Gaucher disease	Spinal Muscular Atrophy
Glycogen storage disease	Tay Sachs disease
Haemochromatosis	Thiopurine methyltransferase TPMT Exon 7/10
Low Density Lipoprotein Receptor	Very High Density Lipoprotein
Marfan syndrome	Williams syndrome

More and more tests are being performed each year, as shown in figure 30. The incremental increase is +25% new tests performed each year since 2000.

More and more tests are being performed each year, as shown in figure 31. The incremental increase is of +25% new tests performed each year

14. Rob Elles, 2004.

MOLECULAR GENE TESTS PERFORMED, BY YEAR
- 18 OECD COUNTRIES (figure 31)



since 2000 (the data is derived from the number of samples accessioned/patient/year reported by laboratories).

Major findings of the survey were the considerable flow of samples across borders and the geographic disparity in availability of tests across OECD countries (see figure 31).

Geographic disparity does not seem related to differences in disease prevalence. A first major determinant is the economic context.

In 2003, 8.6% of Gross Domestic Product (GDP) was spent on average on health care across OECD countries. Public share in health expenditure

represents about 72% of the total. As all governments are adopting measures to control costs, this translates into budget cuts and controls on genetic testing.

The provisions to regulate genetic testing are very similar to those applied in other sectors of health care.

Another determinant is the absence of a clear and rational way in which governments control when potential tests are ready to move from the research phase to a clinical laboratory setting.

Finally, a contributing element is also progress in human genomics and knowledge on the genetic background of diseases. More than 10 000 genetic disorders have been catalogued by Online Mendelian Inheritance in Man (OMIM) to date, and about 1 700 of these have been ascribed to specific mutations in the human genome. The large numbers of genetic disorders, combined with the need to design diag-

Many tests are available from only one laboratory in the world. This is an accepted reality to which we need to find solutions.

nostic assays for each, precludes any one single country from offering a complete range of diagnostic tests for all known genetic conditions.

→ RESULTS/ OUTCOMES

The OECD survey confirms that rare disorder specimens are frequently sent to another country to be tested. Exchanges of samples are on going at an international level. Sixty-four per cent of respondents (529 laboratories), distributed across all the countries participating in the survey, receive specimens from outside their borders.

74% of this exchange is for rare diseases, and 24% for research purposes. More than 18 000 samples were exchanged in 2002 across the 18 participating countries.

→ KEY BARRIERS IN THIS EXCHANGE

1. There is no strategic framework for the designation of rare disease testing services internationally. This is linked to the debate on centres of reference and their criteria.
2. There is no mechanism in place to assist referrals, but only informal professional networks. Still, to ensure quality and effective availability of tests it is important to avoid unnecessary duplication of the provision of the testing.
3. No uniformly adopted funding or reimbursement mechanism.

→ CONCLUSIONS AND SOLUTIONS

- International exchange is a wide spread feature of the rare diseases testing service provision. "Internationalisation" of testing is a reality and will stay with us.
- Trans border testing involves a large majority of laboratories.
- For policy makers, one of the greatest concerns is the lack of internationally agreed Good Practice for quality assurance. When a sample reaches another laboratory in another country, it should be treated and handled with at least a comparable level of quality assurance standards.
- Efforts need to be considered to improve access, coverage and reimbursement for all tests that proved their clinical utility. But there is no shared understanding on how to assess the clinical validity and utility of a test and this is a major task at both national and international levels.

→ FINAL REMARK

The OECD is following up on this survey with the development of best practice guidelines for quality assurance in genetic testing. A public consultation on the guidelines will be launched early 2006.

7.4 Focus on Daily life



Elisabeth Wallenius, Sällsynta Diagnoser, the Swedish Association of Rare Disorders

S P E A K E R

The national association for people with rare disorders in Sweden was founded on the 7th of November 1998. The objectives of the association are to improve the quality of life of people with rare disorders, to make them heard, and to improve their situation by co-operating. To do so, Sällsynta Diagnoser launched a survey to evaluate the perceptions and impact of rare disorders in daily life.

→ THE GOALS OF THE SURVEY WERE TO MEASURE :

- the everyday situation for the members
- the scope of the problems
- what problems they face in daily life
- what similarities and differences there are between different diagnoses

A questionnaire was sent to Swedish patients, and 1660 returned it (answer rate: 60 %). Respondents represented some 30 different diagnoses.

→ CONSEQUENCES OF THE DISEASE FOR THE FAMILY

Practical and time-related consequences

Some rare diseases are enormously time-consuming, e.g. ichthyosis, a skin disorder, for which ointments are available but are time-consuming to apply, and in addition cleaning and washing up represent an important part of day time.

Time for paperwork to obtain reimbursement, telephone calls to obtain a visit or a specialised examination etc. must also be considered. Emotional, social and financial consequences were also mentioned by respondents and more research should be conducted in these fields to better document on the impact of rare diseases.

Questions for the patient himself were focusing on specialised care, rehabilitation, primary health care and dental care and explored the satisfaction for these services.

When unsatisfied, the patients reported:

- as most common reason, the physicians being unfamiliar with the diagnosis
- and finally all symptoms are considered to derive from the diagnosis, thus "nothing can be done"
- then a feeling of not being taken seriously

Again, the necessity to obtain an exact diagnosis as early as possible was stressed.

8 NATIONAL POLICIES AGAINST RARE DISEASES

Summary comparison of national plans and practices

This presentation is based on information collected thanks to a specific questionnaire elaborated by the EMEA and collected by Dr. Ségolène Aymé for the Rare Disease Task Force, and from a survey performed by the NEPHIRD project, supported by the Public Health Programme of DG Health and Consumer Protection, and coordinated by Dr. Domenica Taruscio.

The comparison of national initiatives was possible for some but not all member states: Belgium, Denmark, Estonia, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom.

No standardised definition of Rarity

Where the EU Regulation 141/2000 on Orphan Drugs defines a rare disease using the epidemiological threshold of 5/10 000, some member states use different thresholds: 1/10 000 in Sweden, 1/50 000 in the United Kingdom.

→ MAIN CHARACTERISTICS OF THE NATIONAL PLANS BY MEMBER STATES

Member state	
Belgium	<ul style="list-style-type: none"> • 8 centres for human genetics affiliated to Universities • 6 publicly funded university hospital-based units for inborn metabolic errors • National Fund for Scientific Research has a contact group on rare diseases
Denmark	<ul style="list-style-type: none"> • 11 Working Groups were set up to establish treatment programs for 11 specific rare diseases to work as models • Working group set up by the National Board of Health to produce recommendations for the organisation of diagnosis and care • Two reference centres • Reference programmes for individual rare diseases or groups of RD • Orphan Drug Committee



Dr. Domenica Taruscio,
National Centre for
Rare Diseases, Italy

S P E A K E R

Estonia	<ul style="list-style-type: none"> • Estonian Science Foundation provides research grants (approx. 40 to 50 000 over 4 years) • Neonatal DNA diagnostics, newborn screening • Annual governmental support to Patients' Association of Estonia. • Patients' organisations can apply the resources for different projects from gambling tax • Orphanet member
France	<ul style="list-style-type: none"> • National Plan for Rare Diseases 2005-2008 (see presentation by Alexandra Fourcade below)
Germany	<ul style="list-style-type: none"> • National funding scheme for rare disease research: started in 2003, 5 million euros in 2004 • Funding of 10 networks for rare diseases for an initial 3 years with possible extension after 2 years • There is also a publicly funded programme on clinical trials and innovative therapies • Orphan drugs in public database (AMIS) • German legislation on medicinal products provides for the rapid authorisation of medicinal products of major interest for public health and this also applies to medicinal products intended for the treatment of orphan diseases. • Pre - authorisation access to orphan drugs will be implemented through amendment to German drug law expected in Oct 2005
Italy	<ul style="list-style-type: none"> • 2 National Health Plans 1998-2000 and 2003-2005 • Regional Health Plans • National Network for Rare Diseases (2001-ongoing) • Agreement between the Ministry of Health and Regions (2002-ongoing) • National Committee on RD • National Research Projects for RD • International Research Projects for RD • National Research Fund for Orphan Drugs <p>The National Network for Rare Diseases, decree 279/2001, consists in:</p> <ul style="list-style-type: none"> • The implementation of prevention activities (e.g. folic acid) • The development of epidemiological surveillance • The implementation of both diagnosis and care intervention • The promotion of citizens' information and physicians' training • The National Registry for Rare Diseases at the Istituto Superiore di Sanità • About 500 RD are fully covered (diagnosis and treatment) • Several Networks of Rare Diseases (e. g. Cystic Fibrosis)

<p>The Netherlands</p>	<ul style="list-style-type: none"> • The Steering Committee on Orphan Drugs: <ul style="list-style-type: none"> ◦ established in 2001 (Minister of Health) ◦ to encourage the development of orphan drugs ◦ to improve the situation of patients with RD • Clinical reference centres: <ul style="list-style-type: none"> ◦ the 8 academic medical centres are the main clinical reference centres ◦ Also other hospitals may function as centres (e.g. 16 haemophilia centres, 1 for Gaucher and Fabry disease). • Funds from the Ministry of Health, Welfare and Sport <ul style="list-style-type: none"> ◦ to prepare a programme on RD and orphan drugs, ◦ at the Netherlands Organisation for Health Research and Development (ZonMw) (up to 250.000) • Innovation research incentives scheme (1996-2011): <ul style="list-style-type: none"> ◦ Granted projects on RD: - 7% (50 / 729 total projects) in 1998-2004 ◦ annual budget of 9-10 million Euros • Gene therapy research scheme (2005-): <ul style="list-style-type: none"> ◦ 2 projects are assigned to rare diseases ◦ budget 2 million Euros • New programme on rare diseases and orphan drugs, Ministry of Health (2005/2006): <ul style="list-style-type: none"> ◦ preparation of the programme ◦ budget 250 000 Euros • BioPartner FSG/STIGON programme: <ul style="list-style-type: none"> ◦ To establish high-tech businesses in life sciences, including medicinal products for chronic and rare diseases. ◦ Funded by several ministries and scientific institutions (budget about 9 million). • Steering Committee on Orphan Drugs grants money for rare disease research (50,000 Euros) • An orphan business developer started in 2005 to stimulate Dutch academic researchers and pharmaceutical industries to develop orphan drugs <ul style="list-style-type: none"> ◦ Project funded by the Ministry of Health for 4 years • For Information: • www.orhandrugs.nl: general information on rare diseases and orphan drugs • www.erfocentrum.nl: information on specific rare diseases • The Steering Committee on Orphan Drugs functions as an information centre for rare diseases and orphan drugs • The Dutch patient alliance VSOP started a Working group for rare diseases in 2000 and functions as a information centre for patients with a rare disease • The Stichting Fonds PGO subsidises national patient organisations, including specific and umbrella patient organisations for RD. This foundation is funded by the Ministry of Health
<p>Spain</p>	<ul style="list-style-type: none"> • Period 1999-2003 • National Agency Health Research: <ul style="list-style-type: none"> ◦ Projects ◦ RETICS (Research Networks) • Project "Special Needs on Rare Diseases" (Ministry of Social Affairs) • National Research Rare Diseases Institute (Instituto de Salud Carlos III) • European Projects • Period 2004 - ongoing • National Rare Diseases Centre (Ministry of Social Affairs) • 12 Research Networks (e.g., Fanconi anaemia) • New national strategy on Rare Diseases is under discussion • National Research Rare Diseases Institute (Instituto de Salud Carlos III) • Steering Committee on Rare Diseases (12 Networks) • List of orphan drugs available on REPIER website • National neo-natal screening programme • Directory of diagnosis centres on genetic and metabolic diseases (INERGEN website, REC-GEN) • Public and private funds to support patient organisations (FEDER) • Discussion started on centres of reference
<p>Sweden</p>	<ul style="list-style-type: none"> • Criteria for rarity: 100 / 1million (1 / 10,000) • The Swedish Research Council Medicine supports research on rare diseases (1,1 M / 2005) • Actions Nationally funded: <ul style="list-style-type: none"> ◦ The Swedish Rare Disease Information Database (Swedish National Board of Health and Welfare): information on RD, services, etc. (www.sos.se/smkh) ◦ The Swedish Information Centre for Rare Diseases Smågruppscentrum, Sahlgrenska academy, Gothenburg University (smagrupscentrum@sahlgrenska.gu.se) ◦ Ågrenska AB (www.agrenska.se): Ågrenska's newsletter; Educational projects • Measures in prevention / early diagnosis / management of Rare Diseases: <ul style="list-style-type: none"> ◦ National neonatal screening for PKU, galactosemia, congenital hypothyroidism, congenital adrenogenital hyperplasia ◦ Centres: Reference Centres listed in a National Catalogue • National coordination: <ul style="list-style-type: none"> ◦ Working party for inborn errors of metabolism (The Swedish National Association for Paediatricians) ◦ Nordic Network for Cystic Fibrosis ◦ "Sällsynta Diagnoser" (Rare diagnoses) Swedish umbrella organisation for rare diseases, associated with EURORDIS, receives support from The Swedish Board of Health and Welfare, 110 000 /year (for about 40 RD) ◦ Plus additional Patients Organisation for RD

<p>United Kingdom</p>	<ul style="list-style-type: none"> • No global category of “Rare Diseases” • Many regional initiatives, no national project • National Specialist Commissioning Advisory Group (NSCAG) scheme for reference centres for very rare diseases : <ul style="list-style-type: none"> • Definition: prevalence 1 : 50,000 or lower • Need for planning at national level • Services for 32 very rare diseases or treatments (e.g. major organ transplants) are specially funded and monitored (system has been operating for over 15 years) • Services are designated following consultation with medical profession and with patient groups and development service standards • Careful attention to five basic sets of quality monitoring, including patient satisfaction surveys and mapping of access rates from remote areas
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8.2 The Flemish model

Initiatives to improve care of rare diseases: the Flemish model
 The Centre of Human Genetics brings together different key activities:



- clinical work (department of clinical genetics)
- collaboration with patients/ carers organisations
- molecular work (cytogeneticists and molecular geneticists)
- scientific research
- teaching

→ IN SUMMARY

ACTIONS	BE	DE	DK	EE	ES	FR	IT	NL	SW	UK
National Plans / National Centres			2		X	X	X			
Nat. Networks / Nat. Registries		X			X	X	X			
Public funded structures on RD (specific RD or groups)	X		X	X	X	X	X	X	X	X
Steering Committee on RD at Ministry level						X	X			
Steering committee on Orphan Drugs			X			X	X	X		
Databases on RD				X	X	X	X	X		
Databases on Orphan drugs		X		X	X	X	(X)	X		
Research: Specific Schemes	X	X				X	X	X		
Research: RD as priority topic				X	X	X			X	
Public support to patients' organisations			X	X	X	X	X	X	X	

→ CONCLUSIONS

- Different member states, different approaches:
 - Variability of policy attitudes
 - Variable evaluation of national needs
- Many Countries have public funded structures
- Few Countries have national plans
- Scarce epidemiological data / information at EU level
- Need for targeted research schemes at EU level (E-Rare)
- National policies should give adequate attention to the role of patients organisations

→ CLINICAL ACTIVITIES



Dr. Annick Vogels,
 Centre of Human Genetics, Leuven-Belgium

S P E A K E R

The Genetic Clinic of Leuven offers a multidisciplinary-based genetic counselling service with special interest in syndromic forms of rare developmental disabilities (e.g. integrated service for 60 persons with Prader-Willi syndrome, over 200 individuals with 22q11 deletion syndrome). This service was created twenty years ago. This Genetic Clinic is a meeting place for all those interested in rare genetic diseases. The Centre for Human Genetics of Leuven provides a place for all disciplines with a shared interest in rare genetic diseases and enables them to meet and work together and includes genetic scientists, health professionals, molecular scientists, psychologists, nurses and social workers. It brings together those interested in the clinical, ethical and social aspects of rare genetic diseases

→ RESEARCH ACTIVITIES

The Department of Clinical Genetics of the Centre for Human Genetics is an international authority in:

- The identification of new malformation syndromes (dysmorphology)
- The identification of genes involved in the pathogenesis of congenital malformations, mental retardation (mainly X-linked forms) and developmental disabilities in general (mainly autism).

→ TEACHING / EDUCATION

The centre promotes teaching and research in the field of rare genetic diseases through training of doctoral and postdoctoral students, genetic education of health professionals, seminars, meetings, reports and papers

→ EXAMPLE OF HOW THE CENTRE FUNCTIONS

The Velo-Cardio-Facial syndrome: a multidisciplinary approach

The approach at the centre is centred on the patient himself: for this genetic disease, the geneticist is the referent specialist in close contact with the patient.

Then a first circle of other specialised doctors participate in care: a cardiologist, an oto-rhino-laryngologist, a speech therapist, and a psychologist. On an as needed basis, a second circle of health care professionals can also intervene: an orthopaedist, a child psychiatrist, a physiotherapist or an endocrinologist.

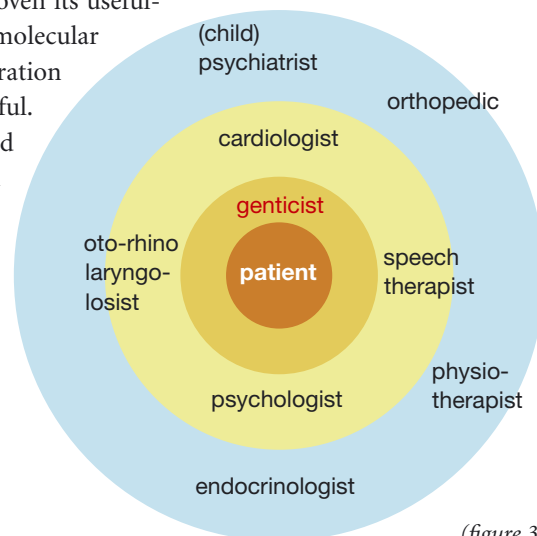
As a complement to the clinical management, the centre also offers other services:

- Group sessions for parents and carers (diet, physical health, emotional issues, behavioural problems, update on scientific research...) and for children (diet, education, emotional issues)
- Visit to the school or institution
- Collaboration with the parent's association (day to day problems, meetings, research, information)

The same approach is organised for some other diseases: Fragile-X syndrome, Williams syndrome, Prader Willi syndrome, Neurofibromatosis, Myotonic Dystrophy, Smith Magenis Syndrome, Turner Syndrome, Angelman syndrome, and Rett syndrome.

→ CONCLUSION

The integration of care, research and other services useful to patients and carers in the same facility has proven its usefulness. The interaction of clinical work, molecular work, research, teaching and collaboration with the parent's association is fruitful. Patients are satisfied and diagnosed early: during the last twenty years, all children with Prader Willi syndrome have been diagnosed excepting for one before the age of 2 years in Belgium and their weight is well controlled.



(figure 32)

8.3 Centres of reference in Denmark

Centres of reference are only a part of the overall health care organisation, but they are an important one. They are part of the puzzle, amongst many other institutions.

In 1993, the Danish board of health initiated a report on how to best organise care for rare diseases.

From 1994 to 1996, 11 working groups were set up to establish state-of-the-art treatment programmes for 11 specific diseases to work on as models. From this reflection, state-of-the-art guidelines were produced:

- Best practice on diagnosis, treatment and care monitoring
- Data collection, scientific knowledge, and coordination.
- Description of social, psychological, educational and occupational problems were also included

In 1997, a working group was set up by the National Board of Health with the mandate to make recommendations on the future organisation of diagnosis and treatment of rare diseases. Health care professionals and patients representatives composed the working group.

→ THESE RECOMMENDATIONS INCLUDED :

1. The establishment of two centres for rare diseases, one in Eastern Denmark and one in Western Denmark
2. The development of state-of-the-art reference programmes for specific rare diseases or for classes of rare diseases

3. A distribution of responsibilities between centres of reference and regional/local hospitals:

- Regional hospitals
 - Primary contact, preliminary diagnosis, referral to centre of reference
 - Monitoring the patients (especially children) as far as the overall growth and health status is concerned, including contact with the local social and educational authorities
 - Carrying out the regular check-ups
 - Acute problems
 - Contact with the family doctor
- Centres of Reference
 - Specialised diagnosis, treatment and monitoring
 - Overall planning and monitoring of the patient's treatment
 - Coordination of the action taken by the various specialities in a multidisciplinary team function as well as the coordination between the central level and the regional level
 - Counselling including genetic counselling



Torben Grønnebak,
President of Rare Disorders, Denmark

SPEAKER

- Collection, registration and dissemination of knowledge for diagnosis and treatment
- Research and development, quality development, training
- Development of reference programmes for other diseases
- International cooperation

Some of these respective responsibilities still need further clarification :

- Who is responsible for the overall care management (diagnosis, treatment, contents and timing of check-ups, etc.)?
- Who is responsible for the coordination of care?

→ THE SITUATION TODAY IN DENMARK

1. Denmark has two centres of reference (the Centre for rare diseases at Aarhus University Hospital, the Clinic for rare disorders at the Copenhagen University Hospital). There are remaining issues, as not all problems were solved as soon as the centres were created : in 2003 Rare Disorders Denmark carried out a survey among 900 people suffering from rare disorders. Patients from 24 organisations took part and the response rate was 71 per cent. It investigated the scope of health care offered to patients with rare disorders and their overall satisfaction with their course of treatment

2. Positive results were described by respondents: patient satisfaction was higher when they were treated at one of the two centres.

- Individual action plans improved patient satisfaction
- Coordination and coherence were considered as extremely important
- The coherence in care management needed a personal coordinator

3. And less positive outcomes were also mentioned :

- Reference programs still only exist for 11 diseases
- Agreements between centres and regional authorities do not exist
- No regional coordinators have been assigned
- Only a small percentage of the rare patients have an individualised action plan

→ CONCLUSIONS

- It has taken nine years to establish a report
- The report can be copied as it is and can apply to other national situations with few modifications as writing another report would take even more time!

- Government bodies have not surveyed the implementation process
- The management on the two University hospitals where the centres are placed have paid no attention to report requests
- Personnel at the centres should be better trained: there is room for improvement in coordination of care, planning, dialogue with local doctors
- Patient organisations have not been given any formalised role in the implementation process
- It is like bringing up children, small children need constant attention every day, every minute....

8.4 A key action of the French National Plan for Rare Diseases 2005 – 2008

Care management of rare diseases is one of the 5 national strategic plans selected from the public health law adopted in France in August 2004 (other priorities were Cancer, Road safety and Accident Prevention Policy, Handicap, and Environmental Health). Objective n°90: « to ensure equality in the access to diagnosis, treatment and provision of care ». Project management by the Ministry of Health including: patients' organisations, health professional and scientific representatives, national and private health insurances, and the Ministry of Research.



Dr. Alexandra Fourcade,
Department
for Health Care
Organisation, Ministry
of Health

S P E A K E R

- A lack of knowledge and information of health professionals and patients responsible for inaccurate diagnoses
- No global strategy for rare diseases health care: clinical pathways based on individual choice rather than organised specialised pathways.
- Differences in the reimbursement, compensation and access to medical products.....
- Lack of epidemiological surveillance of these diseases
- Ongoing inventory of current research projects (Scientific Interest Group, Pr A. FISCHER).
- Lack of adaptation between therapeutic innovations and their funding (Hospital Funding Reform).

→ STRATEGY

- Health care organisation (Pr. L.GUILLEVIN, Hôpital Cochin, - Cochin Hospital, Paris)
- Information, Education (Dr S.AYME, ORPHANET)

- Research (Pr. A. FISCHER, GIS - Institut des maladies rares – Institute for Rare Diseases)
- Epidemiological surveillance (Dr. J. BLOCH, INVS)
- Screening strategies (Pr. D. SICARD, National Committee on Ethics)
- Social and psychological support and access to medical products (Alliance Maladies Rares, Eurodis)

→ 10 AXES

- Increase knowledge of the epidemiology of rare diseases
- Acknowledge the specificity of rare diseases (registration on the list of long term illnesses)
- Improve information for patients, health professionals and the public
- Improve training of health care professionals
- Organise screening and access to diagnostic tests
- Improve access to health care
- systems and quality of care
- Keep up the Orphan Medicinal Product (OMP) development efforts
- Answer specific patient's needs in reforms for the handicapped
- Improve dynamic research and innovation
- Improve development of national and European partnerships

→ FUNDING

Priority 1 Increase knowledge of the epidemiology of rare diseases	2 million €
Priority 2 Acknowledge the specificity of rare diseases (registration on the list of chronologic long term disorders)	
Priority 3 Develop information for patients, health professionals and the general public concerning rare diseases	3.2 million €
Priority 4 Train health care professionals to better indentify them	0.4 million €
Priority 5 Organise screening and access to diagnostic tests	20 million €

Priority 6 Improve access to the health care system and to quality health care	30 million €
Priority 7 Keep up with Orphan Medicinal Product (OMP) development efforts	22.5 million €
Priority 8 Respond to the specific needs of rare diseases patients	0.6 million €
Priority 9 Promote the advancement of research and innovation	20 million €
Priority 10 Develop national and European partnerships	0.16 million €
TOTAL	98.86 million €

→ CENTRES OF REFERENCE

- Organise health care around a few “labelled centres of reference” :
- Leading centres networking with other points of care, including sanitary and social support,
- Leading centres for scientific expertise (clinical research, evidence-based medicine.)
- 18 groups of rare diseases selected by an expert committee,
- 90 to 100 “labelled centres of reference” by the end of the plan.
- Centres of expertise for one rare disease or a group of rare diseases,
- Sub national, national or European level.

1. Missions

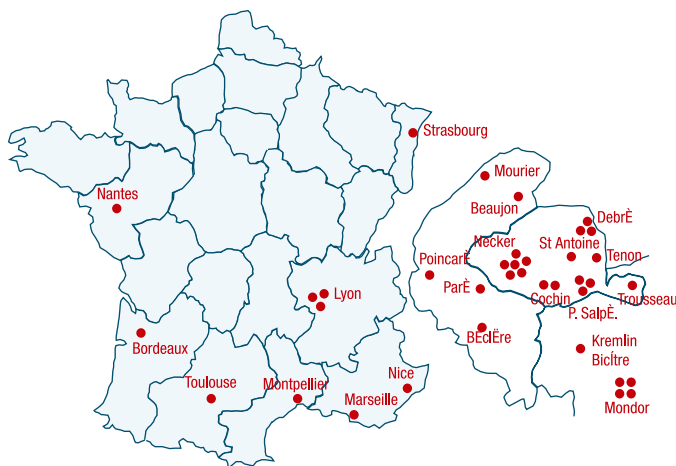
- Second opinion to establish or confirm diagnosis,
- Production and circulation of clinical and organisational guidelines,
- Information and education of health professional's patients and their families,
- Research and epidemiological surveillance,
- Coordination of sanitary and social networks.

2. Evaluation criteria

- Activity (number of patients) health professionals, networks.)
- Organisation of the medical management process
 - Multidiscipline, expertise,
 - Prescription and follow-up of high cost Orphan Medicinal Products,
 - Technological platform (highly specialised biological tests, molecular biology)
 - Network coordination
 - Information / training (patients, health professionals, networks.)
- Research :
 - publications
 - funded clinical and research projects
- Production of good practice guidelines
- Epidemiological surveillance, development of relevant health indicators.

3. Selected centres: no geographical criteria

Figure 33: centres of reference for rare diseases management situated at university hospitals



4. Rare diseases selected

- One extremely rare disease : Ondine's syndrome (1 national accredited centre of reference)
- Or neuromuscular diseases : 2 centres accredited in 2004. About 10 by the end of the plan.

→ **CONCLUSIONS** : Rare disease labelled centres

- an opportunity to implement a clinical pathway for patients and their families,
- a place for the definition and production of clinical and organisational guidelines,
- a place for the initial prescription of orphan drugs,
- An expert network on rare diseases to advise the National Health Insurance Scheme in France.

8.5 Reference centre in Bulgaria

Importance of reference centres as promoters of rare diseases awareness in Europe

The number of specialised centres for rare diseases in Europe is extremely limited; however their impact on public health is enormous:

- They provide patients, relatives and doctors with up-to-date high-quality information about the disease.
- They develop databases of hospital settings, genetic and clinical laboratories and prominent medical teams.
- They provide information on the epidemiology of rare diseases.
- They serve as a bridge between the patients and the public health care systems by advocating for the right to receive quality care.

The Information Centre for Rare Diseases and Orphan Drugs in Bulgaria was created in October 2004. It is the first in Eastern Europe, operates in Bulgarian and English languages and provides free information to patients, relatives and medical professionals. ICRDOD is building databases of doctors, associations, clinical centres and teams, building databases of patients with rare diseases, thus facilitating the contacts for establishing self-support groups, lobbying for adequate national health policy for rare diseases, national and international collaboration and networking.

An expert group submitted an official proposal to the Bulgarian Ministry of Health for establishment of National program for rare diseases and orphan drugs.

Together with the Foundation for Prevention and Treatment of Fatal Angioedematous Disease (Hungary), organised the First Workshop on Hereditary Angioedema (HAE) in Bulgaria. As a result, a HAE centre was established, immunological tests donated, several clinicians were trained in order to increase the quality of healthcare.

The first Eastern European Conference on Rare Diseases and Orphan Drugs was organised in Plovdiv, May 27th 2005, to raise governmental and public awareness in Eastern Europe on rare diseases and orphan drugs.

14 speakers, 132 registrations, 97 attendees (representatives from academies (73%), government (14%), patient associations (8%) and industry (5%)) attended the conference. The Union of Bulgarian Philatelists issued a jubilee first day cover and a special postmark.

Such an event is important to increase awareness on rare diseases. This conference had a great impact in the public opinion.

Poster 1,
Dr. Rumen Stefanov,
MD, PhD, Information
Centre for Rare Diseases
and Orphan Drugs
(ICRDOD), Bulgaria.

Centre of reference
Hereditary Angio-oedema

In conclusion, the creation of centres for rare diseases in each member state should be encouraged, because member states are very different (in respect to healthcare system, language, economical status, traditions etc.) and a unified approach at European level is difficult.

8.6 Regionalisation of the health care system in Spain

The authors explored the consequences of regionalisation in access to care.

The 1978 Spanish Constitution establishes in its Article 2 the acknowledgement of the autonomy of the regions. Article 148 lists the competences that Autonomous Communities may exercise, among them Health. Article 149, paragraph 16 defines the exclusive competences of the State for health: “Foreign health, basis and general co-ordination of health; legislation on pharmaceutical products.”

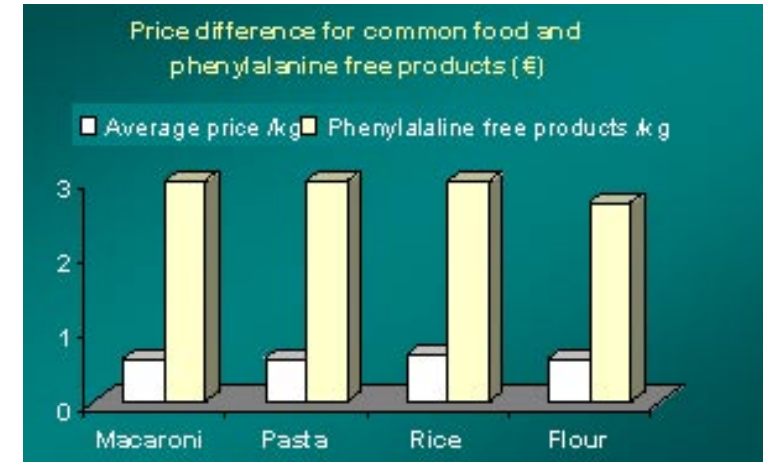
In the case of phenyl-ketonia as an example of the consequence of regionalisation of health care, early detection in newborn is essential in order to prevent the further development of complications, including severe mental retardation and brain damage, mental illness, seizures and tremors, and cognitive problem. A specific diet protein restriction can be established since the first days of life as a secondary prevention (patients require phenylalanine free products).

This adapted diet is not a pharmaceutical product per se, therefore it is not the competence of the central state. Still, phenylalanine free products are much more expensive than common products (see figure 34). Products specially manufactured with a reduced content in Phenylalanine have an extra cost that causes an economic impact for the families. Thus availability and access (reimbursement) vary from one region to the other.

Different regions in Spain have different schemes for the distribution of such products: cooperative-like pharmacy, partial reimbursement or not... Even when products are available at cost price, they remain more expensive than common products.

Poster 57,
Cristina Salinas,
Facultad de Farmacia,
Universidad de Barcelona.

Figure 34: cost of four phenylalanine free products compared to usual products.



8.7 Organisation of care for children in Luxembourg

Therapeutic intervention at preschool and at school in Luxembourg

Liz Gondoin-Goedert explained how social care for children with a rare disease is organised in Luxembourg. Once the evaluation of a child's problems has been made in hospital, his/her parents contact a support group or social worker, who informs them about their rights. These rights include a doubling of family allowance (financial compensation), in certain situations the parents can obtain a supplementary period of days off, or a possibility of tax reduction.

→ EARLY MEDICAL INTERVENTION FOR CHILDREN IN LUXEMBOURG

Children can stay for a certain time at hospital, where early intervention can begin.

When he/she comes back home, a team from a medical organisation (hospital, centre for rehabilitation, or association for early intervention) takes responsibility for the child.

At the age of 4 years, the child will be enrolled into an educational organisation.

Many services are available for these children: There are several services responsible for children with special needs during early childhood. There are services for functional or pedagogical therapy.



Liz Gondoin-Goedert, President of the "Association Luxembourgeoise pour les personnes Atteintes de maladies Neuromusculaires et de maladies rares" ALAN asbl

SPEAKER

Early therapy is a method of systematised apprenticeship where the development of different functions like mobility, perception and communication through language and thinking, are learned and trained step by step, in sequences defined in a therapy program

- The Service for Preschool Therapy and Help for Children
- The Service for Ortho-pedagogic Preschool Intervention (SIPO)
- Study and Help Group for Child Development (GEADE)
- Service for Preschool Education of the Speech Therapy Centre
- Ambulant Services for Early Therapeutic Intervention at school (SREA)

Importantly, early therapy is proposed to these children.

1. The service of preschool therapy gathers different specialists (doctors and paramedical staff: pediatricians, physiotherapists, speech therapists, occupational therapists, pedagogues and psychologists) responsible for babies and children from 0-4 years, presenting one or more problems of:

- Motor difficulties
- Sensorial difficulties
- Behavioral difficulties
- Developmental difficulties
- Communication and language problems
- Problems of deglutition

2. The aim of the Ortho-pedagogic Preschool Intervention Service, created in 1980, is to offer to babies and young children with motor deficiencies or retarded children, a pedagogical stimulation within the family. Early intervention is for children (from 0 – 4 years), showing developmental problems or deficiencies in one or more fields (motility, behaviour, language, perception).

3. Another service is the Study and Help Group for Child Development. The aim of this service is to reduce and improve as early as possible (between 0 and 4 years) developmental problems related to social and family environment: information - services operate for any questions concerning a problem of a young child, and game-groups with educational animation are offered.

4. The Service for Preschool Education of the Speech Therapy Centre is designated to children from 2 - 4 years and focusing upon speech and / or hearing problems.

5. The Ambulant Services of Early Therapeutic Intervention at school (SREA) co-operates with different services of early intervention. The

ambulant service takes place at the moment when a child enters school. It determines whether or not the child has the potential to follow the school programme.

With this service, a child can be taken in charge between 3 to 12 hours a week.

- for educational support
- for pedagogical support
- to foster the child's integration into school

The aim of this service is to help children to continue normal school education (from preschool to college).

Children who need paramedical care, need to empty the bladder, to clean tubes etc. can obtain adapted interventions during school breaks.

Physiotherapist groups offer their service for children at school, but they will need the permission of intervention from the teacher, the headmaster or the mayor of the village or town.

Physiotherapists can also offer their services to nurseries if the following interventions are necessary: respiratory therapy, therapy for Plexus Facialis children, and therapy for children with neuromuscular diseases.

→ FINANCIAL ASPECTS

In general, the associations have signed a contract with the Luxembourg State, and by that convention most of the offered services are financially covered.

→ SPECIALISED DEVICES AND MEDICAL EQUIPMENT

Cases where patients are confronted with a large offer of specialised medical equipment are numerous (neighbouring countries provide a large choice). However even their doctor is not always aware of the enormous choice.

Once new equipment is chosen, patients are confronted with the difficulties of refunding if the device is not covered by insurance.

Even if health insurance systems are very open to integrate new inventions and techniques when they have proven their utility for the patient, it takes the lengthy time of administrative procedure before the device will figure in the official catalogue of reimbursed devices.

The role of a patient organisation is important here, as the organisation is helping families for the administrative burden they have to go through to obtain the medical devices they need and then to be refunded for the purchasing of the device.

→ CONCLUSIONS

In general, we would wish that all the other services would get together to foster treatment intervention at school, during lunch breaks or during sport lessons.

It is very important to help these children to develop a normal social life and to be able to participate in free time activities like other children.

We would wish that more if not all schools would participate in this program.

8.8 Veneto region: The Italian law 279/2001

→ INTRODUCTION

The Italian law 279/2001 created a special regime of benefits for patients affected by rare diseases. According to this regulation, the Italian regions have the responsibility to create a hospital network for patients affected by a rare disease, using the existing structures of proven excellence for care and research.

Since 2000, the Veneto Region - North East of Italy, 4.5 millions inhabitants, implemented an area-based monitoring system for rare diseases. This system is providing:

- Specific treatments and care for rare disease patients, based on a network of health services, each one specific to a particular group of rare diseases
- Free-of-charge diagnostic tools, orphan drugs and other pharmaceutical products
- Information system connecting hospitals, local health districts, pharmacies, 3 500 general practitioners, paediatricians with an on-line patient's clinical record
- Services supplied directly at patient's home
- Epidemiological data useful for policy makers to health planning and evaluation processes.



Poster 116,
Paola Facchin,
Epidemiology and
Community Medicine Unit,
Department of Paediatrics,
University of Padua

→ THE SYSTEM

1. Technological framework.

Located in the university-hospitals and in the regional ones, the selected centres for Rare Disorders are connected by an Intranet to 55 local health districts, pharmaceutical services and 3,500 general practitioners, and they populate a unique central Oracle database through a 3-levels architecture with a web-browser Java application.

2. Information contents, flows & management

All collected data are patient-centred. Each newly identified patient is recorded into the system by diagnosis and certification of his/her disease. This is the starting point of his/her health clinical record. In real time, information about clinical and management plan defined by the centre of excellence, and all other clinical data, are immediately available for the health districts, the general practitioners and for the patient, through a specific individual key-code. Drugs and dietetic products prescriptions are sent to patients directly at home. All the information collected is stratified increasing the knowledge on rare disorders natural history.

→ ACTIVITY

From 2000 to October 2004:

- 4.5 million inhabitants monitored
- 8 961 patients recorded
- 8 012 health clinical records (and treatment plans) available on-line
- 4 234 drugs/dietetic-products prescriptions

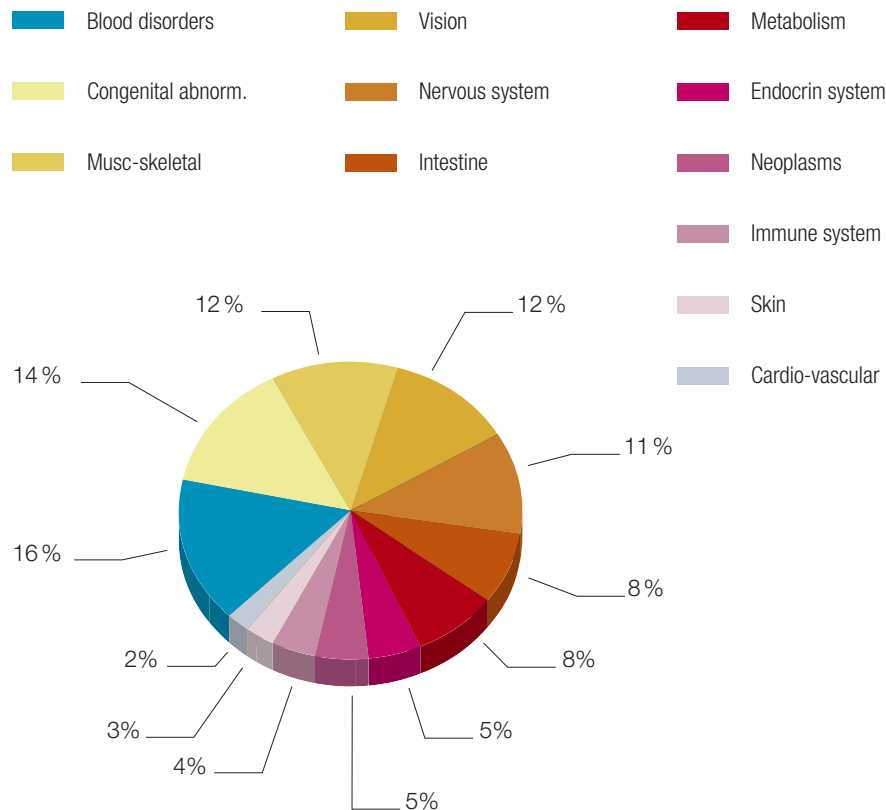
The age distribution of the 8,961 certified patients, shown in fig. 1, ranged from few days of life to 96 years of age, with two peaks: from 5 to 9 years of age (10% of the certified patients), and from 25 to 39 (25%). The mean age at certification is 33 years. Paediatric patients (0-18 yrs) represent 30.2% of all patients with a rare disorder recorded in the register.

From October 2004 up until now, with the creation of the Wide Area (WA) dedicated to rare diseases (inclusion of the Friuli Venezia Giulia Region and Trentino Alto Adige Region (Trento & Bolzano Provinces):

- 7 million inhabitants monitored
- 14 141 patients recorded

DISTRIBUTION OF DISEASES

9000 rare disease patients-Veneto region 2001-2004 (Figure 35)



Participants at the conference

Poster 8,
Philippe Juvin, Nicole
Lhermitte, Gérald
Genthon-Troncy

9 PATIENT NETWORKS

9.1 Living with a Rare Disease

importance of the role played by an association

AMSN (Association des Malades atteints du Syndrome Néphrotique)

→ IDIOPATHIC NEPHROTIC SYNDROME

Idiopathic Nephrotic Syndrome (NS) is characterised by massive proteinuria. The prevalence is about of 16/100 000 in children and probably less in adults. The cause of idiopathic nephrotic syndrome remains unknown, but evidence suggests it may be a primary T-cell disorder that leads to glomerular podocyte dysfunction. Genetic studies in children with familial nephrotic syndrome have identified mutations in genes that encode important podocyte proteins.

→ TREATMENT

In order to avoid the dramatic effects of proteinuria, drugs used in the treatment of nephrotic syndrome include corticosteroids, levamisole, cyclophosphamide, mofetil and cyclosporine. The response to corticosteroids correlates with the histologic type of nephrotic syndrome. Those medications have heavy consequences. Complications of high dosage corticosteroid treatment include obesity; retarded growth and increased susceptibility to infections, hypertension, osteoporosis, cataracts and diabetes mellitus.

→ AMSN OBJECTIVES

The association was created in January 2003 with the objective of:

- Breaking the NS patient's isolation and putting them in contact with each other.
- Acting together to improve treatments and support research.
- Enabling dialogue and providing information centres for the constraints and secondary effects of the treatments

→ AMSN PROJECTS

- An information leaflet to be released in nephrology units
- NS research facilitation (funding, prizes)
- A practical booklet for the families

- Actions with authorities and laboratories for NS medication to be recognised and costs reimbursed (e.g. growth hormone effective against impaired growth in children due to corticosteroids)
- Vigilance against the abandonment of low profitability products like levamisole.
- An annual information meeting between families and doctors, researchers

10 TRAINING AND INFORMATION

10.1 Best practice guidelines for care and management

help-lines and written information

When parents and patients are going through the experience of a rare disease, there is important information they need immediately:

- on the accuracy of the diagnosis, reference are to be found,
- whether any research is being done,
- where specialists or centres of excellence / centres of
- what treatment options there are,
- what the future may hold.



SPEAKER

Lesley Greene, Climb National Information and Advice Centre for Metabolic Diseases

→ WHO NEEDS TO KNOW?

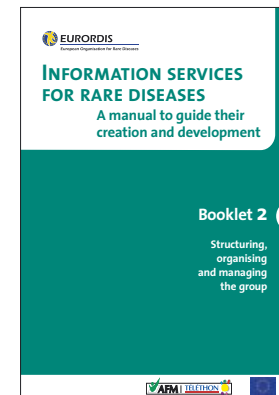
Patients and parents differ by the rare and ultra rare conditions, different cultures and languages, geographic localisation, etc.

In order to survey the needs for information, Eurodis launched a project in 2003, the PARD3 project, with the support the Rare Disease Programme of Directorate C “Public Health and Risk Assessment” & AFM (Association Française Contre les Myopathies –French Association for Muscular Dystrophy).

→ THE PARD SURVEY

Programme and Actions for Rare Diseases (PARD 3) consisted in:

- A Qualitative Survey interviewing 31 associations
- A Quantitative Survey: analysis of 372 questionnaires returned from 18 countries, an overview of needs, information sources, tools, services and expectations



(figure 36)

Two solutions were brought forward:

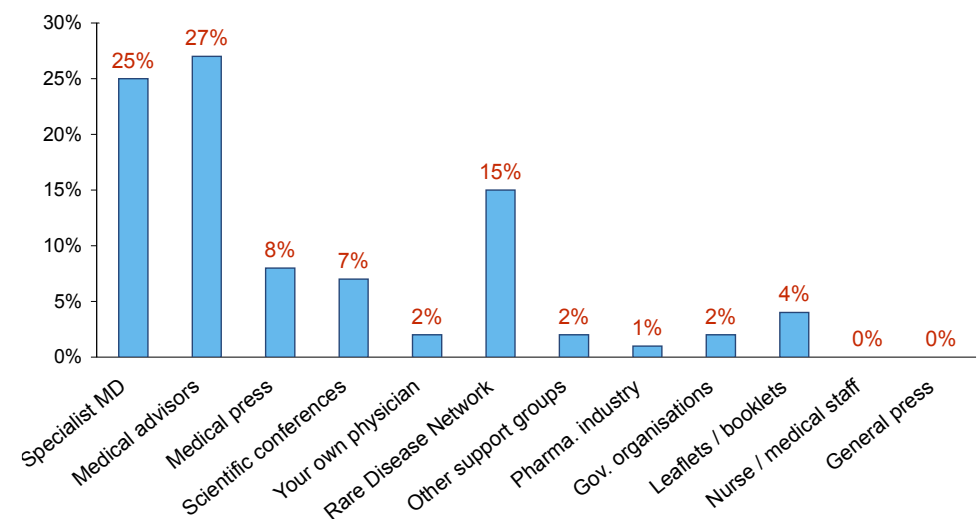
→ **SOLUTION ONE : A MANUAL AND GUIDELINES** (see figure 36)

One of the main objectives was to identify the knowledge base for help-lines. There were two main sources: a specialised doctor, and medical advisors. The rare disease network came next (see figure 37). Web sites were only fourth. “Own physician” and “Governmental organisations” were poor information providers for rare diseases: this demonstrates to what extent the rare disease community is lacking in information.

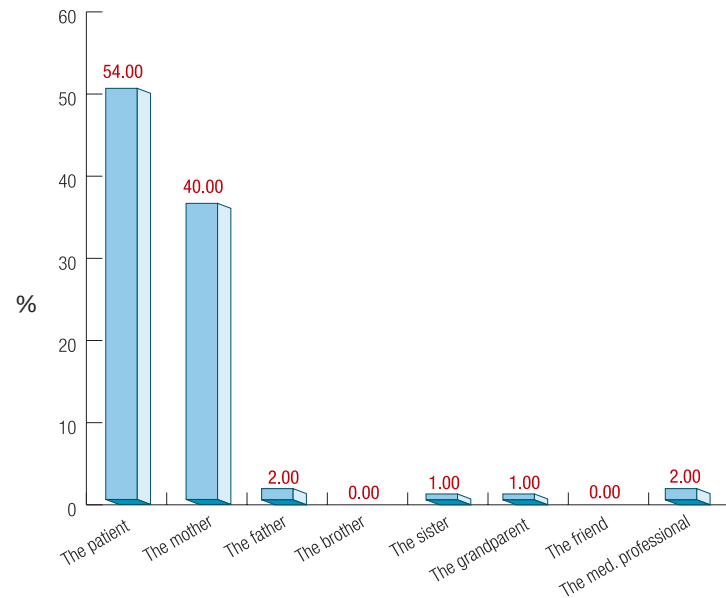
1. Sources of funding

The survey also explored funding sources for services: organisations mainly relied on member and private donors, followed by fundraising events. Private and public administrations represented secondary sources for funding. Countries with regional governments (Spain, Italy) expected the region to be the funding source, and where support for research by groups was greater (Western Europe), industry might have funded more. Governmental organisations and European institutions were a long way down the list. Fragile sources of funding means that any service is going to have problems with consistency in being able to continue to work effectively.

MAIN SOURCES OF INFORMATION (figure 37)



PERSONS WHO ASK FOR INFORMATION (figure 38)



2. Quality of helplines

Another important aspect was to assess how quality of help-lines was achieved and monitored. 63% of help lines used volunteers, and for 81% of help-lines the service was in a confidential area. 86% kept track of the enquirer so they do develop a relationship with the enquirers.

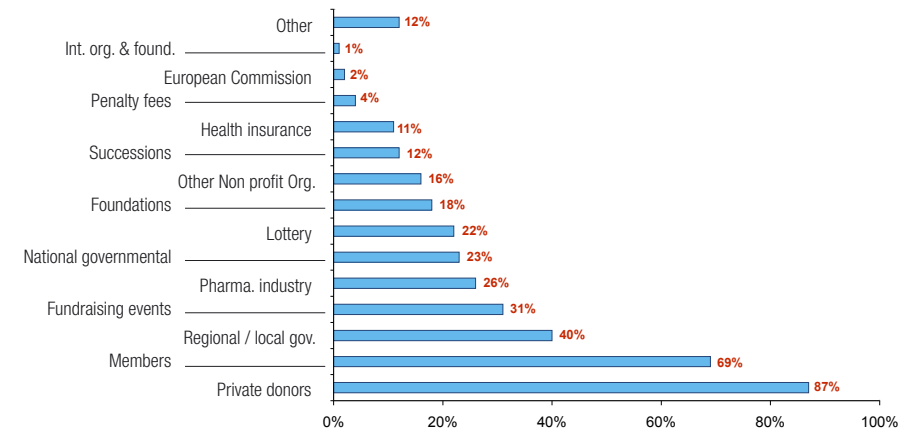
3. Who are the persons who ask for information?

Patients themselves are actively searching for information: they represented 54% of enquiries, even though rare diseases are often disabling. There was a clear difference between mother and father: roles are distributed between the mother as the carer and the father as a source of income for the family. Fathers may sometimes refuse to acknowledge the disease.

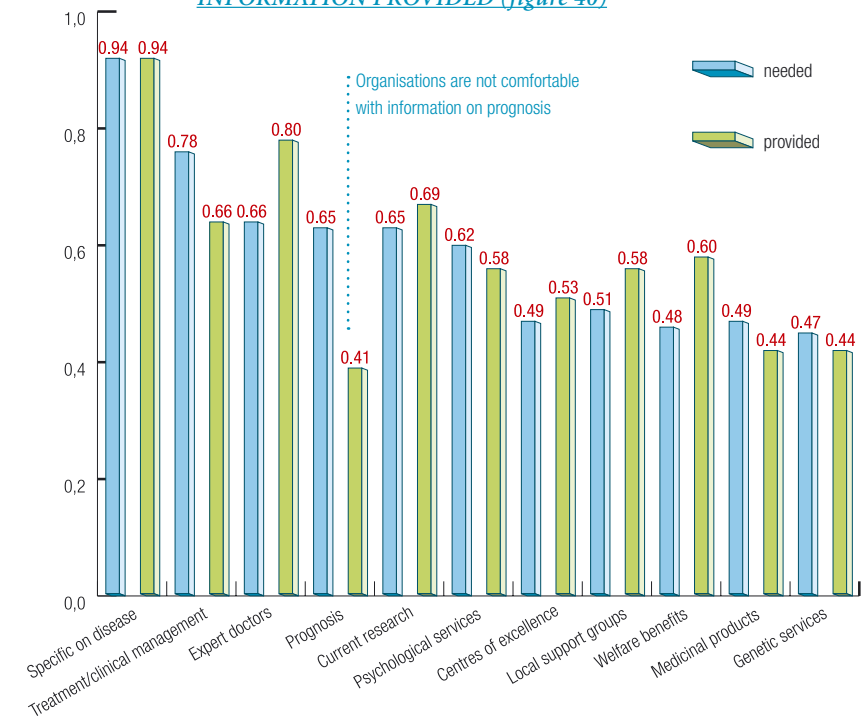
4. To what extent were the help lines accessible?

Help lines run at home by unpaid people are available 24 hours per day seven days a week. Once you get paid staff in, probably because the help lines develop the e-force (web site, etc.), then help lines operate at office time.

SOURCES OF FUNDING: percentage of organisations quoting source (figure 39)



INFORMATION NEEDED COMPARED TO INFORMATION PROVIDED (figure 40)



5. To what extent were the needs of the enquirers met?

Overall the needs of the enquirers were met, and the help lines were able to give the information needed. The organisations showed reluctance to discuss or reveal information on prognosis.

6. What is the impact of lack of information?

The very negative impacts of the lack of information are listed below:

Type of impact	Mentioned by % of respondents
Isolation/inappropriate care	63%
Wrong decision making	59%
Frustration	58%
Powerlessness	49%
Fear	48%
Insufficient financial support	36%
Anger	32%

7. Conclusions

Help lines and written information are the main services provided by patient organisations with patient and mother as primary users.

To ensure quality of help lines, the following requirements were agreed on:

- Volunteers and paid staff need to be trained and the delivery monitored and evaluated
- Help lines need to develop a common tool
- Mature services can mentor developing ones
- The funding base needs to be supported by governments and the EC for stability and continuity

To ensure access to help lines:

- Patient groups, as the most reliable source of information, need to increase networking
- Interested professionals need a central source to which they can refer with confidence
- Leaflets need to be uniform, high quality, in a language appropriate to users in each region (also appropriate to the level of education)
- Websites need to be user-friendly and linked to each other for maximum delivery

→ SOLUTION TWO : A NEW EURODIS INITIATIVE, THE RAPSOODY PROJECT

Rhapsody: Rare Disease Patient Solidarity (project submitted for the 2005 call for proposals, EC public health programme).

This project aims at improving access and quality of essential services at EU level. Within this project, a concerted action for rare disease help lines in Europe (CARHE) is planned.

- It will establish an EU network of rare disease help lines (paid and unpaid)
- It will develop standardised tools for collection of profiles

- It will give pilot training for helpline advisors
- It will build a European Observatory to collect process and record data
- And it will develop a system of identifying and networking very isolated patients

10.2 Internet resources for the rare disease community

Internet is a powerful tool, both to disseminate information To all stakeholders, with potent tools to adapt it, so that global outreach can become very large.

It also creates virtual networks

- To end isolation
- To promote collaboration
- To create communities

→ INTERNET NETWORKS

From 1997 to 2004, DG Health and Consumer Protection Directorate-General has supported networks that largely use internet as a communication tool. To mention a few ones that could not function without Internet:

- Rare pulmonary diseases: set up of diagnostic criteria and reference / training centre (Prof. Popper, Austria)
- Information network for immune-deficiencies (Prof. Vihinen, Finland)
- Euromusclenet: muscle diseases as a prototype of rare and disabling disorders: creation of a European information network (Prof. Spuler, Germany)
- Severe Chronic Neutropenia: European network on the epidemiology, pathophysiology and treatment
- (Dr Schwinger, Germany)
- Paediatric rheumatic diseases: a European information network (Prof.. Martini, Italy)
- Transfer of expertise on rare metabolic diseases in adults (Prof. de Valk, NLD)
- Rare congenital anaemia: European information network (Prof. Vives Corrons, Spain)
- Charge association and Usher syndrome in Europe (Mr. Hawkes, UK)
- Rare forms of dementia (Alzheimer Europe)

All projects run by health professionals included more or less the same type of approach:

- Production of information for patients and health care professionals
- Directory of services (clinics, laboratories, support groups)



Prof. Jörg Schmidtke,
Coordinator Orphanet
Germany, Institute
of Human Genetics,
Hannover Medical
School

SPEAKER

- Web-based system for collecting epidemiological data
- Discussion forum between professionals

→ **LIMITS OF INTERNET AS A SOURCE OF INFORMATION**

Drawbacks are often mentioned when referring to internet as a potent source for information

- not too little but too much information
- no validation rules
- can take time to find the information sought for
- can be a frustrating experience

Therefore an important question is...

→ **HOW TO SURF (IVE) IN THE AREA OF INFORMATION ON RARE DISEASES ?**

One solution is proposed by Orphanet :

- single-entry point for all documented rare diseases
- peer-reviewed information
- revised annually
- updated permanently

The service is not just providing information. An ambitious goal is to identify the gaps that exist in fighting rare diseases and to structure the information in a way that facilitates collaborations and contacts e.g. :

Issues addressed	Tools provided
Lack of information	Encyclopaedia of rare diseases <ul style="list-style-type: none"> • review articles and abstracts • expert-authored • peer-reviewed • over 1300 diseases
Scarce expertise	Experts' directory
Too few collaborations and partnership	Directory of research projects (OrphanXchange, see infra)
Difficulties in enrolling volunteers in clinical trials	Directory of clinical trials On-line recruitment service

Selected further Internet-based information and educational tools

- www.eshg.org (ESHG)
- www.genetests.org (Genetests)
- www.kumc.edu/gec/prof/genecour (University of Kansas)
- www.humgen.umontreal.ca/int/ (Prof. Bartha M. Knoppers)
- www.vh.org (Virtual Hospital)
- www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM (OMIM)

ISSUES ADDRESSED	TOOLS PROVIDED
Lack of information	Encyclopaedia of rare diseases <ul style="list-style-type: none"> • review articles and abstracts • expert-authored • peer-reviewed • over 1300 diseases
Scarce expertise	Experts' directory
Too few collaborations and partnership	Directory of research projects (OrphanXchange, see infra)
Difficulties in enrolling volunteers in clinical trials	Directory of clinical trials On-line recruitment service

Orphanet is also a directory of services, in 20 countries :

- Clinics
- Tests
- Research projects
- Support groups
- Networks
- Registries
- Clinical trials

The participating countries joined the project in a staggered manner, due to financial constrains :

- 1997 France
- 2001 Belgium, Italy, Switzerland, Germany
- 2002 Spain, Austria
- 2003 Portugal
- 2004 Ireland, United Kingdom, Finland, Denmark, Estonia, Latvia, Romania, Greece, Turkey, Bulgaria, the Netherlands, Hungary

→ **ORPHANET USERS' TYPOLOGY**

Among 12 000 daily users in March 2005					
Patients and families	33.3%	Health professionals	51.6%	Others	15.1%
Patients	14.1%	Medical doctors	30.4%	Other professions	7.3%
Parents	8.3%	Non MDs	16.0%	Others	7.8%
Family	10.9%	Medical students	5.2%		

→ CURRENT CONTENT OF THE DATABASE

- 3 713 diseases and synonyms
- 2 463 abstracts (translation ongoing)
- 624 review articles
- 751 diagnostic labs for 943 diseases
- 1 952 research projects on 1 154 diseases
- 858 patients organisations linked to 1 431 diseases
- 1 312 specialised clinics
- 4 832 health professionals
- 4 379 other web pages

→ FUTURE DEVELOPMENTS

- to move towards comprehensiveness of data
- to establish a lay-people oriented encyclopaedia
- to obtain additional national funding
- to edit and distribute country specific print versions
- to establish itself as a partner of stakeholders in rare diseases at national levels

10.3 Training families and carers in Norway

→ A WORD ABOUT FRAMBU

- Frambu is a national centre for rare disorders
- It covers approximately 60 disorders
- It offers services to the users, families and to the local/regional professionals
- It also offers supplementary services to health and social services
- It is financed by the Ministry of Health and Care Services
- Frambu is one of 17 centres for rare disorders in Norway

Norway is benefiting from a long experience in National plans for rare diseases, the initial one was launched in 1990 and lasted until 1993; the most recent was launched between 1994 and 1997.

→ CLUSTERS OF DISEASES COVERED BY FRAMBU

- Genetic syndroms and disorders with developmental delay
- Sex chromosome disorders
- Overgrowth syndroms
- Muscular disorders with appearance in childhood



“ Britta Nilsson,
Frambu centre for rare
disorders, Norway

S P E A K E R



- Progressive encephalopathies
- Neurocutaneous syndroms



→ A PLACE FOR DIALOGUE

Frambu is a place of dialogue for the users, the families, the siblings and the professionals. Users/families can acquire knowledge, consult with professionals, exchange experiences, discuss different topics, enjoy physical activities, focus upon coping, relations, self-esteem, and empowerment and make lasting friendships.....

→ IN-HOUSE ACTIVITIES

Frambu is offering a wide range of services to its users:

- information courses for users and families
- summer camp
- school and kindergarten
- seasonal gatherings for
- representatives of the user organisations
- workshops, seminars and conferences

→ HOW MANY PEOPLE PARTICIPATE TO FRAMBU ACTIVITIES?

Information courses for families and users: altogether 1 160 persons stayed at Frambu in 2004; 453 users (patients), 499 parents and 208 siblings.

Four different summer camps were organised in 2004, for 101 children aged 10 – 16 years and for 74 others aged 17 – 30 years. These camps lasted for two weeks and the children attend the camps on their own, no parents and no siblings are present.

→ TRAINING

Courses for users and families

The main training is related to the diagnosis but not only that: there are social rights and prognosis, genetics and daily life are also covered. It consists in a two week introductory training course followed by a one week course on schooling, social rights, friendship, moving to your own house, technical aid, leisure time...

When parents are listening to lectures, participating in discussion groups or consulting with experts, children are in kindergarten or at school. Both kindergarten and school welcome children with a disease along with their siblings. Special educators have been trained for more than twenty years.

« At Frambu participants can stay awake all night to discuss, to cry, to love, to encourage, to support and to make lifelong friendships. »

→ **OUTREACH ACTIVITIES / TRAINING**

Information dissemination, collaboration and counselling in the local community where the user lives:

- Workshops and seminars in different regions, communities
- Collaboration with clinical and research institutions

A total of 150 users and their professionals were able to be visited from Frambu in 2004. Usually two professionals, for instance a medical doctor and a special educator, travel to the user's home-community for a one- or two-days information dissemination and collaboration with the local and regional professionals.

- Genetic syndroms and disorders with developmental delay
- Sex chromosome disorders
- Overgrowth syndroms
- Muscular disorders with appearance in childhood
- Progressive encephalopathies
- Neurocutaneous syndroms

→ **RESEARCH**

- data collection on every day experiences
- research projects

→ **DOCUMENTATION AND INFORMATION**

- Internet and intranet
- Publications - booklets, brochures, books
- Videos
- Videoconferences
- Online information (telephone, internet)

→ **LEARN MORE ON FRAMBU**

www.frambu.no Most of the site is in Norwegian.



10.4 The Ågrenska Foundation: a family programme



Anders Olauson,
Ågrenska Chairman,
Göteborg

S P E A K E R

A child's disability affects all members of a family; therefore the Family Programme at Ågrenska is directed towards the entire family. The Family Programme offers a unique opportunity for families to meet and exchange experiences concerning the same rare disease.

During the stay, the parents are offered a programme containing the most recent medical and psychosocial information, information on the consequences of the disorder and on the support offered by society.

Professionals from the child's home environment are invited to attend the parental programme for two days. The siblings and the children with the disease are offered a programme that suits their needs.

To better integrate children with a rare disease in our society, educational tools themselves must be considered as part of the treatment.

"In order to understand how it is to be a parent to a disabled child, you have to be a parent of a disabled child yourself!"
Åke Martinsson

The objectives of the Family Programme developed by the Ågrenska Foundation in Sweden are to obtain information on educational consequences and spread it to teachers, pre-school teachers and others who meet the children in daily activities

→ **METHODS**

- Using a controlled and validated observations material which is approved by the University of Göteborg.
- Systematic observations of the children with the same diagnosis are performed in Ågrenska school activities, during the family programme.
- Lectures of the syndrome to parents and the children's accompanying professionals.
- Report back and connection with the children's local teachers at home.

→ **RESULTS**

- From 1990 to 2004, 140 different rare diagnosis's were observed at Ågrenska
- From all parts of Sweden
- More than 2 200 visiting families
- More than 3 300 visiting parents
- More than 2 400 visiting children/ adolescents with a rare diagnosis
- Nearly 3 000 visiting siblings

→ RESULTS FROM THE FAMILIES' PERSPECTIVES

- Parents feel "normal"
- Families feel "In power", by meeting others in the same situation
- Parents obtain new knowledge, in order to be in control of their own lives
- The diagnosed children meet others who have the same diagnosis
- Siblings meet other siblings

→ OVERVIEW OF THE FAMILY PROGRAMME, AUTUMN 2005

Week 35	Achondroplasia
Week 37	Usher's syndrome, type 1
Week 38	Osteogenesis Imperfecta (OI)
Week 40	22q11 - deletion syndrome
Week 41	Neurofibromatosis, type 1
Week 43	Spastic paraparesis
Week 45	Dysmelia – Limb deficiency
Week 46	Langerhans cellular histiocytosis
Week 48	Hydrocephalus, (without Myelomeningocele, MMC)
Week 49	Anal atresia

→ NEWSLETTER

A journalist at Agrenska summarises and compiles lectures and information from the parents programme during a Family Programme for a newsletter on the disease.

Before the information is made available to the public, the lecturers read and register their opinions on the summaries. The medical information is updated continuously, in cooperation with the lecturers. A single case description is included in the newsletter on every disease, describing the every day challenges that the family meet.

→ OTHER PROJECTS

Agrenska launched an initiative with a designer school to help find ergonomic solutions for all sorts of disabilities that people with rare disease may encounter in life.

As an illustration, figure x shows some of the ideas suggested by the participating students. Not all will become reality, but at least this demonstrates that efforts to improve the daily life of disabled persons are possible: eating, washing up, expressing yourself, finding your way, having fun.

10.5 Training on genetic medicine, new technologies

European Courses in Genetic Medicine and Genetic Interest Groups

During the last 50 years the scientific achievements in all areas of life sciences have led to a common basis of unified knowledge and also to common methodological approaches including the specialised areas of medicine. The central role of genetics/genomics in medicine is now widely acknowledged both for biomedical research and for the advanced training of the new generations of scientists. Thanks to the results of the Human Genome Project, the genes responsible for an increasing number of rare diseases can now be identified. The term "genetic medicine" implies that the use of genetics as a tool in biomedical research and in advanced training is becoming one of the main features of modern medicine.

The European School of Genetic Medicine (ESGM) is at the leading edge of advanced training in the field of Genetic Medicine and its courses have been attended by more than 5000 students during the last 18 years (see www.eurogene.org). During the last three years the ESGM training has been marked by the experimentation of new technological and methodological approaches. Using web-casting technology the ESGM is now offering its courses to virtual participants unable to travel to the Main Training Centre located in Bertinoro (Italy). Following this model the virtual version of the courses will be web-cast to Satellite Training Centres all over the Europe. This "hybrid courses" format is intended to attract new participants at the ESGM courses

without requiring them to invest time and resources for travel.

In the near future the ESGM, in collaboration with professional associations and patient organizations will offer a series of courses aiming at increasing awareness and understanding of genetic disorders and intends to collaborate with Genetic Interest Groups in the application for European grants.

Poster 60,
Giovanni Romeo
– European Genetics
Foundation – Bologna

Participants at the conference



11 PATIENTS' RIGHT : mobility, care in a foreign country. Decisions of the European Court of Justice.

11.1 Trans-border access to care: a view from the European Court of Justice

→ SUMMARY

The organisation of healthcare and social security is a matter for which the Member States have not transferred powers to the European Union. In the organisation of their national healthcare systems, Member States must however take into account basic principles of European law, such as the right of patients to free movement. In a series of judgments, starting with the Kohll and Decker cases, the Court of Justice made clear that any national rule which makes reimbursement of medical treatment provided abroad dependent on prior authorisation, must be justified by objectives of general interest such as the financial balance of the social security system and the need to maintain a balanced medical and hospital service open to all.

Whereas prior authorisation may thus be justified for hospital treatment abroad, this is normally not the case for ambulatory care abroad. In the latter case, the requirement of prior authorisation will be an unjustified restriction of the freedom to receive services, irrespective of whether the home State applies a system of reimbursement or benefits-in-kind.

Even though European law does not preclude a system of prior authorisation for hospital care abroad, it requires any such system to be based on objective and non-discriminatory criteria. Under this condition, Member States are free to determine which treatments will be paid for by their social security system. Where prior authorisation is dependent on the necessity of the treatment abroad, authorisation may be refused only if treatment which is the same or equally effective for the patient can be obtained without undue delay in the home Member State. Prior authorisation cannot be refused solely because there are waiting lists on the national territory, that is to say undercapacity. The existence of waiting lists is central to the pending Watts case, in which the Court of Justice has been asked whether the need to allocate resources according to medical priorities might justify refusing certain patients to receive treatment abroad at the expenses of the national health service.



“ Dr. Piet van Nuffel,
Legal Secretary at the
Court of Justice of the
European Communities,
Luxembourg of the
European Communities,
Luxembourg

SPEAKER

Rights to medical care abroad under EC regulation :

1. If insured person abroad needs treatment in State of stay (E111 form)
2. If insured person is authorised to go to other State to receive there treatment (E112 form)
 - Entitlement to benefits under terms of the host State
 - Authorisation not to be refused by home State if:
 - benefits covered in home State
 - treatment not available there within time-limit medically justifiable given patient's state of health

→ RIGHTS TO MEDICAL CARE ABROAD OUTSIDE EC REGULATION :

1. Kohll and Decker case: patient did not seek for authorisation prior to care in state different from state of residence
Articles 30 and 36 of the EC Treaty preclude national rules under which a social security institution of a Member State refuses to reimburse to an insured person on a flat-rate basis the cost of a pair of spectacles with corrective lenses purchased from an optician established in another Member State, on the ground that prior authorisation is required for the purchase of any medical product abroad.

Requirement of authorisation under scrutiny:

- As it can be considered as a barrier to free movement of goods or services
- Can it be justified? In general, member states object that in the absence of such an authorisation,
- Financial balance of social security system could be impaired,
- Thus endangering the objective of maintaining a medical and hospital service open to all.

Art. 22 Reg. 1408/ 71 is intended to allow an insured person, authorised by the competent institution to go to another Member State to receive there treatment appropriate to his/her condition. It is not intended to regulate and hence does not in any way prevent the reimbursement by Member States, at the tariffs in force in the competent State, of the cost of medical products purchased in another Member State, even without prior authorisation.

The obligation to obtain prior permission must be categorised as a barrier to the free movement of goods, since they encourage insured persons to purchase those products in the national territory rather than in other Member States, and are thus liable to curb their import. They are not justified by the risk of seriously undermining the financial balance of the social security system, since reimbursement at a flat rate of the cost of spectacles and corrective lenses purchased in other Member States has no significant effect on the financing or balance of the social

security system, nor are they justified on grounds of public health in order to ensure the quality of medical products supplied to insured persons in other Member States, since the conditions for taking up and pursuing regulated professions have been the subject of Community directives.

2. Requirement of authorisation justified for hospital care (Smits/Peerbooms and Van Riet cases)

This requirement for hospital care is considered as justified, as the impact of foreign visitors consulting or seeking care can be significant:

- necessity of planning the number of hospitals, their geographical distribution, their mode of organisation, their equipment and the nature of the medical services
- aim of controlling costs and preventing wastage of financial, technical and human resources
- ensuring sufficient and permanent access to high-quality hospital treatment

→ CONDITIONS FOR AUTHORISATION

- Hospital care must be insured and reimbursed in state of origin (Smits/Peerbooms)
- Requirement of « necessity » for treatment abroad (Smits/Peerbooms)
- No necessity if same or equally effective treatment available without undue delay
- Are waiting lists relevant? (Müller-Fauré/Van Riet; Watts?)

→ WHEN IS AN INSURED PERSON COVERED FOR TREATMENT ABROAD?

- Treatment while staying abroad
 - no authorisation needed (E111)
 - covered under host State terms
- Ambulatory care abroad
 - if authorised with E112: covered under host State terms
 - without prior authorisation: reimbursed under home State terms
- Hospital care abroad: prior authorisation needed
 - if authorised with E112: covered under host State terms
 - reimbursed under home State terms if authorised otherwise

→ PATIENTS' MOBILITY RIGHTS : CHALLENGE FOR HEALTHCARE?

- Administrative complication
- Stimulus for structural change?
- Will the Court eventually get guidance from our political representatives?

→ CONCLUSION

The Court's case law has prompted the Commission to include provisions on patient mobility in its proposal for a Directive on services in the internal market. In the current political context, it is all but sure that discussion of this "Bolkestein proposal" will result in any codification of the Court's case law. Still, legislative intervention in this field would certainly enhance transparency and legal certainty for all stakeholders.

12 STRATEGIES FOR PREVENTION

12.1 Strategies based on the assessment of epidemiological evidence

Prof. Helen Dolk,
EuroCat, University of
Ulster

Prevention of rare diseases is possible, to some extent.

1. Primary Prevention consists in:

- pre-disease
- Attacking basic cause(s) of disease
- Altering environment or resistance/susceptibility

2. Secondary Prevention consists in:

- Disease has started but symptoms have not appeared
- Detecting and treat early to prevent disease development
- e.g. newborn screening for phenylketonuria

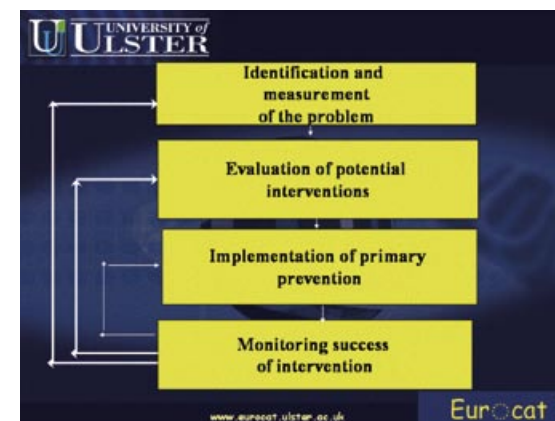
3. Tertiary Prevention consists in:

- Disease has become symptomatic
- Curing, controlling or preventing complications

Epidemiology in relation to primary prevention strategies:

- What is the incidence of the disease in the population?
- What distinguishes who does and does not get the disease in the population?
 - Age, sex, time, place, social status
- What causes the disease?
 - Environment, genes, and their interaction
 - Causal pathways and networks
- How much and why do populations differ in incidence?
- How much disease could we prevent with different prevention strategies?
- How would different prevention strategies affect inequalities in disease incidence?
- How successful has the implementation of a prevention strategy been in relation to its potential in reduction of disease and reduction in inequalities in disease?

figure 41:
an action plan
for prevention, from
problem identification
to the monitoring
of the success.



→ **EUROCAT : EUROPEAN SURVEILLANCE OF CONGENITAL ANOMALIES.**

- European network of population-based registries for the epidemiologic surveillance of congenital anomalies.
- Started in 1979, now funded by EU Public Health Programme
- More than 1.2 million births surveyed per year in Europe
 - 40 registries in 19 countries
 - 30% of European birth population covered
- Quality at the expense of completeness of geographical coverage

→ **POSSIBLE PRIMARY PREVENTION STRATEGIES**

- Periconceptual folic acid supplementation
- Vaccination e.g. congenital rubella
- Preconceptional and pregnancy care for high risk women e.g. diabetes, epilepsy
- Genetic counselling for high risk families
- Reduction of abuse of recreational drugs/alcohol
- Pre-marketing drug testing, pharmacovigilance and health technology surveillance
- Reduction of exposure to environmental pollutants (precautionary where necessary) and enviro-vigilance

→ **IN CONCLUSION**

- Epidemiology underpins planning and evaluation of all levels of prevention
- Primary prevention of rare diseases is as much an equality issue as secondary and tertiary prevention
- Termination of pregnancy following prenatal diagnosis should not be an alternative to primary prevention
- Whole population measures may sometimes be needed to prevent rare diseases
- Population-based registries, networked at a European level, provide the means to carry out epidemiologic research and surveillance for prevention

12.2 Prevention of genetic diseases

→ **TO PREVENT THE CLINICAL OUTCOME OF A LATE-ONSET GENETIC DISEASE**

Gene	Disease	Treatment
BRCA1-2	Breast cancer	Mamectomy
RET	MEN	Thyroidectomy
MHC1-L	Hemochromatosis	Iron chelators
Myosin	Cardiomyopathy	Follow-up
n	Deafness / blindness	Special schooling

“ Prof. Stanislas Lyonnet, Hôpital Necker, France.

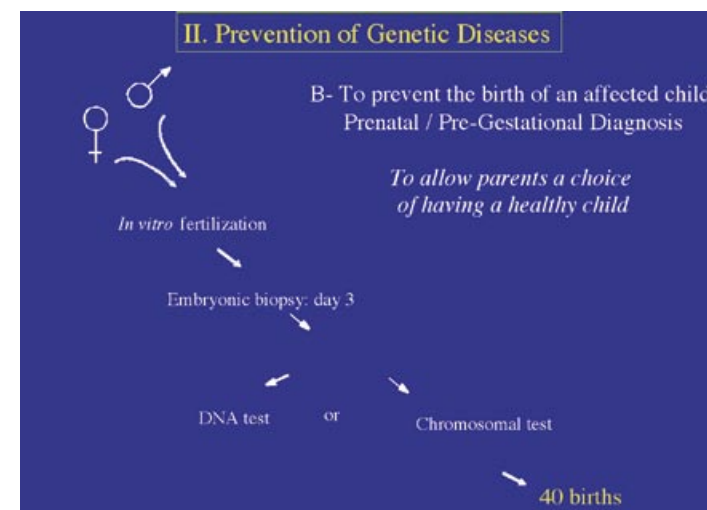
Detection of a genetic risk is best indicated in families where the risk exists, i.e. where cases are already diagnosed. Individualised follow-up can then be implemented. For people who are carrying detrimental genes like those favouring blindness or deafness, even though no treatment exist, early detection of the genes helps deciding how to organise the life of the person years before the disability/disease becomes symptomatic. Schooling for example can be adapted to the needs of the person.

→ **TO PREDICT OR TO SLANDER?**

- Who wants to know?
- When duly informed about the utility of testing, not all patients or persons at risk decide to undergo genetic testing. For Huntington Chorea for example, only 18% of persons at risk and who are consulting for genetic testing actually do the test.
- What do we know? Modifier genes exist, they can be detected, they do not provoke a disease but may increase or decrease the expression of detrimental genes. Predictions are then difficult.
- What is the social impact of prediction? Insurance companies, employers could divert genetic testing from its medical purpose.

Prenatal and pre-implantation genetic testing

Figure 42: Pre-implantation testing has nothing to do with cloning. It consists in *in vitro* fertilisation, for parents who are at high risk to give birth to a sick child. One cell is captured (embryonic biopsy) and analysed (DNA test, chromosomal test), and if the genes are healthy, then the corresponding embryo is



13 CLOSING OF THE CONFERENCE

13.1 Moving forward in Europe

My first message is simple: “Europe, Europe and Europe”, and I am very sorry to be from a member state which missed the point a few weeks ago by rejecting the Constitutional Treaty. It is obvious that for rare diseases this is the only level where we can achieve something meaningful. Even if some citizens have not understood the message, we want to work at the European level, and even better, at the global level.

Then, as health care professionals, we have several messages to the Commission:

- To DG health and consumer protection: we are very satisfied for the support and initiatives in the field of information and surveillance, and this should be continued. However solutions to ensure sustainable and longer term funding are expected, as most of the initiatives really useful for the rare diseases community are developed to collect data and disseminate information and results and these are long-lasting efforts. If funding can only be granted for 2 to 3 years, it may not be worth starting the project at all.
- To DG research: in the recent years, few research projects were supported on rare diseases. In FP7, new research projects on rare diseases are expected to be funded. We need to advocate in order ensuring that no budget cuts will affect this good will. If the research budget has to be decreased, we hope this will not affect projects on rare diseases.
- Currently, rare diseases appear in the genomics strand of the research programme. Genomics is an important part of research but it does not constitute all what we need. Research in epidemiology, health care provision and services are equally important.
- Expectations are very high in the rare diseases community, and sometimes the researchers’ agenda does not totally coincide with patients and families’ agendas. Immediate needs of the community should be listened to.
- Efforts to provide information exist and are welcome; they may not always be adapted to all publics. Paramedical professions, patients and



Dr. Ségolène Aymé,
Orphanet,
Inserm SC11, France.

S P E A K E R

their representatives for example need adapted information. Collaboration and partnership between information sources are certainly a way to address this issue.

- The need for more imagination: even complex problems always have a solution. Even when the damage is present at birth, there are therapeutic solutions that can help and improve the quality of life. More solutions can be found.
- Messages from the Task Force on Rare Diseases: the DG Health and Consumer Protection created this task force and we all welcome this initiative. Funding has been granted and a newsletter thus created to convey information to all stakeholders. It is a link for all of you, so please register if you haven't already done so. The URL where to register is: www.rdtf.org. You are invited to send information to the newsletter team if you wish to disseminate it through the community.
- Other actions of the Task Force for the coming years are ambitious as well: coding and classification of rare diseases. We want a code for each of the rare diseases; all deserve to be visible in the health care systems. We will be working on health indicators, in order to compare outcomes in different member states, and to benchmark best practices in Europe. Of course we will act as advisors to the European Commission, and your participation is key. The force will come from you.

13.2 A society where rarity does not affect opportunity

After one year of preparation and a two day conference, we now have a clear vision for rare diseases: ten years from now, people living with rare diseases across Europe will have the same opportunities as their fellow citizens in European society.

→ HOW CAN WE REACH THIS GOAL?

By enforcing a number of very practical changes in the health care systems across Europe:

- Well trained doctors or paediatricians able to detect a rare condition right away,
- Diagnostic laboratories exchanging blood samples,
- tissues, DNA and results across the EU,
- Radiologists sending medical images from any care centre to a specialised centre,



Christel Nourissier,
Eurordis

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- Accurate diagnosis being made as early as possible with the support of telemedicine,
- If necessary, patient and family travelling to the centre of reference, regardless of borders. Or better still, professionals from the centre of reference training local doctors and their families.
- Simpler paperwork to obtain financial compensation, care, etc.
- Financial aspects being handled with the help of social workers,
- Families getting the support of a local patient group and meeting with other families.

→ **WE WANT A CLEAR PATH FOR PATIENTS AND THEIR FAMILIES:**

- Necessary support, immediately after the diagnosis, during critical situations, and for the duration of the patient's lifetime
- Local health professionals with access to treatment and care guidelines for medical and paramedical care
- Emergency units using updated information from medical web sites, telephone lines,
- Adequate information and training at school, at the work place, at home and in residential homes.

→ **TO MAKE OUR DREAM BECOME A REALITY, EUROPE CAN CERTAINLY HELP:**

- With the co-ordination of public health and research programmes, ensuring continuity of actions
- With the collection of epidemiological information (Morbidity and Mortality Working Party and the Task Force for Rare Diseases)
- With a permanent support of a network of European reference centres connected with national / regional centres of reference
- With the definition of best practice guidelines for care,
- for the integration of children at school, for the integration of adults at the work place
- With the cartography of existing resources: hospitals, respite care, summer camps, and the identification of urgent needs together with patient associations
- By providing a strong European environment for innovative therapeutic interventions and innovative medicines

→ **MANY ACTIONS ARE TO BE IMPLEMENTED**

AT A NATIONAL LEVEL IN EACH MEMBER STATE :

- Encourage national plans for rare diseases,
- Support information centres with more public funding,
- Train and educate health care professionals, and
- also volunteers and staff for patient groups,
- Create and support national or regional centres of reference for rare diseases,

- Facilitate access to medical and paramedical care, devices and equipment,
- Improve access to already marketed orphan drugs; continuously push for the development of other orphan and paediatric drugs,
- Better compensate disabilities: human resources and technical aids
- Empower rare diseases patient groups, inform and educate patients.

→ **ALL THESE EFFORTS WILL NOT ONLY BENEFIT RARE DISEASES, BUT EFFORTS FOR RARE DISEASES CAN PLAY THE ROLE OF A CATALYST FOR OTHER DOMAINS :**

- European networks of biobanks, patient registries and centres for clinical research
- Rare diseases as models for more common diseases
- Pluri-disciplinary research aiming at a better life for patients
- Innovative methods for clinical trials, innovative drugs
- Involvement of strong, active and well supported patient groups

→ **HOW CAN PATIENTS AND THEIR FAMILIES GET THERE?**

- At national level: by strengthening groups and national alliances,
- At European level: with Eurordis representing the rare disease community,

→ **OUR STRATEGY : A GLOBAL APPROACH OF THE PATIENTS**

- Integrate patient networks, research, diagnosis, and treatment structures.
- Make the best use of our current knowledge, of medical and paramedical care, of education and rehabilitation schemes
- Publish and publicise best practice guidelines, when and wherever they exist
- Involve patients at all stages: clinical trials and research protocols, dissemination of outcomes.

Our rare diseases community will meet again to discuss achievements and plans for the future at the next European conference for rare diseases, in Lisbon, Portugal, October 2007.

13.3 The word of the European Commission

The Commission would like to thank the organising committee of this conference, Eurordis, all partners involved, and also the Luxembourg government and in particular the health minister Mars di Bartolomeo, for what I think has been a very successful EU level event.

I wanted specially to complement the cultural performance which was an excellent show, very professional and inspiring.

I also wanted to thank the other sponsors, who helped us to build up this conference together with the EU health programme.

For 2 days we have been taking through what is really going on in many areas in the field of rare diseases. Those participating have been able to get a valuable of where the problems lie.

We learned the results of the Eurordis study on the delays in diagnosis, identifying sometimes considerable time lags before rare diseases are identified and treated, where appropriate and when possible.

There was also a discussion on bench marking initiatives to improve care, comparison of national plans, practices on trans-border access to care, leading to a discussion on the need for and the role of reference centres in the context of rare diseases.

Targeting research to improve quality of life, increasing the coherency of research by avoiding fragmentation, establishing larger networks, and the contribution of our EU research programme where other issues which were discussed. I can confirm that rare diseases per se will be included as an eligible disease category within the next framework programme of the Commission proposal for the period 2007 to 2013. The Commission will also take forward the conclusions of the research workshop which took place on April 13th.

We also heard about the problems encountered in data collection and management. How and why you need to improve coding and classification, a challenge not only for the European Union but other countries around the world and our international partners such as WHO. The specific aspects of registries were examined; and national and trans-national options were looked at. We looked at clinical trials, treatments using orphan drugs, and access issues.

Finally I must mention the important statement given to us just now by Dr. Ségolène Aymé who is the chairman of our Rare Diseases Task Force within DG Sanco which plays a very important role for our work and we hope to include its recommendations in our forthcoming work plan.



S P E A K E R

John F. Ryan,
Head of Health
Information Unit,
Public Health and Risk
Assessment Directorate,
DG Health and
Consumer Protection,
EC

On behalf of the Commission's public health services, I have been most interested together with my colleagues to hear the very high level presentations during these last two days. This conference has given us a better direction, defining priorities in the projects that can be made, and also in the context of our new programme for 2007-2013.

I have been encouraged by some of the presentations to see where we could play a bigger role at EU level in supporting the work of health professionals in improving training, sharing information resources, and providing concrete resources and supports for patients and carers.

You may have seen outside on our information stand some of the completed projects' reports that the Commission has financed and we are very happy that this is given some recognition and publicity to those efforts. We also hope that the future EU health portal which we hope to launch this year will be another step in this direction.

It is our hope that the recommendations made during this conference will be implemented in the coming years, we hope that the future Rare Diseases White Book that you are hoping to develop according to the results of this conference, will bring together these ideas and strengthen European cooperation. We also commit ourselves to taking forward the work within the Task Force that we have set up last year.

The Commission is finally convinced that this is not a single or a one-off event, we are very happy to hear about the announcement of the Lisbon event in 2007 and we would look forward to seeing everybody there and giving our support again.

Thank you ladies and gentlemen, thank you minister.



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