TABLE OF CONTENTS

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ASSOCIATION FRANCAISE CONTRE LES MYOPATHIES AFM/TELETHON

FOR EURORDIS:
Christel Nourissier, Project Leader
Yann Le Cam, Chief Executive Officer
François Houjiez, Project Manager
Patrice Régnier, Finance Officer
Flaminia Macchia, European Public Affairs Officer
William Gibon, Assistant
Media Contact: Stefan Chrobok and Aart van Ierssen

OUR PARTNERS
ALAN in Luxembourg, Alliance Maladies Rares, Agreniska,
Federacion Espanola de Enfermedades Raras, Rare Diseases Denmark,
Czech Agency for Drug Control, Orphanet and Eurocat
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THE MEMBERS OF THE PROGRAMME COMMITTEE

AND ALL ECRD2005 PARTICIPANTS

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4/RARE, BUT EXISTING

4.1 No code, no name, no existence .............. 49
4.2 Why do we need to code rare diseases? .... 50

5/RESEARCH AND CARE

5.1 Research for Rare Diseases in the EU ........ 54
5.2 Fighting the fragmentation of research ....... 65
A multi-disciplinary approach .......................... 55
Transfer of academic research towards industrial development ......................... 60
Strengthening cooperation between academia and industry ........................... 62
Researchers’ networks brought together by a patients’ organisation .................. 64

5.3 Lessons learned from EU framework programmes for research ............ 65
5.4 Research networks ............................ 67
European integrated project on spinocerebellar ataxias (EUROSCA) ............... 67
Wilson Disease: Creating a European Clinical Database and designing randomised
targeted clinical trials ................................ 68
EUGINDAT ........................................ 69

5.5 Establishing networks in myology:
Give more muscle to myology! ........................ 70
5.6 Research and success stories .................. 72
Clinical trials: research on specific domains/pathologies, the ESCAPE trial ........... 72
Rare Infectious Diseases that can be cured ... 73
Collecting and sharing tissue and DNA: EuroBioBank ................................. 74
Data collection for the European Network on Brain Demyelinating Diseases ENBD ... 76

5.7 Collecting and sharing registry data .......... 78
5.8 Building a technology platform:
Centre National de Génotypage .................... 80

6/TREATMENT AND CARE

6.1 Targeting research to improve quality of life .......... 82
Importance in making an accurate, simpler and easier diagnostic ................ 82
Therapeutic solutions that already exist for genetic diseases ..................... 83

6.2 A response to the need of the clinical trial community .................. 87

6.3 Treating with orphan drugs ..................... 91
7 / ACCESSING APPROPRIATE CARE : organisation of care

7.1 Disability: are financial compensations adapted to Rare Diseases? ....... 117
7.2 Clinical networks as a response to scarcity of databases and guidelines for best practices ............. 121
7.3 Access and availability of molecular genetic tests: uncovering the rationales for trans-border testing ............. 125
7.4 Focus on daily life .................................. 129

8 / NATIONAL POLICIES AGAINST RARE DISEASES

8.1 The Flemish model .................................. 135
8.2 Centres of reference in Denmark .......................... 137
8.3 A key action of the French National Plan for Rare Diseases 2005-2008 .................................. 139
8.4 Reference centre in Bulgaria .......................... 143
8.5 Regionalisation of the health care system in Spain .................................. 144
8.6 Organisation of care for children in Luxembourg .................................. 145
8.7 Veneto region register: the Italian law 279/2001 .................................. 148

9 / PATIENT NETWORKS

9.1 Living with a Rare Disease: importance of the role played by an association .................................. 151

10 / TRAINING AND INFORMATION

10.1 Best practice guidelines for care and management .................................. 152
10.2 Internet resources for the rare disease community .................................. 157
10.3 Training families and carers in Norway .................................. 160
10.4 The Agrenskja Foundation: a family programme .................................. 163
10.5 Training on genetic medicine, new technologies .................................. 165


11.1 Trans-border access to care: a view from the European Court of Justice .................................. 166
11.2 Rights to medical care abroad under EC regulation .................................. 167

12 / STRATEGIES FOR PREVENTION

12.1 Strategies based on the assessment of epidemiological evidence .................................. 169
12.2 Prevention of genetic diseases .................................. 170

13 / CLOSING OF THE CONFERENCE

13.1 Moving forward in Europe .................................. 172
13.2 A society where rarity does not affect opportunity .................................. 173
13.3 The word of the European Commission .................................. 176

RARE DISEASES MENTIONED IN THIS REPORT .................................. 178

PARTNERS

Organisers / Partners

EURODIRD (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, EURODIS’ 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.eurodis.org

ÄGRENSKA 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. Ägrenskas’ family program is directed towards families who have children with rare disabilities, and arranges about twenty family stays with different diagnosis each year. www.agrenskas.se

ALAN, the Luxembourg Genetics Association 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. www.alan.lu

FEDER, Fedération Espagnole 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 database that deals with rare diseases and orphan drugs. ORPHANET aims to improve the diagnosis, care and treatment of patients. ORPHANET includes an encyclopedia and a directory of services: specialised outpatient clinics, clinical laboratories, research activities and support groups. www.orpha.net

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

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

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MINISTRY OF HEALTH, Luxembourg

AFM Association Française contre les Myopathies, is the French Neuromuscular Association (AFM). In 1958, the French Neuromuscular Osteodystrophy Association (AFM) is a non-profit organisation 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

AFM TELETHON

LIONS INTERNATIONAL
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 Olausson, 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, Instituto Superiore di Sanità, Italy
- Josep Torrent-Farnell, Committee for Orphan Medicinal Products, EMEA, European Union

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, Tuberous Sclerosis Association, Greece
- A health professional’s testimony
  - Prof. Helena Kääriäinen, Turku University Hospital, Finland
- Disability: are financial compensations adequate?
  - 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 Cabrnoch 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

**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

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  - Prof. Christian Ohmann, ECRIN, Germany

**Discussion**
• Specific difficulties in access to:
  • Access and availability of molecular genetic tests:
    uncovering the rationales for transborder testing
    - Dr Elettra Ronchi, OECD
  • Medical devices and equipment
    - Liz Gondoin Goedert, ALAN, Luxembourg
  • Education: educational implications of rare diseases
    - Anders Olauson, Agrenska, Sweden

Discussion

Building technology platforms
• Building a technology platform
  - Dr. Judith Fischer, National Centre for Genotyping, France

Building strategies for prevention
• Strategies based on the assessment of epidemiological evidence
  - Prof. Helen Dolk, Eurocat, United Kingdom

Discussion

Session 7
BENCHMARKING INITIATIVES TO IMPROVE CARE: BEST PRACTICES GUIDELINES FOR CARE MANAGEMENT (continued)
- Co-chair: Lesley Greene, United Kingdom
- Co-chair: Dr. Manuel Posada, Spain

Information and training
• Help phonelines and written information
  - Lesley Greene, Children Living with Inherited Metabolic Disorders, United Kingdom
• Internet resources
  - Prof. Jörg Schmidtke, Medizinische Hochschule Hannover, Germany
• Training families and carers
  - Britta Nilson, Frambu, Norway and Anders Olauson, Agrenska, Sweden

Discussion

Session 8
FIGHTING THE FRAGMENTATION OF RESEARCH (continued)
- Co-chair: Alan Vannoxell, DG RES
- Co-chair: Jose Luis Valverde

Building a community of patients and professionals
• Patient representatives: examples of patients’ organisations that successfully brought together researchers’ networks
  - Dr. Tsveta Schyns, Alternate Hemiplegia network, Austria
• Establishing larger networks
  - Dr. Serge Braun, Association Francaise contre les Myopathies AFM, France

Discussion

Session 9
TREATING WITH ORPHAN DRUGS
JOINT MEETING OF ALL INTERESTED PARTIES: THE EUROPEAN ENVIRONMENT FOR ORPHAN MEDICINAL PRODUCTS
- Co-chair: Prof. Henri Metz, Luxembourg
- Co-chair: Thomas Lönngren, EMEA

• Status report and health benefits after five years of Orphan drug legislation
  - Dr. Melanie Carr, EMEA, Scientific Advice and Orphan Drugs

Panelist views 1: Experience gained by stakeholders
• 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

Panelist views 2: Access to drugs and responsibilities of Member States
• 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

Data collection and management
• Diseases with no code: the perspective of patients
  - Annet van Betuw, The Rare Chromosome Disorders network, The Netherlands
• Why and how to code and classify rare diseases
  - Dr. Ségolène Aymé, Orphanet, France

Discussion
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

Co-ordinating funding initiatives
• Rare funding initiatives for rare diseases
  - Prof. Hans Hilger Ropers, Max Planck Institute for Molecular genetics, Germany
• DG Research: lessons learned from FP5 and FP6, plans for FP7
  - Prof. Kitty Schwartz, Inserm, France

Discussion
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.

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).
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.
• Mr. Terkel Andersen, Chair of the Board of Directors, Eurordis. terkel.andersen@newmail.dk
• Dr. Séguine Aytré, Director of Orphanet, France, and Leader of the Task Force on Rare Diseases. aytre@orpha.net
• Mr. Mars di Bartolomeo, Minister of Health of Luxembourg. ministeerre-sante@lms.etat.lu
• Annet van Betuw, President of the European Chromosome 11q Network, The Netherlands. avbetuw@wxs.nl
• Prof. Oddle Boeplug-Tanguy, European Leucodystrophy Association and Child Surgery Department, Clement Ferrand hospital, France. odin.boeplug@farmenu-ciermeant199.fr
• Dr. Serge Braun, Director of Research and Therapeutic Development, Association Française contre les Myopathies AFM, France. straum@afm.genethon.fr
• Dr. Milan Cabmouch, Member of the European Parliament, Czech Republic, cabmouch@cabmouch.cz
• Melanie Carr, Pre-Authorisation of Medicines for Human Use, Scientific Advice and Orphan Drugs, EMEA. melanie.carr@emea.eu.int
• Prof. Helen Doik, Faculty of Life and Health Sciences, University of Ulster, Eurocat and Deputy Leader of the Task Force on Rare Diseases. h.doik@ulster.ac.uk
• Catarina Edjlaj, Orphan Drug Working Group and Action, Switzerland. catarina.edjlaj@action.com
• Prof. Anders Fathth, Prof. of Pediatric Immunology, The Queen Silvia Children’s Hospital, and Member of the Task Force on Rare Diseases, Sweden. anders.fathth@pediav.gu.se
• Dr. Ilse Feenstra, MD, Clinical Database Manager European Cystogenetics Association Register of Unbalanced Chromosome Aberrations ECARUCA, The Netherlands. ilsefeenstra@artrg.umcn.nl
• Dr. Judith Fischer, National Centre for Genotyping, Inserm U429, France. judith.fischer@cgr.fr
• Dr. Alexandre Fourcade, Policy Officer for the National Action Plan for Rare Diseases, Ministry of Health, France. alexandre.fourcade@minardes.gouv.fr
• Liz Gondoin Goedert, President of the Association for Neuro-muscular Diseases of Luxembourg, Luxembourg. alanisebild@pt.lu
• Lesley Greene, Children Living with Inherited Metabolic Disorders, United Kingdom and former Project Leader PARDBI, Eurordis. lesley@lclimb.org.uk
• Torben Gromnebaek, President of Rare Disorders Denmark, Denmark. bgromnebaek.dk
• Prof. Anthony Holland, Senior Lecturer, Department of Psychiatry, University of Cambridge, United Kingdom. a.jh1008@cam.ac.uk
• François Hojsijez, Policy Health Officer, Eurordis. francois.hojsijez@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@ons.gsi.gov.uk
• Prof. Helena Kääriäinen, Professor, Department of Medical Genetics, Turku University Hospital, Finland. helena.kaariainen@ktlu.fi
• Dr. Veronica Karcagi, Head of Department Molecular Genetics and Diagnostics “Fodor Jozsef” National Centre for Public Health, Hungary, and EuroBioBank network. karcagiv@dkk.artsz.hu
• Dr. Ylika Kodra, National Centre for Rare Diseases, Istituto Superiore di Sanità, Italy. nephili@iss.it
• Dr. Modulin Kroneman, Researcher, Netherlands Institute for Health Services Research Nivel, The Netherlands. mkroneman@nivel.nl
• Marilena Lambrani, President of the Tuberculosis Associations Greece, tsarlasb@ath.forthnet.gr
• Yano Le Cam, Chief Executive Officer, Eurordis. yano.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
• Thomas Lönngren, Executive Director, EMEA. thomas.lonngren@emea.eu
• Prof. Stenistlas Lyonnet, Department of Genetics, Necker Hospital for Sick Children, Paris, France. lyonnet@hocher.fr
• Sarah McFee, Director of Quality of Life Department, Cystic Fibrosis Association, France. smcfee@vaincrelamuco.org
• Prof. Henri Metz, Member of the COMP/E UME, Luxembourg. metth@bcp.lu
• Dr. Bruce Morland, Chair of the UKCCSG New Agents Group and Consultant Paediatric Oncologist, Birmingham Children’s Hospital, United Kingdom. bruce.morland@bhamchildren.wmids.nhs.uk
• Britta Nilson, Director of Information, Frambu, Norway. britta.nilson@frambu.no
• Christel Nourissier, General Secretary, Eurordis, France and Member of the Task Force on Rare Diseases. prof.nourissier@wanadoo.fr
• Dr. Piet van Nuffel, European, Legal secretary, Court of Justice of the European Communities, Luxembourg. piet.van.nuffel@curia.eu.int
• Prof. Christian Ohmann, Coordination Centre for Clinical Studies (KKS), Germany, and European Clinical Research Infrastructure Network ECRIN. christian.ohmann@ibi-duesseldorf.de
• Anders Olsson, President Agenska, Sweden. anders.olsson@agenska.se
• Prof. José Luis Oliveira, Instituto de Engenharia Electrónica e Telemática de Aveiro, Portugal and InfoSanMed. jlo@det.ua.pt
• Prof. Manuel Palacin, Prof. Dr. Biochemistry and molecular Biology, University of Barcelona, Spain. mpalacin@pob.uc.es
• Dr. Manuel Posada, Instituto de Salud Carlos III, Research Institute on Rare Diseases, Spain and member of the Task Force on Rare Diseases. mposada@isciii.es
• Severine Rastoul, Maladies Rares Info Service, France. srastoul@maladiesrare.org
• Prof. Hans Hilger Ropers, Max Planck Institute for Molecular Genetics, Germany. ropers@mpimp.mpg.de
• Dr Elettra Ronchi, Coordinator Health and Biotechnology Activities, OECD. elettra.ronchi@oecd.org
• John F. Ryan, Head of Unit, Health Information, DG Health and Consumer Protection, European Commission. john.fryan@ec.eu.int
• Agnès Saint Raymond, Pre-Authorisation of Medicines for Human Use, Head of Sector-Scientific Advice and Orphan Drugs, EMEA. agnes.saint-raymond@emera.eu.int
• Rosa Sanchez de Vega, Vice-president of Federación Española de Enfermedades Rares (FEDER), Spain. asanchezdeveg@feder.es
• Fernand Sauer, Director for Public Health, DG Health and Consumer Protection, European Commission. fernand.sauer@ec.eu.int
• Prof. Reinhold Schmidtke, Clinical Immunology, University of Hannover, Germany. schmidtke.reinhard@mh-hannover.de
• Prof. Dr. Jörg Schmidtke, Medizinische Hochschule Hannover, Germany. schmidtke.jorg@mh-hannover.de
• Prof. Pascal Schneider, Associate Professor, Biochemistry Department, University of Lausanne, Switzerland. pascal.schneider@unil.ch
• Prof. Kelly Schwartz, Vice-president of the Board of Directors, Inserm, President of The Scientific Council of the Association Française contre les Myopathies, and Research Director at the “Institut Myologie, 5ème-Salpêtrière Hospital” (Inserm U 567) France. k.schwartz@myologie.chups.jussieu.fr
• Dr. Tsveta Schyns, Coordinator at the European Network for Research on Alternating Hemiplegia in Childhood, Austria. ts.schu@yahoo.net
• Dr. Eva Stelianova-Foucher, Descriptive Epidemiology Group (DEP), The International Agency for Research on Cancer (IARC) and Member of the Task Force on Rare Diseases. stelianova@iarc.fr
• Dr. Domingena Tarusci, Responsible of the Italian National Centre for Rare Diseases, Istituto Superiore di Sanità, Italy and Member of the Task Force on Rare Diseases. tarusci@iss.it
• Dr. Valérie Thibaudet, Project Manager, Database Manager, Orphanet, France. vthibaudet@orpha.org
• Prof. Jose Luis Valverde Lopez, Faculty of Farmacia, University of Granada, Spain.
• Alan Vanvossel, Head of Unit, Major Diseases, DG Research, European Commission. alain.vanvossel@ec.eu.int
• Prof. Joan Luis Vives Corron, ENERCA, Spain, and Member of the Task Force on Rare Diseases. jlvives@cnic.es
• Dr. Annick Vogels, University Hospital Leuven, Belgium. annick.vogels@b.u-leuven.ac.be
• Dr. Yoland Wagener, Ministry of Health, Luxembourg and Member of the Task Force on Rare Diseases. yoland.wagener@mos.etat.lu
• Elisabeth Wallenius, Säkymya Diagnost, Sweden. elisabeth.valleinius@nykoping.nu
• Dr. Corneila Zedler, Clinical Consultant, Secure Chronic Neuropenia International Registry Germany and Member of the Task Force on Rare Diseases. nzeder.comelia@mhi-hannover.de
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 or 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 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, amytrophic 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 epilepsia (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”.

INTRODUCTION
1 OVERTURE

1.1 The word of the President of Eurordis

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.

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
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

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 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 study

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

→ METHOD 3 : limitations of the study

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

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 350 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

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Estimated Prevalence (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rendu-Osler-Weber disease</td>
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<tr>
<td>Dermatitis herpetiformes</td>
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<tr>
<td>Atresia of small intestine</td>
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<td>Duodenal atresia</td>
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<td>Ehlers-Danlos syndrome, classic type</td>
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<td>Hirschsprung disease</td>
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<td>Microdeletion 22q11</td>
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<td>Spherocytosis hereditary</td>
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<td>Turner syndrome</td>
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<td>Breast cancer, familial</td>
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<td>MELAS syndrome</td>
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<td>Leucrosis</td>
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<td>Acyl-CoA dehydrogenase, medium chain, deficiency of</td>
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<td>Lennox-Gastaut syndrome</td>
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<td>Fragile X syndrome</td>
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### Disease Name

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<tr>
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<td>Stargardt disease</td>
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<td>Proximal spinal muscular atrophy</td>
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<td>Saether-Catznot syndrome</td>
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<td>Kennedy disease</td>
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<td>Cystosis</td>
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<tr>
<td>DISEASE NAME</td>
<td>Estimated prevalence (/100,000)</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------------</td>
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<tr>
<td>Amaurosis congensis of Leber</td>
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<tr>
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</tr>
<tr>
<td>Kartagener syndrome</td>
<td>2.5</td>
</tr>
<tr>
<td>Niemann-Pick B disease</td>
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</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>2.5</td>
</tr>
<tr>
<td>Leigh disease</td>
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<td>Peutz-Jeghers syndrome</td>
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<td>Autosomal dominant spinocerebellar ataxia</td>
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</tr>
<tr>
<td>Abnormal ocular</td>
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</tr>
<tr>
<td>Alport syndrome</td>
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</tr>
<tr>
<td>Crouzon disease</td>
<td>2</td>
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<tr>
<td>Deletion 4p</td>
<td>2</td>
</tr>
<tr>
<td>Klippel-fei syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
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</tr>
<tr>
<td>Nal-patella syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Persistent hyperinsulinemic hypoglycemia of infancy</td>
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<td>Aniridia, sporadic</td>
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<tr>
<td>Fabry disease</td>
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<td>Vanishing phthryia</td>
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<td>Budd-Chiari syndrome</td>
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<tr>
<td>Darier disease</td>
<td>1.5</td>
</tr>
<tr>
<td>X-linked severe combined immunodeficiency, T- B-</td>
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<tr>
<td>bile ducts paucity, syndromic form</td>
<td>1.4</td>
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<tr>
<td>Cat-eye syndrome</td>
<td>1.35</td>
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<tr>
<td>Apert syndrome</td>
<td>1.25</td>
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<td>Spastic paraplegia, familial</td>
<td>1.25</td>
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<tr>
<td>Adult Onset Sjögren’s disease</td>
<td>1.23</td>
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<tr>
<td>Polycystic kidney disease, recessive type</td>
<td>1.2</td>
</tr>
<tr>
<td>Pierre Robin syndrome</td>
<td>1.2</td>
</tr>
<tr>
<td>Glycogen storage disease type 2</td>
<td>1.1</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type 3</td>
<td>1.1</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>1.1</td>
</tr>
<tr>
<td>Neophrinophisitis</td>
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<tr>
<td>3-hydroxy-3-methylglutaryl-CoA dehydrogenase, long chain, deficiency of</td>
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<td>Albers-Schonberg disease</td>
<td>1</td>
</tr>
<tr>
<td>Angiokeratotic edema</td>
<td>1</td>
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<tr>
<td>Ataxia telangiectasia</td>
<td>1</td>
</tr>
<tr>
<td>Chondrodysplasia punctata, rhizomelic type</td>
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</tr>
<tr>
<td>Coloboma, ocular</td>
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<tr>
<td>Emery-Dreifuss muscular dystrophy, X-linked</td>
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<tr>
<td>Fanconi anemia</td>
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</tr>
<tr>
<td>Gaucher disease</td>
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</tr>
<tr>
<td>Gorlin syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Hypotrichic periodic paralysis</td>
<td>1</td>
</tr>
<tr>
<td>Isolated acacemia</td>
<td>1</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type 1</td>
<td>1</td>
</tr>
<tr>
<td>Neuraminidase mucopoly</td>
<td>1</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>1</td>
</tr>
<tr>
<td>Thomsen and Becker disease</td>
<td>1</td>
</tr>
<tr>
<td>Chung Strauss syndrome</td>
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</tr>
<tr>
<td>Ellis Van Creveld syndrome</td>
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</tr>
<tr>
<td>Jeuber-Böthlauher syndrome</td>
<td>0.85</td>
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<tr>
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<tr>
<td>Ebstein anomaly</td>
<td>0.75</td>
</tr>
<tr>
<td>Hyperkalemic periodic paralysis</td>
<td>0.75</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>0.75</td>
</tr>
<tr>
<td>Mucolipidosis type 2</td>
<td>0.75</td>
</tr>
<tr>
<td>Albright hereditary osteodystrophy</td>
<td>0.72</td>
</tr>
<tr>
<td>Menkes disease</td>
<td>0.7</td>
</tr>
<tr>
<td>Niemann-Pick C disease</td>
<td>0.7</td>
</tr>
<tr>
<td>Glycogen storage disease type 4</td>
<td>0.6</td>
</tr>
<tr>
<td>Alpha-sarcoglycanopathy</td>
<td>0.57</td>
</tr>
<tr>
<td>Beta-sarcoglycanopathy</td>
<td>0.57</td>
</tr>
<tr>
<td>Delta-sarcoglycanopathy</td>
<td>0.57</td>
</tr>
<tr>
<td>Gamma-sarcoglycanopathy</td>
<td>0.57</td>
</tr>
<tr>
<td>Tetrasomy 16p</td>
<td>0.55</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>0.5</td>
</tr>
<tr>
<td>Veroedema pigmentosum</td>
<td>0.5</td>
</tr>
<tr>
<td>Acanthoplasminaemia X-linked</td>
<td>0.45</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>0.45</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>0.45</td>
</tr>
<tr>
<td>Christ-Siemens-Touraine syndrome</td>
<td>0.45</td>
</tr>
<tr>
<td>Glutaryl-CoA dehydrogenase deficiency</td>
<td>0.4</td>
</tr>
<tr>
<td>Homocystinuria due to cystathionine beta-synthase deficiency</td>
<td>0.4</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type 4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### Diseases without prevalence data available but with published cases

<table>
<thead>
<tr>
<th>DISEASE NAME</th>
<th>Number of published cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klippel treaurey Weber syndrome</td>
<td>1000</td>
</tr>
<tr>
<td>Whipple disease</td>
<td>1000</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td>750</td>
</tr>
<tr>
<td>Alcari syndrome</td>
<td>500</td>
</tr>
<tr>
<td>CADASIL</td>
<td>500</td>
</tr>
<tr>
<td>LI-Trémati syndrome</td>
<td>400</td>
</tr>
<tr>
<td>Silver-Russel, syndrome de</td>
<td>400</td>
</tr>
<tr>
<td>Caddleman disease</td>
<td>400</td>
</tr>
<tr>
<td>Calls maromarla lietangectatica congenita</td>
<td>300</td>
</tr>
<tr>
<td>Mitus syndrome</td>
<td>300</td>
</tr>
<tr>
<td>Albritin syndrome</td>
<td>300</td>
</tr>
<tr>
<td>Kabuki syndrome</td>
<td>300</td>
</tr>
<tr>
<td>Ondine syndrome</td>
<td>300</td>
</tr>
<tr>
<td>Job syndrome</td>
<td>250</td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>223</td>
</tr>
<tr>
<td>Xanthomasitis cerebrellinicus</td>
<td>200</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>200</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DISEASE NAME</th>
<th>Estimated prevalence (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leisch-Nyhan syndrome</td>
<td>0.38</td>
</tr>
<tr>
<td>Pfeiffer syndrome</td>
<td>0.38</td>
</tr>
<tr>
<td>Severe combined immunodeficiency Y- B</td>
<td>0.35</td>
</tr>
<tr>
<td>Anemia congenital hypoplastic, Blackfan-Diamond type</td>
<td>0.32</td>
</tr>
<tr>
<td>Akatuporina</td>
<td>0.3</td>
</tr>
<tr>
<td>Lissencephaly, type 1, due to LIS 1 anomalies</td>
<td>0.3</td>
</tr>
<tr>
<td>Dopa-responsive dystonia</td>
<td>0.3</td>
</tr>
<tr>
<td>Lipodystrophy, Berardinelli type</td>
<td>0.25</td>
</tr>
<tr>
<td>Progeria</td>
<td>0.25</td>
</tr>
<tr>
<td>Granulomatous disease, chronic</td>
<td>0.2</td>
</tr>
<tr>
<td>Jeune syndrome</td>
<td>0.2</td>
</tr>
<tr>
<td>Natrium due to growth hormone resistance</td>
<td>0.2</td>
</tr>
<tr>
<td>Neurodegeneration with brain iron accumulation (NBIA)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Diseases with prevalence data available

<table>
<thead>
<tr>
<th>DISEASE NAME</th>
<th>Estimated prevalence (/100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creutzfeld-Jakob disease</td>
<td>0.19</td>
</tr>
<tr>
<td>Lowe syndrome</td>
<td>0.19</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type 6</td>
<td>0.16</td>
</tr>
<tr>
<td>CHARGE association</td>
<td>0.14</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>0.13</td>
</tr>
<tr>
<td>Bartter syndrome</td>
<td>0.12</td>
</tr>
<tr>
<td>Muscular dystrophy fukuyama type</td>
<td>0.12</td>
</tr>
<tr>
<td>Walker-warburg syndrome</td>
<td>0.12</td>
</tr>
<tr>
<td>Muscle eye brain disease</td>
<td>0.12</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperelementemia, familial (homogous form)</td>
<td>0.08</td>
</tr>
<tr>
<td>Fabry disease, osicificans progressive</td>
<td>0.08</td>
</tr>
<tr>
<td>Synesthesia type 1</td>
<td>0.05</td>
</tr>
<tr>
<td>Factor XII deficiency, congenital</td>
<td>0.04</td>
</tr>
<tr>
<td>Factor XIII deficiency, congenital</td>
<td>0.04</td>
</tr>
<tr>
<td>Perintal hypophosphatasia</td>
<td>0.03</td>
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</table>
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

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Cases</th>
<th>Crude rate</th>
<th>ASR-W</th>
</tr>
</thead>
<tbody>
<tr>
<td>C33</td>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>C37</td>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>C30</td>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>C72</td>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>C88</td>
<td>3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>C08</td>
<td>4</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

INCIDENCE OF RARE CANCERS IN GRANADA, 1998-2001. FEMALES

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Cases</th>
<th>Crude rate</th>
<th>ASR-W</th>
</tr>
</thead>
<tbody>
<tr>
<td>C33</td>
<td>1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>C37</td>
<td>1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>C30</td>
<td>1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>C72</td>
<td>1</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>C88</td>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>C08</td>
<td>1</td>
<td>0.1</td>
<td>0.0</td>
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</tbody>
</table>
3.1 EurordisCare2: patients lose confidence in health care systems

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

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 5,980 to Eurordis, (5,300 analysed).

This study was the first approach on this matter

METHODS

Table below shows the main characteristics of the diseases:

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Prevalence /10000</th>
<th>Main clinical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn</td>
<td>2-15</td>
<td>digestive</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Inheritable</td>
<td>3</td>
</tr>
<tr>
<td>Duchenne</td>
<td>Inheritable</td>
<td>1.2</td>
</tr>
<tr>
<td>Ehlers Danlos</td>
<td>Inheritable</td>
<td>-</td>
</tr>
<tr>
<td>Fragile X</td>
<td>Inheritable</td>
<td>1.5</td>
</tr>
<tr>
<td>Marfan</td>
<td>Inheritable</td>
<td>2</td>
</tr>
<tr>
<td>Prader Willi</td>
<td>Sporadic</td>
<td>0.5</td>
</tr>
<tr>
<td>Tub. sclerosis</td>
<td>Sporadic Anher</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

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 1997.

4. This study has been partially funded by ISCIII: PI020569, REpIER Network (SG03/129) and RCESP Network (C03/09).
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 _ in Ehlers Danlos syndrome), and on the country (1/3 in Finland, Spain, United Kingdom and Ireland versus _ 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 _ 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

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 over representation of the management and teacher sectors, and under representation 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.

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CONCLUSIONS

• Diagnostic delays exist and may have serious consequences.
• 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.
• 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.
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 bear 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 Immune-deficiency (P) 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 Immune-deficiency 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 Immune-deficiency.

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

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 a 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, 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 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.

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There was a need to create the Greek Association of 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 Eurodis 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 loosing 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 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 POSSUM) 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 issues (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.
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. Some of these have non-specific forms of XLMR which do not include associated somatic, metabolic, or 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 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
• Phenotype/genotype correlation
• Population genetics, new gene identification
• Gene expression during odontogenesis
• Mouse/Human correlations

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”
A specialised clinic for Rare Diseases: the RD Outpatients’ Clinic (RDOC) in Italy

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%.

4 RARE, BUT EXISTING

4.1 No code, no name, no existence

Most of rare diseases do not have a WHO code.

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-

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The exchange of data to establish evidence based medicine is also an example of how coordination and active communication can improve health outcomes. Through the creation of registries and databases, researchers can share information about rare diseases, leading to a more comprehensive understanding of these conditions.

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 cooperation.

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 benchmarking.

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

- Indexing medical diagnoses for use in databases
- Planning and decision support
- Audit of health care services
- Development of expert knowledge systems

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 pre-symptomatic cases

→ MAIN CODING/CLASSIFICATION SYSTEMS IN USE

- International classification of diseases (health data)
- ICPC (International Classification of Primary Care)
- SNOMED (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.
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/polinevritis...)
- By aetiology (e.g.: Congenital malformations / genetic syndromes / Chromosomal / teratogenic / unknown...)
- By mechanism (e.g.: metabolic disorders: Transports / cell cycle / repair defects...)

Therefore they are not universal.

5. Orphanet classification
Current situation: link between ICD-10 and OMIM classifications.
- Unique Identifier
- No hierarchy
- Unique Identifier
- Indexation:  
  - OMIM
  - ICD-10
- Poly-hierarchy
- Indexation:  
  - MeSH
  - ICD-10
- List of signs/symptoms
- List of signs/symptoms
- Expert classifications

- Unique Identifier
- Indexation:  
  - mode of inheritance
  - age at onset
- Genes

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