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**International conference  
of the Network of Public Health Institutions  
on Rare Diseases (NEPHIRD)**

**Istituto Superiore di Sanità  
Rome, September 20-23, 2006**

**Proceedings**

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2008, v, 192 p. Rapporti ISTISAN 08/11 (in English and Italian)

NEPHIRD (Network of Public Health Institutions on Rare Diseases) is a project funded by the European Commission for a 5-year period (since November 2001). Fifteen European and European Union associated countries participated in the project: Armenia, Belgium, Croatia, Denmark, Finland, France, Germany, Italy, Lithuania, Malta, Netherlands, Portugal, Spain, Sweden and UK. NEPHIRD aimed at analysing the epidemiological data in participating countries, and at focusing on health care services accessibility and quality of life of Rare Diseases (RDs) patients. To achieve these objectives, the following research activities were undertaken: assessment of the situation of RDs in participating countries including information on the surveillance systems for RDs and the data sources available for the epidemiological data collection of RDs; estimation of epidemiological indices; evaluation of the quality of and accessibility to health and social care for patients (and families) with RDs; assessment of the quality of life of patients (and families) with RDs; approach in assessing health indicators on RDs.

*Key words:* Rare diseases, Quality of life, Surveillance

Istituto Superiore di Sanità

**Congresso internazionale Network of Public Health Institutions on Rare Diseases (NEPHIRD). Istituto Superiore di Sanità. Roma, 20-23 settembre 2006. Atti.**

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NEPHIRD (Network of Public Health Institutions on Rare Diseases) è un progetto finanziato dalla Commissione Europea della durata di cinque anni, iniziato novembre 2001. Quindici paesi europei ed associati all'UE hanno partecipato a questo progetto: l'Armenia, il Belgio, il Croatia, la Danimarca, la Finlandia, la Francia, la Germania, l'Italia, la Lituania, Malta, i Paesi Bassi, il Portogallo, la Spagna, la Svezia ed il Regno Unito. NEPHIRD ha focalizzato la sua attività sull'analisi dei dati epidemiologici, dell'accessibilità ai servizi sanitari e della qualità di vita nelle persone con malattie rare e delle loro famiglie, intraprendendo le seguenti attività di ricerca: raccolta di informazioni sulla disponibilità di sistemi di sorveglianza per le malattie rare e delle fonti di dati disponibili per la raccolta di dati epidemiologici nei paesi partecipanti al progetto; stima degli indici epidemiologici (prevalenza ed incidenza) per alcune delle malattie oggetto di studio del progetto; valutazione dell'accessibilità ai servizi sanitari; valutazione della qualità di vita; definizione di raccomandazioni per la definizione e valutazione degli indicatori di salute per le malattie rare.

*Parole chiave:* Malattie rare, Qualità della vita, Sorveglianza

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## INTRODUCTION

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In the last 10 years the European Union (EU) and each individual country have increased their efforts to address Rare Diseases (RDs), however gaps still remain and information on the epidemiology, the natural history, the diagnosis and the potential prevention and treatment strategies for RDs are still needed.

In this regard, the collaboration among European and non-European countries needs to be strengthened in order to promote better and coordinated research (to provide scientific evidence addressing the existing information gaps) and to ensure access to treatment and care to patients in need. The collaboration among countries is essential to share information, to develop diagnostic and therapeutic guidelines and to conduct relevant research. The coordination and the establishment of networks at the European level are essential in order to maximise the limited resources and to address the problems related to the “rareness” of the RDs: few cases, limited information on the disease vs the great number of rare diseases (approximately 6,000).

NEPHIRD (acronym derived from “Network of Public Health Institutions on Rare Diseases”), project funded by the European Commission, gave an important contribution to tackling the problem of RDs in public health. Fifteen European and European Union associated countries participated in the project: Armenia, Belgium, Croatia, Denmark, Finland, France, Germany, Italy, Lithuania, Malta, Netherlands, Portugal, Spain, Sweden and UK. Moreover, EUROCAT (acronym derived from its original name European Concerted Action on Congenital Anomalies and Twins) gave an important contribution to NEPHIRD activities.

NEPHIRD aimed at discussing and analysing the epidemiological data collection for RDs in participating countries in order to identify and suggest possible approaches for estimating epidemiological indices (incidence and prevalence). It aimed also at analysing the state of the art with regard to RDs focusing on health care services accessibility and quality for RDs patients and undertaking a specific assessment of the quality of life of RDs patients.

In the frame of the project, the Istituto Superiore di Sanità (the National Institute of Public Health in Italy) organised a 4-day conference to discuss the results of the NEPHIRD project and to continue the discussion on strategies and actions required to address RDs.

The conference was organized in plenary section in the morning and discussion working group in the afternoon on the topics addressed in the morning. Plenary sessions focused on the following: prevention and epidemiology; diagnosis and treatment; social aspects and quality of life.

Each discussion working group was composed of about 10 participants with a discussion leader and a rapporteur; the latter was in charge of reporting the outcomes of the group work in the plenary. The summary of all contributions during the discussion working group are reported in the project website.

Moreover, a full day was dedicated to seminars on each of the RD studied in NEPHIRD in order to increase the knowledge about these diseases (neurofibromatosis, Cornelia de Lange syndrome, Rett Syndrome, Prader-Willi syndrome, myasthenia gravis).

The conference confirmed RDs as an important and relevant public health problem that needs to be addressed in a comprehensive and collaborative way.

The Conference concluded that strategies and solutions need to be discussed and developed in collaboration; however each country has a major role to play in the implementation of such recommendations.

**SESSION I**  
**Prevention and epidemiology**



## Session I. Plenary lecture

# PRIMARY PREVENTION: THE MODEL OF FOLIC ACID

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## Introduction

Birth defects are an important public health problem with an incidence of around 3%. A group of birth defects are Neuronal Tube Defects (NTDs) which are one of the major causes of perinatal mortality.

NTDs include certain central nervous system malformations such as anencephaly, encephalocele and spina bifida, which occur during embryonic development and neural tube closure between the 17th and 30th day after the conception.

The location of the defect along the neuraxis determines the specific anomaly presented: if the cephalic end of the tube is affected, the outcome is the lethal condition anencephalus, or more rarely encephalocele or iniencephalus; if any of the remainder is affected, the outcome is spina bifida. Many neonates with spina bifida and encephalocele survive but the vast majority has lifelong moderate or severe disability including lower limb paralysis, poor bladder control, and intellectual impairment.

Approximately 4,500 pregnancies every year in Europe result in a LiveBirth (LB), StillBirth (SB) or Termination of Pregnancy (TP) of a baby/foetus affected by a NTDs, mainly anencephaly and spina bifida.

In Italy, the anencephaly prevalence was 2.23/10,000 LB, SB, TP from 1996 to 2002, while the prevalence of spina bifida was 3.28/10,000 and 0.80/10,000 for encephalocele. These data have been elaborated in the frame of a collaboration among the National Centre for Rare Diseases of the Istituto Superiore di Sanità and Italian Registers of Congenital Malformations, namely: Campania Register of Congenital Malformations (Registro Campano dei Difetti Congeniti, RCDC), Emilia-Romagna Register on Congenital Malformations (*Indagine sulle Malformazioni congenite in Emilia Romagna*, IMER), North-East Italy Register of Congenital Malformations (*Registro Nord-Est Italia delle malformazioni Congenite*, Registro NEI), Sicilian Register of Congenital Malformations (*Indagine Siciliana Malformazioni Congenite*, ISMAC) and Tuscany Register of Congenital Malformations (*Registro Toscano dei Difetti Congeniti*, RTDC) (1).

NTDs have a multifactorial aetiology, i.e., they arise from the interplay between genetic predisposition and environmental risk factors. The genetic basis is indicated by a number of evidences such as the significantly increased risk of recurrence in families that already had an affected child. Among environmental factors, the inadequate intake of Folic Acid (FA), appears to play a major role; as a consequence, increasing the intake of FA, in the periconceptional period can represent a powerful tool for primary prevention of NTDs.

## Folic acid

FA (or B9 vitamin) is a vitamin belonging to the B group. It is essential for metabolism of sulphur-amino acids and nucleic acids: accordingly, biological processes with high cell proliferation rate are specifically vulnerable to FA deficiency, such as haemopoiesis and embryogenesis. FA is present as folate in several green-leaf vegetables and other food commodities such as spinach, chard, asparagus, artichokes, bruxelles sprouts, citrus, oranges, strawberries, beans and nuts.

Evidence of a possible association between folic acid and NTDs has been described in the scientific literature for more than three decades.

Increased folic acid intake is associated with significantly fewer NTDs in combination with another major birth defect, particularly orofacial clefts, cardiac and limb defects and omphalocele (2).

Folic acid deficiency has been suspected as contributing to NTDs as far back as the 1970s, but the conclusive proof was not demonstrated by large intervention studies until the mid-1980s and early 1990s. In 1976, Smithells *et al.* (3) published an early paper suggesting that deficiencies in FA and/or other micronutrients may predispose developing foetuses to NTDs. In a subsequent paper in 1980, Smithells *et al.* (4) reported on possible prevention of NTDs by periconceptional vitamin supplementation.

In the 1990s, multiple intervention trials demonstrated a substantial reduction in the incidence of NTDs with preconception folic acid treatment (2).

These studies include a British Medical Research Council (MRC) study in which women with a previous history of a pregnancy affected by an NTD were treated with large doses of FA (3). This trial has been estimated that improving folate status sufficiently would result in the prevention of 72% of all NTDs.

In a systematic review effected by Lumley *et al.* (6) has been estimated that periconceptional folate supplementation reduces the prevalence of neural tube defects substantially: relative risk (RR) 0.28 (95% confidence interval (CI) 0.13, 0.58). The reduction is both for occurrent defects (those where the mother has not had a previously affected foetus or infant) RR 0.07 (95% CI 0.00, 1.32) and for recurrent defects (where the mother has had a previously affected infant) RR 0.31 (95% CI 0.14, 0.66).

The trials had very low power to identify differences in limb reduction defects RR 0.59 (95% CI 0.04, 8.34), conotruncal defects RR 0.74 (95% CI 0.16, 3.32), or orofacial clefts RR 0.76 (95% CI 0.24, 2.37) or all other major birth defects combined RR 0.76 (95% CI 0.38, 1.51) (6).

Normal daily requirement for FA is 0.2 mg but it doubles during pregnancy, due to the higher requirement for embryonic development. FA is currently used in several Countries for primary prevention of NTDs; much evidence exists that a significant reduction in the incidence can be achieved, especially in the high-incidence areas. In Italy, this public health practice has still an insufficient development.

Three approaches could be adopted to increase folic acid consumption among women in fertile age:

- The first is increase dietary intake of folate rich foods such as green leafy vegetables and fresh fruit.
- The second involves population health promotion programs to encourage women to take FA supplements periconceptionally, whose effectiveness is supported by a large number of studies. It is noteworthy that effectiveness could be further increased by the proper identification of factors (e.g., drugs, metabolic conditions, lifestyles) that may enhance FA requirements and/or impair FA metabolism.
- The third is the fortification of foods with FA. The food fortification (especially of wheat flour) adopted as a mandatory policy in several non-EU countries (USA, Canada, Chile

and Costa Rica) to provide a supply of FA to all women in fertile age, independently from pregnancy planning. Compared to supplementation, fortification gives a lower risk reduction whilst covering a wider basis of population.

## Promotion of folic acid intake in Italy

In Italy, a network for the promotion of FA for the prevention of congenital defects has been formed and coordinated by the National Centre for Rare Diseases (Istituto Superiore di Sanità, Rome, Italy) together with other institutions. The Italian network for FA promotion was established in April 2004, in order to integrate and optimize the many different activities in course at local or regional level. Different organisations including research institutes, university departments, scientific societies, registers, regional offices and councils, patient associations and newspapers met together to propose and agree recommendations regarding folic acid supplementation. 190 national and 2 international organisations are now part of the network (Figure 1).



**Figure 1. Distribution of the Italian Network organizations by Region**

The Network operates through the following working groups: “Advocacy”, “Pharmaceuticals and diet integrators”, “Education of health care workers”, “Information of the general population”, “Research”, “Surveillance and evaluation”.

Some activities undertaken by the Italian network for the promotion of FA are as follow:

- development of communication strategy for FA promotion;
- development of information, education and communication materials;
- organisation of an awareness week on prevention on neural defects;
- risk and benefit analysis of the folic acid;
- evaluation of the prevalence of congenital malformation preventable by the intake of folic acid;
- development of an education model for the promotion of acid folic in schools.

The recommendation regarding FA supplementation was approved in November 2004 and is as follows:

it is recommended that all fertile women that plan a pregnancy or do not actively exclude the possibility take at least 0.4mg a day of FA. It is fundamental that FA is taken starting at least a month before conception and for the whole first trimester of pregnancy. Women who have had prior NTD-affected pregnancy are at higher risk of having a subsequent affected pregnancy as well as women affected by diseases such as diabetes, etc should assume 4-5 mg of FA every day.

The recommendation, together with more details (why, how much, when, foot notes explaining the choice) and a list of scientific publications that support the recommendation is now freely accessible at <http://www.iss.it/cnmr/>.

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## Session I. Plenary lecture

# SCREENING FOR RARE METABOLIC DISEASES IN THE NEWBORN: EXPERIENCES IN FINLAND

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## Introduction

The genetic background of the Finnish population is characterized by genetic isolation and population bottlenecks which has led to a unique epidemiology for some of the rare hereditary disorders (1).

Some mainly autosomal recessive diseases that are extremely rare elsewhere are relatively common in Finland. On the other hand, some genetic disorders relatively common elsewhere are practically absent in Finland. In particular, the incidence of phenylketonuria (PKU) is low, between 1:100,000 to 1:200,000.

For this reason PKU is not screened for in the Finnish population. The only metabolic disease that is being screened in newborns is hypothyreosis from the naval cord blood. Screening for other metabolic disorders requires that the blood sample is taken after the infant's own metabolic processes have started – at the age of a few days.

## Objectives

A proposal to start a pilot study on screening with tandem Mass Spectrometry (MS/MS) – a new method which enables screening for several rare metabolic disorders simultaneously from one blood sample – necessitated a Health Technology Assessment (HTA) project to estimate the effects of such screening in Finland. The full report (2) is available in Finnish at the Finnohta website and an English summary has been published (3).

The results of this HTA assessment were used as the basis for national health decision making by the National Screening Committee of the Ministry of Social and Health Affairs.

## Methods

The HTA project group consisted of methodological and content experts.

The content experts selected five diseases for the cost-effectiveness evaluation: congenital adrenal hyperplasia (CAH), medium chain Acyl-CoA dehydrogenase deficiency (MCADD), long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD), glutaric aciduria type 1 (GA 1) and PKU.

The selection was based on estimated disease incidence in Finland (Table 1), their expected natural course and the benefit of early detection and treatment.

**Table 1. Estimated incidences of newborns with the rare metabolic disorders selected for screening in Finland**

Disease	Lowest possible	N./10 years	Basic estimate	N./10 years	Highest possible	N./10 years
DD	1:360000	1.5	1:84000	6.5	1:18500	30
LCHADD	1:84000	6.5	1:84000	6.5	1:56000	10
PKU	1:200000	2.5	1:112000	5	1:100000	6
GA 1	1:200000	2.5	1:84000	6.5	1:56000	10
CAH	1:15000	36	1:13500	45	1:13500	45
Total/10 years		49		69.5		101
Total/one year		5		7		10

The form and cost of building up a new screening organization and its annual running costs were calculated with the help of experts. The experts evaluated the quality of life in both genders using the 16D (4). The estimate for length of life in severe handicap was based on a Finnish study (5). The number of Quality-Adjusted Life Years (QALY) was estimated for each disease for the worst current practice, the best current practice and the best screening effect. The cost per QALY was calculated for each scenario as annual screening costs divided by QALYs gained.

Current treatment costs until 16 years of age were modelled for a case with severe multi-handicap with the help of a neuropsychiatric rehabilitation team.

The ethical consequences of screening or not screening were identified together with the HTA project group during the process of producing the report. The perspectives and values of individuals, families, health care professionals, society and health policy decision makers were considered.

## Results

It was estimated that by screening 56,000 newborn per year, 5 to 10 children with a rare metabolic disease could be identified. Early death could be prevented in one to three of these cases and severe handicap in one to five. The total costs of the screening (starting costs included) would be 2.5 million euros per year, or 45 euros per newborn. The cost per QALY gained would be 5,500-25,500 euros. The reduced treatment costs were not included in the estimation. The prevention of one child from being severely handicapped would decrease the costs per QALY to 3,900-18,000 euros.

Based on the results three scenarios were presented to the National Screening Committee: 1) no changes to current situation; 2) expanding screening for CAH; 3) expanding screening for all five disorders. For each scenario the project group estimated the effects on health care system, health, costs and health care politics.

## Conclusion

The estimated cost-effectiveness of screening for rare metabolic disorders in Finland was based on several assumptions. The project group felt, however, confident in concluding that the incremental cost-effectiveness ratio is a maximum of EUR 25,500 per QALY gained. In

addition, preventing one severe handicap would reduce the costs per QALY gained to a maximum of EUR 18,000. Finnish public health care is currently providing treatments at similar costs.

Due to the rarity of PKU in Finland, there is a lack of infrastructure for blood spot screening and sufficient cost-benefit ratio is more difficult to reach. Congenital hypothyroidism is screened from cord blood, which means that introducing blood spot screening would require a new screening organization. Currently the diagnosis and treatment of rare metabolic disorders is not centralized in Finland. Implementing MS/MS screening in Finland would require extensive education of the health care system from primary care level to special clinics. This would also increase knowledge of other disorders caused by inborn errors of metabolism.

The National Screening Committee was critical about the limitations identified in the HTA report - true incidence of the diseases or effects of early detection and treatment in comparison to current practice in Finland are not known. The effect of early detection and treatment on the length and quality of life can only be an estimate as the research in this field is still sparse.

The current course of the diseases in Finland is reasonably well known for CAH and LCHADD (6, 7). For MCADD we do not know which mutations (8, 9) might be relevant in Finland. The incidence of GA 1 in Finland is not known; so far all diagnosed cases are severely handicapped or have died. PKU is not identified in Finnish children before a child shows symptoms of developmental delay. It was thus estimated that currently PKU cases would suffer from permanent cognitive damage.

The National Screening Committee organized a seminar with content experts and critical questions concerning the expertise in metabolic disorders in Finland were discussed. The Screening committee requested for a detailed plan on how to collect the missing evidence. A new working group was founded to produce this research plan. It was estimated that a randomized controlled study enrolling all Finnish newborns for 8 years would be needed to answer the preset questions. Major ethical issues were raised as to conducting the study.

The National Screening Committee identified that currently the best achievable level evidence on effectiveness comes from the interrupted time series studies. Based on the high costs of the screening, limited knowledge on the incidence of the rare disorders in Finland and on the effect of early detection and treatment, the National Screening Committee decided, that screening for metabolic disorders in newborn should not be expanded in Finland for the moment. However, the Screening Committee decided to follow the ongoing research in this field and be prepared to re-evaluate their decision when new research evidence is available.

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Session I. Plenary lecture

## EPIDEMIOLOGICAL REGISTRATION AND SURVEILLANCE OF RARE MALFORMATIONS: THE EUROCAT MODEL\*

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The European network of Registers for the Epidemiologic Surveillance of Congenital Anomalies (EUROCAT, acronym derived from its original name European Concerted Action on Congenital Anomalies and Twins) is funded by the Public Health Programme of the European Commission (*Grant Agreement N. 2003219 of DG Sanco Public Health & Consumer Protection*). EUROCAT is a WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies. Started in 1979, it is now including 39 registers in 19 countries, surveying more than one million births per year in Europe.

Providing essential epidemiologic information on congenital anomalies in Europe, co-ordinating the establishment of new registers throughout Europe collecting comparable, standardised data, co-ordinate the detection and response to clusters and early warning of teratogenic exposures, evaluating the effectiveness of primary prevention, assessing the impact of developments in prenatal screening, providing an information and resource centre and ready collaborative research network to address the causes and prevention of congenital anomalies and the treatment, care and outcome of affected individuals.

Main reasons of the collaboration are to provide pooling of data, comparison of data, common response to public health questions, sharing of expertise and resources.

EUROCAT is a population-based registers network: 25% of European birth population is covered by high quality multiple source registers, ascertaining terminations of pregnancy and births by a standardised questionnaire.

Data, documents and publications are reported in the EUROCAT website (<http://www.eurocat.ulster.ac.uk>). An editor data manager programme developed for the central register and the participating centres is accessible on request by external collaborators.

EUROCAT activity on rare diseases regards both routine collection, registration, analysis of and *ad hoc* studies on rare congenital anomalies.

A draft report on the European prevalence of the Cornelia de Lange syndrome has been prepared and analysis of the epidemiology of Achondroplasia, Thanatophoric dysplasia, campomelic dysplasia, Apert, Osteogenesis Imperfecta Type II and III is ongoing.

The results of a survey of confidentiality and consent issues in EUROCAT registers was presented to the Network of Competent Authorities and the Rare Diseases Task Force, 5-6 July 2005 in Luxembourg, and was published in the BMJ (Busby A, Abramsky L, Dolk H, Armstrong B, Eurocat Folic Acid Working Group. Preventing neural tube defects in Europe: population based study. *BMJ* 2005;330(7491):574-5).

A *cluster advisory service* to manage response to clusters or public health concerns through analysis of central database and co-ordination of extra data collection has been developed.

A study programme on gastroschisis, a rare abdominal wall anomaly for which an increasing prevalence worldwide and an association with young maternal age are reported, is in progress.

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\* Abstract of the lecture

Findings indicating that the phenomenon of increasing trend is not restricted to younger mothers only are in press. A EUROCAT working group on folic acid and congenital anomalies is working on. As member of the Rare Diseases Task Force, it was a partner in organizing the European Rare Diseases Conference, Luxembourg, June 2005, where a presentation on strategies for prevention of neural tube defects by raising periconceptional folate status was given.

A large and validated database on rare congenital anomalies and a wide and experienced network are available for research and public health purposes.

## Session I. Plenary lecture

# EXPLOITING AVAILABLE DATABASES: MORTALITY AND HOSPITAL DISCHARGE

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## Introduction

Public-health research on rare diseases would benefit from prevalence data; however, national-level data are often not available. As an alternative, prevalence rates can be conservatively estimated based on the number of deaths and hospital discharges. Moreover, given that more severe diseases are more likely to be reported on the death certificate, the prevalence estimated based on mortality data are more accurate for these diseases. However, it must be taken into account whether or not the code of the International Classification of Diseases (ICD) is specific for the given disease.

Data on the number of deaths and hospital discharges can be obtained from existing national-level databases, which refer to greater numbers of cases than local databases or studies; this is especially important for rare diseases, considering that they are just that “rare” (1-4).

## Objectives

The objectives of the present study were to estimate the prevalence of selected rare diseases in Italy based on mortality data from two national-level sources and to discuss the implications of estimating prevalence based on mortality and hospital-discharge data.

## Methods

The two data sources were the National Mortality Database (Statistics Unit of the Istituto Superiore di Sanità) and individual multiple-causes-of death records (Istituto Nazionale di Statistica, ISTAT: the National Institute of Statistics).

Both sources take data from death certificates, which, according to recommendations of the World Health Organisation, contain:

- *underlying causes of death*  
(the disease/injury starting the chain of events leading directly to death);
- *non-underlying causes of death*  
(those resulting in the underlying cause, or contributing to death yet not part of the chain of events leading directly to death, or immediately causing death).

The National Mortality Database in Italy has 100% national coverage and is based on data provided by ISTAT. This database contains only the underlying cause of death (codified using

the International Classification Diseases, Revision 9: ICD-9), in addition to important demographic data (e.g., age, gender, marital status, and place of birth, residence, and death). The individual multiple-causes-of death records also have a high national coverage and contain data on all causes of death exactly as written out in full by the medical examiner on the death certificate.

Disease prevalence can be conservatively estimated by totalling the number of deaths for which the disease is reported as the underlying cause and the number of deaths with the disease reported as a non-underlying cause. In the present work, we estimated the prevalence for two rare diseases using 1999 mortality data, specifically, pleural mesothelioma and neurofibromatosis type 1. Mesothelioma is a serious tumoral pathology, which in about 90% of cases affects the pleura, and on rare occasions other sites. Given that the ICD-9 does not morphologically classify tumours, pleural mesothelioma is classified using the code for “Malignant Neoplasm of Pleura”, 163 (163.0-163.9). Neurofibromatosis type 1 (or “Von Recklinghausen’s Disease”) is an autosomal dominant neurocutaneous disease. The ICD-9 code (237.7) is not specific, and includes neurofibromatosis type 2, which is much less common but generally more severe.

For each disease, we first examined the National Mortality Database and selected all deaths whose underlying cause was identified with the ICD code for that disease. Since the ICD code is not always specific, deaths due to other causes with the same code must be excluded. To this end, we examined the underlying cause of death on the multiple-cause-of death records, on which the disease is written out in full, and excluded those not due to the specific disease, which provided us with the number of deaths with the specific disease as the underlying cause. We then re-examined the multiple-cause-of-death records to identify deaths with the disease reported as a non-underlying cause. The record linkage between the two data sources was performed using a univocal numerical code.

## Results

With regard to pleural mesothelioma, in the National Mortality Database, the underlying cause was codified as “163” for 1,080 deaths. Of these, in the multiple-cause-of-death records, only 798 had “mesothelioma” or “pleural mesothelioma” written as the underlying cause (the remaining deaths were from other cancers or mesothelioma of other sites). Thus 798 deaths had pleural mesothelioma as the underlying cause. In the multiple-cause-of-death records, we then identified 66 deaths with pleural mesothelioma as a non-underlying cause. Thus the estimated number of deaths due to pleural mesothelioma was 864 (798 + 66).

Regarding neurofibromatosis type 1, in the National Mortality Database, the underlying cause was codified as “237.7” for 20 deaths. Of these, in the multiple-cause-of-death records, only 18 had “neurofibromatosis type 1” (or a similar term) or “Von Recklinghausen’s Disease” written as the underlying cause (the remaining 2 had “neurofibromatosis type 2”). Thus 18 deaths had neurofibromatosis type 1 as the underlying cause. In the multiple-cause-of-death records, we then identified 43 deaths with neurofibromatosis type 1 as a non-underlying cause. The total was thus 61 (18 + 43).



## Conclusions

With regard to pleural mesothelioma, given that this is a very serious and fatal disease, the estimated prevalence can be considered as fairly accurate. In our study, the analysis of the underlying causes with ICD-9 code 163 showed that about 74% (798/1080) were pleural mesothelioma. This is in accordance with reports that about three out of every four deaths coded as ICD-9 163 are pleural mesothelioma.

For diseases that, like neurofibromatosis type 1, are rarely the underlying cause of death, it is particularly important to consider the non-underlying causes. For diseases, for which limited mortality data are available (again, like neurofibromatosis type 1), mortality databases can also provide other useful information (e.g., mean age at death, also by gender).

Moreover, hospital-discharge data may be used to estimate disease prevalence. In fact, many rare diseases are not fatal; thus, prevalence rates estimated based on mortality data are probably less accurate. In Italy, hospital-discharge data, available since 2001, are obligatory and refer to about 13,000,000 hospitalisations annually. These data also include other information, such as clinical aspects (e.g., diagnoses and symptoms), codified using ICD-9-Clinical Modification (ICD-9-CM). ICD-9-CM is based on ICD-9 but provides additional detailed information on morbidity. For example, neurofibromatosis type 1 has a specific code (237.71) that distinguishes it from neurofibromatosis type 2 (237.72).

In conclusion, since for many rare diseases, prevalence data are lacking, estimates based on available mortality data (though potentially limited in terms of accuracy) are important for public-health purposes. These data are routinely collected in all countries and are exhaustive and of fairly good quality. Such databases could also be used to obtain additional potentially useful information, such as selected characteristics of persons affected by rare diseases (1-4).

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## Session I. Plenary lecture

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# **COLLECTION AND EVALUATION OF EPIDEMIOLOGICAL DATA ON RARE DISEASES IN EUROPE: EXPERIENCE OF NEPHIRD-EUROC COLLABORATION**

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## **Introduction**

Birth defects including chromosomal abnormalities, single gene disorders, and isolated/multiple anomalies due to teratogen exposure or of unknown origin are an important medical and public health problem. They are the leading cause of stillbirth and infant mortality and an important contributor to childhood morbidity in developed countries (1).

Although as a group they represent a significant health care problem, birth defects are an assembly of numerous rare diseases. The studies on the epidemiological characteristics of rare disorders are limited, because they require the analysis of large populations and a well-organized diagnostic network.

To bring together data on the individuals affected by rare genetic disorders and to promote the research to their causes and possibilities of prevention, population-based networks of registers for the surveillance of birth defects have been set in Europe (2-6).

The EUROCAT (European Network of Registers for the Epidemiologic Surveillance of Congenital Anomalies) now covers 1,5 million births per year, a third of births in Europe. It is designed to provide epidemiological data and to identify genetic and environmental factors important in the etiology of birth defects. Epidemiological data on more than 80 types of congenital anomaly reported among live births, stillbirths, and terminations of pregnancy after prenatal diagnosis are recorded. This makes possible the identification of teratogen exposures and the assessment of the impact of primary prevention and prenatal screening policies and practice at a population level (6).

On the other hand, the Network of Public Health Institutions on Rare Diseases (NEPHIRD) was established with the aim to identify the state of the art of the activities concerning rare diseases in Europe (7). These two networks connected focusing on the analysis on selected rare syndromes as target models of rare disorders in order to create the concept of more effective organization of the public health services for affected individuals by integrating epidemiologic, clinical and scientific knowledge.

## **Objectives**

There is very little documented information on the epidemiology of rare genetic syndromes in literature (8). For effective planning of the public health services, it is essential to identify the total number of affected individuals and the prevalence per disease. We also need to assess the impact of prenatal diagnostic procedures, the natural history and the life expectancy for each

rare disease. The description of epidemiological characteristics of rare syndromes is important for an improved understanding of these conditions and for clarifying findings from a hospital based series of patients.

The objective of this study is the analysis of epidemiological data of selected rare syndromes in European population, including the assessment of prevalence rates, pregnancy outcome, impact of prenatal diagnosis, survival, clinical presentation, and possible teratogen exposures. In this report, the preliminary results of the ongoing study are presented based on example of Cornelia de Lange syndrome, the rare disorder extensively studied by NEPHIRD.

An overall evaluation of the quality of registration and coding of rare syndromes including the role of medical geneticists in diagnosing syndrome cases should be addressed as well in order to assess the accuracy of the diagnosis of the rare syndromes in registers of congenital anomalies.

The methods used and the data collected will serve as a starting point for further scientific research in the field of epidemiology, public health services and clinical practice concerning rare genetic syndromes in European population.

## Methods

The study is still in progress and includes analysis of epidemiological data on 9 rare syndromes that in their classical expression are easily diagnosed within 7 days of birth (Wiedemann-Beckwith syndrome, Cornelia de Lange syndrome, Ellis van Creveld syndrome, Fraser syndrome, Fryns syndrome, Goldenhar (oculoauricular dysplasia) syndrome, Holt-Oram syndrome, Meckel-Gruber syndrome, and Treacher Collins syndrome). Here the methods used and the problems encountered in data collection and interpretation are presented based on the example of Cornelia de Lange syndrome.

The data were provided by 33 registers from 16 European countries that register congenital malformations in live births, foetal deaths with gestational age > 20 weeks and terminations of pregnancy. The study period covered the years from 1980 to 2005.

Registers participating in the study use the same EUROCAT database program and the same epidemiological methodologies. All registers are population-based, with the exception of Campania (Italy), ISMAC (Indagine Siciliana Malformazioni Congenite, Sicilian Surveying of Congenital Malformations, Italy) and North West Thames (UK), which are hospital-based. The cases are ascertained from multiple data sources to ensure complete and accurate information. The data on the contribution of clinical geneticists in the diagnosis of rare syndromes in participating registers were obtained through a questionnaire that was distributed to all the collaborating centres in the course of the study.

The registration forms for the EUROCAT database are completed by members of the medical staff, and contain information regarding the foetus/infant (sex, number of babies delivered, birth outcome, birth weight, gestational length, survival beyond one week of age), and present malformations. Recorded data on prenatal diagnosis include the methods (amniocentesis, ultrasound, chorionic villi sampling) and gestational age at prenatal diagnosis. The data concerning mother (occupation, age at delivery, reproductive history, assisted conception, illness before and during pregnancy, habitual and unusual exposures, drugs taken in the first trimester of pregnancy) and father (age at delivery, occupation) were also registered. In the analysis of the associated anomalies, minor anomalies were not included. The malformations were classified according to the EUROCAT subgroups of congenital anomalies (available from [www.eurocat.ulster.ac.uk](http://www.eurocat.ulster.ac.uk), last visited 20/07/2007).

The data for this study were extracted from the central database on the basis of the ICD/BPA-9 (International Classification of Diseases as adapted by the British Paediatric Association, revision 9) or ICD-10 and MIM (McKusick's classification in Mendelian Inheritance in Man) codes specific for syndrome under study. Medical geneticist reviewed the data on all patients and contacted the local registers for the confirmation and for text information if missing in the central database. Protection of privacy was assured, therefore confidentiality was maintained.

## Results

### **Evaluation of the questionnaires regarding the diagnosis of the rare syndrome cases in European registers**

The role of clinical geneticist in the process of diagnosing, case reviewing, coding and classification within birth defects surveillance program has not been fully assessed (9). A short questionnaire regarding the role of clinical geneticist was sent to registers participating in the EUROCAT programme. We obtained answers from 32 out of 33 (97%) registers.

Clinical geneticists are involved in the diagnosis of most patients with multiple malformations and syndromes in 17 out of 32 registers (53%). In the remaining 15/32 registers (47%) geneticists are involved in the evaluation of some selected patients with multiple malformations or syndromes. In 84.4% (27/32) of registers, there is a further reviewing after the initial diagnosis. Experts participating in reviewing of syndrome cases are mostly geneticists or paediatricians. Clinical geneticists are reviewing the diagnosis of rare syndrome cases in 24 (89%) registers. In 17 (63%) registers, there is routine revision of all rare syndrome cases, while in 7 (26%) registers only some cases are under review. Experts participating in the coding of rare syndromes are mostly geneticists (in 20/32 or 63% of registers), paediatricians (9/32 or 28%) and epidemiologists (9/32 or 28%).

Reviewing of coding is performed in 17 out of 32 (53%) of registers. Coding review is done again mostly by geneticists (11/17 or 65%). Follow-up of syndrome cases is performed in 24 out of 32 (75%) registers. This is also done mostly by geneticists (13/24 or 54% all syndromes, 6/24 or 25% some cases) and paediatricians.

In conclusion, geneticists are actively involved in diagnosing of rare genetic syndromes in all participating registers. In 20 out of 32 (63%) registers they are also involved in coding and in 19/32 (79%) in follow-up of syndrome cases. The average number of geneticists in registers of congenital anomalies participating in EUROCAT programme is  $2.0 \pm 1.47$  (0.15.-5.0) per 10,000 births.

### **Preliminary results on the epidemiology of classical form of Cornelia de Lange syndrome**

Preliminary results of the ongoing study presented based on example of Cornelia de Lange Syndrome (CdLS), the rare disorder extensively studied by NEPHIRD.

We found the prevalence of the classical form of CdLS to be 1.24/100,000 births and estimated the overall CdLS prevalence at 1.6-2.2/100,000 births (1:62,000-1:45,000). This is significantly less than the usually cited prevalence figure of 1:10,000 births (10). The prevalence was stable during the 20 years of monitoring. The most frequent associated congenital malformations were limb defects (73.1%), congenital heart defects (45.6%), central

nervous system malformations (40.2%) and cleft palate (21.7%). Prenatal ultrasound examination detected abnormalities in approximately a quarter of all cases. Live born infants with CdLS have a high first week survival rate (91.4%). In the majority of patients, karyotype was normal. Two identified abnormal karyotypes caused CdLS phenotype by gene disruption. Maternal and paternal age does not seem to be risk factors for CdLS. Almost 70% of patients, born after the 37th week of gestation, weighed less than 2500 g. The low birth weight correlates with a more severe phenotype, including severe limb anomalies, which are significantly more often present in males. All patients were sporadic and there was no evidence of exposure to consistent teratogenic agents.

## **Lessons learned from evaluation of data collected on rare syndrome cases in European registers**

Although results of our study showed that there is enough expertise in evaluation of rare syndrome cases in European registers of congenital anomalies, the analysis of data showed that there is still place for improvement at local and central level. There is a need to develop common guidelines for reporting and coding of the rare syndromes. Firstly, the diagnostic criteria on which the clinical diagnosis is based should be declared. The case report should include text description (detailed report of major malformations, dysmorphic features and minor anomalies), possibly photographs (posing confidentiality problems for some registers), X-rays, molecular tests and all other details relevant for the diagnosis. The prenatal data are also necessary for complete case ascertainment. An extended follow-up of cases will also be useful and informative, as phenotype is evolving and some anomalies may be discovered at a later stage.

There is always possibility that some cases will be left without final diagnosis remaining in the group of multiple malformation syndromes (especially in case of foetal death or termination of pregnancy). Therefore, detailed description and periodical revision of multiple malformation cases is warranted.

In general, knowledge related to the rare syndromes of health professionals other than clinical geneticists involved in the registration of birth defects should be upgraded.

## **Conclusions and proposals**

Epidemiology data on rare syndromes derived from literature studies are mostly based on biased hospital statistics and not on data obtained from the general population. More accurate and high quality registration can be achieved by a team of specially trained and motivated multidisciplinary professionals incorporated into the international network of birth registers. To assess the accuracy of notification of rare genetic disorders it is essential to determine how genetic services are integrated in the registers of birth defects and to what extent they participate in the process of diagnosis.

Surveillance of epidemiological variables of rare disorders enables evaluation of the quality of preventive procedures aimed at reducing the frequency of birth defects (primary prevention, genetic counselling, methods of prenatal diagnosis etc), forming the basis for public health programmes and preventive health services for affected individuals. The improvement of the methodology of registration of syndrome cases will facilitate in future the use of databases for research into the causes of specific patterns of malformations. International cooperation in data

collection and exchange of expertise will allow us to address relevant issues of interest, such as prevention and service delivery for rare disorders at a European level.

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## Session I. Plenary lecture

# NATIONAL AND REGIONAL REGISTERS: LOMBARDY NETWORK ON RARE DISEASES EXPERIENCE\*

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In the last years, the need to promote network of reference centres for rare diseases has been considered a priority in several countries. Italy has officially adopted the concept of centres of reference for rare diseases with a national plan in 2001.

The plan includes:

- accreditation of reference centres in each region, for one or more diseases;
- establishment of (inter)regional coordinating centres;
- register of patients with rare diseases at the Istituto Superiore di Sanità (ISS) in Rome.

Lombardy Region, an area of 9 million people in Northern Italy, started to identify regional expert centres in December 2001. The Clinical Research Centre for Rare Diseases *Aldo e Cele Daccò* of the Mario Negri Institute was nominated as Regional Coordinating Centre.

Patients with rare diseases registered at the reference centres do not pay tickets on diagnostic/follow-up procedures and receive drugs free of charge.

The first call for proposals was mainly addressed to university/teaching hospitals. In following calls, there was a focus on trying to increase geographical coverage. Twenty-nine reference centres were identified on the whole.

The number of diseases covered by each centre differs. Six centres cover more than 100 different diseases; the other 23 centres are very specialized in a small number of diseases. Currently all regional centres are disease oriented covering all aspects of the patients' needs, from diagnosis to therapy.

This complex network is monitored regularly by the Coordinating Centre.

All the referral departments and physicians located in one of the 29 hospitals are listed on the website of the regional network (<http://malattierare.marionegri.it/>).

A regional register for rare diseases has been implemented and data will be collected by physicians at reference centres. In addition, the Coordinating Centre has to manage the regional register of rare diseases and to send the epidemiological data at ISS in Rome.

The structure of the regional database will be presented.

Expected results include the possibility to:

- improve epidemiological knowledge about rare diseases;
- evaluate the activity of reference centres;
- collect clinical data about patients with rare diseases and find potentially eligible patients for clinical studies on rare diseases.

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\* Abstract of the lecture

## Session I. Plenary lecture

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# ENHANCE NETWORKING AMONG SCIENTISTS TO THE PROFIT OF BOTH GROUPS OF RESEARCHERS AND THE PATIENTS

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## Introduction

The Piedmont Regional Register for Rare Diseases is part of a larger project, the Regional Network for Rare Diseases, whose aims include developing diagnostic protocols to be shared among physicians in the Region, providing information on care and legislation to health professionals, single patients and patient associations and collecting data for epidemiologic studies. Another important aim of the network is to address a rational distribution of health care funds.

The development of the Regional Network of Rare Diseases was based on the promulgation of two Regional laws (1, 2). The first one involved setting up a widespread Regional Network that included all the public health facilities in the Region. It also established that the co-ordinating role would be assigned to the “Centro di Ricerche di Immunopatologia e Documentazione su Malattie Rare” in Turin. The tasks of this co-ordinating centre include managing the Regional Register for Rare Diseases, promoting medical education in this field, and cooperating with the Istituto Superiore di Sanità, the Ministry of Health and patients’ associations.

The uniqueness of the Piedmont organisation of rare diseases is the potential involvement of every specialist in the Network. Indeed, each specialist working in the Regional Health System is obliged to fill in a computerised form in order to register patients who are diagnosed as having a rare disease. This procedure allows the patient to obtain health care free of charge.

## Objectives

The Register was developed to collect data on about 700 diseases. Data analysis should provide us with epidemiologic estimates and an evaluation of diagnostic criteria, as well as with information about therapeutic approaches and possibly about the costs related to disease management. Attempts to evaluate the entire amount of health costs related to peculiar diseases (direct and indirect expenses) by employing data mining techniques are ongoing.

## Methods

Setting up the Piedmont Register for Rare Diseases was carried out in two phases.

The first one lasted 6 months (between June and November 2004) and involved six experimental Centres in the metropolitan area of Turin. During this phase, data concerning 832 patients affected by rare diseases were collected.



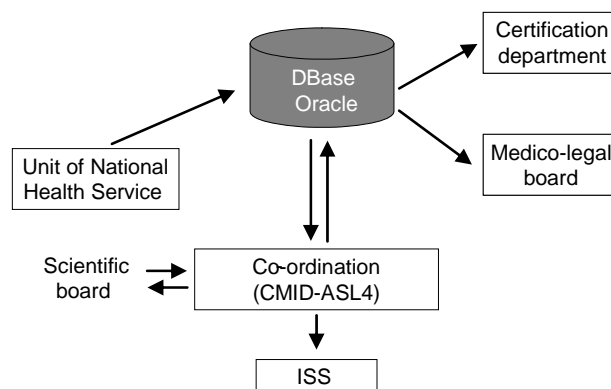
The second phase started in January 2006, and is currently ongoing. This phase (Table 1) involves each Public Health facility in Piedmont and 244 health professionals trained in 15 courses that were organised by the Regional Agency for Informatics of Piedmont (Centro Studi Informatici, CSI).

**Table 1. Health professionals involved in the first 12 months of activity of the Piedmont Register for Rare Diseases**

Medical research centres	n. of operators
Local area facilities and hospitals	104
Main regional hospitals (including University Hospitals)	131
Public research centres (excluding Piedmont Universities)	9

Software for registering patients was developed by CSI. It is based on an Oracle Database that can be accessed via web. The software installed in each Local Health Unit (Azienda Sabnitaria Locale, ASL) of the Regional Health Service was produced using net technology. Access to the database is gained through a Regional Virtual Private Network called Rupar. In compliance with the Italian Privacy Laws, the patient's personal data and medical information are stored separately in the database.

A unique key allows the operator to access all data. The Co-ordinating Centre can access and validate anonymous data in order to carry out epidemiologic studies. Anonymous data are also sent to the National Register for Rare diseases run by the Italian Istituto Superiore di Sanità (Figure 1). The patient's data are also available to the Local Health Services Certification Department, to provide certification allowing patients to obtain health care free of charge.



**Figure 1. Data flow chart used for the Piedmont Register of Rare Diseases**

The Register collects the patient's personal, social and disease-related data (including dates of onset and diagnosis), information regarding clinical signs and symptoms and, interestingly, diagnostic criteria as well.

Different kinds of computerized forms are available. One of the forms is used to register patients who are suspected of having a rare disease, but for whom a definitive diagnosis cannot be made due to a lack of clinical data or because genetic evaluation is incomplete. A second form is used when all the diagnostic criteria have been met and an established diagnosis has been made. The last of the forms is used to register cases which had been diagnosed in the past.

The Register also includes information about the therapy that patients are currently being administered.

## Results

During the first 12 months of activity, i.e., between January 2006 and January 2007, 1,932 files on patients affected by rare diseases were collected: 1,221 concern patients with an established diagnosis and 634 regard patients with a past diagnosis of a rare disease who had been registered as "historical cases". Seventy-seven patients were lacking a definitive diagnosis, however a strong clinical suspicion did exist. Careful evaluation led us to exclude 402 forms from validation due to missing mandatory information.

Tables 2 and 3 summarize data distribution among Regional Health Facilities, and the distribution according to the ICD-9-CM (International Classification of Diseases, revision 9, Clinical Modification).

The hospitals involved in certification activity include the main University Hospitals, i.e.: San Giovanni Battista Hospital (which treats adults); Sant'Anna and Regina Margherita Hospital (which treat children).

Diseases of the musculo-skeletal system and connective tissue were the most commonly represented ones in the first year of activity of the Piedmont Register, followed by diseases of the blood and blood forming organs including haemoglobinopathies and genetically transmitted coagulation disorders.

**Table 2. Number of validated certification forms in Piedmont hospitals (January 2007)**

Hospital or health facility	n. validated forms
ASL 1 - Torino	5
ASL 3 - Torino	23
ASL 4 - Torino	110
ASL 9 - Ivrea	21
ASL 10 - Collegno	8
ASL 17 - Savigliano	5
ASL 19 - Asti	3
ASL 21 - Casale Monferrato	1
ASO Ospedale San Giovanni Battista - Torino	406
ASO OIRM Ospedale Infantile Regina Elena) / Ospedale San Anna - Torino	414
ASO Ospedale S. Luigi - Orbassano	193
ASO Ospedale Maggiore della Carità - Novara	54
ASO Ospedale SS. Antonio e Biagio / Ospedale Infantile Cesare Arrigo - Alessandria	25
ASO Ordine Mauriziano di Torino	262
Total	1530

ASL: Azienda Sanitaria Locale (Local Health Unit); ASO: Azienda Sanitaria Ospedaliera (hospital)

**Table 3. Numer of certification forms according to ICD-9 classification**

Type of disease	n. patients
Infectious and parasitic diseases	92
Neoplasms	139
Endocrine, nutritional, and metabolic diseases and immunity disorders	188
Diseases of blood and blood-forming organs	219
Diseases of nervous system and sense organs	168
Diseases of circulatory system	72
Diseases of respiratory system	84
Diseases of digestive system	11
Diseases of genitourinary system	15
Diseases of skin and subcutaneous tissue	48
Diseases of musculoskeletal system and connective tissue	293
Congenital anomalies	201
Total	1530

Congenital abnormalities collectively represented the third type of registered pathologies, followed by endocrine, nutritional and metabolic diseases and immunity disorders which also included genetically transmitted diseases such as disorders of aminoacid metabolism or congenital immunodeficiency. Diseases of the nervous system only represented the fifth most common type of pathology described in the first year of prospective data collection. Rare neoplastic disorders accounted for 139 cases, mainly neurofibromatosis, whereas other rare neoplasms, which are not included in the list of Ministerial Decree 279/2001, were registered by the “Registro Tumori del Piemonte e Valle d’Aosta”. The registered cases of infectious and parasitic diseases were mainly represented by sarcoidosis (an obvious case of inappropriate disease allocation), whereas true rare infections, such as Hansen’s disease, represented only a negligible amount of cases. Diseases of the respiratory and circulatory systems were mainly represented by pulmonary idiopathic fibrosis or pulmonary hypertension and vasculitis, respectively.

## Discussion

Clinical features and social data collected in the register were chosen in order to carry out an analysis of the epidemiological, clinical, and financial aspects of rare diseases in Piedmont.

The patients’ personal data can be useful to help us estimate local incidence and prevalence of disease, as well as to identify possible clusters or outbreaks of cases. More specific insight into the diseases, including dates of onset and diagnosis are critical for calculating diagnostic delay and revealing the level of general knowledge about rare diseases. Information on signs and symptoms allow us to verify whether the case has been diagnosed correctly. Diagnostic data are important to evaluate the accuracy and uniformity of the criteria that are adopted in Piedmont. The final goal of this part of the certification form of Rare Diseases is to develop shared diagnostic criteria to be employed by each Institution.

The use of three different forms (for provisional, established and historical diagnosis) should allow for correct follow-up of registered patients. The provisional forms allow us to estimate how many patients are suspected of being affected by rare diseases, and, by comparing these forms to the forms regarding established diagnosis, we can estimate how many suspected cases will be confirmed. Registration of historical cases is useful in order to develop a historical

reference database that can be compared to current and future data regarding the incidence and prevalence of a rare disease.

The information concerning which drugs are supplied to patients allows us both to estimate the pharmaceutical costs of rare diseases, and to monitor side-effects.

The main problems we encountered in this initial experience concerning the management of personal data. On the basis of this law, each individual must provide written consent, even if his/her health data are simply used for statistical purposes. Obtaining written consent was not always easy on account of various reasons.

Another problem is the underestimation of cases, which is mainly due to the partial involvement of specialists. In order to solve this problem, meetings with several health professionals throughout the Region are currently ongoing. Finally, developing unique diagnostic criteria among all the specialists involved in the diagnosis of rare disorders represents a critical target of the regional Network. The development of consensus statements on diagnostic parameters may benefit from the analysis of the “Diagnostic Criteria Forms”.

## Conclusions

To date, the Register has collected data on about 2,000 patients. Of course, the collected data do not suffice to make epidemiological estimates of patients affected by rare diseases in Piedmont.

The key factor for developing an accurate and complete Register of Rare Diseases is the involvement of all specialists, as well as general practitioners and pediatricians in an integrated network aimed at providing the best available health care to patients, but also looking for the “Zebras on the commons” diseases (4).

Attempts to cross reference data with other regional databases such as the “Hospital Discharge Forms” and the “Regional Register of Disability Challenged Patients” have been made in order to estimate hospitalisation rates and costs of procedures and devices for patients affected by rare diseases, while the Register of Deaths have been studied in order to estimate mortality rates of selected rare diseases. Work is currently in progress to develop specific data mining programs.

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## Session I. Plenary lecture

# ITALIAN NATIONAL REGISTER FOR RARE DISEASES

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The Centers for Disease Control and Prevention defines public health surveillance as (1):

The ongoing systematic collection, analysis, and interpretation of epidemiological data is essential to the planning, implementation and evaluation of public health programmes, closely integrated with the timely dissemination of these data to those who need to know. The final link of the surveillance chain is the application of these data to prevention and control. A surveillance system includes a functional capacity for data collection, analysis, and dissemination linked to public health programs.

It is clear from this definition that a surveillance program has to point out the aims to implement the procedures how data should be collected, analysed, disseminated and used. A legal support is important to implement these activities.

Following art. 3 Ministerial Decree 279/2001, the National Health Institute of Italy (Istituto Superiore di Sanità, ISS) establishes the Italian National Register for Rare Diseases (Registro Nazionale Malattie Rare, RNMR) (2).

The principal objectives are to estimate the incidence, prevalence and geographical distribution of Rare Diseases (RD), but also to design a new model of prevention, diagnosis, treatment and rehabilitation. Therefore, the data from the RNMR will be helpful for planning and evaluating healthcare programmes, for research activities (case-control-study, clinical trial), but also prioritise the allocation of health resources. Even more, the RNMR will harmonise the dishomogenous information that exists on the morbidity indices of RDs in the national territory (3).

The RNMR aims also to evaluate the diagnostic and therapeutic protocols, in order to improve awareness of diagnosis, treatment and assistance for RD. A national aggregation of experience, with the necessary international discussion and exchange of views, will allow better research to overcome the many obstacles to the development of diagnostic approaches, therapies and ways of providing healthcare. In Table 1 the main aims of the RNMR are shown.

**Table 1. RNMR main aims**

Fields	Aims
Epidemiologic	Estimate the prevalence and incidence Know the spatial and temporal distribution of RDs Assessment of mortality associated with RDs
Public health	Health planning: need for services (burden of disease and patient's migration) Evaluation of diagnostic and therapeutic protocols
Clinical research	Case-control study Clinical trials

A key role in the surveillance is identifying data sources that are able to make appropriate diagnosis of the RD. In Italy, each Region identifies hospitals and others structure, within its territory by legislation mandate, as a potential data sources. Moreover, a Regional linkman will have the responsibility of coordinating data collection at regional level.

The procedures of data collection, from Italian regional data source to the RNMR, are web-based in respect of privacy Italian law. The software is located at the ISS, and it is able to accept electronic transfer of data files from each regional coordinator. The ISS has elaborated a form for data collection such that each participating health-unit has to collect a minimum data set, including the fifteen variables shown in Table 2.

**Table 2. Type of information collected**

Information concerning	Type of information
<b>Patient</b>	Identification code (fiscal code) Sex Date of birth Province and town of residence Educational level Profession
<b>Disease</b>	Name of the disease Date of onset Date of diagnosis Diagnostic criteria Clinical, laboratory and instrumental examination Treatment given Patient outcome (live or dead)
<b>Institution</b>	The diagnosing centre Institution that sends data

A key role in the establishing the register is related to quality of data collected. The quality depends on case ascertainment and geographical coverage. The RNMR is nation wide. Moreover, the RNMR is a passive case ascertainment and the ISS has not duty in finding and confirming the cases. Even if it will be necessary an “in built” control mechanism that will ensure quality of the collected data, and to elaborate new tools to increase the system’ performance.

In conclusion, the RNMR has several strenght points:

- clearly established objectives;
- correlation of the objectives with data structure;
- web data collection (<http://www.iss.it/cnmr/>);

Moreover, the system can respond to new objective, new diseases and permits to add new questions or variables.

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## Session I. Discussion Group

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### FOCUS GROUP 1.

### PREVENTION: FOETAL ALCOHOL SYNDROME

<i>Discussion leader</i>	Ingeborg Barisic (Croatia)
<i>Rapporteurs</i>	Berenice Doray (France), Rumen Stefanov (Bulgaria)
<i>Participants</i>	Miranda Siouti (Greece)
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	Mario Cicchetti (Italy)
	Elisabetta Dichiacchio (Italy)

## Background

Foetal Alcohol Syndrome (FAS) is an important public health problem and thought to be a leading preventable cause of intellectual impairment worldwide. FAS is a diagnosis given to children who have been exposed to maternal alcohol consumption during pregnancy. The number and severity of symptoms may range from mild to serious. The degree to which a foetus is affected depends on the duration and amount of maternal alcohol intake, greater amounts and a longer duration causing more severe symptoms. However, only smaller proportion of pregnancies exposed to alcohol will result in FAS. This is presumably due to the genetic differences in ethanol metabolism of the mother and the foetus (1).

In 1973, the first diagnostic criteria for FAS were established. Individuals with FAS have 3 basic characteristics: dysmorphic facial features, growth deficiency and central nervous system dysfunction. Prenatal alcohol exposure has been also associated with different cardiac, skeletal, renal, ocular and auditory abnormalities (2). There have been several updating of guidelines for referral and diagnosis of FAS, the more recent ones being more accurate and based on up-to-date scientific evidence and current clinical experience (3-5). Terms used to describe the spectrum of effects that result from prenatal exposure to alcohol, include foetal alcohol effect, alcohol-related birth defects, and alcohol-related neurodevelopment disorder. For all these manifestations recently a common term has been introduced: Foetal Alcohol Spectrum Disorder (FASD), defined as the range of effects that can occur in an individual whose mother drank alcohol during pregnancy. These effects may include physical, mental, behavioural and/or learning disabilities with possible lifelong implications.

At present FASD is not intended for use as a clinical diagnosis (5). In USA, in 2002 the Centers for Diseases Control and prevention (CDC) organized a scientific working group that issued guidelines for referral and diagnosis of FAS while the work on FASD is in progress (Annex) (5). It seems that these guidelines are now widely accepted in USA. On the other hand, in Europe there is still no definite consensus on the diagnostic criteria for FAS. Some of the diagnostic guidelines or checklist systems use different cut-offs and some of them are not sufficiently specific to ensure diagnostic accuracy leading to the inconsistencies in the FAS diagnosis.

## **Prevalence**

The prevalence of FAS in Europe has not yet accurately documented, due to lack of research, underreporting of alcohol consumption, differences in access and attendance for antenatal and paediatric services, lack of knowledge and standard diagnostic criteria. Nearly all prospective epidemiological studies on FAS have been conducted in USA. These studies report FAS prevalence rates from 0.2 to 2.0 cases per 1,000 births. Using this prevalence rates we can estimate that among the approximately 5 million infants born each year in Europe, around 5000 will be born with FAS.

The high prevalence rate for FAS in the USA (1-2 per 1,000 live births) and the relatively low rate reported in some studies from Europe (0.08 per 1,000) does not correspond to observed alcohol consumption (6). On the contrary, there is evidence that the alcohol consumption in Europe is increasing (7). A recent study from Italian province of Lazio found a prevalence of 3.7 to 7.4 per 1,000 children. The rate of FASD was 20.3 to 40.5 per 1,000 and estimated at 35 per 1,000 overall or between 2.3 and 4.1% of all children (8). This highly exceeds previously published estimates of both FAS and FASD. Thus, despite the progress made in the epidemiology of FAS, the magnitude of the problem in Europe is still not fully appreciated.

## **Pregnancies at risk**

Available data show that low socioeconomic status is strongly associated with women's alcohol use before and during pregnancy. Some populations (e.g. Native Americans or Indigenous Australians) are particularly vulnerable and at the higher risk for alcohol related foetal spectrum of disorders. Women at high risk for alcohol use when pregnant tend to be younger, less educated, single, and unemployed. Other variables associated with high-risk status for maternal alcohol use were past sexual abuse, current or past physical abuse, smoking, using other drugs, living with substance users. Other contributing factors for high-risk classification include feeling sad, believing that drinking any amount of alcohol while pregnant was acceptable, and being able to hold four or more drinks.

## **Alcohol consumption before pregnancy as a risk factor for FAS and FAS-related disorders**

US studies show that 15% of women of childbearing age could be classified as moderate or heavy drinkers. Binge drinking reported about 13% of women (five or more drinks at one occasion). Among pregnant women in America 13% continue to use alcohol, approximately 3% report binge drinking or frequent drinking (i.e., seven or more drinks per week) (9). Alcohol consumption before pregnancy can be considered the main significant risk factor for alcohol consumption during pregnancy. Therefore, this group of women must be regarded as "high risk".

## **Prevention**

Prevention of FAS and related disorders is of paramount public health importance. Estimates of lifetime cost varied from \$596,000 in 1980 to \$1.4 million in 1988 and we can assume that there is a significant increase in the costs from that period (10). Our goals in the prevention of FAS are to define the problem of alcohol consumption in European region, to raise the awareness of the population and health professionals and to develop programs that are effective and targeted to specific populations for reducing the risk of an alcohol-exposed pregnancy.



## **Recommendations by the focus group**

After a thorough discussion and the analysis of recent studies concerning prevention of FAS (11-19), the focus group has recommended the following specific actions, targeting primary, secondary and tertiary prevention of FAS and foetal alcohol spectrum disorders.

The first step is to study the prevalence of FAS in population-based surveys in Europe, and to determine the existing knowledge and state of the art on health education and promotion in the field of alcohol consumption. In this way we can follow up and evaluate the outcome of future preventive strategies and policy development.

At primary level, two types of activities are needed – health promotion and specific actions. Health promotion should be especially aimed at the following target groups: children, medical professionals (in particular primary health care providers), young women, low socio-economic groups and media. A broad variety of health information methods can be applied – leaflets, articles in journals, TV and radio spots, warning labels on alcoholic beverages etc.

Women of childbearing age should be advised to limit their alcohol consumption to no more than one unit a day when they are planning pregnancy and to sustain completely from drinking while pregnant. This can be done by primary health care clinicians (family physicians, obstetricians) while discussing the family planning and other aspects of reproductive health. The integration of information about FAS prevention together with other available and ongoing prenatal programs (for example folic acid) can be easily done with comparatively good cost-benefit ratio and low burden for the national healthcare systems. Above recommendations could be planned, organized and monitored by a working group on FAS at EU level.

Apart from the general information about the harmful effects of alcohol consumption during pregnancy, primary prevention should incorporate specific screening strategies to identify and intervene with women at risk for alcohol-exposed pregnancy.

Specific actions must also include establishment of a unified FAS case definition that will put the basis for the setting up of a surveillance system at both national and international levels. For this purpose a group of experts should evaluate different checklists and agree upon common diagnostic criteria for FAS and FASD providing a balance between too conservative and too broad diagnostic criteria. Studies utilising different diagnostic criteria in a single population will help to define the optimal diagnostic system.

Secondary prevention can be effective if done simultaneously at prenatal and postnatal levels. Pregnant women should be asked about their alcohol consumption during routine antenatal clinic visit. The detection of the women at risk for FAS can be improved by using one of the standard screening tools (e.g. AUDIT, TWEAK, and T-ACE). Even a brief interruption of drinking habits for women at risk can significantly reduce the incidence of FAS.

We should continue to evaluate the usefulness of biomarkers from maternal blood or meconium in the detection of alcohol exposure. A detailed foetus ultrasound screening can detect facial dysmorphism, growth retardation and/or associated anomalies, thus assuring timely diagnosis and adequate follow up of both the mother and child. Apart from this, counselling must be a significant activity within the secondary level prevention of FAS.

The early diagnosis in the neonatal period can be improved by applying age-appropriate evaluation system. Further screening for FAS should be performed in infancy/school period when additional neurological, cognitive and behavioural characteristics may become apparent.

At tertiary level, guidelines for referral and global healthcare management of children with FAS must be elaborated, that will guarantee optimal quality of life and adequate health, social and educational services. Such guidelines can be prepared at EU level by a working group on FAS.

## Annex 1.

### CDC Diagnostic criteria for FAS (July 2004, last revision May 2005)

#### CRITERIA FOR FAS DIAGNOSIS

FAS diagnosis requires all four of the following findings:

**1. Documentation of all three facial dysmorphism**

Based on racial norms, individual exhibits all three characteristic facial features:

- smooth philtrum
- thin vermilion border
- small palpebral fissures

**2. Documentation of growth deficits**

Confirmed prenatal or postnatal height or weight, or both, at or below the 10<sup>th</sup> percentile, documented at any one point in time (adjusted for age, sex, gestational age, and race or ethnicity).

**3. Documentation of Central Nervous System abnormalities**

*Structural*

Head circumference  $\leq$  10<sup>th</sup> percentile for age and sex.

Clinically significant brain abnormalities observable through imaging.

*Neurological*

Neurological problems not due to a postnatal insult or fever, or other soft neurological signs outside normal limits

*Functional*

Performance substantially below that expected for an individual's age, schooling or circumstances as evidenced by:

1. Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3<sup>rd</sup> percentile (2 standard deviations below the mean for standardized testing)

OR

2. Functional deficits below the 16<sup>th</sup> percentile (1 standard deviation below the mean for standardized testing in at least three of the following domains:
  - a) cognitive or developmental deficits or discrepancies
  - b) executive functioning deficits
  - c) motor functioning delays
  - d) problems with attention or hyperactivity
  - e) social skills
  - f) other, such as sensory problems, pragmatic language problems, memory deficits, etc.

**4. Maternal alcohol exposure**

1. Confirmed prenatal alcohol exposure
2. Unknown prenatal alcohol exposure

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## Session I. Discussion Group

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### FOCUS GROUP 2.

## EPIDEMIOLOGICAL DATA COLLECTION OF RARE DISEASES

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<i>Rapporteurs</i>	Elisana Petrela (Albania), Yllka. Kodra (Italy)
<i>Participants:</i>	Erica Daina (Italy) Albert Matevoysan (Armenia) Algirdas Utkus (Lithuania) Paola Zinzi (Italy) Piera Capra (Italy) Ilona Autti-Ramo (Finland) Sirrku Peltonen (Finland)

Data collection of Rare Diseases (RDs) is useful in terms of epidemiology in order to:

- to estimate the prevalence, incidence and mortality of RDs;
- to know the spatial and temporal distribution of RDs;
- to study the natural history of RDs;
- to conduct analytic and clinical trials of potential risk factor;

and in term of public health in order to:

- provide indicators of access and quality of health care;
- plan health interventions;
- estimate costs of RDs;
- prioritise the allocation of health resources.

Mortality data are not adequate to provide information on the indices of prevalence and incidence.

The reliability of mortality data depends on accuracy of the vital registration systems of each country.

The principle topics regarding epidemiological data collection are:

- *Case definition*

Experts have to establish standard case definition applicable for the purpose of data collection. Case definition for the purpose of clinical trial might be different from that of epidemiology.

To better identify cases, there is a need to:

- continuous training for professionals;
- providing guidelines;
- create a network of check points;
- active case finding as much as possible;
- providing incentives to data providers;
- potential use of database on delivery of specific therapies;
- severity of RDs: need for standardization (especially for genetic diseases).

– *Prevalence rate*

The following two conditions are important in the estimation of the denominators and numerators of prevalence rate:

- Estimates of epidemiological relevance can be achieved through the collection of significant numbers of cases from a relatively large population. (Robertson NP 1998).
- Case ascertainment of the best quality is possible when we focus on a limited population and do good follow up and monitoring with active case finding (Zivadinov R, 1998).

Therefore, it is important to balance the two aspects of data collection: quantity and quality.

Personnel required for the establishment of a reliable register of one or more RDs in a population of 10 million is likely to be in the order of 5-10 full time persons, including at least 2 scientists.

– *Inadequacy of ICD-9 and ICD-10*

Effective coding is critical to data collection because subsequent use of data depends *on storage and retrieval of causes using codes*. Problems with coding have a major impact on rare diseases. Only a few inappropriate coded cases can greatly influence rate.

The system of ICD-9 (ICD9-CM) and ICD-10 are still not sufficiently precise for many RDs.

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## Session I. Discussion Group

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### FOCUS GROUP 3.

### EPIDEMIOLOGICAL INDICATORS: MORTALITY DATA FOR RARE DISEASES

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*Rapporteur*            Janos Sandor (Hungary)  
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### From single to multiple causes of death

Cause-specific mortality is one of the most reliable epidemiological indicators and can contribute to developing etiologic hypotheses, to tracing temporal changes in disease patterns, to describing the health status of different population groups, and to estimating disease prevalence (1-3). However, cause of death is often expressed in terms of a single cause. Although this was probably adequate for describing mortality when public-health concerns mainly involved acute and infectious diseases, it has become less appropriate since industrialized nations have undergone the so-called “epidemiologic transition”, that is, the extensive diffusion of chronic diseases and the simultaneous decrease in acute diseases, especially infectious diseases. Consequently, the proportion of deaths due to chronic diseases has increased, yet these deaths often involve a number of coexisting conditions, which may not be linked by a direct etiologic chain, complicating the identification of a single underlying cause.

To more accurately describe mortality when deaths are due to concurrent causes and to better understand the associations among these causes, multiple cause-of-death records can be of use (1, 2). These records contain not only the underlying cause (i.e., the disease/injury starting the chain of events leading directly to death) but also non-underlying causes (i.e., those resulting in the underlying cause, or contributing to death yet not part of the chain of events leading directly to death or immediately causing death). In some countries (e.g., Australia, South Africa, and the United States), multiple cause-of-death data have been routinely produced for a number of years. In Italy, though these data are not routinely collected or codified, ISTAT (the National Institute of Statistics) collects data on all causes of death exactly as written out in full by the medical examiner on the death certificate, beginning with 1995 mortality data.

### Multiple cause of death data for rare diseases

Multiple-cause-of-death records are particularly useful in studying rare diseases. For example, some rare diseases are seldom the underlying cause of death (e.g., neurofibromatosis type 1, NF1, one of the rare diseases studied in NEPHIRD); thus, data on non-underlying causes

are particularly important. Moreover, for rare diseases that have been the focus of very few mortality studies (again, such as NF1), routinely collected mortality data can provide additional information, such as the mean and median age at death and the most common conditions associated with death (4).

### **Codification of rare diseases and data linkage among various sources**

Mortality data are generally codified according to the International Classification of Diseases (ICD), though the specific version of ICD may vary by country. However, in ICD-9 and ICD-10, not all rare diseases have their own specific code. For instance, in ICD-9, a single code is used to classify both types of neurofibromatosis, two diseases that differ for a number of aspects, including lethality, although in ICD-11, specific codes for hundreds of rare diseases are expected to be added. For this reason, it would be useful to link mortality data with data on deaths from other sources, such as hospital discharge records and disease registers. Linkage would also be useful for acquiring a more complete description of the impact of the disease being studied.

### **Limitations in the use of mortality data**

The validity and reliability of data are important concerns even when considering only a single cause of death; when considering multiple causes, there are obviously more data, which could mean more potential problems. The quality of mortality data depends of course on the accuracy of the death certificate, which in addition to causes of death includes other medical information, such as the sequence of conditions that resulted in death and other contributing medical factors. Demographic data are also recorded, such as age, gender, place of residence, marital status, and occupation.

Moreover, mortality data, which must be collected for all deaths and are generally verified by statistics institutes, are made available with a certain delay (usually a few years). However, this limit is only relative, given that trends in mortality are evaluated over long periods of time, except for severe or fatal diseases that emerge relatively suddenly (e.g., the onset of the AIDS epidemic in the mid-1980s). Another limitation concerns data linkage, which must be performed taking into account laws and regulations for safeguarding privacy.

Finally, for describing those rare diseases that are not lethal, other data sources - besides mortality information - must be taken into account.

### **Final recommendation**

The final recommendation of the Discussion Group is to contribute to the understanding of rare diseases by using mortality data, which are routinely collected in all countries and are exhaustive and of “fairly good” quality. Particular attention should be paid to multiple cause-of-death data, which can allow researchers to maximize the use of the diagnostic information on the death certificate and provide ways of looking at mortality data that go well beyond the typical examination of the underlying cause of death. Linkage of mortality data with data from other registers should also be considered, to combine the high quality of data from specific pathology registers with the completeness of mortality data.

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**SESSION II**  
**Diagnosis and treatment**



## Session II. Plenary lecture

# DIAGNOSTIC TEST: PRINCIPLES OF VALIDATION AND QUALITY

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## Introduction

Diagnostic tests carried out in medical laboratories may have a significant impact on the clinical decision-making process and therefore on the health and wellbeing of individuals or groups. This applies and is of the utmost importance in the field of rare diseases, a highly heterogeneous category of diseases representing a relevant cause of morbidity and mortality in childhood and adulthood (Health-EU - The Public Health Portal of the European Union, [http://ec.europa.eu/health-eu/health\\_problems/rare\\_diseases/index\\_en.htm](http://ec.europa.eu/health-eu/health_problems/rare_diseases/index_en.htm)). Within the European Union, a disease is considered as rare when it affects less than 5 out of 10000 individuals. Seven thousand rare diseases have been recorded to date. As a consequence, although each disease may be rare, the number of patients suffering from rare diseases may be high (Health-EU).

The seriousness of the problem and public concern led the European Union to set up a specific action programme (1999-2003) and under the new Public Health Programme (2003-2008) the European Union continues to promote optimal prevention, diagnosis and treatment of rare diseases in Europe. By creating networks, sharing experience and training, and disseminating knowledge, the EU hopes to achieve an integrated approach and deliver a coordinated response to this major concern (Health-EU).

Advances in genetics, analytical chemistry and technology, in recent decades have allowed the implementation of genetic tests and new diagnostic tools, which, when available, contribute to improve also in the field of rare diseases: i) diagnosis in symptomatic individuals, ii) prediction of risks of future disease in asymptomatic individuals and iii) chances for early treatment, reduced impairment and genetic reproductive counselling. To these aims, both screening and confirmation tests are necessary and their reliability is of the utmost importance. For this reason laboratory tests must be validated before their application as diagnostic tools and their quality maintained throughout use, usually by operating under a quality management system and obtaining, whenever possible, formal accreditation.

## Objectives

Nowadays a range of different analytical techniques (chromosomal, chemical: e.g. chromatography and tandem mass spectrometry, biochemical: e.g. enzymatic methods, immunoassay, and/or molecular/DNA-based tests: e.g. cellular cultures and fluorescence in situ hybridization, FISH; polymerase chain reaction, PCR) is applied by clinical laboratories all over the world for the diagnosis of rare diseases and new tests are continuously being developed. The main objective, from a public health perspective, is the reliability of the results obtained with such techniques. Reliable information on the validation of diagnostic tests and the expected

quality of the results, including considerations of the ethical, legal and social implications should be made available to policy makers for decision making.

According to the international standard ISO 9000 (1), quality is defined as “degree to which a set of inherent characteristics fulfils requirements” and the term validation, in its broader sense refers to the “confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled”. According to ACCE (a specific CDC-Sponsored Project carried out by the Foundation of Blood Research: available at: <http://www.cdc.gov/genomics/gTesting/>, last visited 9/05/2008), the validation of a diagnostic test involves four components: analytical validity, clinical validity, clinical utility and associated ethical, legal and social implications.

For a specific clinical disorder and setting in which the testing is done, analytical validation will define the ability of the test to determine accurately and reliably the genotype of interest. The process involves the definition of the requirements and the knowledge of the performances of the chosen method. Four specific elements should be considered: analytical sensitivity, analytical specificity, quality control and assay robustness.

Clinical validation defines the ability of the test to detect or predict the associated disorder, involving, in addition to analytical validity, clinical specificity, clinical sensitivity, prevalence, penetrance, positive and negative predictive values and effects of (genetic or environmental) modifiers.

Parameters to be assessed for the clinical validation of diagnostic tests are as follow:

- *Sensitivity (true-positive rate)*  
The proportion of individuals in a population that will be correctly identified when administered a test designed to detect a particular disease, calculated as the number of true positive results divided by the number of true positive and false negative results.
- *Specificity (true negative rate)*  
The statistical probability that an individual who does not have the particular disease being tested for will be correctly identified as negative, expressed as the proportion of true negative results to the total of true negative and false positive results.
- *False-positive rate*  
The proportion of individuals in a population that will be incorrectly identified when administered a test designed to detect a particular disease; calculated as follows: 100% minus the specificity (percentage).
- *False-negative rate*  
The statistical probability that an individual who does not have the particular disease being tested for will be incorrectly identified as negative; calculated as follows: 100% minus the sensitivity (percentage).
- *Prevalence*  
The total number of cases of a disease in a given population at a certain time.
- *Positive predictive value*  
The probability that an individual with a positive test has, or will develop, a particular disease, or characteristic, that the test is designed to detect; calculated as follows: number of true-positive results/ (number of true-positive results + false-positive results).
- *Negative predictive value*  
The probability that a subject with a negative test result actually does not have the disease; calculated as follows: number of true-negative results/(number of true-negative results + false-negative results).

- *Penetrance*  
The extent to which the properties controlled by a gene, its phenotype, will be expressed.
- *Genetic modifiers*  
Other genes that can influence the phenotype associated with the gene of interest.
- *Environmental modifiers*  
Factors other than genes that can influence the phenotype associated with the gene of interest.

Clinical utility addresses the issues to be considered when evaluating the risks and benefits associated with the introduction of the test in clinical practice.

Finally, ethical, legal and social implications associated with the validation and implementation of the test should also be considered.

The model process stated within the ACCE project is targeted to the evaluation of data on emerging genetic tests, but it can be applied as well to the totality of clinical laboratory tests, taking into account the differences between the analytical validation of qualitative and quantitative tests. In addition, the validation and the quality of diagnostic tests for rare diseases requires specific issues to be addressed, such as strategies for clinical validation, when numbers of patients over geographic areas is not sufficiently wide, and approaches to analytical validation that take into account the lack or scarcity of primary/reference methods, certified standards and reference materials, external quality assessment programmes and commercial quality control materials. Ideally, test results, wherever obtained, should be comparable through their relationship to the same reference (SI units or other agreed standards), taking into account, in case of quantitative tests, the stated uncertainty of the result. Performance targets, including those for the uncertainty of measurement, should be set taking into account the final use of the data.

In this paper, we focus on the aspects of the analytical validation of diagnostic tests and the principles and methods needed to achieve and maintain the quality of analytical results.

## Methods

### Quality management system and traceability

Considerable efforts are carried out internationally to promote the reliability of diagnostic tests. Laboratories can demonstrate their competence by implementing the requirements of specific international standards (2, 3). Both standards require the definition of a quality management system including:

- control of documents, including analytical procedures and test reports;
- education, training and qualification of personnel;
- control of working environment and equipment (metrological confirmation, including calibration);
- use of approved *in vitro* diagnostic devices (subjected to confirmation of repeatability and absence of significant bias within the laboratory) or, if none is available, other validated methods;
- control of handling and storage of testing materials;
- monitoring of analytical procedures by means of internal quality control;
- regular participation in appropriate External Quality Assessment /Proficiency Testing schemes (EQA/PT schemes);
- traceability of test results including the evaluation of the uncertainty of the measurement, whenever possible.

## Analytical validation of diagnostic tests: key issues

The process of analytical validation of diagnostic tests starts with the definition of the requirements for the intended use, in terms of desirable performance characteristics. Typically such requirements may include analytical performances such as detection and quantification limits, repeatability and trueness of the results, but other aspects, such as sample throughput or sample volume may also need to be defined, e.g. according to the intended use of the method for screening or confirmation purposes.

Before any other step is taken, the test to be evaluated should be completely described in a written procedure, so that the necessary experiments can be carried out in a reproducible way and provide reliable information on the performance of the method. No change is allowed during the validation study. The procedure should be as detailed as deemed necessary, in order to be applied consistently throughout routine use.

Parameters to be taken into account for method validation include: identity, selectivity/specificity, limits of detection/quantification; linear and working range; precision (repeatability, intra and interlaboratory reproducibility); trueness; robustness; accuracy of the measurement test; uncertainty.

Since the terminology in this field is rapidly changing, the definition of each parameter, when quantitative tests are considered, is given below (4):

- *Identity*  
The evidence that the signal produced at the measurement stage, which has been attributed to the analyte, due only to the analyte and not to the presence of chemically or physically similar substances or arising as a coincidence.
- *Specificity/selectivity*  
The ability of a method to determine accurately and specifically the analyte of interest in the presence of other components in a sample matrix under the stated conditions of the test.
- *Limit of detection*  
The lowest concentration of analyte that can be detected, but not necessarily quantitated under the stated condition of the test.
- *Limit of quantification (LoQ)*  
The lowest concentration of analyte that can be determined with acceptable accuracy (e.g.  $\pm 10\%$ ) under the stated condition of the test.
- *Linearity*  
The ability of the method to obtain test results proportional to the concentration of analytes.  
Linear regression and residual analysis of the relationship between response (y) and concentration (x) of an appropriate set of calibration standards are usual methods to test for linearity.
- *Precision*  
“The closeness of agreement between independent test results obtained under stipulated conditions” (5).  
Quantitative measures of precision depend critically on the stipulated conditions, repeatability and reproducibility being particular sets of extreme conditions. Precision under repeatability conditions is determined from independent test results obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time. Intermediate precision, also reported

as within laboratory reproducibility, expresses within laboratory variation, i.e. the variation associated with different intra laboratory conditions: different days (temperature, humidity, etc.), different analysts, different reagent lots, etc. Studies of intermediate precision should be planned in such a way as to include the expected variations of conditions that may influence the results in everyday practice, e.g. by analysing the same sample over a longer period of time.

– *Trueness*

“The closeness of agreement between the average value obtained from a large set of test results and an accepted reference value” (5).

Whenever possible, trueness is studied by analysing matrix Certified Reference Materials (CRMs) under repeatability conditions and by comparing the difference between the certified and found values with the uncertainty of the trueness estimate, which combines the uncertainty of the certified value and that of the measured value. The analysis of CRMs also allows to document the traceability of the laboratory result to the corresponding SI unit by means of the chain of comparisons through the CRM.

– *Robustness*

Measure of the capacity of a measurement procedure to remain unaffected by small variations in the experimental conditions.

It provides an indication of its reliability during normal usage and it is usually assessed by deliberately introducing small changes in the analytical parameters and examining the effect on the results. The effect of several parameters can be assessed at once using specific experimental designs (e.g. fractional factorial designs).

– *Accuracy of the measurement test*

“The closeness of agreement between a test result and the accepted reference value” (5).

– *Uncertainty of measurement*

“Parameter associated with the result of a measurement that characterises the dispersion of the values that could be attributed to the measurand” (6).

It represents a quantitative estimate of the accuracy of the result with a defined confidence level. The process of evaluating measurement uncertainty starts from the definition of a measurement model and the identification of possible sources of uncertainty. If the validation experiments cover most sources of variation, data obtained from method validation can be used to evaluate the uncertainty of measurement. Although the concept of uncertainty cannot be applied directly to qualitative test results such as those from detection tests or the determination of attributes for identification, individual sources of variability, e.g. consistency of reagent performance and analyst interpretation, should be identified and demonstrated to be under control and the incidence of false positive and false negative results associated with the tests should be evaluated (7).

Due to the complexity of the validation process, appropriate planning and dedicated (technical and human) resources are necessary to carry out this task. Written documents – such as a validation programme specifying: information (to be) obtained from existing sources and the experiments to be carried out; records of raw data and their elaboration; evidence of the comparison with the requirements and a signed statement that the method is “fit to purpose” – should be prepared, maintained and made available when necessary.

## Results

### Targets for analytical performance

Recently, the debate on how to set targets of performance which are fit for the intended purpose for tests in laboratory medicine led to the organization of a specific Consensus Conference (8) which established the following hierarchy of methodologies, listed from the most to the least relevant:

- effect of analytical performances on clinical outcome of tests in specific clinical situations;
- effect of analytical performances on clinical decisions, based on biological variability components or opinions of clinicians;
- recommendations published by international or national organisations or local experts (individuals or groups);
- quality specifications stated by government or regulatory bodies or EQA/PT schemes organisers;
- state-of-the-art, based on results of EQA/PT schemes, scientific literature or experience.

### International initiatives for traceability in laboratory medicine

The EC Directive 79/98 stated the provisions for the quality and metrological traceability of *in vitro* diagnostic devices (9). For the scope of the Directive ‘*in vitro* diagnostic medical device’ means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, to be used *in vitro* for the examination of human specimens, for the purpose of providing information: concerning a physiological or pathological state, or concerning a congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures. In this context, the manufacturer must assure that “the traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order” (9).

Several international standards have addressed specific issues related to the quality and traceability of analytical results in laboratory medicine, including terminology, reference materials, reference methods and reference laboratories (10-14).

Specific recommendations have been developed by the 21th Conférence Générale des Poids et Mesures ([www.bipm.fr](http://www.bipm.fr)) concerning: the use of SI units in human health and the development of metrology in chemistry and in biotechnologies. As a consequence, a new Working Group on Bioanalysis of the Consultative Committee for Amount of Substance (CCQM) is addressing since 2001 the issue of international comparability of measurements of biomolecules. National Metrological Institutes (NMIs) and other laboratories designated by NMIs that do not have in-house expertise are actively engaged in biotechnology standardization efforts; definition of key target biomeasurements and their prioritisation for CCQM studies; planning and performing of pilot studies for the assessment of the measurement capabilities for key measurands (DNA, proteins) and to address key issues in the standardization of biomeasurements (circular dichroism, fluorescence, extraction procedures, uncertainty estimates); planning of and performing key-comparisons to document current measurement capabilities for relevant measurands.

The International Committee of Weights and Measures (CIPM), the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC), and the International Laboratory Accreditation Cooperation (ILAC) have agreed to cooperate to establish a Joint Committee for



Traceability in Laboratory Medicine, with the acronym JCTLM: available at: <http://www.bipm.org/en/committees/jc/jctlm>; last visited 9/05/2008). The goal of the JCTLM is to provide a worldwide platform to promote and give guidance on internationally recognized and accepted equivalence of measurements in laboratory medicine and traceability to appropriate measurement standards. The Committee consists of two working groups, one assessing the current state of reference materials and methods, the other devoted to the establishment of Networks of reference laboratories.

The US Centers for Diseases Control has established a Genetic Testing Reference Material Coordination Program (GeT-RM available at: <http://wwwn.cdc.gov/dls/genetics/rmmaterials/default.aspx>; last visited 9/05/2008) previously The Genetic Testing Quality Control Materials Program (GTQC), with the goal to coordinate a self-sustaining community process to improve the availability of appropriate and verified materials for: quality control (QC), proficiency testing, test development & validation, research. The purpose is to help the genetic testing community to obtain appropriate and verified QC materials, to facilitate and coordinate information exchange between users and providers of QC materials, to coordinate efforts for contribution, development, verification and distribution of QC materials for genetic testing.

The European Research Network ERNDIM available at: <http://www.erndimqa.nl/InfoFrame.php>; last visited 9/05/2008) is addressing the issue of monitoring the performance of laboratories performing “rare” analyses in the field of inborn errors of metabolism, by organising specific External Quality Assessment Schemes, run at a European level. Beside quantitative Schemes (e.g. for amino acids, organic acids, purines, pyrimidines etc.), qualitative Schemes focus on the qualitative interpretation of laboratory tests. In these schemes, participants must select relevant analysis based on the clinical details provided and interpret the analytical results to indicate a presumptive diagnosis.

## **A complete test validation in practice**

Inborn errors of metabolism represent a good example on how the approach has been put into practice. Newborn screening for inborn errors of metabolism, since the screening for phenylketonuria has been introduced in the 1960s, has saved many children from disability and death thus representing one of the major health advances of the past century in the paediatric field. With the advent of tandem mass spectroscopy in the 1990s, the variety of conditions for which screening is available has increased dramatically. Recently the American College of Medical Genetics has published guidelines for newborn screening programs based on tandem mass spectrometry, including 29 disorders (15):

1. Phenylketonuria
2. Maple syrup urine disease
3. Homocystinuria
4. Citrullinemia
5. Argininosuccinic acidemia
6. Tyrosinemia type I
7. Isovaleric acidemia
8. Glutaric acidemia type I
9. Hydroxymethylglutaric aciduria or HMG-CoA lyase deficiency
10. Multiple carboxylase deficiency
11. Methylmalonic acidemia due to mutase deficiency
12. Methylmalonic acidemia cbIA and cbIB forms
13. 3-Methylcrotonyl-CoA carboxylase deficiency
14. Propionic acidemia

15. Beta-ketothiolase deficiency
16. Medium-chain acyl-CoA dehydrogenase deficiency
17. Very long-chain acyl-CoA dehydrogenase deficiency
18. Long-chain 3-OH acyl-CoA dehydrogenase deficiency
19. Trifunctional protein deficiency
20. Carnitine uptake defect
21. Sickle cell anemia
22. HB S/Beta-Thalassemia
23. HB S/C disease
24. Congenital hypothyroidism
25. Biotinidase deficiency
26. Congenital adrenal hyperplasia
27. Classical galactosemia
28. Hearing loss
29. Cystic fibrosis

These guidelines are the result of years of research which ended in the definition of:

- analytical validity of tandem mass spectrometry for the simultaneous expanded screening of members for more than 20 disorders, including a broad range of amino acidemias, fatty acid oxidation disorders and organic acidurias, using the blood available on a single newborn screening card;
- clinical validity of tandem mass spectrometry with: a false positive rate for phenylketonuria screening of 0.05% in comparison with a 0.23% false positive rate of enzymatic phenylalanine determination; a false positive rate of 0.33% for the whole expanded newborn screening (> 20 disorders, overall prevalence 1:2400) (16);
- definition of clinical utility of tandem mass spectrometry in terms of evaluation of the impact of a positive (or negative) test on patient care;
- evaluation of social implication of screening in terms of: anxiety or other negative effects produced in families (in case of false positive results); reduction of expenses for hospitalization and medications due to the application of the screening program.

## Conclusion and proposals

The principles underlying the validation and quality of diagnostic tests are set out by the international standards for the competence of testing and medical laboratories. An increasing number of medical laboratories is accredited according to the above mentioned standards.

The European Directive 79/98/CE (9) established the principles that *in vitro* diagnostic devices should be reliable and traceable to higher order measurement method or materials in order to provide comparable results.

Joint efforts at international level are in place to promote the reliability of analytical results in laboratory medicine. Improvement in analytical techniques and a wider application of quality principles allowed to achieve important improvements in many fields of laboratory medicine, of which an example is the early diagnosis of inborn errors of metabolism.

Education and training on the issues of quality and metrology at all levels of medical laboratories may speed the process of transferring such improved scientific knowledge into everyday practice.

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## Session II. Plenary lecture

# GENETIC TESTS\*

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Italy is the only European country, which has settled a comprehensive and long range monitoring of genetic testing at the national level, starting from 1987.

The data collected by the last census of year 2004, on the behalf of the Italian Society of Human Genetics included the activities of 88 clinical centres, 160 cytogenetic and 183 molecular genetic laboratories, hosted by 256 structures, 16% of which were private. Only 42% of them fulfilled the requirements of current Italian legislation.

Genetic tests included 283,601 cytogenetic analyses. There have been 120,238 invasive prenatal samplings, 84% of which were amniocenteses. A significant north to south decreasing gradient of all these activities was apparent. This study has also surveyed 190,610 molecular genetic tests. CFTR (*Cystic Fibrosis Transmembrane conductance Regulator*) analysis accounted for 23% of prenatal and 29% postnatal molecular tests. The analysis of three thrombophilia genes accounted for 25% of analyses, HLA (*Human Leukocyte Antigen*) for 9%. In total, 420 different genes have been investigated, 10 of which accounted for three quarter of all this activity. More than 10% of molecular tests were performed on foetal samples, the analysis of CFTR, DMD (*Duchenne Muscular Dystrophy*), FRAXA (FMR1 gene), FRAXE (FMR2 gene) and GJB2 accounting for 83% of all prenatal molecular tests.

These results reflect a commercial activity fostered by the private health market. In general, the demand of genetic tests has increased by a figure of about 10% each year, starting from 1997. Only 16% of cytogenetic and 12.5% of molecular tests have been followed by genetic counselling.

This survey remarks the need of some basic intervention in the general organisation of the genetic structures in Italy, which should be rationalised, in respect of the national guidelines, and the need of constant training of the general practitioner and education of the consumer to the appropriate use of genetic testing.

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\* Abstract of the lecture

## Session II. Plenary lecture

# QUALITY ASSURANCE OF GENETIC TESTS: THE ITALIAN NATIONAL PROJECT

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## Introduction

During recent years, numerous disease-specific External Quality Assessment (EQA) schemes have been designed to address standards in molecular genetics (1-9). Proficiency testing of laboratories has been assessed on the basis of the ability to accurately detect genotypes and clinical interpretation of the results. EQA schemes for cystic fibrosis showed that 20% or more of laboratories made at least one technical and administrative error (3). In contrast to EQA schemes for gene diseases, other EQA programmes have been designed to evaluate the implementation of molecular diagnostic techniques relevant to all laboratories (10). Raggi and coll. monitored performance in DNA extraction and amplification; the results presented showed that only 10% of laboratories ranked in the excellent category versus 33% ranked as good, 38% ranked sufficient, 8% were poor and 10% were unacceptable. In addition, the results reported by the Multi-National External Quality Assay (EQA) Programmes in Clinical Molecular Diagnostics, based on three different programmes of EQA in molecular methods, showed considerable variations in expected outcomes from participants for all three programmes (11-13).

As regards cytogenetic tests, the first scheme for External Quality Assessment in cytogenetics was established in the UK in 1982 (14). In 1993, a nationwide cytogenetic External Quality Assessment program, based on the British scheme, was initiated in the Federal Republic of Germany (15). In the last few years Finland, France, The Netherlands and Spain have established EQA schemes in constitutional and/or oncological diagnosis (16). In 2005 EuroGentest, a network for test development, harmonization, validation and standardization of genetic testing (including cytogenetics) in Europe, started its activity.

Here we describe the Italian Project for quality assurance and standardization of genetic tests in molecular genetics and in classical cytogenetics coordinated by the Istituto Superiore di Sanità (ISS) (6, 9); main results obtained in four years of activity, 2001-2004, will be shown.

## Objectives

The main objectives of the Project are:

- to control quality assurance of genetic testing in Italian Public laboratories performing diagnostic molecular genetic and cytogenetic tests;
- to develop recommendations for a permanent programme in quality assurance;
- to contribute to the harmonisation of protocols.

## Materials and methods

The Project started in 2001; Italian Public Laboratories distributed throughout all 21 regions were enrolled on a voluntary basis (6).

The following diagnostic genetic tests were selected: a) molecular genetics: Cystic Fibrosis,  $\beta$ -Thalassemia, Familial Adenomatous Polyposis Coli (*APC* gene) and Fragile-X; b) pre- and post-natal cytogenetics, including cancer cytogenetics.

Participating laboratories were grouped into six regional Working Units, each with its own local coordinator; each laboratory could participate for one or more tests.

The Project coordinator chaired the Project Steering Committee, which was constituted by the local coordinators plus reference experts.

### Setting up the external quality control

For the setting up of the External Quality Control (EQC), we standardized procedures as follows:

- *Molecular genetics*

DNA samples, obtained from peripheral blood or from lymphoblastoid cell lines using standard protocols, were collected by the ISS through the Working Units Coordinator or biobanks (11-12). Two independent Working Units within the ISS were responsible for DNA sample processing and validation. The ISS sent to participating laboratories six validated samples together with clinical and technical information; laboratories were required to analyse each sample, interpret the results and write a report within 2 months, using current methods and nomenclature.

- *Cytogenetics*

The scheme is retrospective and structured into three parts, i.e. postnatal, prenatal and cancer cytogenetics; each part of the scheme stands alone and laboratories may subscribe to any combination of parts. Laboratories were asked to send five images and reports relative to one clinical case (three metaphases and two karyotypes reconstructed from the three metaphases) by e-mail or by post. Cases were randomly selected, according to a fixed schedule (e.g., in 2001 ISS asked the 10th case analysed in January 2001 for prenatal diagnosis EQC) (11).

- *Data evaluation*

For each disease, a panel of experts reviewed the results including the raw data, reports and nomenclature. All data were treated anonymously, and at no time were the identities of laboratories revealed; technical, analytical and interpretative performances were reviewed either in molecular genetics (6,9) and in cytogenetics. Following assessment, participating laboratories received comments about the quality of the raw data, the interpretation and the written reports; in case of poor performance suggestions to improve the analysis were included. Laboratories, assessors and the scheme organizer meet in order to discuss results relative to the EQA, during the annual workshops.

## Results

Overall responding laboratories were 60, 69, 77 and 79 in 2001, 2002, 2003 and 2004 respectively.

### Molecular genetics

Responding laboratories were 42 in 2001, 46 in 2002, 54 in 2003, 52 in 2004, and 53 in 2006. Over the four years, 2001-2004, the percentage of samples not correctly genotyped was: 0.7% for Cystic Fibrosis, 4.5% for Fragile X, 0.5% for Beta-thalassemia and 4.8% for APC gene.

Reports were often not accurate and not homogenous among laboratories; in 2004 a standard model of report in molecular genetics, approved *per consensus* by experts and by the Steering Committee, was proposed to participating laboratories.

### Cytogenetics

The number of participating laboratories was: 36 in 2001, 46 in 2002, 49 in 2003, 51 in 2004.

Overall quality of images was satisfactory; however reporting was variable with a high percentage of laboratories not returning complete and accurate reports.

In 2004 a standard model of report in constitutional cytogenetics, approved *per consensus* by experts and by the Steering Committee, was proposed to participating laboratories.

## Conclusions

Our study demonstrates a good level of analytical quality for Italian laboratories.

In order to improve the quality in reporting and to standardize the list of information to be included, a model of a standard report in constitutional cytogenetics and in molecular genetics (9) was elaborated and approved *per consensus* by the Steering committee and by national reference experts.

In 2003, the model was proposed to participating laboratories and it was adopted in the third and fourth trial assessment. The output of this corrective action will be evaluated in a few years time.

Our experience confirms and stresses the importance of the participation in EQA, in order to standardize and to assure quality in genetic testing. Moreover, our initiative has been very useful to educate laboratories to participate in EQA programs: the number of participating laboratories has been increasing over the four years, except for the APC gene EQA.

Annual Workshops, where assessors and participating laboratories meet to review data relative to the EQA and discuss issues regarding the quality of genetic testing, may have contributed to the educational process too.

### Acknowledgements

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## Session II. Plenary lecture

# **COUNSELLING AND RISK COMMUNICATION\***

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Given the genetic origin of 80% of rare diseases, genetic counselling appears to be the appropriate setting for information and tests to be offered to patients and families.

Although most people working in the field of medicine are familiar with the term “genetic counselling” and have some idea what it mean, it is surprisingly rare to see it actually defined. Enquiries among patients and colleagues show a wide variation in people concepts of what the process of genetic counselling actually entails.

According to Harper, “Genetic counselling (CG) is the process by which patients or relatives at risk of a disorders that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it and the ways in which this may be prevented, avoided or ameliorated”.

The main elements of CG will be discussed: diagnostic and clinical aspects, documentation of family and pedigree information, recognition of inheritance patterns and risk estimation, choice of appropriate diagnostic, presymptomatic or predictive genetic test, communication to patients and families, information on available reproductive options, support in decision-making and for decision made.

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\* Abstract of the lecture

## Session II. Plenary lecture

# **INFORMED CONSENT\***

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The concept of Informed Consent goes away back to World War II, when unethical clinical trials were done and the need for the field of bioethics was envisaged.

Informed consent is designed to protect individuals participating in clinical research trials. An individual interested in participating in a clinical research trial will receive a Participant Information Sheet that provides a summary of the clinical trial and explains the rights of the participant. It is designed to begin the informed consent process, which consists of conversations between the participant and the research team. The participant should be able to review the Participant Information Sheet with doctors and ask questions about things they do not understand.

Official consent to participate in the trial is given when the Participant Consent Form is signed. However, the process of informed consent should not end there. Informed consent for a clinical trial involves much more than just reading and signing a piece of paper. Rather, it involves a whole process.

The informed consent process provides the participant with ongoing explanations that will help him make the best decision as to whether to begin or continue participating in a trial. Researchers and health professionals know that a written form alone may not ensure that the participant fully understands what participation means. Therefore, before the participant makes a decision, the research team will discuss with him the trial's purpose, procedures, risks and potential benefits, and his rights as a participant. If the participant decides to participate, the team will continue to update him on any new information that may affect his situation. Before, during, and even after the trial, the participant will have the opportunity to ask questions and raise concerns.

Thus, informed consent is an ongoing, interactive process, rather than a one-time information session.

What happens if the prospective participant in a clinical trial is a minor or an adult who is unable to give consent himself?

This presentation is going to focus on the general process of informed consent and in particular on the provisions relating to giving informed consent on behalf of minors and adults who are unable to consent for themselves (referred to as "incapable adults"), including the role and responsibilities of legal representatives.

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\* Abstract of the lecture

## Session II. Plenary lecture

# PHARMACOGENOMICS AND PHARMACOGENETICS

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## Introduction

Everyone answers in various ways to a determined drug. This is testified by the notes “adverse reactions to drugs” (ADR, adverse drug reactions) that constitute one of the most common cause of death in the western countries. Epidemiological studies indicated that only in United States, each year at least 2 million people show adverse reactions to drugs. Similarly, to many other human traits, drug response is genetically defined and can be attributed to the inter-individual variability. The mapping of the human genome and the definition of the variability at molecular level have recently supplied the tools to understand this phenomenon.

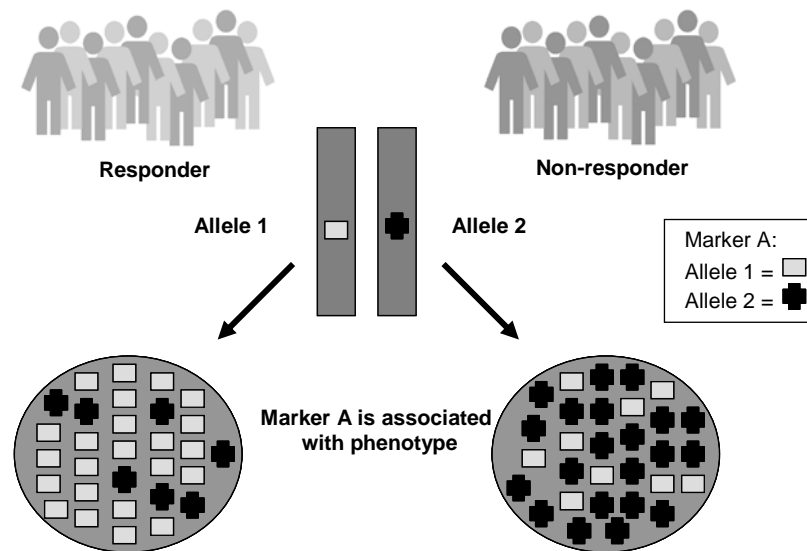
The inefficacy of a drug and the anomalous response to it are a direct consequence of the genetic variability. This variability reflects the different absorption, metabolism and elimination of a drug. Not only, but the genetic variability also determines the different modality for which a drug exerts its effect. In fact, the genetic variability modifies the structure and the function of receptors, enzymes, and proteins involved in the action and in the metabolism of a drug. The genetic variability resides just in the ability of our genes to codify various proteins on which the natural selection acts, rewarding them or eliminating them to the second of their greater or smaller adaptability to the environment in the interest of the same individual. Just this ability, this variation (polymorphism) exists within populations and therefore among the individuals, providing the basis of pharmacogenetics and pharmacogenomics (1).

Vogel, a German geneticist, has introduced for the first time the Pharmacogenetics (PGt) term, trying to explain the reaction that characterizes the effects of drugs. Classical examples of PGt are the studies of the effects of isoniazid, antimalaric drugs, some anticoagulant drugs and anaesthetic agents. The isoniazid it is one of the most important drugs used in the treatment of tuberculosis (1, 2).

However, users of this drug can be distinguished in two classes: ‘rapid inactivators’ and ‘slow inactivators’. A “slow inactivator” person is homozygous for a slow inactivator allele; the ‘rapid inactivator’ person may be either homozygous or heterozygous for a rapid inactivator allele at the NAT2 locus. This characteristic is genetically transmissible. In the United States and Europe 50% approximately of the population is constituted by slow inactivators. They carry a mutation that impairs the NAT2 enzyme production. Only at the end of the 80s after the cloning of the gene coding for debrisoquine hydroxylase, or CYP2D6, the PGt has been asserted as an independent discipline. The availability of the entire genome, has successively allowed the extension of the PGt concept introducing the pharmacogenomics (PGx). Recently, the ICH (International Conference of Harmonisation), has coined the exact definition of these terms: PGx is defined as the “study of the variations to level of DNA or RNA correlated to the answer to a drug”. PGt is defined as “a subset of PGx in order to study the variations of the DNA sequence correlated to the answer to a determined drug” (2, 3).

The reasons of great interest of this discipline reside in the fact that the acquaintance of responsible genes of effectiveness and toxicity of drugs could allow clinicians to establish the appropriate dose and/or the right drug for every individual, being reduced the risk of the side

effects or lack of effect. Such predictive ability, will allow clinicians to avoid long and risk processes in searching the correct dose for a patient. The possibility to eliminate or drastically reduce the side effects is crucial in terms of healthcare and costs. The information on the genetic answer characterizes them to a particular drug that could become integrating part of modern pharmacology (Figure 1).



**Figure 1. The pharmacogenetics concept**  
(it is clear that all patients do not equally respond to these treatments)

## “Genomic biomarkers”: tools for PGx and PGt

A genomic biomarker is defined as: “A measurable DNA and/or RNA characteristic, that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other intervention”.

A genomic biomarker could be, for example, a measurement of:

- the expression of a gene;
- the function of a gene;
- the regulation of a gene.

A genomic biomarker can consist of one or more deoxyribonucleic acid (DNA) and/or ribonucleic acid (RNA) characteristics.

DNA characteristics include, but are not limited to:

- Single Nucleotide Polymorphisms (SNPs);
- variability of short sequence repeats;
- haplotypes;
- DNA modification, e.g. methylation;

- deletions or insertions of (a) single nucleotide(s);
- copy number variation;
- cytogenetic rearrangements, e.g. translocations, duplications, deletions or inversions.

RNA characteristics include, but are not limited to:

- RNA sequence
- RNA expression levels
- RNA processing, e.g. splicing and editing
- microRNA levels

The definition of genomic biomarker is not limited to human samples, and includes viruses and infectious agents *as well as animal samples, i.e. application of genomic biomarkers to non-clinical/toxicological studies*. The definition of genomic biomarker does not include the measurement and characterisation of proteins or low molecular weight metabolites (1, 4).

## Examples of pharmacogenetics

The metabolism of drugs is a complex biochemical process that happens mostly in the liver. The enzymes, involved in drugs metabolism, are classified according to the stage of metabolic reaction they catalyze. In this respect, the P450 cytochromes (i.e. CYP2D6, CYP2C19 or CYP2A6) are particularly important. These enzymes take part in numerous processes of composed pharmacokinetic modification of various drugs. All cytochromes, except the CYP2D6, are inducible and dose-dependent. SNPs at genes coding for CYP proteins, determines the enzyme production of this class of enzymes (3, 5).

Other important examples regard the enzyme TPMT active during the detoxification of the (drug) azathioprine, used to prevent transplant rejection and some autoimmune diseases such as Crohn's disease. The active metabolite of the drug, is the 6-mercaptopurine (6-MP), produced in the liver. TPMT transforms the 6-MP in its derived inactive 6-MMP (6-metilmercaptopurine) by methylation. Many alleles of the TPMT gene have been characterized to influence enzymatic activity. The most common include TPMT\*2, TPMT\*3A and TPMT\*3C. Individuals (less of 0.3% of the population) carrying two copies of TPMT\*3° (homozygous) have reduced enzymatic activity. These subjects accumulate high amounts of the nucleotide (6-TGN) that, being toxic, can turn out fatal for some patients. For this reason, it is recommended to provide little amount of drug.

Recent studies on PGt have identified associations between genotypes and antipsychotic and antidepressant drugs. The genes mainly studied include those associated to pharmacokinetics (metabolism, transport and elimination) or pharmacodynamics (specific molecular targets) of this class of drugs. Different allelic combinations of genes coding for serotonin receptors (5HT2A, HT2C, SLC6A4) and for histamine (H2) have been identified. These findings are relevant for anti-psychotic drug therapy. These allow previewing the therapeutic effectiveness of a particular atypical anti-psychotic (clozapine) with a reliability of approximately 80%. Similarly, a PGt test will come soon used in order to establish the dose of warfarin in the anticoagulant therapy. This drug, prescribed in million doses in the world, is famous for the difficulty to establish the dose, varying from 1-15 mg/day, because the great variability among patients.

The exact dose for every patient is fundamental, since an excessive dose could cause serious haemorrhages, while a reduced dose could be revealed to be ineffective or even dangerous from the therapeutic point of view owing to the formation of thrombi. Currently the correct dose is established through the dosage of the prothrombin or by means of the appraisal of the INR. The pharmacokinetic of the warfarin is mainly due to the action of cytochrome CYP2C9 in the liver (3,

6). SNPs in this gene, considerably, influence the metabolism of the drug. Subjects with CYP2C9\*2 or CYP2C9\*3 alleles show a reduced metabolism compared to other subjects, and therefore they need lower dose of drug. The frequency of these alleles is variable in the populations, and it can be approximately 8% in the Europeans. Recently, the effectiveness of the warfarin has been demonstrated to be linked to the presence of alleles within the VKORC1 gene, codifying the main target of the drug. Subjects carrying mutations in this gene turn out insensitive to the warfarin action, and need elevate doses of the drug (beyond 10 mg/day). Our group has recently demonstrated that the simultaneous analysis of both genes, CYP2C9 and VKORC1, allows establishing with good accuracy the correct dose of warfarin for the patient (3, 6, 7).

American investigators have recently demonstrated the reason why some patients with lung tumor, very well answer to the treatment with gefitinib, an inhibitor of some protein kinases, while in others the treatment is ineffective. This effect was due to the presence of specific somatic mutations in the EGFR gene. A test able to identify EGFR mutations could be useful in precisely selecting patients to be treated with this drug and to address to other therapies those who do not show mutations in this gene.

## Conclusions

The PGt and PGx, constitute an important advance in the history of pharmacology. Many of the concepts of sensitive/not sensitive will be replaced by biological approaches defined at genetic level. It is expectable that next 5-10 years, some drugs will be available in the market with an appropriated genetic kit in order to estimate specific genotypes and therefore the correct dosage of a particular drug (1, 7).

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## Session II. Plenary lecture

# INNOVATIVE THERAPIES ON RARE CANCERS\*

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Malignant transformations of normal cells rise from acquisition of a series of specific genetic changes which lead to impairment of signal transduction, cell differentiation, apoptosis, DNA repair, cell cycles progression, angiogenesis and cellular adhesion. The chemotherapy in the last decades has established/achieved a meaningful improvement in cancer treatment nevertheless it reached its limits. Drug resistance of tumours and side effects on normal tissue limits its effectiveness.

The war on cancer has been declared some years ago with weapons that are more specific: targeted therapies. The goals of the targeted treatment could be all the above-mentioned mechanisms. The treatment could be individualized according to tumour type, histology and disease stage. Target-based drugs can be classified into small molecules that have specific molecular weights and structural formulas, and macromolecules that include antibodies, gene therapy, cell therapy, immunotherapy etc. Tumour-specific target-based therapy modifies tumour-specific molecular change while tumour-non-specific therapy modifies molecular changes in the tumour environment, like antivascular endothelial growth factor (VEGF) antibody or VEGF tyrosine kinase inhibitors.

The main progress and implementation in clinical daily practice has been made with introduction of monoclonal antibodies and small molecules targeting receptor of tyrosine kinases, which are crucial for cell proliferation and cell survival.

The first approved monoclonal antibody was rituximab, antiCD20 antibody for the treatment of Non-Hodgkin's lymphoma in 1997, followed one year later with trastuzumab for breast cancer. Alemtuzumab, anti CD52 antibody is now available for the treatment of chronic lymphoid leukaemia. The research reached further step in introducing radiolabelled antibody, which carries the radionuclides – a source of beta particles, to the cancer cells leaving cellular free radicals killing the tumour cell.

The most successful example for targeting treatment with small molecules is represented by imatinib for the treatment of chronic myeloid leukaemia and GastroIntestinal Stromal Tumour (GIST).

Recently sunitinib, a multitarget drug, has been approved for the treatment of imatinib-resistant GIST and for the treatment of advanced renal cancer resistant to cytokines therapy.

However, despite a boom of this new anticancer strategies based on profound translational research which shift the biology from a descriptive to a quantitative and predictive biology and pathobiology we are still far away from the understanding of cellular networks because of their enormous complexity and multiplicity and from the goal to win the battle against cancer.

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\* Abstract of the lecture



## Session II. Plenary lecture

# RARE DISEASES: THE ROLE OF THE MEDIA \*

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We can read on one of the EURORDIS (*EUROpean Organisation for Rare DISeases*) Statement: “It is time for public authorities to consider rare diseases as a Public Health priority and to take action to concretely support patients and families affected by rare diseases”. Mass media are a powerful instrument for disseminate new knowledge and to empower people. Nevertheless, there are many cases of misrepresentation of medical researches and of the reality of diseases. We can observe this problem also in the field of rare diseases.

The goals to pursue are:

- finding out how frequently the most important Italian newspaper deals with rare diseases.
- analysing the quality of the media reports on genetic and rare diseases, from the scientific and psychological points of view.

The method utilised has been data mining in the web via Google and Scholar Google.

The results showed that in in the Italian press, the articles about rare diseases are as rare as the diseases themselves.

Generally speaking, the quality of media coverage of rare diseases topics is low, often unbalanced and incomplete, both for the evidence based and for the narrative based criteria that we selected. In particular, we found the lowest quality scores for TV reports. The factors, which may contribute to the poor quality of this kind of journalism, include not appropriate length of the articles, few scientific writers in the staff, and so on.

Therefore, mass media rarely can fulfil the mission of correctly inform public opinion on rare diseases. We propose some ideas in order to lobby in a more effective way the issue of rare diseases and to increase the “human” and scientific quality of media reports on these topics.

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\* Abstract of the lecture

## Session II. Discussion Group

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### FOCUS GROUP 1. DIAGNOSTIC TEST

<i>Discussion leaders</i>	Algirdas Utkus (Lithuania), Francesca Torricelli (Italy)
<i>Rapporteur</i>	Marco Salvatore (Italy)
<i>Participants</i>	Luisa Russo (Italy) Rumen Stefanov (Bulgaria) Miranda Siouti (Greece) Vincenza Falbo (Italy) Rosella Tomanin (Italy) Barbara Gavazzi (Italy) Valentina di Pietro (Italy) Marina Patriarca (Italy) Elisabetta Lendini (Italy)

### Diagnostic test

Genetic testing is the analysis of a specific gene, its products or function, or other DNA and chromosome analysis, to detect or exclude an alteration likely to be associated with a genetic disorder.

Diagnostic testing are fundamental to make a diagnosis (e.g. telomere analysis), to confirm a clinical hypothesis (e.g. Miller-Dieker syndrome and del17p13.3), to subclassify a disease (e.g. genetic deafness), to assess the disease severity (e.g. cystic fibrosis), to establish genotype correlations and plan the clinical follow-up (e.g. PTPN11 mutations in Noonan and Leopard syndromes), to prenatally diagnose chromosomal and single gene disorders.

Genetic testing services in the EU have substantially increased their activity in the past few years. Several External Quality Control (EQC) schemes have been funded either by international groups or by national governments or by private subscription.

Some important topics have been discussed within the focus group “Diagnosis and treatment: diagnostic test”, whose discussion leader were Algirdas Utkus (Department of Human and Medical Genetics of Vilnius University, Vilnius, Lithuania) and Francesca Torricelli (Piastra dei Servizi Azienda Ospedalieri Careggi, Florence, Italy).

### Clinicians’ vs geneticists’ role in diagnostic tests

Since heterogeneity of some mutation (e.g. CFTR gene in cystic fibrosis, BRCA1 and 2 genes, etc) a whole and huge knowledge of pathology is essential in order to perform correct and complete analyses. Therefore, clinicians and geneticists have to be considered at the same level and should share their knowledge and information. A full understanding of the pathophysiological and genetic aspects of pathology is good prerequisite for molecular diagnosis testing of rare diseases.

## **Metabolic screening vs genetic testing**

Cystic fibrosis screening in USA was lead by Dr Utkus as example of successful transition to detect some of the most frequent mutations present at national level in US, where a precise number of mutations (25 mutations) were introduced in the minimum CF carrier screening panel.

In Italy a law of 1993 (no. 548, of 23 December 1993) established the development of programmes for the prevention and care of patients affected by cystic fibrosis. The programmes were to include primary prevention measures and the establishment of CF centres in each Italian region or group of smaller regions. CF neonatal screening programmes have been operating in some regions for many years, in some for a more limited period. Neonatal screening is based on an immunoreactive trypsinogen test, followed by genetic analysis (1, 2).

Nevertheless, also on the basis of the personal experience showed by the component of the discussion group, genetic testing activities have to be performed only when a therapeutic approach is available for the pathology; furthermore, population metabolic screening are too expensive.

## **Genetic test selection and diffusion of information at EU level**

The number of analyses performed during recent years, has been increased in all EU Countries; in Italy, for example, the number of cytogenetic tests performed increased from 150,000 to 250,000, from 1997 to 2004 and, during the same period, the number of molecular analyses performed increased from 50,000 to 200,000 and three-quarter of analyses referred to only 10 genes (3).

Therefore, medical community, professional organization and health strategies should be adopted in order to promote diffusion of correct information about genetic test.

## **Diffusion of genetic “passport”**

The diffusion of a genetic passport has to be considered as a tool to have complete and detailed information on a person is important to study the correlation between particular alleles and the capability of metabolizing various compounds. These problems are the subject of pharmacogenetics, an individual field of current genetic research.

The genes that determine the response to carcinogens and endotoxins code for proteins involved in metabolism (deactivation and detoxification) of xenobiotics. Such genes are known as environmental, or metabolism, genes and are characterized by a considerable population polymorphism. Examples of genetic passport are present in Russia (4). Nevertheless, discussion group recognized that the use of genetic passport should be limited at legal reasons.

## Recommendations

Recommendations should be adopted in order to assure safe and effective genetic testing of rare diseases in EU and to implement National experience with international ones

## Laboratory accreditation

Laboratory tests must be validated before their application as diagnostic tools and their quality maintained throughout use, usually by operating under a Quality Management System, including, whenever possible, formal accreditation. Programs should be in place to assist the development from new research findings to diagnostic tests.

Furthermore, specific protocols should be shared by laboratories and standardized methods should be available and used by all genetic testing laboratories.

## Networking activities

A network for all pathologies should be organized in order to send patients to specific reference centres. This networking activity should assure a reduction of error rate in the performance of analyses and a reduction of laboratories, which perform the same analyses thus contributing to the creation of specific centres for detection of pathologies.

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## Session II. Discussion Group

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### **FOCUS GROUP 2. CANCER GENETIC COUNSELLING AND RISK COMMUNICATION**

<i>Discussion leaders</i>	Ignacio Blanco (Spain), Albert Matevosyan (Armenia)
<i>Rapporteur</i>	Paola Zinzi (Italy)
<i>Participants</i>	Berenice Doray (France) Gareth Evans (UK) Elisana Petrela (Albania) Simonetta Pulciani (Italy) Janos Sandor (Hungary) Miranda Siouti (Greece)

Genetic counselling can be defined as the *communication process* which deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family (1, 2).

It is important to point out that the communication process has to be Non-Directive 3. The patients' autonomy in decision-making is an important issue in genetic counselling and has to be promoted by non-directive communication (1-3). Non-directiveness is a strategy to assist individuals to achieve a personal decision, discussing all relevant opinions in a relationship based on reciprocal trust and respect.

This communication process involves an attempt by one or more appropriately trained persons to help the individual or family:

- to comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management;
- to appreciate the way heredity contributes to the disorder, and the risk of recurrence in specified relatives;
- to understand the alternatives for dealing with the risk of occurrence;
- to choose the course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards, to act in accordance with that decision;
- to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

In genetic counselling we have to deal with risk continuously. But, what is the meaning of risk? Risk is a concept based on probability. It is the chance that an event, i.e. a disease, will occur within a given time period.

Dramatic advances in our understanding of the genetic basis for cancer have led to the development of new methodologies and tools for genetic cancer risk assessment. Cancer risk assessment is developing into a distinct discipline in which established empiric risk models are recast along with rapidly evolving genetic technologies for estimation of individual cancer risk. Identification of persons at increased risk for cancer allows application of potentially life-saving surveillance or preventive measures (1-4).

The basic premise is that cancer is a complex disorder, both biologically and socially.

Hallmarks of familial cancer include occurrence of cancer at an unusually younger age, (or in the less usually affected gender), vertical transmission of cancer within a family multifocal or

bilateral disease in paired organs, multiple primary cancers in an individual, and clustering of unusual or rare cancers (4, 5).

Comprehensive cancer risk assessment requires consideration of both personal risk factors (reproductive/hormonal history, exposures such as tobacco, and treatments such as radiotherapy) and thorough family history.

The most straightforward risk calculation is Mendelian risk in the setting of a known familial mutation (50% for first-degree relatives, 25% for second-degree relatives, and so forth).

A more sophisticated approach takes into account age-specific penetrance estimates in a Bayesian modification of risk. In short, if a woman is unaffected at the age of 80 years, then the probability that she or any of her offspring is a carrier of a highly penetrant gene mutation is diminished. Bayesian calculations also can be used to gauge the significance of a negative result in an unaffected individual if the family diagnosis is certain (but the mutation is unknown) and the sensitivity of the genetic test well established.

Genetic testing for inherited susceptibility mutations is the most recent addition to the tools used for risk assessment and has the potential to provide more accurate risk estimation than any empiric risk-assessment tools (5, 7).

Once we have calculated the risk we have to communicate it, and risk can be a difficult concept to explain, especially in the clinical setting. Usually, patients request certainties. But unfortunately, it is impossible to predict exactly what will or will not happen to an individual. People seeking for genetic counselling can be in a condition of great distress, vulnerability, anxiety, and they could be facing very stressful life events related to high-impact existential themes: health, disease, death or reproductive choices. They are not always capable or feel themselves capable to understand all these problems nevertheless they have to do important and urgent choices for their lives.

In the field of Medicine and in particular in Medical Genetics rarely we can provide certainties. In a context of different grades of uncertainty, what we can do is provide the information we have in an accurate, useful, understandable way not forgetting sensitivity and empathy toward who is trying to make his personal sense to this loss of control on his life and cope with.

It can be challenging for a health care provider to convey information in a way that is both personally *relevant* and *motivating* to individual patients.

The form in which risk is communicated may influence both decision-making processes and motivation to change behaviours such undergoing testing or other medical procedures, engaging in behaviours that will protect or harm health, and adhering to recommended treatment or lifestyle advice.

Because of that, it is important that providers and patients understand *what risk is and how it can be altered*.

Difficulties in communicating diagnostic information are inherent in doctor-patient interactions. A very *specialized knowledge* has to be *interpreted* and *understood* by patients. The difficulties in such task are further exacerbated when the *diagnosis* is a *risk* for a severe disease as cancer is. Diagnosis of a cancer (or just the risk of developing it) produces important psychological and relational reactions in people involved, individuals, couples, families. Intensity and quality of these reactions may vary considerable but if we just stop to think it would be the same for all of us like human beings (7, 8).

When healthy “potential patients” are told of their risks for future disease, this can be a sensitive situation, prone to many *dilemmas* with *ethical* consequences (8).

In scientific contexts, risks are calculated on the basis of a variety of systematically established factors; while the risk judgments of individuals are assumed to be influenced to a greater extent by *personal experiences*, *moral values* and *social norms*.

The determination of risk status of an individual for development of a future disease is a complex process, involving *negotiation* between *different modes of explanation*. The health care professional in clinical practice has a mediating function between objective and relatively unambiguous scientific knowledge on statically based risk (measurable uncertainty) and the individual's experiences of ambiguous risk (unmeasured uncertainty). It is important to recognize that *tolerance* of risk varies greatly from person to person, and *patients' risk perceptions* are often very different from their actual risks, leading to over – or underestimations of risk (8-10).

The amount of effort that patients are willing to make to *alter disease* risk may depend on their perceptions of *personal risk* and their *perceived ability* to make effective change.

There are many different ways to discuss risk.

We can use:

- qualitative expressions,
- quantitative expressions,
- absolute risk,
- relative risk,
- risk over different time periods.

But again, it is important to remember that it can be very challenging to communicate information in a way that is both *accurate* and *useful*.

In order to help counselors in the communication process, several authors have tried to establish guidelines for this communication process. For example, Schwartz and colleagues published some principles for cancer risk communicators that can be used in other types of risk communication.

These principles included:

- to make clear the main message;
- to provide context;
- to acknowledge uncertainty;
- to remember health.

First at all, we have to delineate the main message clearly.

We have to define the outcome under consideration: *diagnosis, heredity, specific morbidity, or death from disease*. The risk can be presented in numbers or in words. If it is presented in numbers, we can use percentage or proportions. But also, the risk can be framed in negative or in positive terms.

Breast cancer risk framed in negative terms of lifetime incidence and lifetime mortality (Table 1) of breast cancer in developed countries.

**Table 1. Lifetime incidence and lifetime mortality of breast cancer in developed countries**

Cases	Probability of developing breast cancer (ages 20-80)	Proportion	Probability of dying for breast cancer (ages 20-80)	Proportion
No affected relatives	7.8%	1:13	2.3%	1:42
One affected first degree relative	13.3%	1:8	4.2%	1:24
Two affected first degree relatives	21.1%	1:5	7.6%	1:13

Breast cancer risk framed in positive terms of lifetime chances of not having breast cancer and not dying because of breast cancer in developed countries (Table 2).

**Table 2. Lifetime chances of not having breast cancer and lifetime chances of not die because of breast cancer in developed countries**

Cases	Probability of developing breast cancer (ages 20-80)	Proportion	Probability of dying for breast cancer (ages 20-80)	Proportion
No affected relatives	92.2%	12:13	97.7 %	41:42
One affected first degree relative	86.7%	7:8	95.8 %	23:24
Two affected first degree relatives	78.9%	4:5	92.4 %	12:13

In addition, we have to provide the period. It is not the same the risk for the next year (*e.g.*, in the next 5 year or lifetime). The best way of risk communication depends on the individual client and the aim of genetic counselling and the right way of framing risks must be tailored to the individual client and the specific counselling situation (6,7,8).

The data have to be presented clearly, we have to clearly specify to whom the data apply (*e.g.*, gender, age, risk factors), and we have to present benefit and harm symmetrically.

We have to present both chance of diagnosis and death or morbidity to reflect disease lethality. We can also specify important competing risks for death, compare the risk with familiar events or compare the risk factor or intervention under consideration against other known factors to be clear that not all factors change risk by the same amount.

We should acknowledge uncertainty and remember that risk is only a measure of probability and not an absolute answer. One of the main objectives of medical care is to improve the health of the population and scary messages do not make people feel healthier and may generate unrealistic expectations about disease risk and treatment benefit.

The fundamental purpose of risk communication is to provide individuals with the facts they need to make personal informed decisions. Increasing the public sense of vulnerability to inspire a healthy behaviour undermines well-being and may result in net harm.

Communicators should be sensitive about the potential side effects of their messages.

Several clinical cases were used to point out some of the problems dealing with Counselling and risk communication:

– *Case 1*

A 36-year-old man presented with a 6-month history of palpitations and headaches and high blood pressure refractory to calcium channel blockers and beta blockers.

Urine studies showed elevated catecholamines and a CT revealed bilateral 6-cm adrenal masses suspicious of pheochromocytoma. His past medical history was significant for retinal hemangioma in the right eye. His family history was significant for a father and aunt who died of adrenal tumors. His father was also diagnosed of both retinal and cerebellar hemangiomas. His aunt also had retinal hemangiomas. At the end of the visit the patient demands genetic counselling.

– *Case 2*

A 70 year-old woman and her 42 year-old daughter sought consultation regarding cancer risk.



They reported that the niece of the mother, recently affected by ovarian cancer, tested “positive” for *BRCA1*, but did not want to discuss any of the details of the testing or the specific results. The woman and her daughter who sought consultation could not afford to pay out of pocket for *BRCA1*, which was not covered by their insurance.

– *Case 3*

Mary, a 50 year-old woman, sought consultation regarding her breast and ovarian cancer risk.

She reported that her sister was diagnosed of breast cancer when she was 48. Her mother and grandmother were also diagnosed of breast cancer. Recently, her sister was tested “positive” for *BRCA2*, and after a very short counselling process Mary decided to be also tested for the same mutation. Two days ago Mary received her test result that was negative for her sister *BRCA2* mutation.

– *Case 4*

A 31 year-old woman sought genetic counselling and testing.

She had breast cancer at age 30, renal cancer at age 31, and recently she has been diagnosed of soft tissue sarcoma at age 31. Her mother died of a sarcoma at age 32. Her father is healthy at the age of 60. However, two uncles and her grandfather were diagnosed of colorectal cancer.

– *Case 5*

A 31 year-old man and his family sought genetic counselling.

He has recently been diagnosed of colorectal cancer in the context of a Familial Adenomatous Polyposis (more than 2.000 polyps in the entire colon). His brother has been diagnosed of having more than 1.000 polyps in the entire colon by a screening colonoscopy.

From the real clinical cases discussed in the focus group emerged a common sense of how complex is the communication in the context of genetic counselling and, with more tips from the facilitator about the cases carried on, how the reality is always more complex than expected (1-6). Experiences like this, with health professionals working in the genetic field, from different countries and different backgrounds, could be very useful in sharing personal experiences and best practices (5-10).

As conclusions we would like to remark that:

- Counselling is a non-directive communication process which deals with the human problems associated with the occurrence, or risk of occurrence, of a disorder.
- Risk is the probability that an event will occur within a given time period.
- Risk messages can be communicated in many different ways.
- Risk information can be used to help individuals identify factors that influence health,
- It can be very challenging to communicate information in a way that is both accurate and useful.
- Its important to pay attention to psychological, ethical social, legal aspects involved in genetic counselling and risk communication

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## Session II. Discussion Group

### FOCUS GROUP 3. THERAPIES AND REHABILITATION

<i>Discussion leader</i>	Juha Peltonen (Finland)
<i>Rapporteur</i>	Alberto Loizzo (Italy)
<i>Participants</i>	Katerina Kubackova (Czech Republic) Sirkku Peltonen (Finland) Annalisa Trama (Italy)

Many barriers undermine the access to treatment of patients with rare diseases. Among the others it is worth mentioning the availability of health care centre, the delay in diagnosis, the limited knowledge and experience of health care workers, the availability of a specific drug for the disease and, when available, the cost of the drugs. The aspects on health maintenance organization shall be privileged in the present discussion.

Our discussion receives great help from the EURORDIS (*EUROpean Organisation for Rare DISeases*) care survey, which collected a series of important information, with the aid of the rare disease associations and patients. Some of these questions are of great importance to understand which problems are to be solved first, and may be of great help for, in the management of rare diseases:

1. *Delay from early symptoms to confirmatory diagnosis*

The 25% of patients had to wait between 5 and 30 years, and the 40% of patients first received an erroneous diagnosis. This leads to erroneous medicinal treatment for 33% of patients, to surgery for 16% of patients, to 10% for psychological care.

2. *Patient mobility*

The 25% of patients had to travel to a different region to obtain the confirmatory diagnosis, 2% to a different country

3. *Communication of diagnosis*

Terms or conditions were communicated in unsatisfactory or unacceptable way in 45.5% of cases. The genetic nature of the disease was not communicated to the patient or family in 25% of cases (given the genetic origin of 80% of rare diseases).

4. *Genetic counselling*

Genetic counselling was performed only in 50% of cases.

Discussion on the diagnosis and genetic risk was engaged in 40% of cases.

Patients or their parents engaged in debate within their family to help diagnose or prevent other cases in 80% of cases.

Within the latter conditions, discussion helped diagnose other family members in 30% of cases (10% affected; 20% healthy carriers).

From this information, a series of important questions arise; among these, chiefly two key questions:

1. how to identify persons with rare diseases as early as possible;
2. how to ensure optimal treatment of patients with rare diseases.

Rare diseases hit only a limited number of persons. Only few specialists, often scattered all over a country, are able to put forward correct diagnosis and therapies, however also these

specialists may end up in visiting only few cases during their life. In order to respond to such a problem, the common idea promoted so far, was to identify big institution, with personnel and facilities (infrastructure and equipment) able to manage rare diseases. In a way patients with rare diseases will most likely access to one centre, increasing the number of cases treated in there. This would better expose health care workers to rare disease cases, increasing their knowledge, experience and therefore ameliorating their ability to understand and manage the specific disease.

Several indications are given by different countries, under different public health administrative structures. We propose a discussion on some of these, even though we are aware that some solutions we propose require time, money and good will, but these are part of a practical scheme for social improvement, not utopia.

The Neurofibromatosis clinic established in Turku and described by Dr. Peltonen provides an example of such a referral hospital for patients with Neurofibromatosis 1 (NF), which is a model to expedite the access to adequate treatment.

NF clinic includes one coordinator-consulting specialist of different fields when necessary. The range of specialities available is listed below:

1. genetic counselling
2. orthopaedic
3. dermatology
4. ophthalmology
5. paediatric surgery
6. paediatric neurology
7. neuropathology
8. laboratory investigation
9. etc.

Institutions dedicated to a single rare disease have advantages and disadvantages. Some of these are:

– *Advantages*

- One institution has great visibility. Everybody knows where it is and therefore it is easy to access.
- One institution collects all clinical cases in the territory. The doctors and other personnel belonging to the institution are expert in all aspects of the disease.
- One institution can manage the different clinical aspects of the disease, can undertake clinical research (because of the number of patients that is more likely to recruit).
- One institution can provide comprehensive care to patients including referral to patients associations and to other institution/organisations dealing with the social aspects of the disease.
- One institution can better manage the follow up within the territory: for example establishing linkages with General Practitioners.

– *Disadvantages*

- One single institution is physically far from the great majority of patients. Patients must travel long distance; sick children need the support of their parents who are forced to stay out of their house, far from their other children with a very high economic and emotional cost.
- Often patients looking for help in a country need a first tentative diagnosis in order to be properly referred to the specific specialised centre. This is a great weakness of the system considering that appropriate diagnosis is still a major problem in many

countries as general practitioners and specialists are not able to recognise the disease and therefore to properly advice patients.

- There are some 7000 rare diseases, and there is a need to build and widespread a big number of specialized institutions all over the EU.
- There is the need of establishing which criteria should be used to prioritise some rare diseases.

## Discussion

At present, several highly specialized and well-known institutions exist and perform important job in EU. Some of them (as the one here described by Drs. Juha and Sirrku Peltonen during our Meeting in Roma) are dedicated to a “single syndrome”, as neurofibromatosis is. This condition is optimally studied from several clinical and experimental points of view, including genetic counselling, and offer an excellent answer to the needs of patients. This solution has a very strong cultural and expertise basis, and is a rich resource for the community. Some other institutions can have a wide cultural background, e.g., leukodystrophies, i.e., a wide group of diseases which can be studied with analogous cultural instruments. In both cases patients need these highly specialized institutions, and other “intermediate” structures, as well. They need at first, a wide cultural basis for the diagnosis; they need also a clinical help near their home, to perform therapy and follow-up controls.

Nowadays, which centralised structures are presently working?

Some structures do exist in the field of rare diseases, and we need to know how many, and for what diseases, and where they are. We suggest that the first step can be to have a better knowledge of existing structures, and an inventory list of such specialised Institutes can be outlined. A list for rare diseases organisations is working within EURORDIS, and is referred to more than 260 rare disease organisations. Perhaps these organisations may help compiling such a list, and suggesting further connections within these Institutions.

Moreover, another suggestion can be forwarded. For instance, these organisations may propose adding, on the web, the names of those doctors, scattered all over the territory, who performed studies on one or another particular disease, and can facilitate the management of patient recruiting-diagnosis-treatment. For example: If I write the word “neurofibromatosis” on a research motor as google, the Turku Institute should appear. Clicking on it, further indications can enrich the cultural weight of the Institute: the name(s) of institutions/doctors who may be of help for neurofibromatosis, nearest to the city of patients; and the names and addresses of associations of patients, and so on. In any cases, patients need more than highly specialized institutions. They need also “intermediate” structures able to provide a diagnosis; to provide clinical help near their home, to perform therapy and follow-up controls on a daily base.

Is it possible to identify criteria to develop a list of priorities for the selection of rare diseases on which highly specialized institutions should be built? May be we can, in certain circumstances. Apart from cases of well known and stabilized Institutions, which are part of the cultural heritage of a Nation, we can suggest to adopt at least three criteria to identify priority rare diseases:

- the existence of new effective treatment and/or diagnostic or screening procedures and/or drugs for a certain disease;
- the possibility of grouping several rare diseases, which may be studied together, because of their clinical expression (e.g., central nervous system, or cardiovascular system, and so on) and/or their aetiology (e.g., genetic-metabolic);

- the possibility of collecting large amounts of resources (funds, personnel, equipments) from private/public sources, and the contemporary availability of a critical mass of investigators expert on a specific disease or a group of diseases.

In order to promote the establishment of such centres, it could be important to consider the provision of incentives such as the release of certification or the allocation of financial support, as well. Different Countries in Europe put forward interesting proposals in the field of rare diseases/orphan drugs (e.g., Denmark, France, Germany, Hungary, Italy, Poland, Spain, Sweden, The Netherlands, United Kingdom). Several countries launched a national plan for rare diseases, and within the Plan, some of them designed a number of referral departments/centres located within universities/hospitals, whereas others chose providing funding to specialised centres of reference, or to patients' organizations, or to support clinical research into rare diseases.

Which perspectives for the future? Much work needs to be done:

- a) Information for the great public
- b) Information for the workers in health structures and for the medical schools
- c) Information for the “continuing medical education”

Can we suggest that a National Plan for rare diseases should be adopted in all EU countries?

All these points shall receive help through the web correct diffusion

## **Other important issues in the context of care and treatment**

### **Rehabilitation**

In addition to the pharmacological treatment of the disease or of its signs and symptoms, it is essential to support the reintegration of the patients within the society. This would imply an appropriate physical rehabilitation, when necessary, and a continued or *ad hoc* psychological support to patients. Assistance and help should be given also to the family of the patients as they are directly involved in the management of the patients and often it is a heavy, constant physical and psychological burden difficult to coop with.

It is therefore important to consider the impact of the disease on the quality of life of the patient to understand how to ameliorate it with treatment, care and any other non-clinical support needed.

The integration of the patients within the society should receive more attention as it is the base to ensure a normal and meaningful life to person that too often are marginalised because of their disease. In this optic, it is important to work towards the establishment of an enabling environment including a better school system, a better workplace as well as a better social support for people affected with rare disease.

### **Education and information**

The enabling environment previously envisioned cannot be achieved without the engagement of the general population. It is important to better sensitise the general population on such important issues as it will help to increase the understanding of the problems, to avoid discrimination, to share important preventive information and to build a critical culture on rare diseases.

The continue training of health care workers is a “*conditio sine qua non*”. It is a essential to increase the skills and knowledge of the health care workers; different approaches can be suggested such as the inclusion of rare diseases within the curriculum of the medical school and the development of specific training sessions on rare diseases.

Because, always more often, clinicians, patients, mothers, friends and many others, look for information on the web, it would be important to ensure the development of website of controlled, good quality. The website could include e-forum that would form the basis to strengthen the collaboration among doctors, could be used to share information, experiences and may be to establish networks among patients, doctors and/or others in need.

In order to sensitive and provide appropriate information, it is important to develop information, education and communication materials to be distributed in hospitals, schools and any other relevant opportunities. Newsletter, brochure, pamphlet, poster are only few examples of written information materials. Also the engagement of the media could be further explore as often people rely on the information given by newspaper, magazine or the radio.

In this context the patients' association can and should play a major role. There is need to strengthen the linkages between general practitioners, health centres, schools and patients' associations. In addition patients' association should be more involved when issues related to rare diseases are discussed as they have a unique insight that derived from their personal and direct experience.

## Session II. Discussion Group

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### FOCUS GROUP 4.

### CASE STUDY: HAEMOPHILIA

<i>Discussion leader</i>	Massimo Morfini (Italy)
<i>Rapporteurs</i>	Erica Daina (Italy), Simone Baldovino (Italy)
<i>Participants</i>	Elisa Rozzi (Italy) Ezio Vallana (Italy) Federica Censi (Italy) Renato Scarinci (Italy) Paolo Salerno (Italy) Maria Antonietta Trasia (Italy) Angela Passafiume (Italy) Franco Noli (Italy) Marotta Lucia (Italy)

## Introduction

There are about 38,000 haemophilia patients in European Union, the incidence of haemophilia being 1/10,000 inhabitants. Each year, about 750 babies are born with this disorder. Approximately 85% have haemophilia A (FVIII deficiency) and the remainder has haemophilia B (Factor IX deficiency). The severity of haemophilia is related to the amount of the clotting factor in the blood. About 70% of haemophilia patients have less than one percent of the normal amount and, thus, have severe haemophilia.

The phenotype of the patients is based on assay of factor VIII or IX, by means of clotting (one-stage method is the most popular) or Chromogenic substrate methods. The genotyping is now easily achieved by means of screening tests, as CSGE or DHPLC, in order to select patients positive for Intron 22 inversion (about 40%) and, in the negative, to detect the exon carrying the mutation. The sequencing of the mutated exon allows the exact definition of the mutation.

The knowledge of mutation, in the frame of affected family, is particularly important to detect the facultative carriers before or during the pregnancy. This allows the prenatal diagnosis by means of villocentesis at 10-11 week of pregnancy. The voluntary interruption of pregnancy is particularly frequent in under development countries (about 80%) and less frequent in the developed countries (about 30%) where good facilities are available for the treatment of the disease.

## What is the problem?

The most important challenges facing today the haemophilia patient, health care providers, and research community are safety of products used for treatment, management of the disease including inhibitor formation, irreversible joint damage, and life-threatening haemorrhage, and progress toward a cure. In the past 10 to 15 years, advances in screening of blood donors,



laboratory testing of donated blood, and techniques to inactivate viruses in blood and blood products have remarkably increased the safety of blood products used to treat haemophilia.

Although treatment-related infection with the AIDS virus or most of the hepatitis viruses is a thing of the past, these measures do not completely avoid viruses such as hepatitis A and Parvovirus B19. There is a great deal of concern about Creutzfeldt-Jakob disease (CJD), a rare transmissible nervous system disease that is inevitably fatal, being transmitted through transfusion. Recombinant factor VIII/IX, are manufactured by a process entirely free of human or animal proteins.

Although the cost of these products exceeds that of the blood-derived product, it is clearly the treatment of choice for those, such as newborns, who have been not yet exposed to blood products or, if previously exposed, not yet infected patients. All haemophiliacs of European countries have now available a treatment for bleeding which is totally free of any contaminating agents.

On the contrary, the haemophiliacs of on development countries do not have these facilities, neither plasma-derived clotting factor concentrates: 80% of haemophiliacs world wide are lacking any form of therapy. While current treatment has greatly improved the outlook for most haemophiliacs, the development of antibodies (inhibitors) that block the activity of the clotting factors has complicated treatment for some patients. Approximately 15 percent of severe haemophilia A patients and 2.5 percent of haemophilia B patients develop such antibodies after exposure transfused factors. When inhibitors are present in large amounts, the patient may require very high and expensive quantities of transfused clotting factors to stem bleeding, and, in some instances, even that may not be effective. Immune Tolerance Induction (ITI) protocol have been developed with aggressive therapeutic approaches, which are terribly expensive (about € 1.10<sup>6</sup>/year for a 20 kg child).

The major cause of disability in haemophilia patients is chronic joint disease ("arthropathy") caused by uncontrolled bleeding into the joints. Life-threatening haemorrhage is a constant risk.

Traditional treatment of haemophilia is "on-demand" treatment, since patients are received factor replacement only after bleeding symptoms are recognized. In several European countries, the haemophiliacs receive periodic infusions (prophylaxis) regardless of bleeding status. This approach maintains the factor level high enough that bleeding, joint destruction, and life-threatening haemorrhage can be almost entirely avoided. The prophylaxis cost is huge, more than € 200,000/year/patient by the second decade of life. Even higher, is the cost of Immune Tolerance Induction (ITI), about € 4,000,000/year/patient. The treatment decisions are not easy.

## Conclusion

The final goal is a cure for the disease. Gene's transfer is the challenge. Since normal genes transferred into patients could produce the normal clotting protein. A small amount of active factor produced by the patient's own body will correct the disease.

Although much must be done before such treatment can be offered to patients, there are already many studies performed on animals. For instance, factor VIII and IX genes, inserted in mice and dogs, can produce the proper blood product for periods exceeding one year.

Major issues, still to be resolved, include the low level of production of the clotting factor, reduction of immune reactions that stop the production after a period, and development of ways to insert the gene directly into the body without manipulating cells outside the body.



**SESSION III**  
**Social aspects and quality of life**



### Session III. Plenary lecture

## PSYCHOSOCIAL IMPACT OF RARE DISEASES

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Elizabeth Ettorre

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### Introduction

You may remember that two years ago I gave a talk on sociological aspects of rare diseases to a similar NEPHIRD (Network of Public Health Institutions on Rare Diseases) conference and some of you in the audience attended. In that talk, I argued for the development of a social perspective on rare diseases and showed how this development revolved around a discussion of three key areas including: 1) identifying people involved with supporting those with Rare Diseases (RDs) as well as Associations for people with RDs (APRD); 2) establishing the need for a new language on RDs; and 3) beginning to answer the question ‘What is involved in the culture of RDs?’

This issue will deal about the psychosocial impact of rare diseases. It focuses again on the question ‘What is involved in the culture of RDs?’ Before I begin, I should say that as a sociologist I am more familiar with the ‘social’ part of ‘psychosocial’ and will talk more about the ‘social’. However, you should know that I am keenly aware of the ‘psycho’ part of ‘psychosocial’ as well. What I hope to do in my talk is look at four topics:

1. Why is there a need to talk about psychosocial impact of RDs? ;
2. How we are able to use the notion ‘psychosocial impact’ of RDs in a political way;
3. What are the implications of using ‘psychosocial impact’ of RDs in a political way and lastly
4. The importance of sentimental work in the field of RDs.

### Need to talk about psychosocial impact of RDs?

When psychologists talk about the psychosocial impacts of diseases they tend to link this issue to a patient’s quality of life. Subsequently, they argue that psychosocial factors impact upon the development and progression of diseases and that psychosocial interventions will improve the quality of life of patients with established diseases. They suggest further that psychosocial interventions may even influence biological processes thought to delay disease progression (1).

However, I would argue that this picture shifts dramatically when we are talking about the psychosocial impact of RDs. This is for a variety of reasons. There are probably many but I focus on two, which are relevant for my purposes. Firstly, research on psychosocial impact of RD is still in infancy and furthermore, lacks any sociological input. As a sociologist, I think this is most interesting because I think sociologists, particularly medical sociologists, should have a lot to say on the experiences of those with RDs; how the discourses on chronic illness and disability shape these experiences and the impact of RDs on the medical profession. I think some of my colleagues in the field of medical sociology are more interested in diseases/illnesses, which are accessible in research terms. (I find this quite curious as

EURORDIS estimates that 30 million people in Europe are affected by rare diseases throughout Europe).

Secondly, and related to this last point, while quality of life is a key issue when we talk about persons with RDs, research on people with RDs tend to fall off the face of the earth because researchers find it much easier to access large populations of those who are sick with more common diseases such as heart disease, cancer, HIV/AIDS. In the field of RD, we often don't have the luxury of large-scale clinical trials. Thus, it is difficult to argue, as those researching more common diseases do, that only large-scale clinical trials are able to determine the extent to which psychosocial interventions may impact quality of life, morbidity and mortality (1).

## **Use of the notion 'psychosocial impact' of RDs in a political way**

While the idea of 'psychosocial impact' shifts dramatically when we talk about RDs, I would argue that we should begin to use the notion 'psychosocial impact' of RDs politically in 2 ways:

1. to sensitize those in society without RDs to what living with RDs is all about;
2. to attempt in some way to de-medicalize RDs.

### **Sensitizing those in society without RD to what living with RDs is all about**

The everyday person in society should be aware of what it means to have a RD, the difficulties one with a RD faces as well as those around him/her; the oftentimes, diminished prospects for a good quality of life, the stigma one with a RD experiences especially if there is a visible physical disability for all to see. (After all, they are the ones whose tax money will be used to provide medical services in some countries). Also, I think what would be interesting here would be to get circulated into the public domain research on those who care for those with RDs. While I may have painted a gloomy picture here – gloom and doom are not always the case, as we know from research on carers of those who are disabled. Caring for those with chronic illness and disabilities (here I would include those with RDs) can be a joyful and empowering experience.

In some of my recent work on narratives of acute illness I show that for all of us (whether or not we have a RD), the many layered texture of illness is shaped in our daily lives as a way of enduring and actively engaging with anxiety, despair, disgust and agony as well as triumph, hope, joy and pleasure. Acute illness narratives can generate useful ways of creating knowledge about suffering and of grappling with not only the intricate, interior language of wounding, despair and moral pain but also the victory of living with an illness or in our case RD. This often gets left out of the picture.

Besides knowing about the victory of living with a RD, those in society need to be sensitised to how RDs are constructed as disabilities and how the notion of dis-ability and disablism are embedded within society. Here I use Carole Thomas's definitions to make my point (2). Disability is not the condition or functional consequence of being physically or mentally impaired. Rather, dis-ability refers to the disadvantaging affects – referred to by many as the 'social barriers' – faced by people with impairments flowing from disablism which is 'the ideological antipathy to what is considered to be undesirable physical, sensory or mentally – related difference or 'abnormality' in western culture'. These definitions of disability and disablism are very useful as a basis for further development of an understanding of RDs in society.

## **De-medicalizing RDs**

What I mean by de-medicalising RDs is that while we accept that RDs are medical conditions, we help to raise the awareness of medical professionals to the need for psychosocial as well as medical interventions in the field of RDs. Medical professionals should not only be interested in how RDs affect the human person as an organism or developing interventions that reduces mortality or morbidity. They should be aware of how a psychosocial intervention can have a huge impact over the course of a lifetime for person with RD who benefits. There is a marvellous opportunity to make a difference.

Here, I would ask: What model of disability does the medical professional use? Does the medical professional uphold the individual model or the social model of disability? Do the medical professional locates the problem of RD within the individual and see the cause of the problem as stemming from the functional limitations or psychological losses which are assumed to arise from disability/RD? Does the medical professional uphold the 'personal tragedy of disability' which suggests that disability/RD is some terrible chance event which occurs at random to unfortunate individuals? Or does the medical professional uphold the social model of disability rejecting the individual model of disability and accept that it is not individual limitations of whatever kind which are the causes of the problem but society's failure to provide appropriate services and adequately ensure the needs of disabled people are fully taken into account in its social organisation.

If the latter social model is accepted, the medical practitioner sees that disability or a RD is really about all the things that impose restrictions on disabled people/those with RDs - ranging from individual prejudice to institution discrimination, from inaccessible public buildings to unusable transport systems, from segregated education to excluding work arrangements and so on. The social model suggests that people with RDs are disabled by society not by their bodies or diseases.

What about the empowerment of patients with RDs? Do medical professionals have an awareness of support groups for those with rare diseases? Do they facilitate the development of self-help strategies for their patients? Do they employ team working and principles of rational management of their patients' condition? What about their management of the impact of the RD on the individual and society? What do they know about State benefit entitlements; aids and appliances the patient uses or needs; the physical, social and psychological impact of the RD; the genetic implications for the family; medico-legal issues and educational needs of the patient? When they communicate to the patient or give advice are they able to use a psychosocial model to help de-medicalise RDs?

## **Implications of using 'psychosocial impact' of RDs in a political way**

If we use the notion psychosocial impact in a political way we focus very clearly on the complexities which exist in the RD culture. This means that we make it very clear that connections need to be made between society, the individual, the family, the RD, health intervention and medical professional/health personnel. Also, we help to establish the idea that RDs have a major impact on one's identity in society. Here, there is a lot of work in sociology which shows that chronic illness has a major impact on identity (3,4,5). We need to use this work as a basis for our own work in the field of RDs. Also, chronic illness is seen as a radical intrusion into embodied selfhood. Why can't we see RDs in the same or similar way? We need

to be more reflexive about RDs. I would argue that being more reflexive about RDs can become a valuable healing tool for patients and medical professionals alike, regardless of the fact that many RDs do not have a cure. I am talking about the recognition of what those with RDs need on a human level.

## Importance of sentimental work in the field of RDs

So with the backdrop of sorrow and joy, my talk thus far has implied that a focus on the person with RD in a social context is crucial if we want to make any impact or change on the level of social recognition of RDs. If we want to improve the quality of life of those with RDs, we need in my view to begin to raise the consciousness of society on a macro level, as I described above.

On a micro level, we need to recognise that illness narratives have a major role to play in an ill person's quest for authenticity, while experiencing 'a loss of self' (5). This is true for those with RDs. We need to develop in the public domain narratives of those with RDs – narratives which detail physiological changes that occur for the individual, the embodied choices that they make in their lives and the participatory/social frameworks in which these are set. We also need to recognise that when a person is ill or has a RD, there is work to be done by her/him and others. The entirety of work organised over the course of a RD is incalculable. Making embodied judgements is hard work for the patient with RD as is being shaped as the technician of practical and technical knowledge for the medical professional treating the person with RD.

Here, I would like to introduce the concept sentimental work which Anselm Strauss, the American sociologist and his colleagues (6) define 'as any work where the object being worked on is alive and sentient'. While Strauss and his colleagues translate this into the treatment of the chronically ill in what they call the 'technologized hospitals', their ideas are useful in a wider clinical context and specifically, in providing a reflexive context for RDs. Sentimental work suggests the problematization of illness/RDs and desire for health as a powerful force that needs to be morally regulated.

For Strauss and his colleagues, the sources of sentimental work include a perspective on medical professional's trajectory work, both expressive and instrumental. Highlighting different types of moral regulation, they see sentimental work in a space where there is the ever present possibility of clinical awareness, if not danger. Sentimental work is commonly done by strangers to the patient; takes priority over other considerations such as getting to know the patient and has a time expanse which may last for days or even weeks. While this work may be a bit outdated, as evidenced by the recent work in the field of medical sociology (7-10), Strauss and his colleague's work suggest a whole range of ways that medical professionals 'work' emotionally with patients and vice versa. Strauss speaks of interactional and moral rules, trust work, composure work, biographical work, identity work, awareness context work and rectification work, which for me can be translated to the field of RDs and are significant in RD contexts.

For example, that *trust work* is needed in clinical encounters is interesting given that very often the medical professional is usually at first a stranger to the patient and the patient to him/her. There is also *identity work* because RD impacts on one's identity. Is the patient further medicalized or understood and listened to by the medical professional? Does the medical professional speak in a language that is understood by the person with RD? Is there any attempt at restoration of trust or *rectification work* when things go wrong?

Glaser and Strauss (11) coined the term *awareness contexts* when looking at the sorts of interactional difficulties surrounding the dying in hospital. Identifying a range of awareness



contexts, they looked at how social order was maintained in the face of the disruptive threat, death, and how the hospital regime accommodated the unintended consequences of impending death. What sort of awareness contexts are established when working with people with RDs who are not dying? Are there *open awareness contexts* when the person with RD knows what is happening to them and their body and the risks of his/her condition? Is there *closed awareness* (i.e. the staff knows the patient does not about his/her condition and the tendency for staff to believe that the patient does not want to know)? Is there a *suspicion awareness* (i.e. suspicion exists between the medical professional and patient and the status of the RD is unclear); Is there *mutual pretence* (i.e. pretence exists between patient and medical professional)?

What about *composure work*? How does the patient with RD learn to gain calmness and equanimity. There is also *biographical work* when life events may be shared between the medical professional and a person with RD. Is this ever done in a clinical setting?

Usually, the person with RD recognises himself/herself as 'having a disease' in the above encounters, as he/she engages in *interactional work* and learns about *setting moral rules*. In this sense it is not always the medical professional who is in control. Thus, a medical professional's behaviour is capable of change and communications patterns between doctors and patients have been known to transform from strictly medical encounters to those in which engagement in a mutual life world is possible (12). Indeed, health care relationships can be spaces where the expertise of both patients and health professionals are pooled to arrive at mutually agreed goals (13).

In conclusion, for those with RDs their self-identity, emotions and experiences are often shaped by biomedical experts' risk calculations about their diseased bodies. I would contend that some, if not many, of the problems those with RDs encounter are socially constructed and political as well as a personal and biological. I have shown the importance of sentimental work in encounters with those with RDS. Most importantly I have wanted to give testimony to what has been traditionally neglected in the field of RD and to make way for new and more reflective ways of doing patienthood for those with RDs as well as those who treat them.

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### Session III. Plenary lecture

## NARRATIVE MEDICINE: A RIGHT AND A DIFFERENT EPIDEMIOLOGY

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“Memory, defended and educated within ourselves for others  
by way of the autobiography, returns us to the sense of having lived  
and of being able to teach what little we have managed to understand about life”  
(D. Demetrio)

“Listening to a story of disease is not a therapeutic act,  
but it is an act that gives that voice dignity and honors it”  
(A. Frank)

## Background

Illness refers to a person's perception of their health and its context, and illness stories represent the lived experience of patients and families (1, 2).

Research is a response to health needs, collecting personal experiences can be a method to understand therapeutic needs and social inequalities (3).

Through stories, the patients and the clinicians can speak to each other to build new policy solutions, and to enhance the health care workers' approach to patients and their families (4).

Today narrative medicine represents a new tool for research and for patient/family participation (4, 5).

Narrative medicine is a combination of different partnerships: primary care medicine, narratology, and studies of effective doctor-patient relationships.

Narrative medicine has been introduced to improve doctor-patient relationships and it rightly deserves greater consideration in health care systems for a number of reasons (1, 2).

Narrative medicine is a patient-centred approach. Telling stories are a neglected right and are the best way to voice patient's needs (3, 6). The illness stories give an account of a life project; a personal experience, and how patients and their families experience diseases. The illness/life stories give the opportunity to see situations from a different point of view: from the standpoint of storytellers.

In addition, the stories can assist and guide the physician in formulating better diagnostic and treatment options, since they are informative situations to put clinical data and needs in a real perspective (7, 8).

Illness stories provide visibility to people, and their unmet needs (4, 8).

Furthermore, the narrative approach can have a therapeutic value and an empowering role (4, 5, 9). Stories therefore could complement data on accessibility and quality of socio-medical services, on quality of life and on needs (3,6,8).

It is important to stress the epidemiological value of the diseases/life experiences (4, 6, 9, 10).

The stories should be collected in a context of collaboration with advocacy groups, families and patients to become a form of “lay/popular/community” epidemiology (7, 8).

Telling/listening to illness stories is a specific methodology of patient/family participation (4, 6, 9).

Traditionally, patients are rarely seen as partners in the therapeutic setting, and in the epidemiological/clinical research (4, 9).

Nowadays, the scientific community has come to acknowledge the importance of patients participation (4, 9).

A more direct and active role of people and patients in formulating health choices, is considered an interesting trend in medicine and society (3, 7, 8).

According to the spirit of the Declaration of Alma Ata, participation is a right. This is an area at risk of being dominated by declarations of intent, wishful thinking while its credibility and contribution are strictly dependent on real experiences (5).

Taking up the word is one of the most significant and ‘elevated’ means of participation.

Telling stories is a way to take up the word, and reserving listening time to them are the means of building paths of real participation (6, 8).

The disease experiences are always part of a ‘project of life’; gathering and comparing them makes it possible to create paths that are truly shared (4, 5, 9).

## Why writing?

“Writing relieves uneasiness. Writing incarnates and produces in any case someone who does not exist until he is born from our pen. [...] Writing sows and generates. It leads us beyond. In any case, writing stops us; it makes us feel even more physically present. [...] we no longer feel liquid. We were so while we were thinking...the pen, the pencil, the keyboard return to us the sensation of not floating in empty space”  
(D. Demetrio)

Writing is a way to speak out, a way to tell the story, calmly, beyond the time limitations of an interview, or the rigid structure of a questionnaire (1-3).

Writing allows to communicate experiences, to reach every one, even those that have difficulty in ‘coming out’, who do not have any help from or connection to support/advocacy (3, 6, 8).

Writing returns centrality to the individual and told stories may offer healthcare providers the possibility to have a more complete perspective of the problems (4).

## The project

In November 2005 the Centro Nazionale Malattie Rare (CNMR, National Centre for Rare Diseases) of the Istituto Superiore di Sanità (ISS, Italian Health Institute), initiated a collaboration project on rare diseases and narrative-based medicine. In our project we stress the importance in the collecting of illness stories as a participatory and inclusive method to better understand unmet needs and to develop public health activities (2, 3, 8).

In other countries many different experiences have been conducted which have centred on the involvement of patients and they have always had very fruitful results (2, 3, 6). The project “Rare Diseases and Narrative medicine: integration with and contributions to projects on public healthcare, quality of life, accessibility to social and healthcare services and formation” is aimed

at promoting a culture of participation in the context of rare diseases through the collection of concrete experiences (3, 6).

The idea of creating a database of diseases began in continuation with several other projects initiated within the European Project NEPHIRD (Network of Public Health Institutions on Rare Diseases), to integrate data already collected within the context of research on accessibility and quality of social-healthcare services in Italy for patients with rare diseases.

## Methods

A 6-month pilot phase has been started within a focus group. Objectives have been discussed during the meeting of the focus group which included a selection of Patient Associations (PA) representing different rare diseases. We have collected a wide variety of personal experiences (stories, paintings, and different materials) inserted into a special database.

## Results and discussion

We have collected a wide variety of personal experiences (63 stories, some paintings, and other materials). From experiences, we can stress that:

- patient and family who turns illness into story transforms problems into experience and experience into resources
- sharing experiences is a good way to find solutions and new projects of life
- in the field of rare diseases, there are many unmet needs and different problems in the areas of diagnosis, information, social support and therapeutic options (2,3,6).

All patients affected by a rare disease share many problems and needs:

- late and difficult diagnosis;
- little knowledge exists on rare diseases in the medical context;
- lack of an effective treatment;
- communication of the diagnosis.

For many people the role/support of association is an important way to have a diagnosis and to find information about hospitals, therapies, social services. Patient Associations provide support and information to patients, their family and carers.

One of the most serious problems is the lack of information. This affects health and the quality of life. The lack of information is a social determinant of health.

In the illness narratives, we have not seen the family doctor actively involved and this is an important problem that we should discuss, at all levels, to understand the reasons, responsibility and remedial proposals.

## Conclusion

In our project, we stress the importance of collecting illness stories as a participatory and inclusive method in better understanding unmet needs and in developing public health activities. If research is a response to health needs, collecting personal experiences is a method in understanding therapeutic, social, relational needs, and inequalities (6,8).

The voice of experience and the voice of an expert can speak to each other to build new policy solutions and to enhance the health care worker approach for patients and families affected from rare disease (4, 6).

The collected data will be fundamental for the National Health Service in order to promote a new direction on health participation and rights, to establish an active participation of patients, relatives, parents, and associations in order to plan relevant programs in public health, to improve the different epidemiological approaches (3, 6, 7).

The data finally collected would become an educational resource for medical students, nurses and other health professionals (3, 5, 6).

In light of the results obtained we will seek to develop projects that include the active participation of patients, their families, and associations in educational workshops or in the preparation of literature that are relevant to public health (4, 6, 9).

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### Session III. Plenary lecture

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## **COPING WITH SOCIAL NEEDS: EXPERIENCE FROM INTERVENTION OF AGRENSKA, SWEDEN\***

Anders Olauson

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When a family gets a child and the child have a disability, everything changes and the whole family is disconnected from all networks, that they previous was a member to.

The family program at Agrenska is an intervention that shows result that goes beyond other interventions that the traditionally healthcare-system offers to these families.

The program, based upon a five-day fulltime, stays and consists of four parallel programs involving the children with the diagnoses, parents, siblings and family related professionals. The target group is diagnoses within the group rare diseases, and involves the whole family and family related staff.

From a pan-EU perspective the results indicate that if all families who have a child with a rare disease participate in a program as the Agrenska model, there will be a significant less strain in these families and their relatives.

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\* Abstract of the lecture

### Session III. Plenary lecture

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## CONTRIBUTION OF PATIENTS' GROUPS ON EPIDEMIOLOGICAL HEALTH DATA: RARISSÍMAS\*

Paula Costa (a), Fernando Guerra (b)

(a) *Portuguese Association For Rare Disorders, Oporto, Portugal*

(b) *Scientific Board of RARISSÍMAS, Department of Medical Genetics, Dona Estefânia Paediatric Hospita, Lisbon, Portugal*

RARISSÍMAS is a Portuguese patients association that provides support of rare disease patients. This patients association has six axis of action: scientific activities; patient's register; raising funds; provide Information to patients, families and health professionals; pressing the Portuguese government; family support.

The development of adequate information about rare diseases is one of the most important tasks of RARISSÍMAS. In the last four years, our association developed a number of activities in Portugal to inform the general population, the rare disease patient's families, and specially the health professionals, about the actual impact of rare diseases in our society dynamics and public health policies.

At this moment, RARISSÍMAS is holding two projects. One on scientific level with the creation of a rare disorders and orphan drugs phone line to help professionals and families with the information available on these subjects. The other one is the construction of a home for young adults with rare disorders. Our First Lady embraces this project and with the support of several sponsors, we, RARISSÍMAS, will build a house/school/activities centre for young adults with rare disorders.

As RARISSÍMAS as no governmental support we contacted private sponsors to support both projects. For "Marcos's House" we launched a fund raising campaign open to population and enterprises.

So far we managed to achieve the locations for both projects. For rare diseases phone line we have almost everything we need and it won't be long to start working. For "Marco's House" we have the location and the project. Now we are raising funds to start building (we will try Feb 16 2007).

Concluding, these two projects are very important to the quality of life of rare disorders carrier's and their families. We think it is also important for doctors and other technicians to know that these children/adults are being conveniently accompanied. We propose that these projects can be adopted in all EU countries.

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\* Abstract of the lecture



### Session III. Plenary lecture

## CRITERIA FOR QUALITY OF LIFE ASSESSMENT\*

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Over the last two decades, clinical and public health researchers have emphasized the need for a thorough evaluation of concepts such as Health Related Quality of Life (HRQoL) to study the impact of chronic illnesses and their treatments on the patient's life. At least four dimensions should be included in a quality of life assessment. These dimensions are physical, functional, psychological, and social health. Different tools were developed to measure HRQoL.

Our aims are to investigate the ability of different patient-oriented questionnaires in measuring patients' perspective and to highlight the criteria for quality of life assessment.

Methods: We critically evaluated papers regarding the process of development and validation of HRQoL tools in order to analyze their own characteristics.

Mainly, three different categories of patient oriented tools exist: generic, disease-specific and "regional" questionnaires. Generic tools are specifically developed to permit a wide assessment of patient's health status, while disease-specific questionnaires detect specific deterioration due to pathology. Disease-specific tools are more sensitive and responsive to changes than generic tools, but they focus only on specific aspects of pathology. "Regional" tools are specifically developed to assess the performance and symptoms of an anatomical area.

In conclusion, the tool must be chosen according to the aim of the research and the characteristic of the studied sample. The best way to avoid risks of errors when we need an accurate HRQoL assessment is the use of both generic and disease-specific tools at a time. When disease-specific tools are not available, regional tools should be used. We think that patient-oriented questionnaires should be used in clinical trials to better define the impact of the pathology on patient's daily life, to investigate natural history, to measure the efficacy of the therapy.

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\* Abstract of the lecture

### Session III. Plenary lecture

## ASSESSMENT ON PATIENTS' NEEDS: RESULT OF NEPHIRD SURVEY

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NEPHIRD (Network of Public Health Institutions on Rare Diseases) is one of the projects financed by the European Commission following the decision (No 1295/99) taken by the European Parliament and Council to launch a programme of community action on Rare Diseases (RDs).

NEPHIRD objectives follow:

- 1) to undertake a situation analysis on RDs at the European level;
- 2) to estimate epidemiological indices (incidence and prevalence);
- 3) to assess the quality of life of patients affected by the selected RDs;
- 4) to assess the access to and quality of health care services for RDs;
- 5) to identify public health indicators for RDs.

Fifteen European and EU associated countries participated in the project: Armenia, Belgium, Croatia, Denmark, Finland, France, Germany, Italy, Lithuania, Malta, Netherlands, Portugal, Spain, Sweden and UK. The project comprised the Project Management Group (PMG) and the Expert Working Groups (EWGs). The PMG was appointed to coordinate, monitor progress and to provide directions to the overall implementation of the project. The EWGs were responsible for taking decision on processes and tools to undertake the activities of the project. PMG had *ad hoc* meetings to monitor progress of the project. The final meeting with all participants of the project was held from the 18<sup>th</sup> to 23<sup>rd</sup> September 2006. Also the EWG had several meetings to discuss methods and agree on and/or develop tools for the different activities of the project.

In the context of the project, the following research activities were undertaken:

- situation analysis of RDs at European level;
- assessment of the prevalence at European level of the Myasthenia Gravis (MG) and of the Cornelia de Lange syndrome (CDL syndrome);
- assessment of the accessibility and quality of health care and social services for RDs patients;
- assessment of QoL of patients with RDs.

Moreover, NEPHIRD contributed to the assessment of health indicators on RDs. In this context, the NEPHIRD project used his network of experts to provide recommendations on the identification of indicators for RDs.

## Situation analysis

The situation analysis on RDs showed that the posture on RDs at the European level is very heterogenous:

- different policy attitudes with regards to RDs;
- few countries have publicly funded structures dedicated to RDs;

- few countries have national plans;
- few countries have a system to collect data on RDs.

In this context, it will be important to advocate for keeping RD a priority in the political agenda by promoting a comprehensive approach for addressing RD.

Strengthening the collaboration among EU countries is another key action to promote. In addition to the collaboration at the European level, the development of national plans at the country level will be essential to ensure the comprehensive approach previously mentioned.

The development of a surveillance system for RDs remains a priority action to promote and support. Establishing a Register for RDs could contribute to the development of a surveillance system, however there are still some obstacles to overcome. Among these obstacles are: a lack of awareness of the Ministry of Health (MOH) on the importance of accurate diagnosis, continuous surveillance, treatment and data collection on RDs; a lack of funds; a lack of a network and referral system for the diagnosis and treatment of RDs.

In conclusion, it will be important to address immediately the obstacles in order to ensure the establishment of a surveillance system at the European level. NEPHIRD experts held various meetings to discuss and agree on the most important issues to consider for establishing a network for data collection among EU countries. Experts discussed and provided recommendations on the following issues: disease selection, type of information to be collected, identification of centres for data collection, information flow, data management and a data quality and coding system.

## **Prevalence of RDs with different approaches**

Two different approaches were used (a review of relevant scientific literature and a population based register) with the aim of comparing the two. The results of NEPHIRD on these topics highlighted that the prevalence evaluated through a review of the literature is useful when dealing with diseases for which a data collection system is not yet in place. However, the literature review is a rapid method, which provides a crude estimation of the prevalence. Thus, results have to be interpreted very carefully. Moreover, the prevalence based on registers is more reliable. It is a common understanding that Registers are the ideal sources of data that give valid and reliable epidemiological information. Only a “population based register” ensures a comprehensive view of RDs. EUROCAT (acronym derived from its original name European Concerted Action on Congenital Anomalies and Twins) is a good example of register. Such registers are distributed quite uniformly throughout Europe; they are good sources of reliable information for several RDs, fulfilling almost all needs, from serving as a tool for surveillance to providing epidemiological estimates. However, running a register is a cumbersome and costly activity that is not always effective and efficient.

## **Accessibility and quality of healthcare and social services**

To assess accessibility and quality of health care and social services a pilot survey involving patients' Associations was carried out in several EU Countries in patients with Myasthenia Gravis, Neurofibromatosis type 1, Prader-Willi Syndrome and Rett Syndrome. The pilot study was undertaken in the following NEPHIRD countries: Italy, Spain, France, and UK. Additional

countries such as Romania and Turkey expressed their interest in being involved in the study and they were welcomed to participate.

The assessment encompassing clinical, rehabilitative, social, educational and legal dimensions identified and confirmed the multidimensional needs of RDs patients.

The overall rate of negative and positive experiences are relatively similar for the four diseases, suggesting that rare conditions have major common problems: a) social services (educational and work); b) lack of health information and c) inadequate provision of legal support. The study confirmed the two-fold advantage of carrying out surveys engaging patients and/or their families: a) it helps healthcare providers to improve the quality of and accessibility to their services and b) it empowers patients.

## Quality of Life

To assess the Health-Related Quality of Life (HRQoL) we selected NF1, MG and Prader-Willi syndrome as case-study. The study protocol was a multiperspective protocol including clinical assessment and patient-oriented measures of QoL.

The objective was to link clinical evaluation with HRQoL measurements in order to identify the clinical aspects that mainly impair QoL. To assess the QoL we administered both, the general and the specific tools for the selected diseases. We used the most validated generic (SF-36, CHQ-PF50) and specific QoL questionnaires (MGQ and Skindex).

The studies confirmed the heavy impact that RDs have on both mental and physical aspects of patients' life. Physical and mental aspects of QoL were impaired in all the diseases studied.

For diseases with more disfigurement such as PWS (presence of characteristics facial features) and NF1 (presence of neurofibromas), mental aspects of quality of life were compromised. For MG, physical aspects of the quality of life were more impaired.

Our data demonstrated also that clinical variables are related to the HRQoL.

## Recommendations on health indicators

To promote the use of mortality data (derived from death certificate) and morbidity data (derived from hospital discharge as they are available in all countries of the EU), two different approaches were used (a review of relevant scientific literature and a population based register) with the aim of comparing the two:

- continuing the discussion to identify a list of health indicators for rare diseases including indicators to assess social support for RDs patients and policy actions undertaken with regards to RDs;
- engaging patients when defining specific indicators on the Quality and accessibility of care.

Although, comparability between countries is a major issue, they can provide information on mortality and morbidity of RDs.

## Conclusions

The results of NEPHIRD activities highlighted major challenges in defining RD prevalence and in identifying RD indicators. We have also described major problems related to the

provision of care for patients with RDs, for instance poor quality of care, lack of information on RDs, limited access to health care, etc. Finally, we confirmed the heavy impact of RDs on QoL of patients with RDs. Based on the experience derived from NEPHIRD activities; we suggest giving priority attention to the following:

- improving the exchange of epidemiological data;
- promoting patient involvement;
- promotion of a multidisciplinary/multi-faceted approach in order to tackle RDs;
- developing information for patients and health professionals concerning RDs;
- supporting research on RDs.

### Session III. Discussion Group

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## FOCUS GROUP 1. SOCIAL ASPECTS

<i>Discussion leader</i>	Andrew Knight (Australia)
<i>Rapporteur</i>	Sirkku Peltonen (Finland)
<i>Participants</i>	Giulia Andreoli (Italy) Maria Bonsignore (Italy) Claudio Buttarelli (Italy) Stephen Groft (USA) Erica Hackenitz (Netherlands) Anders Olauson (Sweden)

The group raised some questions and hypotheses about social aspects, which can be considered to be universal are the following:

- How can a person with a rare disease find a better place in society?
- What do we need to do to support the caregivers of a person with a rare disease?
- How can we support professionals and patient advocacy groups?
- At present social aspects are not recognized as important as they are - or as important as they should be regarded.

The theses can be summarized as follows:

- social aspects of rare disease have to be given greater importance;
- social aspects are very individual and require individual solutions;
- social problems of individuals need immediate solutions;
- Persons with rare disease should be integrated with other people in society.

This will decrease social impact of their disease and increase awareness in the community

Moreover, there are several obstacles regarding attitudes and ethical values in the society:

- people that do not understand and appreciate diversity;
- history of separation of “different” people from mainstream society.

It is important to provide training and education of the population and professionals in diversity and to increase health literacy of the population

Social problems and suggestions for the needs analysed according to different periods of life are reported in the following:

- *Parenthood for a child with a rare disease*

#### *Problem*

The illness pushes you out of “normality” – how do we minimise this for families with a child with a rare disease? Parents face a challenge to be able to live “normally” with their child and to help the child to develop social skills and other abilities required in life.

#### *Suggestions*

Group support for the family and siblings should be available to encourage the socializing process. The services needed should be arranged.

Services should be provided as much as possible at home, and the parents should be helped to learn to take care of the child at home.

Educational programs should be provided for people to learn to accept differences.

– *School*

*Problems*

Families and children with rare diseases face different school systems and different problems depending on where they live.

The general school system is built upon expectations which may not match what a child with a disease can achieve. Children with disease do not fill the criteria necessary for integration into the current mainstream schooling system. Thus, disabled people are differentiated or disintegrated very early from the society.

*Suggestion*

Children with rare disease should be integrated into the general school system as they are part of general society.

To integrate the child, teacher should be trained in promoting and coping with diversity.

Improvement of health literacy in general population.

– *Adolescence*

*Problems*

Transition from childhood to adult life requires learning of a range of social skills, coping etc. and may be delayed in a person with illness. Adolescence is a particularly difficult age in which to accept difference and contains a high pressure to be “normal”.

*Suggestion*

Education towards accepting diversity.

Getting encouragement from patient organizations.

Meeting and sharing experience with other adolescents with the same disease.

– *Studying*

*Problems*

Specific disabilities may prevent people from finishing studies or accessing tutoring systems.

*Suggestions*

Institutions such as universities must provide services to enable those suffering from rare diseases to receive appropriate education.

– *Adult life; work and employment*

*Problems*

Unemployment, repeated short employment due to limited funding support of disabled people ; difficulty in finding permanent work, decreased performance in work, decreased ability to cope, poor transmission of information on the disease at work. Problems keeping or losing the job because the disease has caused changes in performance or requires frequent absences for medical or other interventions.

*Suggestions*

Some solutions already exist in some countries. The best solutions should be identified and spread.

Support systems by government: rights to have health care, own living accommodation, to get personal assistance, etc.

The company should be compensated if it employs a person with a disease. To receive this support, the patient has to have the illness officially recognized. In case of rare diseases, the requirement for recognition may even be refused because of the ignorance of the officials on rare diseases.

The role of professionals can help alleviate social problems faced by people with rare diseases through:

- spreading information on rare diseases among public health system;
- increasing and improving the role of family doctors for people with rare disease
- designing service provision so that as much as possible people can receive care at or close to home;
- research-oriented doctors could investigate whether general platforms of common diseases can be used for rare diseases;
- help and support to and from the patient organisations.



### Session III. Discussion Group

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## FOCUS GROUP 2. QUALITY OF LIFE\*

*Discussion leaders* Luca Padua (Italy), Pietro Caliandro (Italy)

*Rapporteur* Lars Ege (Denmark)

*Participants* Enzo Ricci (Italy)  
Luisa Russo (Italy)  
Marotta Lucia (Italy)  
Franco Noli (Italy)  
Mirando Siouti (Greece)  
Annalisa Trama (Italy)

The group focused the discussion in which setting the Quality of Life (QoL) can be used:

- To assess the efficacy of a medical procedure
- To assess the quality of a therapy
- To make an estimation of the needs of a population
- To improve the clinical decision
- To appreciate the differences in the health status of different patients.

After the introduction on QoL, the following topics were covered during the discussion group:

- *To evaluate QoL in patients with deeply impaired clinical picture*

Evaluating Health Related (HR) QoL can be relevant both when the clinical picture is severe and when it is not severe. One of the major roles of QoL is to detect the evolution of the disease. QoL is used in clinical studies in order to integrate so-called ‘objective’ clinical data with ‘subjective’ scales.

To reach a sufficient number of patients QoL is not good to measure individual persons, but useful to measure the implications of the disease in a sample.

- *To compare QoL of patients with different diseases and living in different countries*

The crucial point is to decide which available measurement should be chosen:

- *Generic instruments.* They evaluate the HRQoL as a whole. Applicable to a wide range of different people with different type and severity of diseases, different cultures. Useful for comparisons and decision-making across different diseases and interventions.
- *Specific instruments.* They have been developed on specific groups. They focus on the phenomenon of interest, can be more sensitive, more acceptable

HRQoL is the most important outcomes of clinical trials; useful to investigate variations in the way the diseases develops and can help the doctors to find out, what might be done.

- *To evaluate the QoL of parents*

Different measures exist for adults and children. For children, the QoL evaluation is based on parents’ reports. Anyway it should be reminded that parents’ perspectives may be different from children’s ones.

- *To utilise the results to improve social conditions.*

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\* Abstract of the lecture

### Session III. Discussion Group

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## FOCUS GROUP 3.

## COMMUNICATION AND NARRATIVE MEDICINE

<i>Discussion leader</i>	Daniela Zarri (Italy)
<i>Rapporteur</i>	Simonetta Pulciani (Italy)
<i>Participants</i>	Simone Baldovino (Italy)
	Claudia Alberico (Italy)
	Elisa Rozzi (Italy)
	Stefanov Rumen (Bulgaria)
	Janos Sandor (Hungary)
	Clara Bonaldo (Italy)
	Donatella Valerio Sessa (Italy)
	Anna Luzzi (Italy)
	Anna Colucci (Italy)
	Ines Vallanzuolo (Italy)

This short report summarizes the very long and productive discussion held during the focus group on “Communication and Narrative medicine”.

The participants to this focus group were physicians, psychologists, patient association members and health operators, coming from Italy, Hungary, and Bulgaria.

This heterogeneous group pointed out different viewpoints on “Narrative medicine” and its role and potentiality for a better therapeutic approach.

All participants agreed on the special power of narration, but not every body agreed on the tasks of Narrative medicine, which prompted the discussion on topics such as Epidemiology and Empathy.

The Narrative medicine could be used as reservoir of disease symptoms data to improve clinical knowledge acquired through epidemiological studies. The steering group analyzed the Narrative medicine concept in order to find a link to compare symptoms data collected from questionnaires, with data extrapolated from the “illness stories”.

Many doubts were argued and expressed on the possibility to categorise and to analyze scientifically the data collected through the narration, which to date vastly differ from epidemiological approaches and protocols.

The Narrative medicine has a long way to go before being widely accepted as tool to improve medical knowledge on diagnosis and therapy. Anyway, several participants have pointed out that it could be adopted as an effective and humane medical model.

The narration concept will devote more time to the therapeutic relational approach and may offer opportunities for empathic medical care.

Physicians, besides diagnosing and treating their diseases, should show more empathy towards those who suffer, and accompany their patients through their illnesses.

Empathy is a type of “emotional resonance”, which permits recognizing, perceiving and feeling the emotions of someone else.

Much consideration was expressed about the meaning of “emotional resonance” and its consequences in the medical-patient relationship.

The physiologists pointed out that “Empathy”, as defined by Carl Rogers, is “to perceive the internal frame of reference of another with accuracy and with the emotional components, but without ever losing the ‘as if’ condition”. Thus, it means to sense the hurt or the pleasure of

another as he senses it and to perceive the causes thereof as he perceives them, but without ever losing the recognition that it is as if I were hurt or pleased and so forth.

“Empathy” is not just a personal sensitivity to the “listening” approach of someone else. The attitude to communicate through “empathic” modalities can be acquired, and are desirable to enrich the narrative approach with other communication techniques, such as counselling.

Surprisingly, the focus group on “Communication and Narrative medicine” concentrated just on the patients being the only narrators. Instead, it would have been better to focus on discussions involving physicians, the patients’ families and other social groups that could use the narrative approach. All these participants through narration could better examine their relationships with each other and that of the patients.

From the “illness stories”, physicians can be aware of the patients’ needs, communicate them to other health care professionals, and establish a communication ties with the public and the institutions to establish a more dedicated health care system.

No consensus was reached on task of Narrative medicine and its potentialities and limits by those participating and time placed a restraint on the fruitful discussions continuing.

However, all participants agreed on the need of a more “humane” medical practice based on a constructive collaboration among physicians, health operators and those involved.

### Session III. Discussion Group

## FOCUS GROUP 4.

## CASE STUDY: PRADER-WILLI SYNDROME

*Discussion leader* Antonio Crinò (Italy), Michele Dentamaro (Italy)

*Rapporteur* Gareth Evans (UK)

*Participants* Graziano Grugni (Italy)  
Paolo Salerno (Italy)  
Vittorio Bonaldo (Italy)  
Franco Noli (Italy)  
Clara Rigetti (Italy)

Prader-Willi Syndrome (PWS) is the most common genetic cause of obesity. The syndrome is related to a paternally derived alteration on chromosome 15. It occurs in approximately 1:15,000-25,000 of births. PWS affects an estimated 350,000-400,000 people worldwide. The PWS Association (USA) is aware of around 3,500 cases in the United States, but the estimated pool of 17,000-22,000. The real prevalence of the syndrome is underestimated because of lack of knowledge about the disease.

In the first part of discussion, the dr. Crinò showed a power point presentation of the disease and a clinical case, where the most important aspects of PWS underlined:

- clinical aspects;
- diagnosis;
- treatment;
- social aspect.

Very important is the role of multidisciplinary approaches to this disease, for instance for the clinical aspects of hypotonia and of the obesity, which is deserve a differential diagnosis (Figure 1).

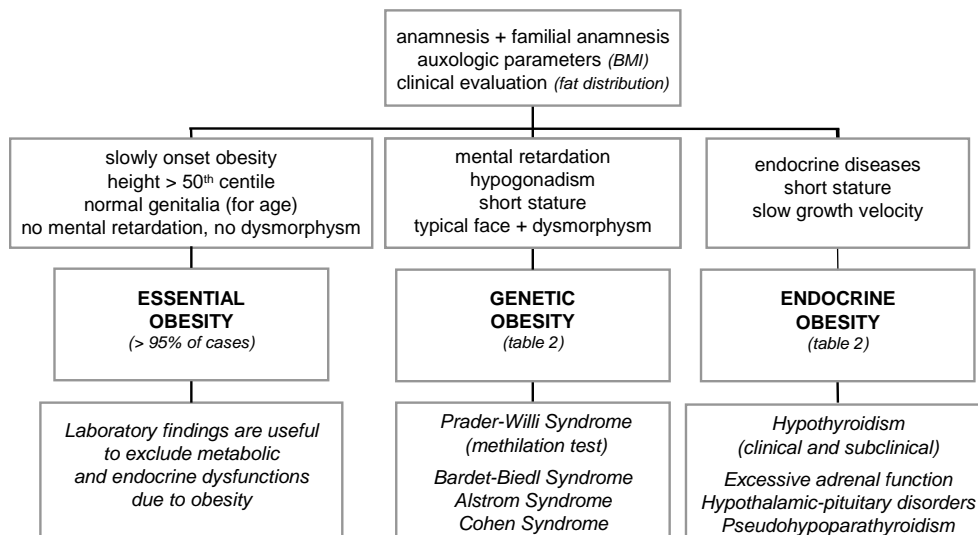


Figure 2. Differential diagnosis of pediatric obesity

**SESSION IV**  
**Rare diseases studied in NEPHIRD**



## Session IV. Plenary lecture

## NEUROFIBROMATOSIS TYPE 1: GENOTYPE PHENOTYPE CORRELATIONS

Meena Upadhyaya

*Institute of Medical Genetics Cardiff University Cardiff, UK*

Neurofibromatosis type 1 (NF1) is a common dominantly inherited neurogenetic disorder that affects about 1 in 3000 individuals world-wide. The condition is characterised by the presence of multiple café-au-lait spots, benign dermal neurofibromas, skinfold freckling and Lisch nodules (1). A variety of other clinical features may also be observed in NF1 patients, including macrocephaly, small stature, learning disabilities, abnormalities of the cardiovascular, gastrointestinal, renal and endocrine systems, a number of orthopaedic problems, facial and body disfigurement, and perhaps most importantly, an increased risk of malignancy. Pigmented café-au-lait spots usually develop during infancy, with most NF1 patients (~80%) manifesting such features by one year of age. The major neurocutaneous feature of the disease are dermal neurofibromas that usually develop later in adolescence, these growths are always benign and develop from the peripheral nerve sheath. The much larger plexiform neurofibromas, which develop in association with the major nerve trunks, usually appear during infancy.

Neurofibromatosis type 1 is caused by inactivating mutations of the *NF1* gene (2).

This large gene spans an ~350kb region in 17q11.2, is composed of 61 exons, of which 4 are alternatively spliced, and encodes a 9-12kb mRNA. Three unrelated genes, *EVI2A*, *EVI2B* and *OMGP*, are located intragenically in intron 27b of the *NF1* gene and are transcribed in the opposite orientation. The role of these genes, whether individually or collectively, in regulating *NF1* gene expression is unknown. Four alternatively spliced exons (9a, 10a-2, 23a and 48a) are occasionally included in the *NF1* transcripts. The *NF1* gene promoter is located within a CpG-island and exhibits a high degree of sequence conservation with *NF1* gene orthologues present in a number of organisms. A number of highly homologous partial *NF1* pseudogene-like sequences have been identified on a number of chromosomes.

Neurofibromin, the *NF1* gene product, exhibits structural and sequence similarity to an evolutionarily conserved family of proteins, the mammalian GTPase activating protein (GAP) related proteins. The most highly conserved region of neurofibromin is the NF1 GAP-related domain (GRD) encoded by exons 20-27a. The neurofibromin GRD stimulates the intrinsic GTPase of p21-RAS-GTP to hydrolyse GTP to GDP thereby inactivating p21-RAS. Therefore the main function of neurofibromin is inactivation of the active RAS-GTP and its signal transduction pathways (3).

More than 820 different *NF1* germline mutations have now been identified using a variety of mutation detection techniques (available from: <http://www.hgmd.org>; last visited 26/07/2007). While a small number of recurrent *NF1* mutations have been found, there is no evidence for clustering of mutations to any particular part of the gene. The efforts required to identify and characterise all the different *NF1* gene mutations are considerable and represent a significant diagnostic challenge, due to the large size of the gene, the lack of any obvious evidence for either mutation clustering or for repeat mutations, and the great diversity of mutation types observed. The presence of highly homologous partial *NF1* pseudogene-like sequences has increased the complexity of PCR-based mutation analyses (4).

About 5-10% of all NF1 individuals are reported to have large genomic deletions within the 17q11.2 region, these deletions remove the entire *NF1* gene, along with a variable number of the immediately flanking genes. Another 5% of the *NF1* mutations are due to smaller single or multi-exon deletions. The sequence complexity of the genomic architecture of the 17q11.2 region poses considerable difficulties for the analysis of the individual genomic deletions. Two major types of *NF1* microdeletions have been so far identified, type-1 deletions encompass 1.4 Mb and are the most commonly encountered *NF1*-associated microdeletion. This deletion is mediated by non-allelic recombination between a pair of low-copy repeats (LCRs), the proximal and the distal NF1 LCRs. Type-2 deletions are smaller ~1.2 Mb, and this deletion involves homologous sequences within the *SUZ12* (*JJAZ1*) gene and its pseudogene  $\Psi$ *SUZ12* ( $\Psi$ *JJAZ1*), two paralogous sequences located adjacent to the *NF1* LCRs (5) Kehrer-Sawatzki *et al.* 2004).

About 5% of NF1 patients have microdeletions spanning 1.4 Mb in 50% of cases (type I) and 1.2 Mb in about 38% of deletions cases (type II). A small number of *NF1* genomic deletions with a variety of sizes (from 1-Mb to >7Mb) have been identified, although the sequence context of the breakpoints of these atypical deletions have still to be determined.

Careful examination of the clinical phenotypes associated with both the common and the several atypical *NF1* gene deletions may help to identify the minimal genomic overlap possibly involved with the expression of specific deletion-associated features. NF1 patients with the common 1.4Mb genomic deletion are reported to present with a more severe form of the disease, often developing severe dysmorphism, a variable degree of mental retardation, the much earlier onset of large numbers of dermal neurofibromas, and a significantly increased risk of developing malignant tumours, especially Malignant Peripheral Nerve Sheath Tumours (MPNST) (6). It should be noted that there are exceptions to this particular genotype-phenotype correlation.

There is no current treatment for NF1 and it is therefore important to determine whether there is any consistent relationship between the size of the *NF1* gene deletion and the severity of the associated features, to enable better clinical management of such patients. Attempts to establish close correlations between specific gene mutations and the clinical phenotype exhibited by the affected patient is one of the most challenging tasks in clinical genetics. In most cases the various molecular and biochemical events that lie between a particular sequence change in the gene and the resultant expression of the associated disease features is just too disparate and convoluted to permit accurate genotype-phenotype correlations. In order to interpret any such relationships, the combinatorial effects of multiple different mutations and polymorphisms of the gene, whether allelic or not, all need to be considered.

There is an additional problem when trying to assess the situation in NF1 because of the wide range of clinical phenotypes often observed in NF1 patients, even between affected family members who all carry the same *NF1* mutation.

While several studies have attempted to address this genotype-phenotype relationship in NF1, no obvious correlations have yet been identified (7). Indeed, efforts to try to identify such genotype-phenotype correlations in NF1 is still in their infancy, due mainly due to the extensive mutational heterogeneity and the labour intensity required for complete mutation screening because of the large size and complexity of the *NF1* gene. This apparent lack of genotype-phenotype relationships may also be due to the variable nature, location and developmental timing of secondary *NF1* somatic mutations that might determine the rate of progression and the disease severity expressed in different tissues.

It is also possible that variable expression of the various alternative *NF1* transcripts in different tissue types, or of abnormal *NF1* RNA editing, may also account for extensive range of clinical features observed in patients. Attempts at finding genotype-phenotype correlations in NF1 may also be confounded by the strong age-of-onset effect observed with many of the



clinical features and also a lack of independence of such features. The wide diversity of pathogenic *NF1* mutations that are distributed throughout the gene, combined with the challenge of trying to classify each mutation according to its expected effect on protein function, may also seriously hamper such studies. Attempts have also been made to quantitatively analyze the familial variation observed in NF1 and these have found evidence for the involvement of unrelated modifying loci, and possibly even the normal *NF1* allele, in the development of particular disease features.

To date, only two relatively consistent genotype-phenotype correlations in NF1 have been reported, the first are those patients described previously with large genomic deletions who often exhibit high tumour burdens for their age, display dysmorphic features, and who may develop severe learning disabilities. Such deleted NF1 patients are also at greater risk of developing MPNST, although this was not confirmed in a recent study. It is interesting to note that in one study, seven of eight type II deletions are mosaic deletions. None of these patients with mosaic deletions exhibited facial dysmorphism and mental retardation and generally exhibited a milder phenotype.

The second NF1 genotype-phenotype correlation was only recently reported, and describes a series of unrelated adult NF1 patients, all with a specific 3bp deletion of the *NF1* gene, in which no cutaneous neurofibromas were found (8). This specific AAT deletion in exon 17 of the *NF1* gene is also associated with a mild NF1 phenotype in the majority of cases. The paucity of cutaneous, subcutaneous, and superficial plexiform neurofibromas in such specifically mutated patients is a striking finding, especially as dermal neurofibromas are a hallmark clinical feature of NF1 and are present in nearly all adult NF1 patients. The clinical data on this cohort of patients show a significant reduction of many NF1 features.

The  $\Delta$ AAT mutation was originally identified in three unrelated NF1 families referred for molecular diagnosis in Cardiff. In the subsequent international collaborative study, an additional 22 unrelated NF1 probands (14 familial and 8 sporadic cases) were identified, all with the same c.2970-2972 deletion AAT (p.990delM) mutation but with neither cutaneous neurofibromas nor any clinically obvious plexiform neurofibromas (9). The in-frame AAT deletion is predicted to result in the loss of one of a pair of methionines at codon 991 and 992 (DMet991). These two methionine residues are located within a highly conserved region of neurofibromin where they might be expected to have a functional role in the protein, although studies have not yet to be carried out to elucidate what this role may be.

It is the physical structure of the disease-associated protein, as well as its interactions with other proteins, usually considered to be responsible for, or to contribute to, the observed variation in the clinical phenotype in a particular disorder. To be able to gain a better insight into any genotype-phenotype relationship, one therefore needs to consider the combinatorial effects of multiple different mutations and polymorphisms, whether allelic or non-allelic. The underlying mechanism by which this specific  $\Delta$ AAT mutation of the *NF1* gene nullifies the development of dermal neurofibromas still remains to be determined.

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## Session IV. Plenary lecture

# PRADER-WILLI SYNDROME

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## Epidemiology and genetic aspects

Prader-Willi syndrome (PWS) represents the most common form of genetic obesity and affects males and females equally. It has been estimated to have a population prevalence of about 1 in 10,000 to 1 in 52,000. More recently, the prevalence, varying from 1:49,911 up to 1:91,802, was found (1).

PWS is a complex multisystem disorder due to the absent expression of the paternally active genes in the PWS critical region on chromosome 15 (2). In approximately 70-75% of affected individuals, there is a deletion of the paternal chromosome 15q11-q13 (del15). In this context, some Authors have identified 2 classes of deletion subjects (3). The type I deletion results in the loss of approximately 500 kb of genetic material in addition to what is missing in the type II deletion. Most of the remaining 25-30% of subjects has a maternal uniparental disomy for chromosome 15 (UPD15). Nevertheless, it has been recently reported a greater proportion of patients with UPD15 in young children with PWS, likely due to the increasing maternal age at conception. Finally, another few percent of patients may have abnormalities of the imprinting centre or translocations involving chromosome 15.

## Clinical features

The PWS is a condition characterized by a range of symptoms, including muscular hypotonia, hyperphagia, progressive obesity, short stature, hypogonadism, mental retardation, behavioural alterations, high pain threshold and dysmorphic features. Although many of the manifestations of PWS might be accounted for hypothalamic dysfunction, the clinical picture differs significantly during lifespan. The classic concept of the PWS is that a two stage disorder with a infantile hypotonic phase with feeding problems and failure to thrive, followed by hyperphagia and weight gain, leads most PWS patients to develop morbid obesity during childhood (4). This has been extended to include both a foetal/neonatal stage and an adolescent phase (5). Taken into consideration that individuals with PWS who have received appropriate attention to medical problems can actually live over 40 years, we would develop this model further to include an adult phase.

### Foetal and neonatal stage

The foetus with PWS is less active *in utero* than a normal foetus. Because of generalized hypotonia and the poor muscle tone, neonates with PWS are profoundly floppy with abnormal

weak or absent cry. These babies show little facial expression and tend to have feeding difficulties lasting for weeks or months, necessitating special feeding techniques. Early in life, their sticky saliva is a helpful pointer to the clinical diagnosis. Genital hypoplasia, with scrotal hypoplasia, cryptorchidism and a small penis in boys is the rule, while it is more subtle in girls and easily missed (6). Thermoregulation in PWS newborn may be a significant problem.

### **Infant stage**

After the neonatal period, hypotonia becomes less evident, but the child remains difficult to feed with consequent failure to thrive. Motor activity gradually increases but development is delayed, particularly gross motor and speech. Children with PWS usually learn to walk between the age of 2 and 3 years. Expressive language and articulation difficulties become evident. The typical facial feature with narrow bifrontal diameter, almond-shaped palpebral fissures, thin downturned upper lip and narrow nose become more pronounced. Some individuals are also hypopigmented, with fair hair and blue eyes.

### **Childhood stage**

This phase is characterized by hyperphagia with consequent obesity and behaviour problems. Growth retardation, a symptom of the hypothalamic GH Deficiency (GHD), became evident in many children between the ages of 3 and 12 years. In fact a reduced Growth Hormone (GH) secretion has been documented in the majority of children with PWS (7, 8). Recently, GH therapy has been approved for the long-term treatment of these patients and it should be started very precociously. Scoliosis and/or kyphosis may develop likely as consequence of hypotonia. The typical facial phenotype, obesity and genital hypoplasia complete the clinical picture at this stage. Skin-picking, in combination with decreased sensitivity to pain, is more frequently observed with increasing age. Caries affecting the primary dentition are common and may be related to the viscous saliva. Mental retardation is often mild and some subjects can attend normal school until secondary school level, after which they will require special education onwards. Reading ability is often reasonable, but arithmetic is usually poor. Many of them have short-term memory difficulties.

### **Adolescent stage**

The adolescence is characterized by a insatiable appetite with compulsive eating and increasing weight that very often lead to morbid obesity. Diabetes mellitus (type 2) frequently appears during or soon after puberty as a complication in 7-20% of individuals with PWS. Behaviour and learning difficulties become more evident at this age. In particular temper tantrum, obsessive/compulsive behaviour can make school and home management very difficult. Scoliosis could be more evident at this age even if only a few of them need surgical treatment. They often fall asleep easily when are inactive. Sleeping disorders (obstructive and/or central apnea), hypoventilation, significant oxygen desaturation, frequent waking up during the night are particularly frequent and not always related to obesity. Pubertal development is delayed and usually incomplete, but few cases of precocious puberty have been reported. Only occasionally, males have voice change, male body habitus, or significant facial and body hair. Testes are generally very small with a volume of less than 6-7 ml and pubertal stage rarely progress over Tanner genital stages 2-3. Menarche may occur spontaneously between the ages of 10 and 38 years.

## Adult stage

The clinical features of PWS adults depend on the success of treatment during childhood and adolescence. Older individuals, born before the syndrome was well established, have been probably diagnosed later than the younger patients, and generally have not received anticipatory care and appropriate treatment of weight excess. The muscular hypotonia improves, but is still present during adulthood. The reduced muscle tone, generally accompanied by decreased muscle mass, may contribute to the lower metabolic rate and physical inactivity. Consequently, adult PWS patients are often characterized by morbid obesity, and die prematurely from complications conventionally related to obesity, including diabetes mellitus, arterial hypertension, sleep apnoea, and cardiopulmonary disorders.

The great majority of subjects with PWS without growth hormone treatment will have short stature by adulthood. An average adult height of 159 cm in males and 149 cm in females was found in German PWS subjects. A slightly lower average height at 155 cm for men and 148 cm for women was reported in American patients with PWS, while shorter stature is reported in Japanese PWS population, i.e. 148 cm in boys and 141 cm in girls. In this context, preliminary studies have demonstrated that GH deficiency may be present in a significant percentage of PWS adults (9).

Hypogonadism is an almost invariable feature of PWS adults. The degree of hypogonadism is variable and is less severe in females than in males. Primary amenorrhea is reported in two thirds of the patients older than 18 years, and oligomenorrhea in the remaining subjects. In both sexes sexual activity is rare and infertility is the rule. Nevertheless, pregnancy and birth have been reported in three cases. As a consequence, of multiple hormone deficiencies (GH and sex hormones), as well as of physical inactivity and dietary abnormalities, individuals with PWS are also at increased risk of osteoporosis.

Finally, in adults, behavioural problems are of major concern, and symptoms of psychosis, such as bipolar disorders, obsessive-compulsive disorders and schizophrenia, can be seen in some patients.

## Diagnosis

Anamnestic and clinical diagnostic criteria established by a consensus in 1993 (4) are very useful; they inform and raise the index of suspicion of clinicians unfamiliar with the syndrome. Three categories of criteria were developed: 8 major (valued one point each), 11 minor (valued one half point each) and 9 supportive findings (increasing the certainty of diagnosis but they are not scored). In children with 3 years of age or younger five points are required for diagnosis of PWS; from 3 years of age to adulthood a total score of eight is necessary for the diagnosis. However, with advances in molecular genetics and the availability of definitive laboratory testing, diagnosis by scoring of clinical symptoms is rarely necessary.

Revised criteria according to age have been proposed in 2001 (10) in order to raise diagnostic suspicion to prompt the genetic tests, avoiding expense of testing unnecessarily. Genetic testing has become the standard because it detects nearly 100 percent of persons with PWS, is highly specific, and can diagnose PWS earlier than would be possible based on clinical criteria.

All three of the genetic abnormalities (deletion, UPD15 and imprinting defect) may be detected by methylation analysis (Figure 1).

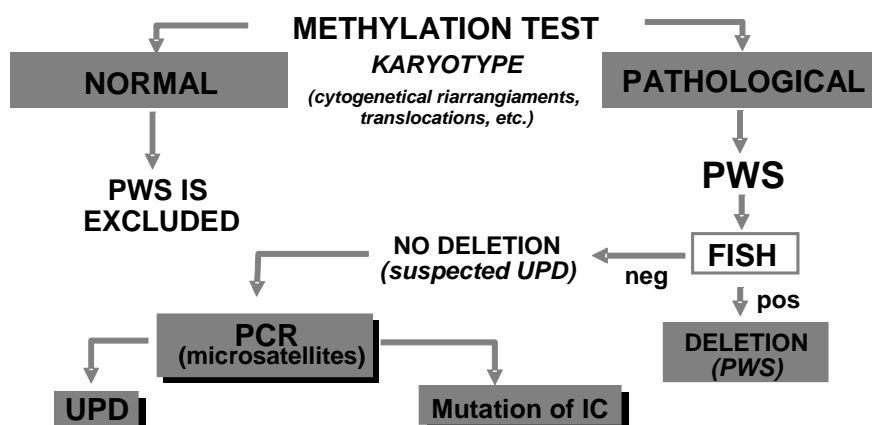


Figure 1. Genetic diagnosis of PWS according to Holmand Cassidy criteria

This test confirms the diagnosis of PWS in all patients with a suspicion of the disease. Fluorescence in situ hybridization (FISH) for chromosome 15 can diagnose only the cases with microdeletion (70-75% cases). However, a high-resolution karyotype is always necessary to identify the cases with translocations or other chromosomal rearrangements.

If an infant is hypotonic and has difficulty feeding, or if a child with this history has excessive food-seeking behaviour, obesity and global developmental delay, a methylation test or FISH for chromosome 15 should be performed. Nevertheless, the presence of cryptorchidism in a child with hypotonia and mental retardation can furtherly sustain the clinical suspicion of PWS and prompt the physicians to perform the genetical analysis.

Precocious diagnosis of the disease is important to prevent the onset and the progression of obesity and related complications and to contribute in improving some clinical features and in particular the behavioural problems.

The risk of recurrence of PWS is very low in individuals affected by microdeletion or UPD15. When a chromosomal translocation or a imprinting defect is present the risk may be higher.

## Therapy

### General approach

Because of its multidimensional problems, PWS should be managed in a multidisciplinary setting that emphasizes comprehensive care. First, enteral gastric tube feeding is indicated in a significant percentage of neonates with PWS. Feeding difficulties commonly occur and may lead to malnutrition if not addressed. Starting from 1-6 years of age, the complications associated with obesity are the recognized main risk factors for morbidity and mortality of patients with PWS. This circumstance prompted many investigators to recommend severe preventive measures for uncontrolled weight accrual. When excessive appetite and compulsive eating become evident, weight management needs to include caloric restriction, usually in the

range of 8-11 kcal/cm/day (cm=height) beyond the toddler years. For adolescents and adults, general recommendations have been from 900 to 1200 kcal/day, and rarely exceed 1400 kcal/day. These nutritional strategies require a complete and absolute control over access to food, as well as a special education for the family and caretakers. On the other hand, none of the appetite suppressant or antiabsorptive agents is generally effective in PWS. In addition, bariatric surgery is not recommended in PWS, because weight gain may recur over the long term in a significant percentage of patients.

Available evidence suggests that obesity in PWS is worsened by reduced energy expenditure and decreased physical activity due to reduced lean body mass. In this context, physical therapy is an essential element of treatment for PWS subjects. Apart from the beneficial effects on hypotonia during infancy and early childhood, structured physical activity is very helpful to increase muscle and skeletal mass as well as to ameliorate physical strength and energy balance. Rehabilitation programs aimed to support the development of motor skills, should be planned in early childhood of PWS subjects. The stimulation of motor activity requires a graded age, weight and strength program for each patient and needs constant monitoring from birth through adulthood.

Appropriate management of behavioural and psychological problems is mandatory, including speech and language evaluation and therapy. Successful behaviour management requires at least three elements: a) a consistent, supportive environment; b) strategies for promoting positive behaviour; and c) tools for changing difficult behaviour (11). In this context, attention must be given to the support of the families caring for patients with PWS.

## Medical and surgical therapies

As above mentioned, most of the medical conditions associated with PWS are related to obesity, such as respiratory dysfunction, diabetes mellitus, gall bladder disease, and cardiovascular disorders. These complications are treated according to conventional therapeutic modalities. On the other hand, scoliosis is often noted in PWS children who are not overweight, indicating that excessive weight is not a causative factor. Therapy of scoliosis generally requires a spinal orthosis (brace) for mild to moderate curves and surgical management for severe curves. Brace treatment in PWS is the same with those for adolescent idiopathic scoliosis. Frequent remodelling is required because weight fluctuations are common, and prolonged brace wear into early adulthood may be necessary. As far as eye abnormalities in PWS are concerned, consultation with an experienced ophthalmologist is required.

Depending from the severity of symptoms, the use of psychotropic medications is an essential element in the treatment of behaviour problems. Unfortunately, there is no syndrome-specific medication. Furthermore, clinical experience suggests that psychotropic agents are neither universally effective, nor without side effects, including hyperphagia. A range of medications is currently available, either singly or in combination: risperidone, haloperidol, thioridazine and selective serotonin reuptake inhibitors (fluoxetine). In this context, an improvement in the amount and severity of skin picking was described with the use of topiramate, a new antiepileptic agent.

Studies during the past decade have improved our understanding of the importance of the treatment of endocrine disorders in PWS. This includes GH therapy and the use of gonadal steroid hormone replacement. A large number of works has shown that GH treatment improves linear growth and final height of children with PWS (12). However, the importance of “non-growth” effects of GH appears more consequential for many of children and adolescents with PWS than changes in height. In fact, GH replacement therapy has been well documented to improve body composition, muscle strength, physical agility and behaviour. Moreover, the

greater benefits on anthropometric parameters, body composition, and psychomotor development were seen in the first years of age so that early institution of GH therapy was recently recommended for PWS children. In spite of these beneficial effects, fatal courses in young patients with PWS have been reported during the first months of GH administration. In this regard, it has been recommended that before GH therapy all children with PWS should have a sleep study and otorhinolaryngological examination (ENT). In addition, we suggest that polysomnography and ENT evaluation should be repeated 6-8 weeks after starting of GH treatment. In fact, the previously published cases of death occurred not before than 2 months of GH therapy. In the case of hyperplasia of lymphoid tissue, adenoidectomy+tonsillectomy should be taken into consideration either before or during GH administration.

Another important question concerns GH doses. In children with PWS the dosage actually recommended is 0.175-0.235 mg/kg per week. In our opinion, GH therapy might start with a lower dose, and dosage could be increased gradually on the basis of clinical response and instrumental assessment. If during therapy with growth hormone children with PWS show signs of respiratory infection, GH administration should be interrupted and aggressive therapy of the infection is mandatory.

Moreover, we suggest a close cardiologic evaluation before and during GH therapy. As far as adult age is concerned, information regarding GH treatment is beginning to emerge (13). We have previously demonstrated that GH administration may improve quality of life and psychological well-being of PWS adults (14) as well as some cardiovascular features, particularly cardiac mass, body composition, and some markers of cardiovascular risk (15). Nevertheless, individual signs of deterioration in right ventricle function should be taken into account and warrant appropriate surveillance. This finding suggests the need of more extensive studies in order to better clarify the role of GH treatment in adulthood.

Replacement therapy of the hypogonadism in PWS is not commonly used, and remains a controversial issue. Most clinicians, however, agree that all cases of cryptorchidism should be evaluated by an experienced pediatric urologist in the first months of age. Medical therapy with gonadotropin administration is generally attempted, but the ultimate success rate of hormonal therapy is low. Consequently, orchiopexy is requested in the majority of children with PWS.

Our experience suggests that the need of substitution therapy in PWS individuals is similar to those requested in non-PWS hypogonadal subjects. Sex hormone therapy should be started at a biologically appropriate time (e.g. adolescence), as a means to stimulate growth and pubertal development as well as to improve the self-esteem of the patient (16).

Moreover, gonadal steroid treatment is necessary for preservation of bone mass and prevention of osteoporosis, both in males and females with PWS. Nevertheless, it has been reported that testosterone treatment might worsen the behavioural problems. In these cases the substitution could be stopped, as well as in females with risk of thromboembolic events. In PWS subjects who are unable to tolerate sex steroid therapy, bisphosphonate treatment may be considered for treatment of osteoporosis. Finally, estrogen replacement therapy (+progestin) should be taken into consideration for women with menstrual cycles, in order to avoid the potential risk of pregnancy.

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#### Session IV. Plenary lecture

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## **MYASTHENIA GRAVIS AND MYASTHENIC SYNDROMES\***

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Myasthenia Gravis (MG) is the most prevalent disorder affecting neuromuscular transmission. The clinical hallmark is abnormal weakness and fatigue, which may be restricted to ocular muscles (ocular myasthenia) or involving additional muscle groups (generalized myasthenia gravis). Myasthenic crisis is a severe exacerbation with respiratory failure and aspiration associated with high mortality. Autoimmune MG is caused by autoantibodies targeting at the neuromuscular endplate the acetylcholine receptor (AChR) present in up to 90% of cases. In approximately 10 to 20%, AChR-antibody positive MG is a paraneoplastic syndrome associated with a tumour of the thymus. Few clinical trials have been performed in recent years to address empirical treatment standards and innovative treatment options.

The aims of our study had been to create a database containing epidemiological, immunological and clinical data, and stratification of patients to identify prognostic factors and response to therapy. The procedure followed had been data extraction from records of a single centre myasthenia clinic from 1980 to 2005, and the analysis of follow up in 5-year cohorts.

Classical autoimmune MG appears to be diagnosed more frequently over time especially in patients with late onset of disease. Based on activities of daily living clinical outcome is good or very good in the majority of cases. A non-classical variant of autoimmune MG can be distinguished by the presence of autoantibodies to the muscle specific tyrosine kinase (MuSK) in a minority of cases and it may be more difficult to achieve good treatment results.

This database is a useful tool providing clinical information on the long-term course of MG and helps to identify target populations for clinical studies evaluating treatment standards.

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\* Abstract of the lecture

## Session IV. Plenary lecture

# RETT SYNDROME

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## Description

Rett syndrome (RTT) was originally described as a clinical entity by Dr. Andreas Rett in 1966 (1). Hagberg and colleagues increased awareness of the disorder in the English medical literature in 1983 with a further description of the condition in 35 girls with strikingly similar clinical features of “progressive autism, loss of purposeful hand movements, ataxia, and acquired microcephaly” (2). RTT is a severe neurodevelopmental disorder characterised by a wide spectrum of clinical manifestation. In the classic form, after a period of normal development, patients show progressive loss of intellectual functioning, fine and gross motor skills and communicative abilities, deceleration of head growth, and the appearance of stereotypic hand movements. Girls with RTT often develop seizures, a disturbed breathing pattern with hyperventilation and periodic apnoea, scoliosis, growth retardation, and gait apraxia. RTT is characterised by a specific developmental profile, with the diagnosis of RTT being based on a consistent constellation of clinical features and the use of established diagnostic criteria (3).

## Variants

With increasing experience, it has become clear that females with RTT may present with a much broader phenotype than originally described. A number of variants have been described, which may be more or less severe than the clinical picture seen in classical RTT.

RTT variants have been described, including the Preserved Speech Variant (PSV), characterised by the recovery of some degree of speech; the congenital variant (recognised from birth); the “early seizure variant” (seizure onset before regression); and the “forme fruste”, with a milder, incomplete clinical course (regression between 1 and 3 years). These variants present some symptoms of RTT, but show considerable variation in type and age of onset, severity of impairment and clinical course.

Among these, the “early seizure variant” was initially described by Hanefeld in 1985, who reported a girl with infantile spasms with hypsarrhythmia in her early development. The Hanefeld variant of RTT presents a phenotypic overlap with West syndrome, also called infantile spasm syndrome, X linked (ISSX). ISSX is characterised by the triad of infantile spasms, hypsarrhythmia, and severe to profound mental retardation. One of the characteristic features of Rett syndrome is the loss during the regression phase of any speech which has been acquired by the affected girl. Occasionally, however, a few words can still be uttered. Although the words are not always used in context this represents a milder form of the syndrome, which has been termed the preserved speech variant (4, 5).

## Epidemiology

RTT is recognised as a panethnic disorder, and it presents an ever-widening clinical phenotype. The frequency of the disorder appears ranging from 1 in 10000 to 20000 females births. It is considered to be the second most common cause, after Down's syndrome, of severe mental retardation in females.

## Causes/genetics

The search for a gene for Rett syndrome was seriously hampered by a lack of familial cases as >95% of cases of the syndrome are sporadic, but by performing linkage analysis on the few available familial cases the region of interest was localised to Xq28 in 1998. This localization was followed by intense screening of the Xq28 region for likely candidate genes until in 1999 Amir *et al* published the first report linking the syndrome to mutations in the *MECP2* gene. Amir *et al* reported mutations in the *MECP2* gene in 5/21 cases of RTT (6). Since publication of the original paper, there have been a series of confirmatory studies detecting mutations in the *MECP2* gene in girls with Rett syndrome from several ethnic groups. The numbers of mutations detected in these varies from 21% in the original paper to >90%.

The search for a gene for Rett syndrome was seriously hampered by a lack of familial cases as >95% of cases of the syndrome are sporadic, but by performing linkage analysis on the few available familial cases the region of interest was localised to Xq28 in 1998. This localization was followed by intense screening of the Xq28 region for likely candidate genes until in 1999 Amir *et al* published the first report linking the syndrome to mutations in the *MECP2* gene. Amir *et al* reported mutations in the *MECP2* gene in 5/21 cases of Rett syndrome (6). Since publication of the original paper, there have been a series of confirmatory studies detecting mutations in the *MECP2* gene, in girls with Rett syndrome from several ethnic groups. The numbers of mutations detected in these varies from 21% in the original paper to >90%. *MECP2* mutations have also been identified in about 50% of PSV cases and in a lower percentage of other variants. In the variant with early development of convulsion described by Hanefeld, *MECP2* mutations have not been published. The *MECP2* gene is located at q28 on the human X chromosome, and has been demonstrated to undergo X inactivation in mice and humans. It encodes a protein of 498 (MeCP2B or MeCP2; encompassing exon 1 but not exon 2) or 486 amino acids (MeCP2A or MeCP2β; encompassing part of exon 2 but not exon 1), depending on the use of alternative splice variants, with MeCP2B being the predominant isoform in brain. MeCP2A may predominate in other tissues, such as fibroblast and lymphoblast cells. MeCP2 is a broadly expressed, nuclear protein binding to DNA methylated at CpG dinucleotides through a conserved methylated CpG-binding domain (MBD). Through its ability to recruit chromatin-remodelling complexes containing histone deacetylase activities (HDAC) as well as histone methyltransferase activities (HMT), MeCP2 is able to abrogate gene expression by modifying chromatin structure. Furthermore, by interacting directly with a component of the basal transcriptional machinery, TFIIB, MeCP2 seems to be able to repress transcription in a chromatin independent manner (7). Eventually, this methyl-binding protein is able to compact a nucleosomal array on its own, suggesting that altogether MeCP2 exerts a number of effects on chromatin structure and gene expression. Mice null for MeCP2, both male hemizygotes and female homozygotes, manifest phenotypes paralleling that of RTT. Importantly, the conditional deletion of MeCP2 in post-mitotic neurons recapitulates these features, demonstrating that neuronal dysfunction is the cause of the deficiencies in these mice. In accordance with this,

MeCP2 expression is particularly high in neurons and its timing of expression correlates with neuronal maturation. Although initially thought to be a disorder exclusively affecting females, males with a Rett-like phenotype have been reported occasionally, including those who also have a 47XXY karyotype, males who are mosaic for severe mutations, and males who may have milder mutations. In addition, other non-RTT phenotypes have been associated with *MECP2* mutations.

## Diagnostic evaluation

The diagnosis of RTT is based upon a thorough clinical evaluation including a complete physical and neurologic assessment; detection of characteristic symptoms and findings; and a careful patient and family history. The discovery of the *MECP2* has made possible the development of a test to aid in accurate diagnosis, detection of asymptomatic female relatives, and detection of the disorder before birth in families with an affected daughter. The diagnostic criteria for RTT were developed by Rett Syndrome Diagnostic Criteria Work Group (1988):

- normal or apparently normal development until approximately age 6 to 18 months.
- head circumference that is within normal limits at birth with subsequent slowing of head growth (acquired microcephaly);
- loss purposeful hand movements, severe impairment of receptive and expressive language, and apparently severe mental retardation;
- development of uncontrolled, persistent (stereotypic) movements, including repeated hand clapping, mouthing, tapping washing and/or wringing;
- impaired ability to coordinate movements required for walking resulting in a stiff, unsteady, widely based gait and possible “toe-walking”;
- fine tremors of the torso and, possibly, the limbs, particularly during periods of agitation.

Supportive criteria for a diagnosis of RTT are:

- breathing irregularities (e.g., periodic apnoea and hyperventilation);
- abnormal brain wave patterns as seen by EEG;
- increasing motor impairment;
- restricted movements of certain muscles due to progressively increased muscle rigidity;
- scoliosis;
- chewing and swallowing difficulties;
- growth retardation;
- teeth grinding (bruxism);
- poor blood circulation to the lower legs and feet (vasomotor disturbances).

According to the recently revised criteria, the clinical diagnosis of RTT is excluded if there is evidence of a storage disorder, retinopathy, cataract, or optic atrophy, an identifiable metabolic or neurodegenerative disorder, an acquired neurological disorder, or evidence of perinatal or postnatal brain injury.

## Differential diagnosis

Diagnostic studies may also be conducted to eliminate possible neurodegenerative, neurometabolic, mitochondrial or other disorder that may have similar symptoms (e.g. Angelman syndrome, Batten disease, organic acidemias, lysosomal storage disease etc.). These

studies may include certain blood and urine test, analysis of CerebroSpinal Fluid (CSF), neurophysiologic test such as Electromyography (EMG) and Nerve Conduction Velocity studies (NCV) and neuroimaging techniques including Computerized Tomography (CT), Magnetic Resonance Imaging (MRI).

## **Clinical course**

In female with classic RTT, the disease course tends to follow a relatively predictable pattern, although the age and symptom severity may be somewhat variable. Four stages of RTT have been defined to help characterize the disorder and improve its recognition and diagnosis. These stages may be described as follows.

### **Stage I. Early onset**

Beginning at approximately age 3 to 5 months (and continuing until about 4 years of age), there is a slowing of head growth (acquired microcephaly). Between about age 6 to 18 months, additional early abnormality may develop that may not be recognized. Affected infants or children may attain certain developmental milestones, such as crawling or pulling themselves up to a sitting or standing position, later than otherwise expected. They may also stop to acquire new skills. Additional early findings may include increasingly diminished muscle tone (hypotonia), decreased eye contact, and inattentive behaviour.

### **Stage II. Regressive stage**

Between 1 and 4 years of age, particularly from about 9 to 12 months, affected infants and children may have a gradual, sudden, or incremental loss of previously acquired skills. This is known as developmental regression. For example, by approximately age 3 years, spontaneous, purposeful use of the hands has been lost as well as most spoken language, such as previously acquired sounds, words, or word combinations. Conscious control of the hands and fingers is gradually replaced with distinctive, uncontrolled, stereotypic movements performed almost continually during waking hours yet cease during sleep. These may include repeated hand clapping, clenching, grasping and releasing, mouthing, patting, rubbing, tapping, or “washing and wringing”. In addition, the tongue may repeatedly twist or contort in ineffective chewing movements, and there may be involuntary grinding, gnashing or clenching of the teeth (bruxism). Children may also be prone to outbursts of laughter, screaming, or crying.

In infants and children with RTT, an impaired ability to consciously co-ordinate purposeful movements, known as apraxia or dyspraxia, may gradually interfere with almost all voluntary motions. For example, relatively early in the disease course, this impaired ability may affect eye gaze, leading to poor eye contact. As mentioned previously, affected children also have severely impaired expressive, as well as receptive, language development. Verbal apraxia/dyspraxia is thought to contribute to the irritability and agitation seen in many RTT patients. Affected girls may also have diminished interest in social interactions, often engage in repetitive rocking motions, and may develop other autistic-like behaviours. Although these RTT characteristic interfere with the ability to obtain accurate assessments of intelligence, many reports suggests that patients with RTT typically have severe mental retardation.

Children with RTT also develop disturbances of balance and difficulties in purposefully performing the motor actions required for coordinating walking (gait apraxia) and trunk

movements. As a result, they may have unsteady walking patterns, such as a widely based, stiff, jerky gait and unusual “toe-walking”. In addition, some children may have severe delays in the ability to walk independently or never gain this ability.

In many children, respiratory dysrhythmia becomes apparent during waking hours, including periodic apnoea, hyperventilation, and air swallowing, which may lead to abdominal bloating. Hyperventilation episodes may also be associated with momentary lapses of awareness (8). Affected girls may also develop sleep irregularities and seizures (9). Once neurodevelopmental regression occurs, most RTT patients also begin to have growth delays and appear abnormally small and thin as compared to other females their age (10).

Many develop chewing and swallowing difficulties and may have associated abnormalities of the digestive tract, resulting in insufficient food intake or impaired utilization of nutrients. There may be poor control of tongue movements and regular entry of food or liquids into the airway during swallowing. Digestive abnormalities may include peristalsis, gastroesophageal reflux, and oesophageal atony. Children with RTT are also prone to infrequent, incomplete, or difficult passage of stools (constipation). In addition, although calcium and vitamin D intake and absorption may be adequate, many RTT patients have decreased bone density and an associated risk of bone fractures.

### **Stage III. Relative stabilization**

During early to mild-childhood, such age 2 to 10 years, neurodevelopmental regression stops and there is a relative stability of symptoms. However, motor difficulties and seizure activity may become more pronounced. In addition, before approximately 8 years of age, scoliosis may develop. Curvature may be mild or become progressively severe during late childhood to early adolescence. There may be modest developmental gains, such as increased attention span or more interest in surroundings. Relative improvements in communication skills may also be achieved and continue into adulthood. Many females with RTT remain in this stage of stabilization.

### **Stage IV. Late motor impair**

Beginning after approximately 10 years of age, some RTT patients may develop increasing motor difficulties. Whereas some girls have never gained the ability to walk (Stage IVB), others may gradually lose this ability (Stage IVA). Other findings may include increasing muscle weakness, spasticity, or joint contractures. Sustained muscle contractions may cause involuntary, potentially painful, twisting or distorted posturing of affected muscles. Additional abnormalities may include irregular, rapid, jerky movements (myoclonus), particularly of the forearms and lower legs, or athetosis. In addition, in patients with scoliosis, particularly those who are unable to walk or are affected by dystonia, the spinal curvature may become progressively severe during this stage.

However, abnormal breathing patterns and seizure episodes may tend to become less pronounced with age, and eye contact and attention span may continue to improve. In some patients, stereotypic hand movements also become less persistent during waking hours and some purposeful hand actions may be recovered.

## Treatment

Medical management of RTT is essentially symptomatic and supportive. The treatment of RTT patient requires an integrated, multidisciplinary approach, aimed at maximising each patient's abilities and facilitating any skills that may be emerging. Management should include physical, occupational, and speech therapy, psychosocial support for the families, development of an appropriate education plan, and assessment of available community resources. Parent support groups are crucial in providing support for families.

The majority of RTT girls lose verbal expressive language, although some retain some speech or single word expressions. Alternative forms of communication that may be used include communication boards, technical devices, and switch activated systems. These are used for making choices and facilitate environmental access. Some girls are also able to communicate through eye pointing, gestures, body language, and hand pointing. These abilities need to be recognised and encouraged (11).

Decreasing repetitive purposeless hand movements can be achieved by the use of various arm restraints, such as soft elbow splints, and are occasionally helpful in training specific hand skills such as self-feeding. These methods are also helpful in decreasing agitation and self-injurious behaviour. Feeding problems are common in RTT. Several factors contribute to this, including poor caloric intake secondary to swallowing difficulties and immature chewing patterns, and energy expenditure imbalances with calories used to sustain motor activities at the expense of growth. Despite a voracious appetite, some girls experience poor weight gain. This may be because the majority of girls are unable to feed themselves, and very few develop mature chewing patterns. A gastrostomy tube may be used as an alternate route to supplement nutrition. Gastro-oesophageal reflux may respond to conservative medical treatment with anti-reflux agents, thickened feeds, and positioning.

Budden (12) found that frequent small feeds during the day with added carbohydrate foods not only maintained growth and weight gain but had a definite influence on agitation and irritability in younger girls. Pharmacological treatments for RTT have included L-carnitine, which may lead to an improvement in patient wellbeing and quality of life, magnesium to reduce the episodes of hyperventilation, and melatonin to improve sleep dysfunction.

Evaluation of the efficacy of these and other potential treatments on the horizon will require carefully constructed clinical trials, using validated instruments for measuring clinical improvements and relevant biochemical markers. Seizure control is a common problem in the care of females with RTT.

A major challenge in diagnosis may be differentiating seizures from the behavioural patterns often associated with RTT. Breathing irregularities such as breath holding and hyperventilation, episodes of motor activity such as twitching, jerking, or trembling, or a cardiac arrhythmia associated with a prolonged QT interval are most commonly confused with seizures. Studies using prolonged video EEG polygraphic monitoring indicate that the occurrence of seizures is overestimated. Most episodes identified by parents represent non-epileptic behavioural events. On the other hand, some actual seizures may be unrecognised by parents or occur during sleep. EEG telemetry and parental education may assist in identifying true seizure events. Prolonged heart rate corrected QT values have been reported in association with RTT. Prokinetic agents (such as cisapride), antipsychotics (such as thioridazine), tricyclic antidepressants (such as imipramine), anti-arrhythmics (such as quinidine, sotalol, amiodarone), anaesthetic agents (such as thiopental, succinylcholine), and antibiotics (such as erythromycin, ketoconazole) should therefore be avoided because of the possibility of precipitating electrocardiogram QT abnormalities and cardiac arrhythmias (13).



Scoliosis is found in approximately 65% of girls with RTT. Some girls require bracing, while others require surgical intervention. Increased tone in the Achilles tendon is one of the earliest manifestations of onset of rigidity, usually followed by toe walking. It is important to maintain ambulation, and so bilateral ankle foot orthoses need to be used to prevent foot deformities, maintain foot alignment, and keep the heel cords lengthened. Physiotherapy is also required to keep the Achilles tendons stretched. Although the girl with RTT will need help for most activities of daily living, she can learn some independent skills.

Despite their difficulties, girls and women with RTT can continue to learn and enjoy family and friends well into middle age and beyond. They express a full range of emotions and show their engaging personalities as they take part in social, educational and recreational activities at home and in the community.

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## **ABSTRACTS**



## **TELOMERE DYSFUNCTIONS AND CHROMOSOMAL RADIOSENSITIVITY IN TWO PATIENTS WITH A NIJMEGEN BREAKAGE SYNDROME-LIKE PHENOTYPE**

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Nijmegen Breakage Syndrome (NBS) clinical signs include growth and developmental defects, dysmorphic facies, immunodeficiency and cancer proneness. NBS is a radiosensitive disorder caused by mutations in the *NBS1* gene, whose product nibrin is part of the MRE11/RAD50/NBS1 complex involved in DNA Double-Strand Breaks (DSBs) response pathway. Genetic heterogeneity in NBS is highlighted by patients showing clinical and cellular features of NBS but without mutations in *NBS1* and normal levels of nibrin.

We describe here two of these patients with an NBS clinical phenotype, chromosomal sensitivity to X-rays but without mutations in *NBS1*. Spectral Karyotyping (SKY) analysis, chromosome radiosensitivity, kinetics of DNA rejoining in cells treated with X-rays, telomeres analysis by TRF and FISH, immunoblot analysis of protein involved in the processing of DNA DSBs and PCR amplification of the *NBS1* exon 6 were performed.

Normal levels of proteins involved in the maintenance of genetic stability (MRN complex, ATM, ATR, LIG4, XRCC4, SMC1) have been detected. Radiosensitivity was mediated neither by DSB rejoining defects nor by NBS/AT-dependent DNA-damage response pathway. We found that cells from both patients displayed telomere dysfunction, in fact, they were either elongated or shortened; however, alterations in telomere size did not affect Gross Chromosomal Rearrangements (GCR) frequency.

Dissecting the clinical and cellular phenotype of NBS-like patients represent a useful tool for the research of new genes involved in the cellular response to DSB response.

## **E-RARE: AN ERA-NET FOR RESEARCH PROGRAMMES ON RARE DISEASES**

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Research on rare diseases is significantly hampered due to lack of suitable resources at multiple levels:

- patients are scattered over large geographic areas making difficult to build cohorts;
- existing databases and material collections are mostly local, small, and not accessible or standardised;
- a low number of scientists work on rare diseases;
- diseases often have complex clinical phenotypes and require interdisciplinary approaches for research;
- therapeutic research is not heavily supported by the pharmaceutical industry despite available incentives;
- funding resources are limited. Therefore, rare diseases represent a perfect example of a research area that could strongly benefit from strong cooperation at a European scale.

E-Rare (ERA-Net for research programmes on rare diseases) is a network of nine partners from eight countries, which are responsible for the development and management of national/regional research programmes on rare diseases. E-Rare is supported by the European Commission, under the Sixth Framework Program ERA-Net scheme for a 4-year period (starting June 1<sup>st</sup> 2006).

E-Rare main objective is to maximize the efficiency and impact of research on rare diseases by providing the environment to bring together clinicians and scientists and gather research infrastructures, patient cohorts and related biological material on a European scale.

E-Rare foresees:

- to set up sustained and long lasting cooperation between partners
- to coordinate national actions in order to overcome the fragmentation of research on rare diseases and promote interdisciplinary approaches
- to harmonize and develop synergies among the national and/or regional research programs of the participating countries
- to develop common research policy on rare diseases
- to sustain a favourable competitive position with regard to research on rare diseases in other regions of the globe such as North America and Asia.

The key stages of the project are:

- creation of a knowledge base for the development of joint and trans-national activities: survey on national programs, global competitiveness of E-rare, development of a program maker information tool, identification of gaps and overlaps among national research programs and activities on rare diseases
- definition of strategic priorities to be included in the research policy agenda on rare diseases and in future research programs and activities at national, trans-national and European levels
- development of trans-national multidisciplinary approaches: opening and support of rotational positions allowing clinicians to get involved in frontier research in the field of rare diseases, networking of technological platforms

- implementation of trans-national cooperation for the funding of research on rare diseases:  
trans-national calls for proposals

E-Rare partners:

- the National Institute for Health and Medical Research (France);
- PT-DLR and The Federal ministry for Education and Research (Germany);
- the Institute of Health Carlos III (Spain);
- the National Fund for Scientific Research (Belgium);
- the Chief Scientist office of the Israeli Ministry of Health;
- the Istituto Superiore di Sanità Italian (the National Institute of Health in Italy);
- the Netherlands Organisation for Health Research and Development;
- the Scientific and Technological Research Council of Turkey.

## **RARE DISEASE: PUBLIC COMPETITIVE RESEARCH FUNDING IN SPAIN. PRESENT SITUATION AND ITS POSSIBILITIES OF MATCHING FOR EUROPEAN AND INTERNATIONAL RESEARCH CO-OPERATION**

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Weak research capacities devoted to Rare Diseases research within a broader historical similar general context, associated to expertise split.

The objective is to improve translational Rare Diseases research in order to get better Public Health, health care and well being results for patients and their relatives, as well as for feeding the policy making process

It has been spent 34,72 M € for Rare Disease research in Spain (2003-2005), by the extramural biomedical and health research funding branch of ISCIII (FIS) upon public open competitive calls (peers' review and strategic assessment).

It is needed a broader more cooperative and cohesive effort on Rare Disease research. At Spanish level, CIBERs (Network of Centres of Biomedical Research), RETICS (Cooperative Thematic Research Network on Health), and other new funding instruments, as well as a research certification process (institutes for health research) are been developed, also based in open competitions and assessment. EU and international research cooperation is in progress, but affected by legal bottlenecks rather than scientific and health issues. Present Spanish requirements for member states' inter-agencies international fund driven research are also presented.



## GUIDELINES FOR RARE DISEASES

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Rare diseases are a wide group of conditions (5-6 thousands), with low prevalence in the population. In European countries, it is considered rare a disease with a prevalence not more than 5 patients on 10.000 inhabitants.

In the last years, new knowledge and expertises have been acquired, and new scientific and social approaches have been developed in rare diseases managements.

Therefore, it is advisable to elaborate appropriate instruments, which could be the suitable doctors' instruments for taking any clinical and therapeutic decisions, according to the new scientific literature. The guidelines would represent one of these instruments.

At the National Centre for Rare Diseases (CNMR), the project "Guidelines for rare diseases" has been approved, with the goal to elaborate, to implement, and to promote the diffusion of guidelines for rare diseases.

These guidelines are meant as the instruments to standardize the clinical behaviours and the social approaches in rare diseases.

The guidelines are meant as instruments to rationalize the clinical assessments. They are "Recommendations" developed in a systematic way to help health operators, patients and their families in taking the decisions on the appropriate management for specific clinical conditions.

The project will be realized through the collection of existing guidelines for specific rare diseases, and the elaboration of new guidelines for specific rare diseases.

Moreover, the project includes selected rare diseases, a systematic and standardized search of the scientific literature and an appropriate elaboration and communication of answers to queries on rare diseases.

The elaboration of these guidelines will be the first step in realizing the following main actions of the Italian National Health Plan 2006-2008 on rare diseases:

- to develop a network among the Medical Centres in order to diffuse and to consolidate the new diagnostic and therapeutic protocols for rare diseases;
- to integrate different competences in order to promote multidisciplinary approaches in clinical and social research and to guarantee the best changes of success;
- to promote useful and appropriate information to Clinical Centres for rare diseases in order to avoid repeated and unsuccessful hospitalization, and to guarantee a prompt and appropriate diagnosis and treatment, involving also the Patients' Associations;
- to promote a continuing training for health operators.

The first project achievement has been the realization of a website dedicated to the guidelines for rare diseases. In this web site it is possible to find out information and documentations (<http://www.iss.it/cnmr> at "Linee Guida").

The guidelines for the rare diseases would have the important role to assure the maximum appropriateness in the medical practices, and to reduce, as much as possible, the variability in the clinical decisions, related to a lack of knowledge or to a personal judgements in social approaches needed.

## **RARE PATIENTS: “I WOULD LIKE TO KNOW SOMEBODY WITH THE SAME HEALTH PROBLEM...” THE ROLE OF THE REGIONAL NETWORK FOR RARE DISEASES AND THE PATIENTS’ ASSESSMENT: PRELIMINARY DATA**

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In 2001 the Clinical Research Centre for Rare Diseases *Aldo and Cele Daccò* of the Mario Negri Institute, was nominated *Coordinating Centre of the Regional Network for Rare Diseases* in the Lombardy Region, an area of 9 million people in Northern Italy.

Since the beginning of its activities, the Centre has established close collaboration with more than 280 Italian Associations dedicated to a specific rare condition. Unfortunately, not all rare diseases have specific associations, particularly those “ultra rare” conditions. Our Centre has therefore activated a special Service aimed to help these twice orphan patients (and their families) to meet other people with the same health problem.

The primary aim of this survey is to verify the real usefulness of this specific Service.

The secondary aim is to investigate about the general and demographic characteristics of this patients’ sub-group with rare diseases and the major problems for these families related to the lack of a specific patients Association.

In our activity as Information Service for rare diseases patients, we routinely provide information and address of patient support group. Whenever we are contacted by people whose disease has not a support group, we ask patients if they are interested in meeting other people with similar problem.

If they agree, they would send us a written authorization. We then favour the exchange of experience between interested parties, by contacting other patients with that given rare disease. The contact is established by the research nurses.

We then investigated the results and the effects of the queries service sending out questionnaires to 112 families we had been in contact with.

By July 31, 2006, we received 61 completed questionnaires (52% of the questionnaires we sent). The great part of respondents (n. 42) were patients’ relatives, usually parents or partners.

Genetic syndromes represent about 1/3 of the diseases for which we received the questionnaires. After their authorization, it was possible to meet other persons for 40 families (about 66% of respondents) and 20 of these families are still in contact.

This experience mainly contributed to improve the exchange of knowledge about the disease and also to give comfort and psychological support. In 4 cases this initiative helped the birth of brand new associations.

These preliminary data confirm the real contribution of this Service for patients and families, above all to improve their knowledge about the rare disease; the Service could be also represents a good way to stimulate the establishment of support groups or specific Associations dedicated to rare diseases.

## **SMÅGRUPPSCENTRUM: THE NATIONAL INFORMATION CENTRE FOR RARE DISEASES AND THE SWEDISH RARE DISEASE DATABASE**

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SmågruppsCentrum is a Swedish information centre for rare diseases, managed under the auspices of the Sahlgrenska Academy at Göteborg University and funded by the Swedish National Board of Health and Welfare. The mission of the centre is to provide high-quality guidance and information in the area of rare diseases.

Smågruppscentrum has been commissioned by the Swedish National Board of Health and Welfare to produce a rare disease database, available at [www.sos.se/smkh](http://www.sos.se/smkh). The database currently contains detailed descriptions of more than 200 rare diseases and is continuously extended and updated. The material is supplied by leading experts on each diagnosis and is reviewed by a scientific advisory board before publication. Patient and parent organizations are important partners. The mission also includes publishing the texts in English.

The main target groups are individuals with rare diseases or disabilities and their families, organizations for the disabled and patient associations, educators and healthcare professionals, including physicians, nurses and researchers. Healthcare professionals are very frequent users of the database.

The database is structured in accordance with the recommendations outlined in the EU programme on public health. The information about each diagnosis is organized under the same headings, including incidence, aetiology, heredity, symptoms, diagnosis and treatment. Each diagnosis entry also contains information about research and development, Swedish specialist clinics and centres of excellence. The relevant organizations for the disabled/patient associations, educational resources, local support, information material and references are also listed in each text.

The number of visitors to the database is steadily increasing. At present, there are more than 45,000 visitors to the site each month.

## **APPROCCIO MULTIDISCIPLINARE IN UN MODELLO DI PATOLOGIA GENETICA RARA: LA MALATTIA DI HUNTINGTON**

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La Malattia di Huntington (MH) (o Còrea di Huntington) è una rara malattia neurodegenerativa ereditaria (frequenza: 5-10/100.000) dovuta ad una mutazione del gene IT-15 (espansione del numero di triplette CAG) caratterizzata clinicamente da disturbi del movimento, modificazioni della personalità e demenza che comportano una cronica e progressiva disabilità. La malattia colpisce soprattutto gli adulti e generalmente compare tra i 30 e i 45 anni di età, ma l'esordio si può verificare a qualsiasi età, dall'infanzia alla vecchiaia. I sintomi neurologici sono la conseguenza della degenerazione e della perdita di neuroni che interessa i gangli della base (soprattutto il nucleo caudato e il putamen) e porta a una diffusa atrofia della corteccia cerebrale e a una riduzione della massa cerebrale. Sono attualmente disponibili vari farmaci per alleviare i sintomi che via via si presentano nel paziente ma non esiste ancora una terapia in grado di fermare la progressione della malattia. Questa carenza nel "curing" ci ha suggerito di attivare un approccio multidisciplinare di "caring" con terapia riabilitativa motoria, cognitiva e logopedica e supporto psico-sociale al malato e alla famiglia.

Il test genetico per accertare la presenza della mutazione è tecnicamente di facile esecuzione e può essere utilizzato sia per la conferma di una diagnosi clinica in un paziente già affetto, sia per prevedere se individui sani a rischio hanno o meno ereditato il gene (test presintomatico) sia per diagnosi prenatali. A fronte della relativa facilità tecnica del test genetico sta la complessità dei problemi psicologici, etici e sociali che vi sono connessi, soprattutto nel caso dei presintomatici, che li rende test assai diversi da quelli comunemente eseguiti nella pratica medica o genetica clinica.

Il test presintomatico per la MH, infatti, non ha alcun valore sul piano clinico (trattandosi di una malattia non prevenibile e non curabile) e non può quindi essere prescritto dal medico, ma solo liberamente scelto dall'individuo a rischio. Questo implica che non può essere eseguito sui minori, e che non vi devono essere condizionamenti esterni da parte di datori di lavoro, familiari o altri.

Per assicurare alle persone a rischio tutto questo si richiede una complessa procedura (definita da apposite linee guida internazionali) consistente in diversi colloqui dell'individuo a rischio con una equipe multidisciplinare, oltre ad un accurato standard di qualità delle analisi di laboratorio. In Italia l'applicazione di questa complessa procedura incontra delle difficoltà che nascono prevalentemente dall'assenza di controlli di qualità per questo tipo di servizi e dai rimborsi dell'Servizio Sanitario Nazionale (SSN) ridicoli rispetto ai tempi e alle professionalità necessarie.

La malattia ha un andamento lentamente progressivo e presenta un complesso quadro clinico caratterizzato da disturbi motori, cognitivi e psichiatrici. L'esordio e il decorso della malattia sono diversi da soggetto a soggetto e dipendono, almeno in parte, dal numero di triplette espanse. Al Policlinico "A. Gemelli" di Roma è attivo da più di 15 anni un ambulatorio dedicato alla MH in cui un'equipe composta da neurologi, psicologi e dietologi segue i pazienti, i

portatori della mutazione ancora asintomatici, i soggetti a rischio e i caregivers dando una risposta integrata medico-psicologica e coordinata ai diversi aspetti della malattia.

Nel 1999 abbiamo avviato un protocollo riabilitativo multidisciplinare per i pazienti affetti da MH presso la Casa di Cura di Riabilitazione “Nova Salus” di Trasacco, nella Regione Abruzzo. I trattamenti riabilitativi interdisciplinari vengono svolti in regime residenziale. La durata standard del programma è di tre settimane ed è possibile effettuare un massimo di tre ricoveri l’anno. L’effetto della riabilitazione è stato valutato sia in termini di prestazioni motorie misurate quantitativamente attraverso apposite scale, sia in termini di valutazione soggettiva da parte dei pazienti e dei loro caregivers.

L’Associazione Italiana Corea di Huntington Onlus (AICH-ROMA) si è costituita nel 1987, in concomitanza con lo studio epidemiologico sulla malattia nel Lazio condotto dal nostro gruppo CNR ed ha perciò tratto notevoli vantaggi dallo stesso rapporto con il mondo della ricerca. Le attività svolte sono state indirizzate a: promuovere la conoscenza della malattia; coinvolgere e responsabilizzare le strutture pubbliche rispetto ai particolari bisogni di assistenza di questi pazienti e delle loro famiglie; potenziare le attività di prevenzione e ricerca.

## **QUALITY OF HOSPITAL SERVICES FOR RARE DISEASES: HOW TO ORGANIZE? THE DANISH SYSTEM AND EXPERIENCES**

Marianne Jespersen

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Rare diseases represent a challenge to all health services. It is difficult to secure knowledge and experiences. The medical staff shall remember the existence of a disease they have never seen before and in some cases not even heard of. In Denmark there is a system with guidelines from The National Board of Health designating diagnoses and treatments, which should be regarded as highly specialized and designation of centres of reference for this conditions. The criterias for establishing such centres is among other things rareness.

Our goals are to achieve an early and accurate diagnosis, the necessary and sufficient treatment, offered at the appropriate time, securing high quality of service rendered, and more satisfied patients.

## **RARE DISEASES: AN AUSTRALIAN GENERAL PRACTICE PERSPECTIVE**

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Australia scores highly on most health indicators and has a relatively well developed and efficient health system. An orphan drug program has operated in Australia since 1998. However there has yet to be developed a coordinated approach to rare diseases such as exists in the United States and Europe.

General practitioners in Australia provide unreferred services to up to 90% of the population in a 12 months period. Given the high prevalence of rare diseases as a group, it is inevitable that general practitioners care for many people with rare diseases. Literature from primary care supports this conclusion. However, there is no published literature on the role of general practitioners in the care of people with rare diseases in Australia or elsewhere.

Patients and families dealing with rare diseases report common negative experiences with issues such as diagnosis, coordination of care, access to expert care and emotional support. General practitioners are well placed to help in many of these areas.

First: there is a need to address Australian national policy with regard to rare diseases. Secondly: we tentatively propose the DAKESA model for a generic general practice approach to patients with rare diseases. General practitioners should: Diagnose, Attend to the whole patient, Know the disease, Empower the patient, Support the family and Advocate for the patient. There is a need for research to test and elaborate this model with practicing clinicians and patients.

## A NEW POWERFUL TOOL TO STUDY MITOCHONDRIAL FUNCTION IN METABOLIC DISEASES

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We examined mechanisms contributing to stimulus-evoked changes in NAD(P)H fluorescence as a marker of neuronal activation in the barrel cortex area of murine thalamocortical slices. An electrical stimulus produced biphasic fluorescence changes composed of an initial transient decrease (“initial component,” 1-3%), followed by a longer-lasting transient increase (“overshoot,” 3-8%).

Both components of NAD(P)H transients were abolished by ionotropic glutamate receptor block, implicating postsynaptic neuronal activation as the primary event involved in generating the signals, and not presynaptic activity or reuptake of synaptically released glutamate. Spatial analysis of the evoked signals indicated that the peak of each component could arise in different locations in the slice, suggesting that there is not always obligatory coupling between the two components.

The initial NAD(P)H response showed a strong temporal correspondence to intracellular  $\text{Ca}^{2+}$  increase and mitochondrial depolarization and treatment with rotenone (an inhibitor of complex I), and a removal of glucose and addition of 2-deoxyglucose (2DG) (10 mmol/L) or iodoacetic acid (IAA, 1 mmol/L), that induced an inhibition of glycolysis, shows that the initial response is strongly influenced by mitochondrial complex I activity.

The overshoot response is probably a postsynaptic measure of neuronal excitation, which is influenced by many factors like impaired glucose utilization, GABA<sub>A</sub> receptor population and  $\beta$ -endorphine receptor population.

Some of these factors, and the initial component for monitoring mitochondrial complex activity, are early symptoms for several metabolic pathologies, especially neuro-degenerative diseases and rare diseases, in pathological murine models, and they can be very useful for pharmacological experiments.

These responses can be matched also by inverted biphasic Flavin Adenine Dinucleotide (FAD) fluorescence transients (mitochondrial complex II activity) and intracellular  $\text{Ca}^{2+}$  movement, and these responses can reveal to be a powerful diagnostic tool in laboratory animals as well as in human tissues.



## DIAGNOSTICS PROBLEMS OF RARE DISEASES IN ARMENIA: THE STATE AND WAYS DECISIONS

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Diagnosis of Rare Diseases (RD) is the important component of all problems of RD in Armenia, especially during the reorganization of the all social and economic structures and systems of the public health services, low level of financing, transition to new market conditions, high corruption administration and protectionism. Despite the presence of highly skilled experts, the problem got worse, bad social and economic conditions of population, absence of health insurance, and national legislation stating the creation of organizations in order to provide a support for patients with rare diseases, etc.

The purpose of this research was studying the opportunities and the diagnostic conditions for RD in Armenia, in order to improve them and to find new approaches in the organization of diagnosis and patients support.

The RD associations and other organizations have studied new opportunities and diagnostic conditions for RD in the Yerevan State medical university after M. Heratsi in cooperation with associations «Neurohereditary Diseases» and other organizations.

This analysis has revealed problems connected with RD diagnosis and treatment. Low level of knowledge of doctors of public health services concerning modern methods of diagnosis, treatment and preventive maintenance, low detection RD, an insufficient level of modern laboratory genetic methods of research and their financing. Available RD centres on neurodegenerative and neuromuscular diseases, Hypothyroidism, Phenylketonuria, Mediterranean Fever, Hemophilia, etc., and function on the basis of University structures and the Medical centres. Their activities are mainly provided by university workers and researchers, patients' organizations, and volunteers. Laboratory genetic methods of research are supported by cooperation and help of foreign medical organizations and centres (Switzerland, Germany, France, Italy).

Remarkably, in the last years, we took part at the European information network, as members of EURORDIS (European Organisation for Rare Diseases), and cooperating in project NEPHIRD (Network of Public Health Institutions on Rare Diseases) and other programs.

Necessity of the complex system approach to the decision on RD problem, assuming association of efforts, knowledge and resources of all structures and the groups were deal with problem RD is marked: bodies of public health services, academic, universities, public and other organizations, and, also separate researchers. The constant exchange of experience and the information underlined the necessity of creating a national centre and an information network for RD, to further cooperate into the European information network and participate in the international programs, trainings and conferences. It is important to involve governmental bodies, especially Ministries of Health, in the RD problems, mainly, through international conferences and programs within the European Union. The results developed by standards and positions on RD, to the recommended countries of the European Union is rather important.

## MEDICAL GENETIC REGISTER: AN OPERATIONAL EXPERIENCE AND PROSPECTS

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The organization of system of revealing, registration, the account and patient's supervision of Medical Genetic Registers (MGR) of patients– with rare diseases, in connection with their low detectability in republic, is one of actual problems of public health services. In this way, it will be possible to collect epidemiological data, to plan and organize support for patients with rare diseases. The purpose of research was studying the efficiency of functioning of the MGR of hereditary NeuroDegenerative and NeuroMuscular Diseases (ND&NMD).

The register has been created 20 years ago on the basis of genetic and neurological data, and gave important results. The register contains the information and a database about more than 360 families and 1200 patients with the ND&NMD and those phenotypically healthy relatives of group of risk from all the states.

The republic's independence changed its social and economic structure, reforming the public health service. This period had been characterized by a transition towards new markets. As consequence, the republic had suffering for a lack of prevention strategies particularly in RD early diagnosis.

The new approach to the organization of the work on genetic registers has shown its efficiency. Although at the initial stage it has increased revealing and applying patients with ND&NMD, growth of awareness of a problem among doctors. In fact, doctors gained awareness of the problem, since more and more patients have been enrolled in the registers.

A special attention had been addresses also to uniform communication with family doctors in order to involve them in the organization of a regional network, and creating both a regional and a national ND&NMD database.our goal are to improve the information network. Therefore, a website had been created: [www.nhmda.am](http://www.nhmda.am).

Training of the doctors and information now became the most important aspect concerning RD problems.

Postdoctoral training, seminars on: modern clinic and laboratory diagnostic, treatment and prevention, medical social problems had been organized.

A special attention has been focused on cooperation with the European information network on RD: in particular, to NEPHIRD programs. The membership in EURORDIS, is providing us modern and valuable information on RD and Orphan Drugs.

In the conclusion, it is necessary to note the importance of creating both national registers, on the basis of the specialized centres, and regional databases under separate forms RD. The organization of an information network, using resources such as Internet will be a support for Ministry and its Institutions of Public Health, with appropriate financing. Considering the rather small territory of Armenia (29743 km<sup>2</sup>) – about 3,5 million people – the offered scheme of the organization of work medical genetic registers and an information network can serve a model for regions with small territory.

## HAEMOPHILIA: A MODEL FOR COMPREHENSIVE CARE OF RARE DISEASES

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There are about 38,000 haemophilia patients in European Union, the incidence of haemophilia being 1/10,000 inhabitants. Each year, about 750 babies are born with this disorder. Approximately 85% have haemophilia A (FVIII deficiency) and the remainder has haemophilia B (Factor IX deficiency). The severity of haemophilia is related to the amount of the clotting factor in the blood. About 70% of haemophilia patients have less than one percent of the normal amount and, thus, have severe haemophilia. The phenotype of the patients is based on assay of factor VIII or IX, by means of clotting (one-stage method is the most popular) or Chromogenic substrate methods. The genotyping is now easily achieved by means of screening tests, as CSGE (Confirmation Sensitive Gel Electrophoresis) or DHPLC (Denaturing High Performance Liquid Chromatography), in order to select patients positive for Intron 22 inversion (about 40%) and, in the negative, to detect the exon carrying the mutation. The sequencing of the mutated exon allows the exact definition of the mutation. The knowledge of mutation, in the frame of affected family, is particularly important to detect the facultative carriers before or during the pregnancy. This allows the prenatal diagnosis by means of villocentesis at 10-11 week of pregnancy. The voluntary interruption of pregnancy is particularly frequent in under development countries (about 80%) and less frequent in the developed countries (about 30%) where good facilities are available for the treatment of the disease.

The most important challenges facing today the haemophilia patient, health care providers, and research community are safety of products used for treatment, management of the disease including inhibitor formation, irreversible joint damage, and life-threatening haemorrhage, and progress toward a cure.

In the past 10 to 15 years, advances in screening of blood donors, laboratory testing of donated blood, and techniques to inactivate viruses in blood and blood products have remarkably increased the safety of blood products used to treat haemophilia. Although treatment-related infection with the AIDS virus or most of the hepatitis viruses is a thing of the past, these measures do not completely avoid viruses such as hepatitis A and Parvovirus B19. There is a great deal of concern about Creutzfeldt-Jakob disease (CJD), a rare transmissible nervous system disease that is inevitably fatal, being transmitted through transfusion. Recombinant factor VIII/IX, are manufactured by a process entirely free of human or animal proteins.

Although the cost of these products exceeds that of the blood-derived product, it is clearly the treatment of choice for those, such as newborns, who have not yet been exposed to blood products or, if previously exposed, not yet infected patients. All haemophiliacs of European countries have now available a treatment for bleeding which is totally free of any contaminating agents. On the contrary, the haemophiliacs of under development countries do not have these facilities, neither plasma-derived clotting factor concentrates: 80% of haemophiliacs world wide are lacking any form of therapy. While current treatment has greatly improved the outlook for most haemophiliacs, the development of antibodies (inhibitors) that block the activity of the clotting factors has complicated treatment for some patients. Approximately 15 percent of

severe Haemophilia A patients and 2.5 percent of Haemophilia B patients develop such antibodies after exposure transfused factors. When inhibitors are present in large amounts, the patient may require very high and expensive quantities of transfused clotting factors to stem bleeding, and, in some instances, even that may not be effective. Immune Tolerance Induction (ITI) protocol has been developed with aggressive therapeutic approaches, which are terribly expensive (about € 1.10<sup>6</sup>/year for a 20 kg child).

The major cause of disability in haemophilia patients is chronic joint disease - “arthropathy” – caused by uncontrolled bleeding into the joints. Life-threatening haemorrhage is a constant risk. Traditional treatment of haemophilia has involved “on-demand” treatment, meaning that patients are treated with factor replacement only after bleeding symptoms are recognized. In several European countries the haemophiliacs are treated by periodic infusions (prophylaxis) regardless of bleeding status. This approach maintains the factor level high enough that bleeding, joint destruction, and life-threatening haemorrhage are almost entirely avoided. The cost of prophylaxis is huge more than € 200,000/year/patient by the second decade of life. Even higher, is the cost of ITI, about € 4,000,000/ year/patient. The treatment decisions are not easy ones. The ultimate goal is to offer a cure for the disease. The challenge is to transfer normal genes into a patient so that they will produce the normal clotting protein. A small amount of active factor produced by the patient’s own body will correct the disease.

Although much remains to be studied before such treatment can be offered to patients, there have been a number of studies done in animals such as mice and dogs in which a factor VIII or IX gene has been inserted and has produced the proper blood product for periods that exceed one year. Major issues that remain to be resolved include the low level of production of the clotting factor, reduction of immune reactions that stop the production after a period, and development of ways to insert the gene directly into the body without manipulating cells outside the body.

# THE IMPACT OF “RARE DISEASE” IN RHEUMATOLOGY: THE EXPERIENCE OF A TERTIARY REFERRAL CENTRE IN ITALY

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Rheumatic diseases are a heterogeneous group of diseases with a broad spectrum of clinical manifestations. Whereas the etiology is unknown (even if is paid a great attention to the infective agents), pathogenesis can vary: degenerative, inflammatory, dismetabolic, autoimmune.

Many rheumatic affections, in particular those which involve the connective tissues, are generally multisystemic and chronic and often determine an important worsening of the quality and the expectation of life. Diagnostic iter may be long and difficult and may need high technology and sophisticate examinations. In most cases, treatment is particularly complicated and needs a therapeutical strategy with associations of conventional drugs and off-label drugs not always easily available. Many rheumatic disorders are rare diseases and the aim of our study was to verify their prevalence in the patients followed at our Unit.

Revision of our database and clinical charts has identified 523 patients affected by rare diseases, actually taken in care in our Unit (Table 1).

**Table1. Epidemiological data\***

Diseases	Followed-up out patients	Patients hospitalized in 2005	DH 2005	Mean disease duration	M/F	Out patients visit
Horton's temporal arteritis	66	15	2	8.2	15/51	198
Takayasu's arteritis	9	2	0	9	0/9	24
Mixed cryoglobulinemia	98	17	2	15.2	13/85	196
Dermatomyositis	40	9	1	4.1	12/28	120
Polimiositis	30	10	2	6.6	11/19	90
Wegener's granulomatosis	13	9	2	7	4/9	39
Behçet disease	95	16	5	12.7	49/46	285
Schonlein-Henoch's syndrome	1	1	0	16	1/2	4
Churg-Strauss' syndrome	19	5	3	9	13/6	57
UCTD	139	23	5	10.5	23/116	347
MCTD	9	5	2	16.4	3/6	22
Retroperitoneal fibrosis	3	2	0	4.6	2/1	15
Good Pastrure's syndrome	1	1	0	2	1/0	0

(\*) Collection of these data has been possible thanks to the precious collaboration of all our staff.

In 2005, on 747 hospitalizations for rheumatic affections, 113 (15.12%) have been for rare diseases. Sometime the same patient has been hospitalized more than once for a disease flare or to start a therapy wich needs a tight monitoring.

Moreover, on a total number of 239 patients seen in day hospital, 24 (10%) had rare diseases, and on a total of 5902 out-patients, 1397 (23.6%) were seen for rare disease.

If we consider Systemic Sclerosis (SSc) and Antiphospholipid syndrome (aPL syndrome) (diseases which are in the process of being classified as rare diseases), on a total of 747 patients

hospitalized in 2005, 198 (26.5%) had SSc, 14 (1.87%) had aPL syndrome. On a total of 239 patients seen in day hospital in 2005, 34 (14%) had SSc and 3 (1.2%) had aPL syndrome.

In the framework of a regional project performed in collaboration with epidemiologists of Istituto di Fisiologia Clinica of the Consiglio Nazionale delle Ricerche (IFC-CNR) of Pisa a form identifying patients with rare diseases has been prepared, and the epidemiological, clinical and serological data of this group of patients have been collected in a computerized database.

Although rare diseases have a very low prevalence, in our Unit they represent a sizeable group of affections, needing great care on diagnostic, clinical e therapeutic approach.

## THE FINNISH NEUROFIBROMATOSIS CENTRE: CONTINUOUS CROSSTALK BETWEEN CLINICAL MEDICINE AND BASIC SCIENCE

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Turku Hospital District has about 450 000 inhabitants located within 100 km of the main hospital, Turku University Central Hospital. The hospital includes all medical specialties, including the Positron Emission Tomography (PET) centre equipped with PET-CT (Computerized Tomography) imaging facility. As NF1 (Neurofibromatosis type 1) is a multi-system disease, many patients visit several specialists in the hospital, in addition to meeting their own family doctors in their own community. Most specialists can provide NF1 patients with high-quality services while very few are familiar with all aspects of the syndrome. NF1 research has been established in the Institute of Biomedicine, University of Turku, in late 1970's. The Institute is located in the close vicinity of Turku University Central Hospital. This background provides an opportunity for close cooperation between the clinicians and basic science.

The goal of this project has been to organize the treatment and follow-up of NF1 patients in Turku area. The main goal since 1999 has been to provide all patients for an access to a coordinating doctor who is familiar with the syndrome. Furthermore, the patients' needs for the consultations in various specialties are evaluated and visits, as well as imaging, are organized without delay. The coordinating doctor is actively following NF1 research and can help in recruiting the patients to research studies. With the consent of the patients, the tissue material removed from the patients can be used for research purposes.

Information on the presence and activities of the NF Centre has been spread through the Finnish NF1 Association. In addition, we have sent an information letter to all local health centres and hospitals in Turku area, as well as to all clinics of the University Hospital.

Since year 2000, about 100 patients have been referred to the NF Centre for a consultation. Many of them have been referred by family doctors, after removal of a skin tumor that surprisingly proved to be a neurofibroma. Among these patients, nine diagnoses of localized NF were made. Most patients however received the relieving information of not having NF. Sixty-five NF1 patients have been registered into follow-up. Two MPNSTs, one astrocytoma in midbrain, and one lymphoma have been diagnosed in NF1 patients, based on the referrals from the NF Centre. In addition, ten patients have been operated in the departments of neurosurgery or plastic surgery. Willingness of the patients to have their cutaneous neurofibromas removed has resulted in the establishment of a Schwann cell bank, as well as a collection of tumor material for various biochemical analyses. Knowledge derived from research, such as high osteoporosis risk in NF1 patients, has had an impact on the counselling with regard to vitamin D and calcium supplementation.

Patients, with a multisintomatic disease, need an own coordinating doctor who knows the various symptoms and complications of the syndrome. Continuous cross-talk with basic science is essential to keep the patients informed on new developments of the research. Close contact with clinic is important for the flourishing basic research.

## SHARING EXPERIENCES AND EXPERTISES: EFFECTIVE COMMUNICATION IN RARE DISEASES

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Rare diseases represent a main issue in public health, and are estimated to be almost 6,000-7,000 in the world. Since a rare disease occurs in or less 5 per 10,000 individuals, there are 6-7 million people in the world suffering for these conditions; the rarities of the diseases pose several needs.

An effective interchange of information among institutional health centres, patients, their families and medical workers could help to focalise needs, and in return fulfil them. In fact, the success achieved by the Patients' Association campaigns has demonstrated the importance of interpersonal relationship based on communication, and sharing experiences.

At the Italian National Centre for Rare Diseases (Centro Nazionale Malattie Rare, CNMR), two activities have started in order to implement an open communication flow with people involved in rare diseases: Information Service, and narrative medicine.

Moreover, among the institutional activities of the CNMR, according to the Public Health Service legislation, there is communication with the public. The Information Service and Narrative medicine, even if with different purposes, distinct characteristic, and their own specific methodologies, can accomplish this institutional duty. The Information Service of the CNMR provides information to patients and their families, and also to physicians, nurses, and other health-care professionals. The information is given by e-mail or conventional mail. The CNMR answers to scientific, medical, and social queries about rare diseases, and related problems. The Narrative medicine is an approach to gather relevant information on diseases from patients, doctors, relatives, and all the public through "Illness stories".

The "Illness stories" will help to point out specific problems and needs of patients and their families, and they may transform problems into experiences.

Finally, the narrative medicine represents a reservoir of disease symptoms data, which could be used to improve clinical knowledge. The communication process of verbal, paraverbal, and nonverbal means is fostered by interpersonal relation. Such a process can be definitely strengthened supplementing the Information Service and the narrative medicine with various communicative modalities, carried out by other subjects involved in rare illnesses treatment on a central, regional and local scale through the help of public structures, patient associations and media.

The final goal of the CNMR is to build "a network" for information exchange on rare diseases, using the knowledge derived from disciplines involving in health communication, always committed to the highest standards of ethical and professional integrity.



Moreover, the Information Service and the narrative medicine, founded in order to implement an open communication flow, will make possible to collect data on needs, and to plan new strategies and new effective interventions on rare diseases.

## INITIATIVES ON RARE DISEASES AND ORPHAN DRUGS IN BULGARIA

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Rare diseases and orphan drugs become an important topic in the public health agenda of Europe. However, still many member states do not have adequate national policy on this topic. The aim of the presentation is to demonstrate the activities on rare diseases in Bulgaria.

Since 2004, a free public multilingual information service on rare diseases (Information Centre for Rare Diseases and Orphan Drugs, ICRDOD) has started, operated by a non-governmental non-profit organization in close collaboration and networking with medical and patient associations.

The service provides personalized replies to requests from patients, families and medical professionals.

The other tasks of ICRDOD include:

- encouraging people with rare disease to establish patient associations, which is the way to protect their human rights and to participate in regulatory actions;
- bridging between patients with rare diseases, researchers and industry;
- lobbying and advocating for adopting of adequate rare disease and orphan drug legislation;
- networking and integrating with the other similar national and international organizations;
- active search for partners for collaboration and support at a national and international level.

Apart from these activities, two Eastern European conferences on rare diseases have been successfully organized. The development of national policy on rare diseases and orphan drugs will be discussed.

## ACTIVITIES OF THE ITALIAN NATIONAL CENTRE FOR RARE DISEASES

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The National Centre for Rare Diseases (Centro Nazionale Malattie Rare, CNMR) leads several activities ranging from laboratory research on specific rare diseases (including rare tumors), to prevention, surveillance and information to patients, families and to the general population.

The main activities of the CNMR are briefly described as follows:

– *Research activities on rare diseases*

Projects are on going to identify molecular markers for diagnosis and prognosis of selected rare tumors (e.g. pancreatic tumors, salivary glands tumors, pheocromocytomas, and hepatoblastom) as well as on the Nijmegen breakage syndrome. The project on Nijmegen breakage syndrome started two years ago in cooperation with the University of “Roma Tre” and “Istituto Angelo Novicelli” (Brescia). Moreover, details on specific projects are available on the web <http://www.iss.it/cnmr>.

– *Quality assurance of genetic tests*

The Italian External Quality Assessment (I-EQA) was financially supported by the Italian Ministry of Health within the Projects: “Italian national project for standardisation and quality assurance of genetic tests” (Italian Legislative Decree 505/92) and “Genetic tests: from the research to clinic”. It is coordinated by the CNMR.

General aims of the I-EQAs are:

- to assure an appropriate use of genetic test in Italian laboratories;
- to elaborate guidelines and recommendations to improve analytical and interpretative performance;
- to facilitate diffusion of technical information and standardization of laboratory methods.

Public Laboratories, covering all Italian Regions, participate on a voluntary basis and participation is free. The IEQA scheme covers Cystic Fibrosis, Beta-Thalassemia, Fragile-X syndrome, the Adenomatous Polyposis Coli (APC) gene and prenatal and postnatal diagnosis, including cancer cytogenetics. Trials are organized once a year; five trials have been performed up to now (2001, 2002, 2003, 2004 and 2006).

– *Primary prevention of congenital defects and folic acid*

The Italian Network for Folic Acid Promotion started in April 2004, in order to integrate and optimize activities already on going at local and regional level. The constituencies of the Network are: research institutes, Italian Ministry of Health, Local Authorities (Regions), Local Health Services, Universities, as well as physicians, journalists and representatives of patients’ Associations. The Network developed and is currently promoting a National Recommendation to increase the intake of folic acid among women in fertile age to prevent congenital defects.

- *Surveillance of rare diseases at national level: Rare Diseases National Register*  
The Register was established by the Ministerial Decree 279/2001 at the CNMR - Istituto Superiore di Sanità (Rome) in 2001, with the following specific objectives:
  - to estimate incidence or/and prevalence of rare diseases in the Italian territory;
  - to develop diagnostic protocols and clinical guidelines for specific rare diseases;
  - to improve collaboration among health care operators to reach consensus on diagnostic criteria and treatment rare diseases. Up to now, we collected epidemiological data on 689 different rare diseases.
- *National Register of Orphan Drugs*  
The National Register of Orphan Drugs was established at the ISS with the aim of: 1) ensuring a post marketing surveillance of the orphan drugs centrally approved by the EMEA and reimbursed by the National Health Service; and 2) monitoring and collecting information on orphan drugs efficacy, safety and appropriate use (for details see page 158).
- *Development of guidelines*  
The Centre leads the project “Guidelines for rare diseases” with the goal to elaborate, to implement, and to promote the diffusion of guidelines for several rare diseases.  
The web site <http://www.iss.it/cnmr> includes a specific section dedicated to this topic.  
Moreover, the Centre is co-ordinating a multidisciplinary group of stakeholders involved in the development and dissemination of multidisciplinary guidelines for diagnosis and management of persons with Down syndrome.
- *Accessibility and quality of health and social services for the patients with rare diseases*  
Collaborative projects are on going among our Centre, Patients’ Groups, Institutions and health/ social operators in order to assess accessibility and quality of health/social services.  
*Ad hoc* questionnaires are elaborated and validated by the CNMR and distributed to responsables of Patients Associations, Patients and their relatives.  
The main studied topics are: accessibility and quality of diagnostic, pharmacological, psychological and rehabilitative interventions; social support; school and vocational training; information to Patients and families.
- *NEPHIRD*  
NEPHIRD (Network of Public Health Institutions on Rare Diseases) is a network of Public Health Institutions working on rare diseases in Europe funded by the European Commission. As the name implies, NEPHIRD was conceived as a forum for public health institutions to share opinions and experiences. Public Health Institution from 18 European Countries participated in the project coordinated by the Istituto Superiore di Sanità. Specific activities of NEPHIRD are described in the dedicated Abstract.
- *Narrative medicine*  
Narrative medicine is a patient-centred approach to gather relevant information on diseases from patients, relatives, medical doctors through “illness stories”. In November 2005, the CNMR launched a collaborative project on rare diseases and narrative – based medicine. In this project we stress the importance to collect illness stories as a participatory and inclusive method (see pages 152-153).
- *Provision of information to patients, families, and to the general population*  
The CNMR provides information and support to patients, families and to the general population. The Centre collaborates with Patients’ Associations to spread knowledge on rare diseases also through the web site <http://www.iss.it/cnmr>, the latter includes a specific focus and a database on the National Patients Associations.

– *Training and continuous education of health care operators*

The CNMR organized on a regular basis courses, national and international workshops to improve training and continuous education to health care operators involved in epidemiological and clinical activities of rare diseases.

Moreover, international Conferences and Meetings for scientists, policy makers, patients' Associations are organized yearly.

## THE ITALIAN ORPHAN DRUGS NATIONAL REGISTER

Domenica Taruscio (a), Alberto Loizzo (a,b), Daniela Pierannuzio (a), Annalisa Trama (a), Stefano Loizzo (a), Luca Ferrari (a)

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The Regulation (EC) No 141/2000 lays down a Community procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the research, development and placing on the market of designated orphan medicinal products. Since 2000, the European Agency for the Evaluation of Medicinal Products (EMA) and its Committee on Orphan Medicinal Products (COMP) has taken on an important role in stimulating the development of orphan medicinal products and in implementing the legislation.

As a direct consequence of such initiatives, the number of orphan medicinal products authorised has increased each year since 2000.

In this context, the Istituto Superiore di Sanità (ISS) established the Orphan Drugs National Register with the aims at 1) ensuring the post marketing surveillance of the orphan drugs centrally approved by the EMA and reimbursed by the National Health Service and 2) collecting information on orphan drugs efficacy, safety and appropriateness of use.

The register collects information on the diagnosis and follow-up of patients in treatment with the drugs under surveillance. The ISS in collaboration with the clinical experts develops the electronic data set per each rare disease with a specific orphan drug available.

The health centres authorised to dispense the reimbursed drugs access to the register through the ISS-National Centre for Rare Diseases website and fill in the data set on line. The ISS collects, verifies and analyses the data ensuring a feedback to all health centres involved and major stakeholders. Privacy is ensured in data collection, analysis and storage. The ISS is actually focusing on the following orphan drugs:

- Aldurazyme (Mucopolysaccharidosis I)
- Fabrazyme e Replagal (Fabry disease)
- Ventavis, Tracleer (Pulmonary arterial hypertension)

**Acknowledgements:** The Orphan Drugs National Register is financially supported by the Italian Drug Agency (AIFA). Special thank to Roberto Raschetti and Marina Maggini (National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, Rome, Italy) for their advice and collaboration.

## THE EUROPEAN RARE DISEASE THERAPEUTIC INITIATIVE (ERDITI)

Elisabeth Tournier-Lasserre, Pascale Borensztein  
*GIS - Institute des Maladies Rares, Paris, France*

The thousands of compounds that have been developed by pharmaceutical companies for more common diseases but that were abandoned or failed to achieve registration for several reasons (such as biopharmaceutical properties, toxicity, lack of efficacy, or strategic reasons) represent a treasure worth exploiting. The availability of such compounds could allow us to shortcut the traditional route of pharmaceutical development and evaluate swiftly – at minimal costs – drug candidates for the treatment of rare diseases.

With this aim, several academic research institutions and pharmaceutical companies (Pharma Partners) have established an innovative partnership called ERDITI (European Rare Diseases Therapeutic Initiative) ([www.erditi.org](http://www.erditi.org)).

ERDITI has three main objectives: 1) to provide academic teams with a facilitated access to available compounds developed by companies; 2) to provide a streamlined facilitated process of collaboration between public and private partners; 3) to guarantee the continuity all the way from pre-clinical research to development and commercialisation of the drug.

ERDITI is under the sponsorship of the European Science Foundation, and is coordinated by French Institute for Rare Diseases Research. To date four major pharmaceutical companies developing a research activity – GlaxoSmithkline, Roche, Servier and Sanofi/Aventis – and about 10 European research institutions or organizations support this initiative.

Participation implies that the partners agree to follow in good faith the working procedure and use the standard agreement as a framework for its contractual relationship with other Partners.

Any academic researcher conducting a project on a rare disease, or a group of rare diseases, who is willing to evaluate the therapeutic potential of chosen compounds for preclinical studies simply needs to apply to participate (at <http://www.erditi.org>). The suitability of the request is assessed by a scientific advisory committee, consisting of European experts from both academic and private sectors. After approval, pharmaceutical company partners are questioned on the availability of molecules belonging to pharmacological classes of interest. If a molecule (or several molecules) is available, a specific agreement is signed between the industry partner and the academic team. Then the industry partner provides reasonable quantities of the molecules required for preclinical studies, together with the necessary information about the molecules. Obviously, transactions with each pharmaceutical company partner are dealt with separately and in confidentiality.

The commitment of the four pharmaceutical companies already involved with ERDITI – who are willing to take up the challenge and to open their compound libraries to academic therapeutic research – really raises hope for future development of new drugs.

## **HEALTH RELATED QUALITY OF LIFE IN PATIENTS AFFECTED BY NEUROFIBROMATOSIS 1: A CROSS SECTIONAL STUDY PERFORMED IN NEPHIRD PROJECT**

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Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen's disease, is an autosomal dominant neurocutaneous disease equally widespread across sex, race, ethnic and national boundaries. The disease manifestations are extremely variable. The primary symptoms of NF1 are neurofibromas, tumours which develop in and along nerves and nerve sheaths. External neurofibromas may be cosmetically disfiguring and associated with considerable stigma for affected persons.

NF1 appears to have a significant impact on Quality of Life (QoL) of the patient through alteration of health and appearance. A cross-sectional study was carried out to evaluate the impact of NF1 on QoL in an Italian population. The aim of the study was to assess the relationship of disease severity and appearance to the measures of QoL.

Recruitment took place in a single Italian Centre, namely at the Dermatological and Neurofibromatosis Clinic of the University of Rome "La Sapienza", Italy. During the time frame from February 2005 to September 2005, 121 patients with NF1 were enrolled.

QoL was measured using the SF-36 – a general health questionnaire and the Skindex – a specific QoL questionnaire, which is especially designed to assess the QoL in skin diseases. Both the Ricciardi and Ablon scales were used to evaluate the clinical data on the severity and the appearance of the disease effects, respectively.

A total of 121 adults with NF1 filled the study questionnaires. They ranged in age from 11 to 70 years (mean  $\pm$  SD, 37.5 $\pm$ 12.7). Patients with more evident NF1 reported more effects on each aspect of their a specific QoL questionnaire: emotion, symptoms and functional (analysis of variance:  $P=0.000$ ;  $P=0.002$ ;  $P=0.0001$  respectively)

Our 121 patients with NF1 were compared to a healthy sample of 2031 subjects representative of general population that had answered the SF-36. For all domains of SF-36 profile, patients with NF1 had lower scores than the control sample; participants with more severe NF1 did not report significantly more effect on the domains of their general health QoL.

Cases were evaluated through a multiperspective protocol by means of clinical assessment (Ricciardi and Ablon scale), and patient-oriented measures of QoL (General Health-Short Form-36 -SF36) and disease-specific questionnaire (Skindex). Both severity (defined as medical complication) and appearance (defined as cosmetic effects) of NF1 could have consequences on patients' QoL.

We emphasize several findings from our study. In general, persons with NF1 reported an effect in all aspects of Skin-disease-specific QoL, but the emotional aspect showed the greatest impact. Patients with more visible NF1 reported more effects on their skin-disease-specific QoL. These findings suggest that Skindex-29 measures certain skin-disease-related aspects of health more specifically and accurately than other generic tools.



## CHEMOGENOMICS WITH ORPHAN TARGETS

Hartmut Zehender, Lorenz M. Mayr

*Novartis Institutes of Biomedical Research, Discovery Technologies/Lead Discovery Centre, Basel, Switzerland*

An overview of the Lead Discovery Process at Novartis/Basel is presented.

The Lead Discovery Centre of Novartis looks for chemical lead structures by means of high-throughput screening (HTS) of disease related genomic targets with libraries of chemical compounds from medicinal and combinatorial chemistry and from natural products.

The objective is to support the development of new drugs for preclinical and, later on, for clinical applications. The presentation is focused on disease-linked targets with a yet unknown biological function (orphan) and on targets for which a functional HTS assay is difficult to assess (non-tractable).

An affinity-selection based, homogeneous, label-free method is presented, which aims in the detection of binder molecules with an affinity to the biological target.

Using a pool of compounds for screening, the binder-target complex is separated from unbound molecules by rapid size exclusion chromatography. Binders are identified by their molecular mass ( $m/z$ ) using mass spectrometry measurements and data evaluation with a special software.

The SpeedScreen HTS method is described and results of a case study with a biological target are shown. At Novartis, affinity-selection based HTS is successfully applied to orphan and non-tractable targets.



**ABSTRACTS**  
**SENT BY ITALIAN PATIENTS' ASSOCIATIONS**



## SINDROME DI EHLERS-DANLOS E ORMONE DELLA CRESCITA

Cinzia Sacchetti

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Una ricerca del 2005 svolta da EURORDIS (*European Organization for Rare Diseases*), che metteva in luce i ritardi nella diagnosi delle malattie rare, ha evidenziato che per la sindrome di Ehlers-Danlos, 1 paziente su 4 ha aspettato per più di 30 anni prima di giungere alla diagnosi corretta. E ottenuta la diagnosi, comunque, non esiste ancora un trattamento specifico e i pazienti devono limitarsi a curare di volta in volta i sintomi che si presentano.

Prendendo spunto dall'esperienza di mio figlio vorrei proporre un progetto sperimentale per curare la sindrome di Ehlers-Danlos nel suo insieme con l'ormone della crescita (*Growth Hormone, GH*).

Tra i sintomi più frequenti della sindrome di Ehlers-Danlos abbiamo: iperestensibilità cutanea; cicatrici allargate atrofiche, papiracee (manifestazioni di fragilità cutanea); ipermobilità articolare, legamentosa generalizzata; grave ipotonia muscolare già alla nascita; acrogeria (invecchiamento prematuro della pelle delle mani e dei piedi); ipermobilità delle piccole articolazioni (mani e piedi); rotture muscolari e tendinee; fistola arteriovenosa; piede equinovaro; vene varicose precoci; pneumotorace; fragilità tissutale con cicatrici atrofiche; facilità di contusioni; aspetto marfanoide; microcornea; grave osteopenia; ecc.

Allo stato attuale della conoscenza dell'ormone della crescita sappiamo che questo ormone serve per ottenere un aumento della statura in età pediatrica e agisce in maniera benefica anche nell'adulto sulla composizione corporea, sulla funzione cardiaca, sulla funzione renale, sul metabolismo lipidico, protidico e glucidico, sulla capacità fisica e lavorativa e sulla qualità della vita. Inoltre, ha anche indicazioni terapeutiche non "convenzionali", cioè farmacologiche (vedi sindrome di Turner e di Prader-Willi). Tra queste possiamo considerare anche: gli stati catabolici gravi, le ustioni estese, l'osteoporosi, l'infertilità, l'obesità, la sindrome da immunodeficienza acquisita.

In conclusione, io vorrei aggiungere a questo elenco la sindrome di Ehlers-Danlos, dando a questi pazienti un'opportunità di cura.

A tal proposito porto l'attenzione soltanto su quanto è dimostrato finora riguardo alle ustioni estese: Herdan e collaboratori, in 80 pazienti pediatriche, ustionate per più del 40%, trattati con rhGH, hanno evidenziato tra i vari effetti anche un aumento della velocità di guarigione delle ferite.

Inoltre il GH risulta coinvolto nella realizzazione del "picco di massa ossea" e quindi utile nel trattamento dell'osteoporosi.

## FIBROSI CISTICA

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Molti sono gli aspetti che coinvolgono un genitore quando al proprio figlio viene diagnosticata una malattia rara ed io, come madre di una bambina di 13 anni affetta da Fibrosi Cistica (FC), desidero approfondire l'aspetto riguardante la sensazione di dolore e solitudine che sin dal momento della diagnosi, ci pervade e ci proietta in una dimensione a noi del tutto sconosciuta. Dopo una prima fase, inizia un percorso alla continua ricerca di notizie, cure e terapie esistenti; in pochi istanti si vorrebbe avere la consapevolezza totale di tutto. Non è sufficiente una semplice parola di conforto da amici e familiari, desideriamo ascoltare esperienze di persone nella nostra medesima situazione, che diano la possibilità di confrontarsi; questo accade spesso, ad esempio, durante un ricovero in ospedale dove cerchi altri genitori come te. Parli con medici, infermieri psicologi, assistenti di reparto ma li senti estranei e la sete è immensa e non è sufficiente.

13 anni fa, enciclopedie, libri e riviste parlavano della FC ma con pochissime righe e le notizie che avevo non corrispondevano a ciò che io cercavo.

Dopo sei anni, accadde che una persona speciale mi prese per mano e mi condusse in un mondo a me sconosciuto: la rete Internet. Mi fece comprendere che avrei potuto dialogare con chiunque e cercare tutto quello che esisteva sulla FC. Con il suo aiuto, iniziai a costruire il mio sogno divenuto realtà. Un luogo dove genitori e pazienti potessero ritrovarsi, scambiare esperienze, notizie, sostenersi a vicenda. Nacque così, nel 2000, il forum di discussione: [fibrosicisticaItalia.it](http://fibrosicisticaItalia.it).

Ritrovarmi a scambiare messaggi, condivisibili e fruibili a tutti, con una donna adulta affetta da FC e sposata, con un suo lavoro, una sua vita e dialogare con famiglie nel mondo condividendo lo stesso mio problema, mi ha trasmesso una carica che prima di allora non avevo avuto. Vedevo un futuro, la mia sensazione di solitudine è divenuta voglia di combattere e di spingere altre persone a farlo e soprattutto intorno a me c'erano persone che comprendevano esattamente il mio "tutto".

Oggi il forum visitato ogni giorno da migliaia di persone italiane e non, è un grande gruppo di amici. Condividiamo e confrontiamo ogni giorno le nostre esperienze e questo è meraviglioso. È radicata in me la consapevolezza che condividere, scambiarsi anche le esperienze più insignificanti, aiuti i genitori e anche i pazienti a sopportare meglio il peso di una malattia rara. Io, come altri frequentatori del forum, non ringrazierò mai abbastanza questo grande strumento che ci permette di continuare a combattere sostenuti da una grande energia derivante dal "non sentirsi soli" e dal "magico" filo di Internet.

Volendo condividere con Voi questa mia esperienza per invitare le autorità politiche, i manager sanitari, le istituzioni, i ricercatori, i medici e tutte le associazioni presenti ad utilizzare molto questi strumenti di dialogo, auspicando ad un confronto e ad una condivisione continua delle esperienze perché a mio modesto parere, in un sano e costruttivo confronto possano venire identificate le soluzioni ai problemi.

Ringrazio gli organizzatori di questa conferenza internazionale ed in particolare la Dott.ssa Taruscio alla quale rivolgo un personale ringraziamento per il concreto impegno che dedica continuamente alle problematiche di noi tutti.

## **IL DIRITTO ALLA SALUTE: DALLA COSTITUZIONE ITALIANA ALLA CARTA EUROPEA DEI DIRITTI DEL MALATO**

Ombretta Fumagalli Carulli

*Associazione "Giuseppe Dossetti: I Valori", Roma, Italia*

Il tema del diritto alla salute è particolarmente complesso, intrecciando diversi livelli di tutela e diverse epoche storiche. Accennerò in questa sede a due livelli, oggi oggetto di particolare attenzione e discussione: quello costituzionale italiano e quello europeo. Lo farò cercando di segnalare con estrema sintesi gli aspetti di maggiore attualità, che si collegano al tema delle malattie rare.

La salute come diritto fondamentale dell'uomo e della società è stata sempre considerata segno di progresso nelle carte internazionali uscite dalla Seconda Guerra Mondiale.

Già nel 1948 l'art. 25 della Dichiarazione Universale dei Diritti Umani affermava il diritto per ogni individuo ad un tenore di vita sufficiente a garantire la salute e il benessere.

Successivamente, negli anni '60 dello scorso secolo, il Patto Internazionale sui Diritti Economici Sociali e Culturali all'art. 12 sosterrà il riconoscimento del diritto di ogni individuo a godere delle migliori condizioni di salute fisica e mentale.

Ma è stata la Costituzione Italiana del 1948 a considerare la salute come un diritto costituzionalmente tutelato e protetto. In discontinuità sia con la legislazione liberale sia con la legislazione fascista, lo Stato democratico afferma con l'art. 32 della Costituzione: "La Repubblica tutela la salute come fondamentale diritto dell'individuo e interesse della collettività; e garantisce cure gratuite agli indigenti". Per lungo tempo la nostra è stata l'unica Costituzione del dopo-guerra che abbia contenuto una norma esplicitamente dedicata agli interessi collegati con la salute dei cittadini. Solo successivamente, disposizioni analoghe saranno contenute nelle Costituzioni di Spagna, Portogallo, Irlanda. Affermare che la salute è interesse della collettività e non solo diritto dell'individuo è stato come porre un sigillo nei confronti di qualunque provvedimento postumo che ne potesse snaturare il reale significato.

Il Servizio Sanitario Nazionale ancora oggi, nello sviluppo regionale realizzatosi negli ultimi decenni, garantisce a tutti i cittadini livelli di assistenza sanitaria e di standard qualitativi tra i più alti al mondo. Esso è frutto dell'art. 32, che in maniera lungimirante i Padri della Costituzione hanno saputo inserire nella Carta quale essenziale aspetto dei "Rapporti etico-sociali" considerati nel titolo II.

Con l'Unione Europea, poi, si è pervenuti nel 2000 alla Carta dei diritti fondamentali (Carta di Nizza). Il suo Capo I detta il principio del rispetto della dignità di ogni individuo: "la dignità umana è inviolabile". Ne deriva un ampio ventaglio di diritti individuali: il diritto alla vita, la condanna della pena di morte, il diritto all'integrità della persona, con la conseguente introduzione dei nuovi diritti della genetica, che impediscono ogni esperimento sugli esseri umani ai quali si garantisce integrità fisica, genetica e psichica, rispettando il "consenso libero e informato" del paziente. Si pone anche il divieto di fare del corpo umano una fonte di lucro. Ai diritti personali la Carta di Nizza aggiunge i diritti sociali, anche se, tutto sommato, ancora timidamente. Così, il diritto alla salute come diritto sociale è configurato dall'art. 53 della Carta di Nizza come "diritto di accedere alla prevenzione sanitaria e di ottenere cure mediche alle condizioni stabilite dalle legislazioni e prassi nazionali". Il timore di mettere in crisi delicati equilibri politici raggiunti nei singoli Paesi europei è trasparente nel rinvio alle legislazioni e

prassi nazionali. Un Welfare europeo insomma fatica ad affermarsi, anche se lo stesso art. 53 stabilisce che l'Unione deve garantire "un alto livello di protezione della salute umana", intendendo la salute come un bene sia individuale che sociale. Se dunque i Governi nazionali europei devono comunque non fermarsi alle soglie di "standard minimi garantiti" ma predisporre ogni mezzo affinché la persona sia garantita nella sua integrità psico-fisica, per il nostro Governo vi è un vincolo in più in favore della tutela della salute: la norma costituzionale dell'art. 32.

Partendo dalla Carta dei diritti fondamentali è stato possibile elaborare a Bruxelles una Carta Europea dei Diritti del Malato. Essi, in sintesi, possono così riassumersi: diritto alla prevenzione, diritto all'accesso, diritto all'informazione, diritto al consenso, diritto alla libera scelta, diritto alla privacy, diritto al rispetto del tempo, diritto al rispetto di standard di qualità, diritto alla sicurezza, diritto alla innovazione, diritto ad evitare sofferenze inutili, diritto ad un trattamento personalizzato, diritto al reclamo, diritto al risarcimento.

La Carta Europea dei Diritti del Malato rappresenta un importante mattone dell'edificio dell'Europa dei Diritti alla Persona, che, insieme all'Unione Monetaria, è un grande servizio a popoli diversi, che vedono messi a rischio quei diritti fondamentali senza i quali il disegno europeo sarebbe una costruzione senza anima.

Liste d'attesa fuori di ogni sopportazione, o scandali nella sanità che molti ritengono ancora terreno di conquista finanziaria e politica, sono fenomeni deteriori che purtroppo continuano a caratterizzare negativamente molti Paesi, il nostro compreso. Essi urtano frontalmente contro i principi contenuti nelle Carte fondanti la nostra comunità civile, che mettono il cittadino e la sua dignità al centro del sistema sanitario.

Certamente una concezione che veda nella sanità solo affari o potere non potrà ammettere che l'Europa dei Diritti si costruisca, aprendo gli spazi alla tutela della persona di ogni età e cultura.

Anche i cittadini affetti da malattie rare hanno il diritto, non solo alle cure, ma alla ricerca di ogni terapia medica che possa rimediare ai danni più profondi causati dall'insorgenza di patologie non diffuse.

Da sempre l'Associazione "Giuseppe Dossetti" ha sensibilizzato l'opinione pubblica, le istituzioni, i mass media a prendere nella dovuta attenzione il tema delle malattie rare, della ricerca farmacologica, dello scambio d'informazioni per rendere effettivo quello che spesso è solo sancito sulla carta. A muoverci non è solo la solidarietà sociale; è anche il rispetto dei diritti. Abbiamo, infatti, tutto il corpo delle norme costituzionali e di quelle europee che ci danno la forza per chiedere l'estensione del diritto alla salute anche alle malattie scoperte da poco ed a quelle che si potranno scoprire in futuro.

Un'ultima e più generale osservazione oggi di specifica attualità: è iniquo pensare di poter assestare il bilancio dello Stato colpendo, direttamente o indirettamente, il diritto alla salute dei cittadini. Ticket sui ricoveri e sul Pronto Soccorso o anche sulle cure farmacologiche colpirebbero soprattutto i cittadini delle fasce sociali deboli (anziani, disoccupati, bambini). Dobbiamo sempre ricordare che, proprio grazie all'art. 32 Cost., le fasce sociali deboli nel nostro Paese hanno avuto la possibilità di ottenere pienamente una tutela della loro dignità, che altrove, anche in società più avanzate come quella americana, non sono neanche immaginabili.

In conclusione: la dignità della persona al centro di ogni sistema è il nucleo del nostro ordinamento sanitario. Esso è frutto anche delle radici cristiane della nostra Europa. La salute e la vita sono per il Cristianesimo dei doni di Dio che la società deve difendere e tutelare a difesa delle persone, senza distinzione di condizioni economiche o culturali.

Queste garanzie valgono per tutti gli uomini e le donne senza distinzione di fedi religiose o appartenenze etniche. L'art. 32 della Costituzione è un valore prioritario su cui fondare il nostro impegno civile e sociale.



Partendo da tutto ciò l'Associazione Dossetti da anni è impegnata nella tutela di una particolare categoria di cittadini malati: quella delle malattie rare.

Attraverso convegni e manifestazioni abbiamo sensibilizzato le istituzioni sanitarie a guardare con maggiore attenzione gli oltre due milioni di persone che in Italia sono colpite da patologie rare.

Grazie anche al nostro impulso è stato varato nel 2001 il Regolamento di Istituzione della Rete Nazionale delle Malattie Rare che contempla parte delle 5.000 malattie riconosciute come rare.

Noi ci battiamo affinché l'accesso ai farmaci, che vorremmo non fossero più chiamati orfani, sia reso possibile senza ulteriori barriere sia di tipo amministrativo sia di tipo sanitario.

Auspichiamo che il Governo ed il Parlamento possano al più presto varare attesi provvedimenti legislativi e regolamentari che mettano i malati di patologie rare sullo stesso piano degli altri cittadini nella tutela del loro diritto alla salute.

## SINDROME DA IPERSENSIBILITÀ AI CAMPI ELETTROMAGNETICI

Anna Zuccherò

Associazione Italiana Elettrosensibili, Padova, Italia

L'Associazione Italiana Elettrosensibili è stata fondata nel 2005; vuole essere un riferimento per le persone che esponendosi ai campi elettromagnetici lamentano una sintomatologia che viene comunemente chiamata sindrome da ipersensibilità ai campi elettromagnetici (*Electromagnetic Hypersensitivity Syndrome*, EHS). L'Organizzazione Mondiale della Sanità nel progetto di studio sui campi elettromagnetici sostiene che il problema è reale, la considera con la MCS (*Multiple Chemical Sensibility*, sensibilità chimica multipla) tra le intolleranze idiopatiche ambientali; non è ancora entrata nella Classificazione Internazionale delle Malattie (*International Classification of Diseases*, ICD). Non si sa se si può ritenere rara poiché manca una stima precisa della prevalenza non esistendo dei criteri standardizzati di diagnosi, certamente si può definire "orfana". L'EHS è stata descritta negli anni '60 in lavoratori esposti a radar da autori russi che la denominarono "sindrome da microonde", successivamente in esposti lavorativi e residenziali a basse frequenze (ferrovia, industria, elettrodotti, apparecchi elettrici) e più recentemente è stata descritta con sempre maggiore frequenza una relazione spaziale e temporale con l'esposizione individuale, lavorativa, residenziale, a tecnologie che utilizzano le alte frequenze (telefonia mobile, sistemi wireless, stazioni radio-base).

Colpisce ogni età (più gli adulti), entrambi i sessi (più le donne) e ogni razza. Particolarmente predisposto è chi porta protesi metalliche o ha avuto traumi cerebro-midollari o shock elettrico; può associarsi, precedere o seguire la MCS. Può portare a grave disabilità: sono stati descritti casi di morte. Non è nota la terapia se non l'evitamento dei campi elettromagnetici.

La clinica, le indagini strumentali, elettrofisiologiche ed istologiche inducono a ipotizzare si tratti di una patologia sostenuta dall'infiammazione con conseguente danno delle fibre sensitive sottili cutanee (diametro di pochi micron); sono colpite anche le fibre C afferenti del sistema nervoso autonomo che inviano impulsi ai centri ipotalamici e limbici, stimolando una risposta efferente autonoma che può spiegare il polimorfismo del quadro clinico: sintomi neurologici, psichici cardiovascolari, respiratori, digestivi, urogenitali, visivi, uditivi, endocrino-metabolici.

Scopi dell'Associazione sono:

1. il riconoscimento scientifico dell'EHS. Riteniamo che l'impostazione della ricerca seguita fino ad ora, focalizzata sul rapporto causa-effetto tra c.e.m e sindrome (tra sostanze chimiche e sindrome nella MCS), abbia determinato pesanti interferenze di interessi economico-politici sugli studi scientifici per l'importanza della chimica e dei campi elettromagnetici nel mercato mondiale; pensiamo invece sia urgente focalizzare l'attenzione degli studi sulla ricerca delle alterazioni anatomico-funzionali che sostengono EHS ed MCS.
2. la definizione di criteri di diagnosi clinici e/o strumentali; è urgente e indispensabile per avviare un'adeguata gestione clinica e socio-previdenziale.
3. il riconoscimento dell'EHS come disabilità, secondo il "Regolamento standard per la parificazione delle opportunità delle persone disabili", risoluzione 48/96, 20/12/1993 dell'ONU. Ciò è possibile prima ancora che la scienza definisca con maggior precisione l'EHS; esso permette provvedimenti volti all'abbattimento delle "barriere elettriche e

chimiche” che impediscono una vita individuale, familiare, sociale, all’elettrosensibile e/o chemiosensibile. La Svezia ha già seguito tale strada.

In questo primo anno di attività in cui l’Associazione non ha ancora potuto accedere a finanziamenti pubblici:

- Sono stati instaurati rapporti con Associazioni di elettrosensibili, Istituzioni e studiosi italiani ed esteri.
- Si è fornito supporto a persone elettrosensibili italiane.
- È stata raccolta una ricca e aggiornata bibliografia scientifica sull’argomento.
- Sono state valutate le diverse metodiche schermanti i c.e.m nonché possibili soluzioni farmacologiche.
- Sono stati fatti interventi pubblici e radio-televisivi.

Ci auguriamo che qualcuno “adotti” queste patologie “orfane”.

## ESPERIENZE GENITORIALI IN RAPPORTO A RICERCA SCIENTIFICA E SANITÀ PUBBLICA

Ines Valanzuolo

*Associazione Italiana Malformazioni Ano-Rettali, Roma, Italia*

La nostra Associazione si è costituita nel settembre del 1994 tra genitori, professionisti e volontari per condividere obiettivi comuni: aiutare a risolvere problemi collegati ad una malformazione congenita, ano-rettale, risultato di difetti congeniti che colpiscono in Italia ogni anno dai 110 ai 130 bambini e che si sviluppa fin dalla VI-X settimana della vita embrionale. Queste malformazioni coinvolgono non soltanto l'apparato intestinale ma anche il vicino apparato urinario e genitale. Si associano frequentemente, infatti, ad altri difetti congeniti presenti, con incidenze variabili a seconda degli organi e apparati interessati. I bambini possono così presentare anomalie riguardanti l'apparato genitale e urinario, difetti alla colonna vertebrale, malformazioni degli arti inferiori e superiori, malformazioni cardiache ed esofagee.

La compromissione dell'apparato sfinteriale/ano-rettale, talvolta di quello vescicale, comporta conseguenze funzionali, psicologiche e sociali facilmente immaginabili. Il bambino e, in seguito, l'adulto possono risultare più o meno incontinenti. Qualsiasi diagnosi di tipo prenatale non risulta affidabile, non consentendo ad oggi alcun grado di prevedibilità.

Un neonato che nasce con Malformazioni Ano-Rettali (MAR), se ha una malformazione bassa, questa viene corretta con un unico intervento; se ha una malformazione alta, alla nascita viene praticata una colostomia per consentire l'evacuazione delle feci; dopo questo intervento l'impegno dei genitori è diretto alla gestione della colostomia a domicilio; ad un'età variabile da tre a dodici mesi viene eseguito l'intervento di anorettoplastica, la colostomia viene lasciata aperta allo scopo di deviare le feci proteggendo in tal modo l'intestino a valle.

Nel periodo post-operatorio, i genitori continuano a gestire la colostomia e, contemporaneamente, a domicilio, praticano le calibrazioni rettali iniziate in ospedale dopo l'intervento. Tre mesi dopo si può praticare l'ultimo intervento: la chiusura della colostomia e la ricostruzione della continuità dell'intestino.

Quindi il bambino è colostomizzato per un periodo limitato ma fondamentale, sia per il suo sviluppo psico-fisico, che per l'equilibrio dei familiari che si trovano, in una situazione di completa ignoranza, a gestire un problema impreveduto. La nostra associazione intende quindi intervenire sia in questo momento iniziale che in seguito e si è associata all'AISTOM (Associazione Italiana Stomizzati) per trovare in sinergia possibilità di interventi efficaci, finalizzati alla soluzione, a breve e a lungo termine, delle problematiche descritte. L'AIMAR (Associazione Italiana Malformazioni Ano-Rettali) riunisce 800 iscritti; è in relazione con 15 chirurgie pediatriche su 52 esistenti a livello nazionale. Non si hanno dati epidemiologici precisi ma se mettiamo in relazione la situazione da noi conosciuta con quella sconosciuta delle altre chirurgie pediatriche nazionali, probabilmente esistono altri 2500 bambini e altrettante famiglie di cui non sappiamo niente, senza poi considerare i casi che vengono risolti all'estero. Non esiste un registro nazionale da cui possa derivare una corretta impostazione degli interventi. Come associazione di genitori non intendiamo fare né pietismo né rivendicazionismo nei confronti delle istituzioni; non ne giustifichiamo però né l'assenza né le scelte sanitarie in base ai numeri (siete pochi? non contate!). Abbiamo le idee chiare su ciò che dobbiamo fare noi e ciò che spetta alla comunità.

Da parte nostra abbiamo cercato di metterci in relazione con centri nazionali e internazionali qualificati circa le problematiche attinenti alle MAR; abbiamo organizzato incontri seminariali tra genitori, medici del Bambin Gesù, infermieri; abbiamo fatto in modo che venissero dagli Stati Uniti Alberto Peña e Kathleen Guardino del *Children Hospital* di Long Island di New York che hanno incontrato genitori e fatto corsi di formazione per medici e infermieri su sperimentate tecniche chirurgiche ma soprattutto su pratiche idonee ad una corretta gestione e riabilitazione intestinale; abbiamo istituito borse di studio per medici laureandi che hanno affrontato il problema genetico ereditario; ci siamo messi in contatto con parallele organizzazioni americane, svedesi, tedesche, olandesi; abbiamo dato informazioni, trasmesso esperienze, indirizzi, approfondito conoscenze, problematiche socio-culturali, legislative attraverso un periodico quadrimestrale "AIMARNEWS"; ci siamo associati con l'AISTOM, per determinare la sinergia necessaria, tra gruppi diversi per problematiche e numero di associati, a superare il senso di impotenza di fronte alle istituzioni e sostenere il disegno di legge n 5663 che risolverebbe numerosi problemi, soprattutto nel momento dell'inserimento sociale dell'incontinente e nel riconoscimento della sua invalidità.

I genitori che devono affrontare con i loro figli i problemi relativi alle MAR e alla conseguente incontinenza si sentono spesso soli, non sanno come permettere loro di avere una vita sociale alla pari dei coetanei.

L'AIMAR fornisce loro una rete di solidarietà che li aiuti a confrontare i loro problemi con l'esperienza di chi li ha già affrontati. Ogni nostra iniziativa, determinata dalla necessità e dalla esperienza, è realizzata con il volontariato e l'impegno personale, senza alcun sostegno istituzionale.

Come associazione, i nostri auspici sono di vedere realizzati in un prossimo futuro i seguenti punti:

- Registro Nazionale delle Malattie Rare effettivamente operante, in particolare per quanto riguarda la raccolta di tutti i dati relativi alle MAR;
- finanziamenti per la ricerca in campo genetico;
- creazione di un centro nazionale ad alta specializzazione con personale medico e paramedico adeguatamente formato, in grado di seguire il portatore di MAR non solo nella fase pediatrica ma per tutta la vita;
- disponibilità di informazioni adeguate nelle chirurgie pediatriche per i genitori in casi di nascita di bambini portatori di MAR;
- assistenza domiciliare nella fase post-partum;
- assistenza nell'inserimento scolastico, sia a livello igienico che alimentare (dieta adeguata nelle mense) e psicologico;
- sburocratizzazione nel riconoscimento della invalidità a fini lavorativi, assistenziali;
- obbligatorietà, nella Commissione di accertamento di invalidità, di presenza medica a conoscenza delle MAR e delle conseguenze dell'incontinenza fecale/orinaria, persistente e spesso accentuata con l'età.

## NARCOLESSIA

Icilio Ceretelli

*Associazione Italiana Narcolettici, Firenze, Italia*

Il nostro intervento vuole portare all'attenzione delle Istituzioni la grave situazione che si è venuta a creare nei confronti delle malattie rare e dell' informazioni sulle stesse.

Nonostante ci si impegni a trovare risorse private per effettuare campagne di informazioni con eventuali spot video, oggi tutto può essere vanificato (come è accaduto alla nostra associazione) dal mancato patrocinio da parte di Pubblicità Progresso che viene richiesto per la trasmissione degli spot.

Chiediamo un impegno da parte del Ministero della Salute e dell'Istituto Superiore di Sanità (ISS) a far sì che ciò non avvenga e che le malattie rare non siano considerate di scarso interesse sociale tanto da definire esagerato il mezzo televisivo per informare su la malattia.

A tal proposito sarebbe opportuno che il Ministero della Salute e l'ISS fossero i primi a concedere il proprio patrocinio per campagne d'informazione che non costano nulla alla Sanità.

## NEOPLASIE ENDOCRINE MULTIPLE DI TIPO 1 E TIPO 2

Lara Gattico

*Associazione Italiana Neoplasie Endocrine Multiple di tipo 1 & 2, Torino, Italia*

In una società che si vuole sempre più attenta al benessere di tutti i suoi cittadini, il ruolo delle Associazioni di Malattie Rare è diventato ormai fondamentale, nel rapporto con le Istituzioni, il personale medico e infermieristico, e soprattutto con i pazienti affetti da questo tipo di patologie.

L'Associazione AIMEN 1 & 2, Associazione Italiana Neoplasie Endocrine Multiple di tipo 1 e tipo 2, si sta impegnando proprio in questa direzione, per garantire una migliore qualità della vita a tutti i malati affetti da Neoplasie Endocrine Multiple (*Multiple Endocrine Neoplasia*, MEN), sindromi rare, caratterizzate dalla presenza di iperplasie/neoplasie di numerose ghiandole endocrine, trasmissibili geneticamente. La rarità della patologia e la peculiarità di essere trasmissibile geneticamente ha suscitato il nostro interesse e impegno. Impegno rivolto soprattutto a garantire l'applicazione del diritto alla salute sancito dalla Costituzione, garantendo pari opportunità di trattamento socio-sanitario a tutti i soggetti malati.

Nostro attuale e primario obiettivo è infatti quello di veder riconosciute istituzionalmente le patologie MEN, attraverso il loro inserimento nell'Elenco delle Malattie Rare, garantendo stesso trattamento sanitario anche ad un soggetto affetto da malattia rara.

Altro nostro importante ed ambizioso progetto è relativo alla "Campagna di Informazione e Sensibilizzazione". Per noi, per la nostra Associazione, questo progetto si muove su due fronti: da un lato, informare i medici di base, gli specialisti del settore e il personale infermieristico, per garantire l'assistenza e le cure più adeguate ai malati, attraverso programmi di educazione sanitaria; questa necessità sorge dalla scarsa conoscenza di questa malattia, con le implicite complicità che ne derivano: errata o ritardata diagnosi, il che comporta spesso un aggravamento della malattia, con conseguenze patologiche e psicologiche molto spesso devastanti; dall'altro lato sensibilizzare l'opinione pubblica in merito all'esistenza di tali sindromi, anche per il loro elevato tasso di trasmissibilità alla prole.

Pensiamo oggi che sia probabile l'esistenza tra la popolazione di un numero di persone affette da patologie MEN superiore a quante effettivamente riscontrate, ma che, per ignoranza e disinformazione, sono trattate come portatrici di altre malattie. Questa considerazione non è arbitraria, ma nasce da quanto abbiamo potuto constatare nella nostra se pur breve esperienza, non solo come Associazione, ma anche e soprattutto come malati.

La nostra attività ci vede sempre più impegnati come "filtro" tra, da una parte, gli specialisti che da anni si occupano a livello clinico e mediante ricerca scientifica dei malati MEN, dall'altra i pazienti: non solo fornendo indicazioni sulle varie attività dell'associazione, ma informando sugli ultimi risultati della ricerca scientifica e sui laboratori che effettuano analisi genetiche.

Siamo consapevoli che l'interesse per questo tipo di problematiche sia scarso, anche per l'incidenza di "nicchia" che hanno sulla cittadinanza, ma siamo anche molto convinti che sia giunta l'ora di ampliare i nostri orizzonti, per garantire il diritto alla salute a tutti i cittadini, a prescindere dal tipo di patologia di cui affetti: riteniamo essere questo nostro dovere civile e morale, e segno di una nuova civiltà attenta ad ogni singola vita, perché ogni singola vita è un tesoro. Proponiamo l'aggiornamento dell'elenco malattie rare e l'istituzione di un documento contenente tutti gli estremi dei centri di riferimento per malattia rara.

## MILLE MODI DI RACCONTARSI

Daniela Zarri

*Chirurgia Pediatrica, Istituto Giannina Gaslini, Ospedale Pediatrico, Genova, Italia*

Da diversi anni all'Istituto G. Gaslini di Genova, nei dipartimenti di Oncoematologia Pediatrica e di Chirurgia Pediatrica, la narrazione viene utilizzata come forma di comunicazione prioritaria con i piccoli pazienti. Il bambino, infatti, utilizza un linguaggio spontaneo che consente di entrare in relazione con il suo mondo più profondo e di avere così accesso ad emozioni e sentimenti che verrebbero negati o celati qualora fossero poste domande troppo dirette. Ciò che la malattia significa, nel presente e nella proiezione futura della vita del piccolo paziente, viene meglio rappresentato quando il bambino o l'adolescente ha la possibilità di esprimerlo attraverso modalità narrative, che possono essere verbali, grafiche, pittoriche, plastiche e drammatiche. Per estensione, ciò che abbiamo visto possibile e conveniente è applicabile anche all'adulto che, stimolato a cimentarsi nella dimensione narrativa e di drammatizzazione, spesso esprime ciò che ritiene altrimenti vergognoso o inefficace. Per questo motivo, come AISP, abbiamo incrementato, nei nostri convegni annuali dedicati alle famiglie, una modalità di comunicazione che permettesse ai piccoli, ma anche agli adulti ed ai genitori, una libertà di espressione metaforica attraverso la conduzione di laboratori nei quali ogni possibile forma narrativa è stata sperimentata.

Per quest'anno abbiamo pensato di affiancare, accanto ai laboratori già collaudati, anche un nuovo laboratorio di narrazione fotografica, pensando in tal modo di ottenere una sequenza emotiva più completa che abbracci passato, presente e futuro, attraverso la quale fornire un messaggio stimolante e rassicurante sulle capacità e possibilità di buona qualità di vita per il singolo paziente e per l'intero gruppo familiare.

I laboratori proposti saranno quelli narrativi, di animazione musicale a terra ed in acqua termale, di costruzione di oggetti dinamici a partire da materiale di recupero e di psicomotricità. Tutti i laboratori sono condotti da educatori esperti nel campo e che hanno già partecipato alle precedenti edizioni, per le quali abbiamo potuto contare su oltre 200 tra pazienti pediatrici ed adulti. Il laboratorio di narrazione fotografica si avvarrà di un nuovo esperto che avrà l'incarico di stimolare l'elaborazione digitale di ritratti ed autoritratti tanto eseguiti sul momento che ricavati da vecchie foto. Ogni elaborazione sarà seguita da un racconto che illustri i motivi della scelta dell'elaborazione stessa.

Analogamente, sarà condotto un laboratorio grafico nel quale l'educatore stimolerà l'autore del disegno alla narrazione che accompagna il segno grafico.

Gli elaborati verranno discussi in gruppo alla fine di ogni giornata congressuale, verranno successivamente raccolti e valutati da uno psicologo supervisore.

Le attività di cui abbiamo parlato ci hanno concesso finora di rispondere a quesiti altrimenti inespresi; ci hanno consentito di rassicurare, rinforzare, ridare speranza.

Basta veramente poco per far sentire nuovamente "persona" chi si è sentito tradito dalla sorte, dal proprio corpo, dai medici e dalla società. Grazie alla narrazione, a volte non occorre neppure che sia un altro a fornire una risposta; chi racconta, che lo faccia con una penna o con un pennello, espone a se stesso ancor prima che agli altri i propri pensieri e la chiarezza che ne può derivare rende meno drammaticamente necessaria una risposta che, comunque, non c'è.



## COMPITI DELLE ASSOCIAZIONI DI PAZIENTI E FAMILIARI

Donatella Sessa

*Associazione per l'Informazione e lo Studio dell'Acondroplasia, Milano, Italia*

Compito principale delle Associazioni è promuovere cultura, sia nei riguardi dello specifico della patologia, in quanto riferimento competente ed esperto per famiglie e medici, che nei riguardi di una cultura volta al sociale a difesa del *diritto* alla diversità/malattia dei propri ed altrui Soci contro le pesanti tentazioni di un onnipotente controllo di ogni aspetto della vita, che caratterizza il mondo di oggi.

Questo compito si realizza nel *tutelare* (dai bisogni ai diritti) il bambino, *ammalato* e quindi *più indifeso*, che ha diritto a:

- crescere in una *famiglia sana*: ha bisogno di essere aiutata;
- *migliore qualità della vita* possibile: massimo impegno della rete dei servizi;
- *buona “assistenza”* (assistere ed stare accanto);
- *speranza* (“nulla deve più essere considerato incurabile”).

Tutelare, nel concreto significa:

- aiutare le famiglie sostenendole nel percorso di accettazione e cura del figlio;
- diffondere il proprio sapere sulla specifica patologia
- promuovere lo studio di protocolli clinici e di reti di cura e di assistenza per una efficace presa in carico multidisciplinare integrata; la ricerca non solo scientifica ma anche antropologica, psicologica e sociale, l'integrazione sociale
- sostenere il *diritto alla diversità/malattia*
- aiutare le istituzioni preposte a dare risposte adeguate ai bisogni delle persone
- diffondere ai tavoli di pensiero ed etici la necessità della ricerca non solo medico, genetica e scientifica, ma anche psicologica e sociale per migliorare la qualità di vita delle persone colpite da Malattie Rare
- promuovere l'idea di una Società maggiormente volta ai diritti dei deboli ed alla integrazione delle diversità
- sostenere la necessità di una buona presa in carico multidisciplinare integrata

Quattro sono i punti di partenza:

1. Le Istituzioni hanno il sapere dato loro dal ruolo e dalle Leggi
2. I medici hanno il sapere dato dalla loro scienza e sapienza
3. Le Associazioni hanno il sapere dato dalle tante storie di vita
4. Le Associazioni devono essere un anello della rete di assistenza volta alla presa in carico multidisciplinare integrata.

Una semplice proposta è una buona assistenza multidisciplinare integrata ed una Rete di Esperti (medici, psicologi, servizi, associazioni) (Figura 1).

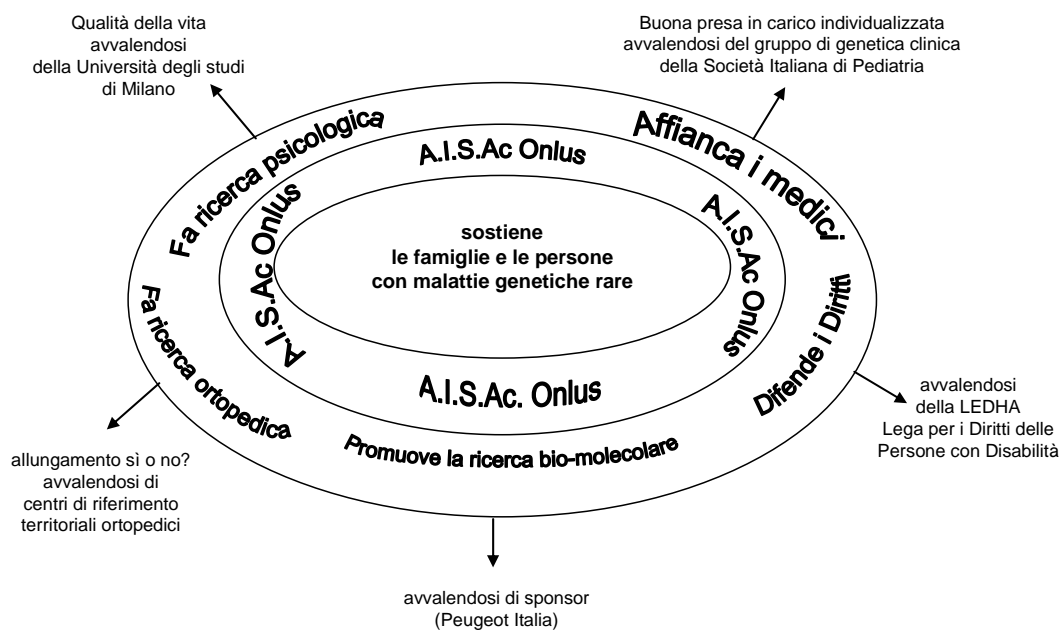


Figura 1. La rete di esperti

## SINDROME DI EMIPLEGIA ALTERNANTE

Rosaria Vavassori

*Associazione Italiana per la Sindrome di Emiplegia Alternante, Lecco, Italia*

L'Emiplegia Alternante (EA) è una malattia neurologica con manifestazioni non solo croniche ma soprattutto parossistiche molto invalidanti, sovente interpretate come disturbi di origine epilettica o emicranica. I primi sintomi si manifestano entro il primo anno di età, nella maggior parte dei casi nei primi giorni di vita e continuano nell'età adulta.

L'EA è una malattia molto rara: meno di 500 sono i casi attualmente conosciuti nel mondo; di questi, circa 40 pazienti vivono in Italia.

Si tratta di una malattia multisistemica, cronica ed altamente invalidante, che provoca disabilità motoria, sensoriale e psico-intellettuale e limita pesantemente l'autonomia e la qualità di vita delle persone che ne sono affette.

Le cause dell'EA sono tuttora sconosciute, non esistono farmaci efficaci né metodi riabilitativi specifici e non è possibile avere indicazioni certe sull'evoluzione della malattia con l'età.

A causa della sua estrema rarità e della sua definizione molto recente, l'EA è ancora molto poco conosciuta dal mondo medico e scientifico, ed è ufficialmente ignorata anche dalle istituzioni pubbliche.

In Italia, questa malattia non è ancora inserita nell'elenco delle malattie rare e non le è stato ancora assegnato un codice di esenzione dalla partecipazione al costo delle prestazioni sanitarie, secondo quanto stabilito dal Decreto per le Malattie Rare n. 279/2001. Non esistono per essa protocolli diagnostici, terapeutici e assistenziali ufficialmente adottati né investimenti specifici per la ricerca.

La nostra richiesta primaria è quindi la seguente: rapido completamento della procedura di revisione dell'elenco delle malattie rare e assegnazione del Codice di Esenzione per l'EA.

Chiediamo inoltre maggiori investimenti per la ricerca per le malattie rare, con particolare attenzione a quelle malattie per le quali vi è ancora poca conoscenza e minore sensibilità da parte dei soggetti privati.

Proponiamo infine una maggiore collaborazione tra le associazioni dei pazienti e le istituzioni (Ministero della Sanità e Regioni), anche attraverso il Centro Nazionale Malattie Rare (CNMR), con particolare riferimento alle seguenti aree:

1. partecipazione attiva e istituzionalizzata delle associazioni nella definizione e gestione della Rete Nazionale Malattie Rare;
2. informazione, ai pazienti e al pubblico in genere; formazione degli operatori del Servizio Sanitario Nazionale (SSN);
3. censimenti e indagini conoscitive sulla situazione dei pazienti e le loro richieste, con maggiore condivisione delle informazioni così ottenute;
4. sviluppo di linee guida e protocolli diagnostici e di assistenza socio-sanitaria da adottarsi ufficialmente da parte dell'SSN;
5. supporto, anche economico, alle associazioni;

Concludiamo, ringraziando in particolare il CNMR per l'impegno attivo in tutte queste aree.

## **LA RICERCA: UN BISOGNO DEL PAZIENTE? QUAL È IL RUOLO DELL'ASSOCIAZIONE?**

Mario Melazzini

*Associazione Italiana Sclerosi Laterale Amiotrofica, Novara, Italia*

Nel campo della ricerca il paziente è visto come materia prima, ma siamo ormai passati a una fase in cui il paziente non ha più solo un atteggiamento di sudditanza nei confronti dei medici, ma di persona correttamente informata.

Perché la ricerca può essere considerata un bisogno del paziente? Uno dei motivi è sicuramente rappresentato dal fatto che il paziente possa usufruire di un'assistenza di elevato livello, di controlli e di esami diagnostici più assidui e di una presa in carico più efficiente, con un ruolo, del paziente stesso e delle associazioni che lo rappresentano, propositivo e partecipativo.

Per concludere, l'obiettivo futuro è che i diversi attori coinvolti nel processo di ricerca (ricercatori, istituzioni, industria e associazioni di pazienti) devono trovare un nuovo modo di lavorare insieme nel rispetto dei singoli ruoli evitando di includere o escludere le associazioni dei pazienti per un cinico esercizio di opportunità politica.

È quindi basilare creare un network per ottimizzare la ricerca su malattie rare e farmaci orfani, tra associazioni di pazienti, istituzioni, istituti di ricerca, società scientifiche e industrie farmaceutiche.

## SINDROME DA FATICA CRONICA E FIBROMIALGIA

Rita Ghiringhelli

*Associazione per conto ammalati di CFS e Fibromialgia, Italia*

Questo intervento è l'esperienza di chi non può raccontare perché la vita è soffocata da un grido di dolore che non gode di benefici terapeutici. È un grido di dolore lasciato vivere nella solitudine della propria casa, diventata una specie di ospedale invisibile. Molto semplice le coordinate dei fatti: dal 1981 al 1998... in cerca di diagnosi. Nel 1998 diagnosi di sindrome da fatica cronica (*Cronic Fatigue Syndrome*, CFS) con sperimentazioni di farmaco costosissimo ed inutile. Nel 2003 complicazione di carattere oncologica con relativo intervento chirurgico ma nessuna terapia di sollievo per una malattia il cui enigma si chiama CFS-Fibromialgia.

In questa occasione dai contorni formali vorrei chiedere alle autorità competenti, a nome mio e di tutti gli ammalati, che sono tanti, troppi, di intervenire là dove nessuno ha mai osato per scoprire perché tante vite (ancor troppo giovani per morire) vengono sacrificate sull'altare dell'indifferenza. Chiedo alle autorità competenti, alle quali mi sono rivolta già troppe volte, di osare, di essere coraggiosi nell'intraprendere la strada della verità di cui noi ammalati siamo inconsapevolmente portatori.

Viene proposta la codifica della malattia, con conseguente coordinamento delle ricerche in atto anche a livello internazionale, al fine di poter adottare una metodologia di intervento terapeutico che renda sostenibile la vita agli ammalati.

## MALATTIE DA INTOSSICAZIONE CRONICA E/O AMBIENTALE

Marco De Santis

*Associazione per le Malattie da Intossicazione Cronica e/o Ambientale, Roma, Italia*

Siamo qui a rappresentare i malati di sensibilità chimica multipla (o MCS, *Multiple Chemical Sensibility*), una patologia che comporta reazioni multiorgano quando si è esposti a sostanze chimiche anche in minime tracce. Alcuni malati hanno reazioni occasionali e modificano solo parzialmente il proprio stile di vita, altri sono fortemente invalidi e vivono praticamente isolati in casa, con enormi difficoltà. In realtà, la MCS è solo l'espressione più grave della Sensibilità Chimica ai prodotti d'uso comune che colpisce, secondo dati danesi e statunitensi il 10-15% della popolazione.

Attualmente la MCS è riconosciuta in quattro regioni. In particolare l'Emilia Romagna e la Toscana hanno avviato delle Commissioni Mediche e hanno individuato dei Centri Regionali di riferimento, che sono però rimasti solo sulla carta. Questo significa che anche in queste regioni, come nel resto d'Italia, i malati non riescono ancora ad accedere alle strutture sanitarie pubbliche, neanche al Pronto Soccorso, a causa della totale assenza di ambulatori adeguatamente decontaminati e della mancanza di personale medico esperto nel trattare questa patologia. Intanto diversi malati hanno ottenuto dalle ASL il rimborso per curarsi nei centri di alta specializzazione in Germania.

Ad aggravare la situazione c'è l'attuale blocco delle diagnosi in queste regioni, in attesa dei risultati di uno studio osservazionale che però deve ancora essere avviato. Le regioni ci dicono che sono in attesa del parere del Consiglio Superiore di Sanità e speriamo che questo avvenga al più presto perché siamo letteralmente subissati di richieste di aiuto da parte di malati che, per esempio, hanno patologie gravi come tumori o cardiopatie e poi ci sono i malati che non hanno nemmeno la diagnosi e si sottopongono a percorsi diagnostici e trattamenti terapeutici spesso inutili e purtroppo a volte dannosi al punto di farli peggiorare. Questo stato di cose danneggia i malati ma anche le casse dello Stato.

Chiediamo, infine, al Ministro per la Salute di fare tutto il possibile affinché venga approvata la Proposta di Legge dell'Onorevole Paolo Cento per il riconoscimento della MCS come malattia sociale.

## UNA RICONCILIAZIONE TRA IL SISTEMA SANITARIO NAZIONALE E I MALATI RARI

Nicola Spinelli

*Associazione Sarda Coagulopatici Emorragici, Monserrato (CA), Italia*

L'Associazione Sarda Coagulopatici Emorragici riconosce l'importanza del momento storico che attraversa il sistema sanitario nazionale. Le linee guida di governo della sanità italiana presentate dal ministro Livia Turco parlano della necessità di rilanciare il sistema con un vero New Deal sanitario basato su di un supremo e globale patto d'intesa e programmatico.

Noi pensiamo che nel marcare profondamente il passaggio tra una vecchia e nuova *era sanitaria* in Italia, ci debba essere anche il prerequisito di una riconciliazione tra il sistema, inteso statalmente, e i pazienti rari e loro familiari. La riconciliazione deve pervenire all'assunzione morale e politica di soddisfazione giuridica nelle grandi controversie legali che vedono contrapporsi i pazienti da una parte e il sistema, con i suoi vari apparati a partire dal ministero, dall'altra. Ancora oggi, dopo molte vicende e sentenze favorevoli, non è stato chiuso il "caso infezioni da uso di emoderivati", che notoriamente coinvolgono tantissimi malati gravi superstiti e familiari di deceduti. Inoltre, come ASCE, abbiamo letto le linee programmatiche governative che il ministro della salute Livia Turco vorrebbe realizzare. Siamo sostanzialmente d'accordo con l'impianto delle linee guida e nell'intervento vogliamo fare alcune riflessioni sugli aspetti generali del programma e in particolare sulla parte dedicata alle malattie rare.

Scopo dell'Associazione è di stipulare un patto programmatico tra i vari attori coinvolti che sfoci in una intesa definitiva di chiusura del contenzioso. La legge di riforma 229/2005 attualmente aperta ai soli vaccinati offre una interessante piattaforma giuridica e politica d'intesa su cui lavorare per raggiungere una sorta di condono tombale sulla vicenda che soddisfi la richiesta di giustizia dalle vittime e riconcili il sistema con i cittadini.

Un altro obiettivo dell'Associazione è che alle linee guida del governo si aggiunga una sorta di New Deal delle associazioni riguardanti le malattie rare affinché operino secondo le esigenze di un nuovo e ancora più elevato e corretto impegno.

## SINDROME NEFROSICA IDIOPATICA

Andrea Sciarcon

*Associazione Sindrome Nefrosica Italia Onlus, Italia*

Associazione nata (anagraficamente) solo da alcuni mesi, ma già attiva attraverso internet da alcuni anni; raccoglie intorno a se alcune decine di famiglie con bambini affetti da Sindrome Nefrosica Idiopatica (SNI), una patologia renale correlata alla risposta autoimmune individuale, più alcuni adulti.

La SNI presenta le caratteristiche di incidenza e prevalenza ritenute necessarie per l'inserimento nel sistema di tutela delle malattie rare come riportato dal DM 279/2001.

Il rationale di questo riconoscimento si basa principalmente sul fattore dell'incidenza della malattia nella popolazione in età pediatrica:

La definizione data dall'Unione Europea di malattia rara, prevede un'incidenza minima di 5 nuovi casi l'anno su 10.000.

L'incidenza stimata della SNI in età pediatrica è pari a 16 nuovi casi l'anno su 100.000.

La prevalenza della malattia nell'intera popolazione non è superiore a quella pediatrica. Il Levamisolo, farmaco tuttora utilizzato per la terapia della malattia, è un farmaco cosiddetto "orfano" inserito nell'elenco dei farmaci orfani.

La Sindrome Nefrosica Idiopatica stabilizzata anche con "farmaci orfani" ha generalmente negli anni una buona prognosi, tuttavia è anche ritenuta una delle cause principali dello sviluppo dell'insufficienza renale cronica, soprattutto per quella percentuale di piccoli pazienti che non rispondono alle terapie attualmente a disposizione, vi è inoltre un'alta probabilità di recidiva della malattia post-trapianto e anche nelle sue forme "benigne" lascia degli strascichi di notevole entità, relativamente ai medicinali assunti nel corso dell'infanzia. Al momento non abbiamo notizia (a parte pochi casi) di ricerche di buon livello in Italia, nè altri studi di settore.

L'ASNIT onlus ha in programma (nei propri limiti) di favorire e dove possibile raccogliere fondi per la ricerca e lo studio della SNI.



## FIBRODISPLASIA OSSIFICANTE PROGRESSIVA

Enrico Cristoforetti

*Associazione Fibrodisplasia Ossificante Progressiva (FOP ITALIA), Sabbionara d'Avio (TN), Italia*

La nostra associazione è costituita da genitori e parenti di persone, principalmente bambini, malati di Fibrodisplasia Ossificante Progressiva (FOP). Il nostro intento è quello di dare un aiuto a tutte quelle persone che come noi si trovano ad affrontare questo problema, attraverso lo scambio di informazioni ed esperienze.

Poiché la FOP è una malattia rarissima (1 caso ogni 2.000.000) e di conseguenza quasi sconosciuta, vogliamo suscitare e mantenere l'interesse pubblico sui problemi dei soggetti affetti da FOP promuovendo e sostenendo la ricerca scientifica, attraverso la raccolta di fondi da destinare alla stessa.

Per una persona colpita da FOP è estremamente importante poter parlare con qualcuno che capisca le difficoltà che deve affrontare; cerchiamo di porre fine all'isolamento del passato mettendo in contatto tra di loro le persone con la FOP.

Contribuiamo inoltre al miglioramento del patrimonio informativo esistente in Italia circa le necessità e i supporti indispensabili per i malati di FOP e le loro famiglie, in particolare informandoli sulle possibilità di cura, terapie, luoghi di assistenza e primo intervento.

Promuoviamo e favoriamo attraverso incontri, dibattiti, conferenze, manifestazioni il sorgere di gruppi di lavoro, associazioni, progetti scientifici medici per lo studio della F.O.P., sollecitando anche l'emanazione di specifici provvedimenti legislativi.

Che cosa è la FOP? È una rara malattia genetica nella quale dei frammenti di ossa si manifestano nei muscoli, nei tendini, nei legamenti e in altri tessuti connettivi.

I bambini colpiti da FOP hanno un aspetto del tutto normale alla nascita, eccezione fatta per una deformazione congenita dell'alluce (ci sono casi simili che non presentano tale malformazione). Entro i 20 anni, dolenti noduli fibrosi si sviluppano nel collo, nel dorso, e nelle spalle. Questi noduli poi diventano ossa con un processo biochimico chiamato ossificazione eterotopica.

In seguito la FOP progredisce lungo il tronco e gli arti, rimpiazzando i muscoli sani con frammenti di ossa dell'aspetto normale. Questi frammenti o ponti bloccano gravemente la mobilità delle articolazioni. Se si cerca di rimuoverli chirurgicamente si scatena un'ulteriore e ancora più aggressiva ossificazione poiché ogni tipo di trauma quale la chirurgia (e perfino una botta, una caduta, o una puntura intramuscolare) accelerano il decorso della FOP.

Il decorso della FOP è altamente variabile e imprevedibile. In alcune persone, la malattia si sviluppa velocemente, mentre in altri il processo è più graduale. Alcune persone possono passare dei mesi, perfino degli anni, senza subire una crisi di ossificazione; per altre persone il processo di ossificazione non dà tregua. Per tutte le persone, l'ossificazione può avvenire improvvisamente o a seguito di un trauma, colpendo qualsiasi muscolo.

La FOP non solo causa la produzione di osso eccessivo, ma porta alla formazione di un secondo scheletro che avvolge i muscoli. Il paziente si trova rinchiuso in una gabbia di ossa senza possibilità di uscirne.

Si stima che nel mondo vi siano 2.500 persone affette da FOP, ovvero una ogni 2 milioni.

Nonostante la rarità di casi, la ricerca ha fatto importanti scoperte per quello che riguarda le tappe fondamentali della formazione scheletrica.

Finalmente dopo molti anni di dure ricerche, alla *University of Pennsylvania School of Medicine* di Filadelfia, è stato scoperto (maggio 2006) il gene che causa la malattia della

fibrodiplosia ossificante progressiva. La scoperta di questo gene chiave, annunciata sulla rivista *Nature Genetics* da Frederick Kaplan e Eileen Shore, è importante per poter far fronte a questa rarissima quanto devastante malattia che imprigiona il corpo del paziente in un secondo scheletro, ma potrebbe essere utile anche per patologie ossee comuni. Gli esperti hanno lavorato anni su famiglie multigenerazionali sparse in tutto il mondo trovando alla fine il colpevole, il gene per il recettore "Activin Receptor Type IA" ACVR1 sul cromosoma 2.

Questo recettore ha un ruolo chiave nel meccanismo di morfogenesi dell'osso e partecipa dunque al funzionamento del sistema di segnalazione delle cosiddette proteine della morfogenesi ossea. I genetisti hanno scoperto che nei pazienti vi è un piccolissimo difetto del gene, difetto che causa un difetto di funzionamento di ACVR1 che porta alla malattia. Adesso gli esperti stanno lavorando alla creazione di un "topo modificato", ossia un modello sperimentale della malattia per capire cosa succede a livello molecolare per la mutazione del gene ACVR1. Una volta compreso ciò, hanno concluso i genetisti, si potrà pensare a cure per questa devastante malattia. "Il primo risultato - commenta Frederick Kaplan, ricercatore-capo - sarà quello di arrivare a rallentare la formazione 'ribelle' di materiale osseo".

La FOP è molto rara ed ha bisogno urgentemente del riconoscimento da parte del Ministero della salute, oltre alla costituzione di un centro specialistico in Italia sia di diagnosi che di cura.

Si propone un intervento urgente per il riconoscimento della malattia e un supporto organizzativo, logistico e finanziario per "costruire" il centro specialistico sopra accennato presso la struttura dell'Ospedale Gaslini di Genova, che tramite il prof. Ravazzolo e la dott.ssa Di Rocco, ha già dato la propria disponibilità iniziando diagnosi certe sul gene. Inoltre nel marzo 2007 verrà organizzato il primo Seminario, sempre presso il Gaslini, sulla FOP.

Crediamo sia utile provvedere all'istituzione di un fondo, organo o comunque porre un'attenzione particolare a tutte le patologie rare o rarissime come la FOP, organismo che dovrà essere promosso, gestito, tutelato e garantito dal Ministero della Salute Sappiamo bene che esistono altri morbi molto rari, verso i quali bisogna provvedere e prevedere anche in un'ottica di grande solidarietà.

## **DISTROFIA MUSCOLARE DI DUCHENNE E BECKER**

Silvia Starita

*Parent Project onlus, Roma, Italia*

I genitori del Parent Project da 10 anni sono impegnati contro una malattia rara, la Distrofia Muscolare Duchenne (DMD) e Distrofia Muscolare Becker (DMB), contribuendo con tutti i fondi disponibili al finanziamento della ricerca scientifica per trovare una cura. Promuove incontri scientifici con lo scopo di eliminare le interferenze che nascono dalla distanza che separa i protagonisti della ricerca seria e rigorosa dai pazienti ed i loro familiari. Da anni Parent Project è impegnato per ridurre questa distanza e favorire l'interazione tra i ricercatori, i clinici, i terapeuti, pazienti e le famiglie. Questo lavoro continua ancora oggi, nella certezza che da questa interazione tutti traggano beneficio ed i risultati non sono mancati, segno che la strada è quella giusta.

Conosciamo l'impegno personale del Ministro Livia Turco in ambito sociale e condividiamo completamente quanto indicato nelle Linee di Programma presentate alla Commissione Affari Sociali della Camera dei Deputati in particolare per quanto riguarda le malattie rare con l'Istituzione del Comitato Nazionale per il quale vorremmo dare tutta la nostra disponibilità perché, insieme, si riesca a sviluppare politiche assistenziali adeguate alla gravità di tante malattie rare.

Chiediamo sostegno economico da parte del Ministero della Salute e dell'ISS, alla stesura di protocolli di trattamento per la DMD/DMB al quale lavoriamo da anni, che possano essere riconosciuti, divulgati ed applicati nei centri di riferimento per le malattie rare.

## FIBROSI CISTICA

Franco Noli

*PRivata Associazione Nazionale per la Ricerca di Cure Efficaci contro la Mucoviscidosi (PrANaRCEM),  
Roma, Italia*

La Fibrosi Cistica è una malattia ereditaria delle ghiandole esocrine. Questa patologia interessa principalmente la funzionalità delle ghiandole che producono muco. Infatti, queste ghiandole secernono un muco denso e vischioso e quindi poco scorrevole, con conseguente ostruzione dei dotti principali. L'insorgenza di gran parte delle manifestazioni cliniche tipiche della malattia sono correlate a queste ostruzioni: come la comparsa di infezioni polmonari, di insufficienza pancreatica, di cirrosi epatica, ostruzione intestinale ed altro.

In Italia i sinonimi per la Fibrosi Cistica sono:

- fibrosi cistica (0% inv)
- fibrosi cistica del pancreas (100% inv)
- Mucoviscidosi (80%inv)
- mucosi (inesistente)
- fibrosi pancreatica (inesistente)

Le proposte avanzate sono:

- adeguamento della legge 548/93 (on. Fumagalli Carulli) alla realtà odierna;
- riconoscimento della patologia con tutti i suoi sinonimi equipollenti;
- applicazione della normativa esistente ed adeguamento della stessa in linea con il riconoscimento dei diritti socio-sanitari dei singoli e delle rispettive famiglie e dell'essenzialità dell'assistenza domiciliare ed in ambienti sociali (scuola, lavoro, altro) anche utilizzando adeguati collegamenti telematici anche per assicurare la frequenza scolastica ed il lavoro;
- attivazione della tessera sanitaria.
- Miglioramento dell'assistenza sanitaria impiegando idoneo personale ed ambienti adeguati per assicurare assoluta impossibilità di letali infezioni nosocomiali.

Si ritiene opportuno indicare anche la normativa correlata ancora inapplicata:

1. applicazione dei disposti di cui alle modifiche alla disciplina sulle Patologie Rare, originariamente contenuta nel Decreto n. 329/1999 (1 paziente su 10.000 abitanti - vedi n. pazienti nel successivo punto 6;
2. aggiornamento della legge 549/1993 (correlata alla circolare ministeriale attuativa n. 500.4/DM.I-407 del 19 aprile 1994) e, in particolare, l'art. 5 della legge 548/1993, al fine di assicurare, in Italia ed all'Estero, l'assistenza sanitaria non solo domiciliare ma anche in ambienti scolastici, lavorativi in genere oltre che in regime ospedaliero continuativo con possibilità di acquisizione del supporto farmaceutico necessario anche di farmaci classe H (non imponendo la fornitura di dosi che coprono tre mesi di terapia acquisibili (art. 3.1. della L. 548/1993), esclusivamente, presso la USL di Residenza e, esclusivamente, su prescrizione di un Centro Regionale Specializzato!!!);
3. predisposizione del ricovero e, in generale, dell'assistenza sanitaria impegnando personale ed ambienti adeguatamente trattati per impedire assolutamente infezioni nosocomiali;
4. compatibilità tra Tessere Personali (vedi art. 4 della legge 548/93) e attuali Tessere Sanitarie (TS) definendone la validità delle TS in ambiente europeo nonché su tutto il territorio Nazionale anche visti i disposti di cui agli articoli 3 e 4 della L. 548/93 sulla

- Fibrosi Cistica nonché agli art. 4.1., del DMS 329/99 e art. 4.2, delle modifiche al DM n. 329/1999;
5. predisposizione di adeguate indicazioni riguardanti “codice fiscale” e “dati identificativi personali” da impiegare per le TS riferite a feti e/o neonati ed aggiornamento delle eventuali tessere personali o altre sostitutive (in applicazione degli art. 4.1. e 4.2. della L. 548/1993);
  6. controllo sull’impiego del finanziamento (art. 10, L. 548/1993) oggi aggiornato con l’art. 3.1 della legge 362/99 [lire 8.500.000.000 a decorrere dall’anno 1999] assegnati, su firma del Presidente Delegato Tremonti, con quote sotto indicate riferite agli anni 1999-2003 [n. pazienti/Importo assegnato/Riferimento Periodo]: N. 3364 / € 57.612.615 /1999-2000 -//- n. 3274 / € 52.956.181 /2001-2002 -//- n. 3274 / € 52.956.181 /2002-2003;
  7. avvio, inderogabile, di adeguate indagini a tappeto su tutta la popolazione italiana al fine di individuare possibili portatori sani e definizione delle espressioni patologiche riscontrate;
  8. informazione adeguata anche i malati e alle rispettive famiglie sui risultati della ricerca sui farmaci nonché sulla disponibilità degli tessi nonché sulle problematiche correlate al trapianto d’organi;
  9. verifica dell’attuazione dei disposizioni del DM del Ministero della Sanità - 8 giugno 2001 (GU 5/7/01 n. 154);
  10. disposizione dell’applicazione dei contenuti dell’ICF-OMS (presentate al Ministro Sirchia nell’Aprile del 2002 a Trieste e ad altri 191 Partecipanti internazionali), anche ai pazienti affetti da problematiche anatomiche, tra cui quelle determinate dalla fibrosi cistica; a questo proposito, sarebbe anche assolutamente opportuno che venisse adottato l’ICF “International Classification of Funtioning, Disability and Health” dell’O.M.S., presentata a Trieste, nell’Aprile del 2002 davanti al Ministro Sirchia ed a 191 Paesi in cui, come punto focale, vengono inglobate nella sfera delle menomazioni anatomiche e corporali (e non più solo quelle della disabilità afferenti esclusivamente ai sistemi corporali);
  11. salvaguardia del diritto all’istruzione ed al lavoro anche nel rispetto delle limitazioni determinate dai frequenti e prolungati tempi di ingravescenza della patologia (febbre, terapia, altro);
  12. applicazione punto 1.1.3.: Esenzioni - 1.1.3.1.a) dell’ADR (trasporto di ossigeno “per uso proprio” su veicoli da trasporto - Direttiva 2001/7/CE della Commissione del 29 gennaio 2001) che riporta: “Esenzioni relative alla natura dell’operazione di trasporto. Le disposizioni dell’ADR (acquisito dall’Italia con la Direttiva 2001/CE della Commissione delle Comunità Europee firmato a Bruxelles il 29 gennaio 2001) non si applicano ai trasporti di merci pericolose effettuati da privati quando queste merci sono destinate al loro uso personale o domestico o alle 100 attività ricreative o sportive” adeguando, il Nuovo Codice della Strada, la Nuova legge 104 e quanto altro.

## SINDROME DEL VOMITO CICLICO

Denys Figliuolo

*Associazione Italiana Sindrome del Vomito Ciclico, Calenzano (FI), Italia*

La sindrome del vomito ciclico è una malattia rara che provoca un'intensa sofferenza causata da attacchi prolungati e violentissimi di vomito che durano da dodici ore fino a cinque giorni, nausea ed una serie di altri sintomi, tutti accompagnati da continue sincopi vasovagali che fanno precipitare il paziente in uno stato definito "coma cosciente".

Gli attacchi si ripetono nella migliore delle ipotesi ogni mese ed il numero di conati di vomito può variare da centoventi a quattrocento in soli due giorni.

La sindrome del vomito ciclico colpisce principalmente in età prescolare iniziando talvolta nei primi mesi di vita.

La sua violenza incontenibile e le modalità di presentazione, mettono a rischio della vita il paziente ogni volta che l'attacco si manifesta.

La nostra associazione è la prima e unica in Italia ad occuparsi della sindrome del vomito ciclico e, in collaborazione con la CVSA-UK (unica ed altra associazione su questa malattia in Europa), stiamo redigendo un primo censimento dei casi conosciuti nel nostro continente.

## IL SERVIZIO SANITARIO NAZIONALE ITALIANO E LE MALATTIE RARE

Renza Barbon Galluppi

*UNIAMO Federazione Italiana Malattie Rare Onlus, Venezia, Italia*

Federazione Italiana Malattie Rare – onlus (“UNIAMO” FIMR) conta al suo interno circa 50 associazioni di pazienti affetti da Malattie Rare (MR). Nonostante le diverse patologie rappresentate, sin dalla sua fondazione (1999) si sono riscontrate le molte problematiche comuni a tutte le associazioni federate: la quasi totale mancanza di fondi per la relativa ricerca, i percorsi diagnostici estremamente lunghi, la scarsa presenza in Italia di esperti su patologie più rare di altre, la difficoltà o addirittura l'impossibilità di reperire i farmaci utili, lo stato di totale abbandono in cui versano le famiglie interessate, il vuoto legislativo sull'argomento. La Federazione si è sempre impegnata a livello istituzionale per promuovere azioni in difesa dei Malati Rari, ricerca, informazione e formazione sulle problematiche in cui sono coinvolti. Gli obiettivi già raggiunti sono:

- la promozione del DDL 1388 “Incentivi alla ricerca e accesso alle terapie nel settore delle malattie rare” nella precedente legislatura;
- l'applicazione dell'art. 9 del Regolamento CE n. 141/2000 del 16/12/1999;
- la partecipazione come membro della Commissione Ministeriale relativa al DM 06/06/03 nel biennio 2002-2003;
- la promozione dell'emendamento “Provvedimenti a favore dei pazienti affetti da MR” della Finanziaria 2004 e in quella 2005;
- la promozione del libro “Malattie Rare – Associazioni in Italia” prodotto da Orphanet Italia e Farminindustria e dell' “Annuario delle MR” (2005).

Oggi la Federazione sostiene la necessità di un cambio di ruoli nel rapporto medico-paziente: non più medico esperto e paziente passivo, ma una vera e propria alleanza tra le due parti, collaborativa, bidirezionale, dinamica e con un approccio diretto alla persona.

È impegnata per un'efficace co-progettazione delle Politiche Locali con lo sviluppo della cultura della “presa in carico” del progetto globale di vita dei singoli - ai sensi della L 162/1998 e dell'art. 14 L 328/1999 (Livelli Essenziali di Assistenza, Piani di Zona e progetti individuali).

Più specificatamente sull'attuazione di politiche inclusive e di interventi coordinati e continuativi, capaci di valorizzare le attitudini e le abilità delle persone per il conseguimento di una pari opportunità di condizioni tra i cittadini, eliminando le discriminazioni sociali e culturali, le limitazioni e gli ostacoli alla fruizione dei diritti, consapevole che nello specifico delle malattie rare è richiesta un'assistenza continuativa e specialistica di tale complessità ed intensità, che non può essere sostenuta solo dalla famiglia ed è pertanto essenziale un importante intervento pubblico, non tralasciando quelle prestazioni socio-sanitarie atte a soddisfare, mediante i percorsi assistenziali integrati, azioni di cura e riabilitazione nonché una tempestiva diagnosi, e una giusta individuazione dell'eventuale invalidità.

Tra i principali progetti nazionali sui quali UNIAMO FIMR è attualmente impegnata:

- Progetto “Insieme”

Il Progetto presentato da UNIAMO in sede ministeriale, è già passato alla prima revisione del Ministero del Welfare: si tratta della possibilità di attivare un protocollo comune fra associazioni federate, per contatti transittivi tra pazienti affetti dalle stesse patologie.

– Progetto “Pollicino”

Presentato da UNIAMO in sede ministeriale, è già passato alla prima revisione del Ministero del Welfare, si propone di istituire una banca dati dove possano emergere tutte le difficoltà dei pazienti affetti da malattie rare nella totalità dei loro percorsi assistenziali.

UNIAMO FIMR è anche impegnata in progetti europei grazie alla sua caratteristica di alleanza nazionale di associazioni di pazienti affetti da patologia rara.



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