



**Ministère des Solidarités,
de la Santé et de la Famille**

Labelled reference centres : a key action of the rare diseases french action plan 2005-2008

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Context

- **Care management** of rare diseases is one of the **5 national strategic plans** selected in the **public health law adopted** in France in August 2004
- **Objective N°90** of the joined report : « To ensure equal access to diagnosis, treatment and quality of care »
- Project managed by the **Ministry of Health** including: patients' organisations, professionals and scientific representatives, national and private health insurances, and research ministry.....

The current situation in France (1)

- **A lack of knowledge and information** of professionals and patients responsible for inaccurate diagnoses
- **No global strategy of health care** for rare diseases: clinical pathways linked to **individual choice** rather than **planned specific pathways**
- **Differences** in the reimbursement, compensation and **access to medical products.**

The current situation in France (2)

- Lack of **epidemiological surveillance** of these diseases,
- Ongoing inventory of current **research projects** (Scientific Interest Group, Pr A. Fischer),
- Lack of adaptation between **therapeutical innovations** and their **funding** (Hospital Funding Reform)

Works in progress (1)

- **Emergence of an orphan drugs mission in 1995**
 - The EU Orphan Drugs Regulation (reglementation rule on orphan drugs),
 - Initiatives for research programs,
 - Development of the ORPHANET database
- **French Ministry of Health initiatives**
 - Support for ORPHANET,
 - Rare disease information phone services,
 - Internet website for professionals, patients and large audience.....

Works in progress (2)

- For **research support**:
 - Hospital clinical research funding programs 2002, 2003 and 2004
- To improve **diagnosis and treatment access** :
 - Competency and resources centres :
 - for Cystic Fibrosis : 45 centres
 - for ALS :17 centres
 - Call for proposals for molecular genetics laboratories, May 2003

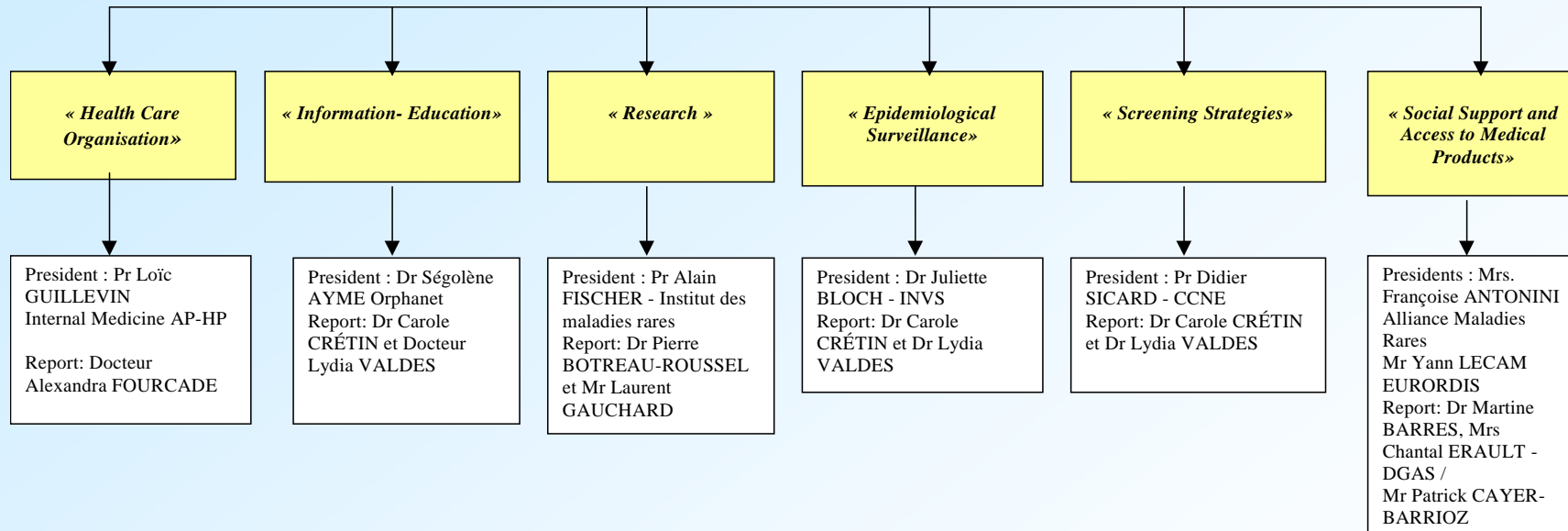
Strategic axis of the action plan

- **Health care organisation** (Pr Guillevin, hôpital Cochin, Paris)
- **Information- Education** (Dr S. AYME, Orphanet)
- **Research** (Pr A.Fischer, GIS-Institut des maladies rares)
- **Epidemiological Surveillance** (Dr J. Bloch, INVS)
- **Screening strategies** (Pr D. Sicard, National Committee of Ethics)
- **Social and psychological support and access to medical products** (Alliance Maladies Rares, Eurordis)

THE RARE DISEASES FRENCH ACTION PLAN

Orientation Committee

President : Ministry of Health (Health Care Organisation Direction)
Report : Dr Alexandra Fourcade



Time table

- **March 2004: First meeting of the Orientation Committee**
- **April-June 2004: Working groups**
- **June 2004 : 2nd Meeting of the Orientation Committee (selection of the main goals and actions)**
- **June-September 2004: Write up of the plan**
- **15 September : last meeting of the Orientation Committee**
- **End of September : presentation of the plan to the Minister of Health**
- **20th of November : launch of the Action Plan, press conference with all stakeholders, hôpital Necker, Paris.**

10 strategic axes 2005-2008 (1)

- **Develop epidemiological issues**
- **Acknowledge the specificity of rare diseases (registration on the list of long-term affections « ALD »)**
- **Improve patients, public and professionals information**
- **Improve education of health care professionals**
- **Organise screening and access to diagnostic tests**

10 strategic axes 2005-2008 (2)

- **Improve access to health care system and quality of care**
- **Keep up with the efforts for the development of Orphan Medicinal Products**
- **Answer specific patient's needs within the handicap reform**
- **Improve dynamic research and innovation**
- **Improve development of national and european partnerships**

Plan funding (1)

Priority 1

Develop epidemiological issues

2 million €

Priority 2

Acknowledge the specificity of rare diseases

Priority 3

Improve patients, public and professionals information

3.2 million €

Priority 4

Improve education of health care professionals

0.4 million €

Priority 5

Organise screening and access to diagnostic tests

20 million €

Plan funding (2)

Priority 6

Improve access to health care system and quality of care

30 million €

Priority 7

Keep up with the efforts for the development of Orphan Medicinal products

22.5 million €

Priority 8

Answer specific needs of rare diseases patients in the handicap reform

0.6 million €

Priority 9

Improve dynamic research and innovation

20 million €

Priority 10

Improve development of national and european partnerships

0.16 million €

Total

Rare Disease Task Force, European Centres of Reference, Friday 3 June

98.86 million € 13

Focus on the Health Care Action Plan

- Organise health care around a few « **labelled reference centres** » :
 - **Leading centres** of a professional care **network**, including sanitary and social support,
 - **Leading centres for scientific expertise** (clinical research, evidence-based medicine....)
- **18 groups of rare diseases** selected by an expert committee,
- **90 to 100 « accredited centres of reference »** by the end of the plan.

The label criteria

- **Expert center for one rare disease or a group of rare diseases,**
- **Subnational, national or european level.**

Missions

- **Second opinion** to establish or confirm diagnosis,
- Production and circulation of **clinical and organisational guidelines**,
- **Information and education** of health professionals, patients and their family,
- **Research and epidemiological surveillance**,
- **Coordination** of sanitary and social networks.

Evaluation criteria (1)

- **Activity** (number of patients)
- **Organisation of the medical management process**
 - **Multidisciplinarity**, expertise.
 - **Prescription** and follow-up of **high cost orphan medicinal Products**.
 - **Technological platform** (highly specialised biological tests, molecular biology)
 - **Network coordination**
 - **Information/training** (patients, health professionals, networks.....)

Evaluation criteria (2)

- **Research:**
 - publications
 - funded clinical and research projects
- **Production of good practice guidelines**
- **Epidemiological surveillance, development of relevant health indicators.**

The Label National Committee

- **Missions :**
 - criteria evaluation,
 - advice on the opportunity about setting a labelled center,
 - advice on the financial requirements,
 - evaluation of the centres.
- **Composition :**
 - experts, patients' organisations and representatives of Health Ministry,
 - designated for five years.

Steps for the selection procedure

- **Call for proposals** to the university hospitals (28):
May 2004
- **3 steps for selection:**
 - **6- 20 September** : 1st selection on administrative criteria (217 submitted applications)
 - respect of the tender,
 - regional advice,
 - fulfilled application > **89 selected applications**
 - **20th September-20 October**: external evaluation (expert/administrative) : « **Respect of the criteria** »

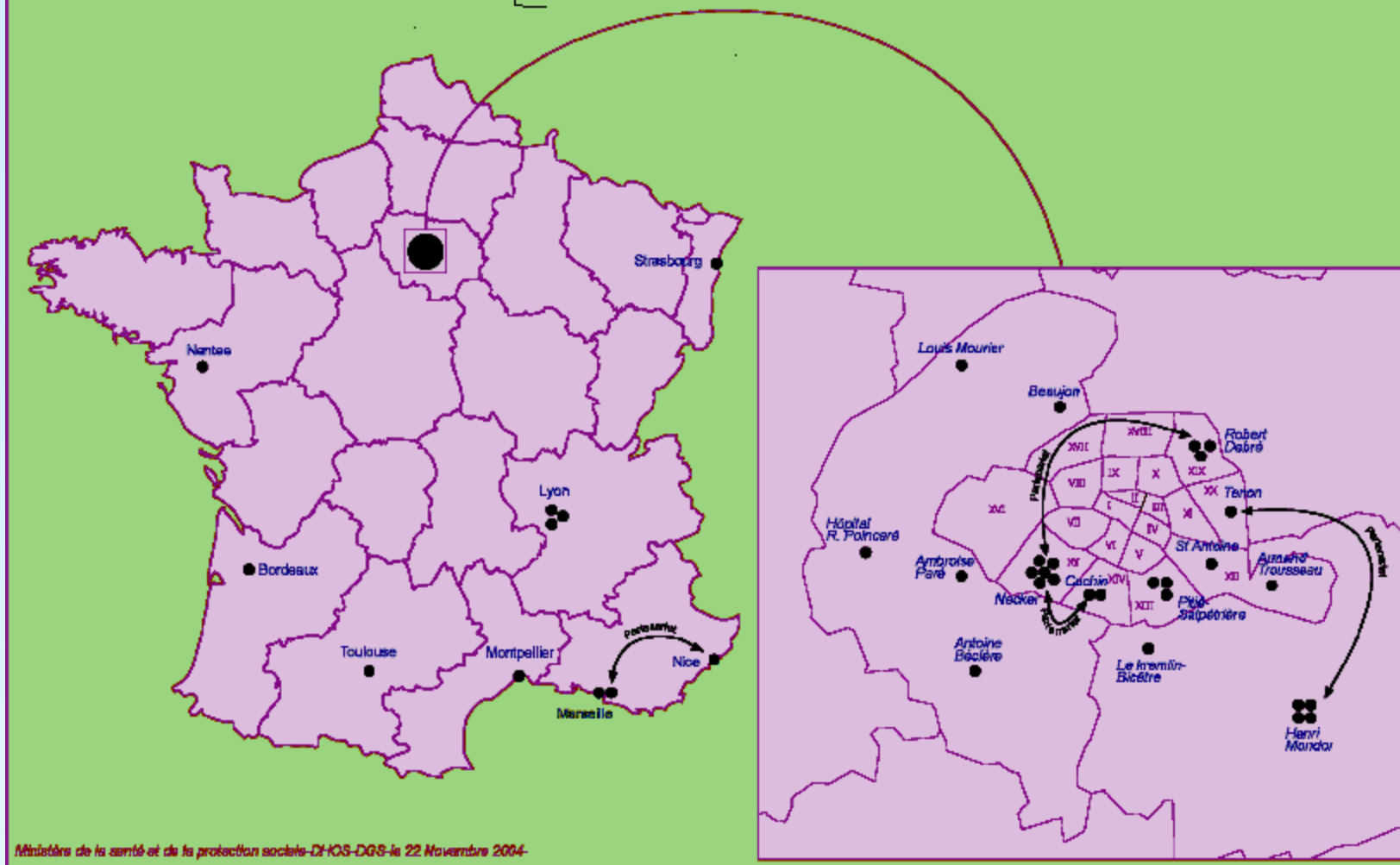
Step 3: Advisory Committee

- **Label opportunity** towards criteria of :
 - medical and scientific excellence,
 - balance between scientific expertise and clinical patient care,
 - relationship between the centre and its network partners,
 - relationship with patients' organisations
- **30 selected centres submitted to the Health Minister**
- Final decision : **34 centres.**

Mapping of the centres accredited in 2004

- No geographical criteria
- **Rare diseases selected**
 - one extremely rare disease: Ondine's syndrome (1 labelled national reference centre)
 - or neuromuscular diseases: 2 centres labelled in 2004. About 10 by the end of the plan.

Centres of reference for rare disease management situated at university hospitals (CHU), which were accredited in 2004



Challenges for 2005

- **Coordinate** existing rare disease networks (ALS, Cystic Fibrosis, etc.),
- Implement **clinical pathway** between labelled centres and other health care organisations,
- Promote **sub-national organisation** of labelled centres.

Conclusion

- **Rare disease labelled centres :**
 - an opportunity to implement a **clinical pathway** for patients and their family,
 - the primary place for **definition and production of clinical and organisational guidelines,**
 - a place for the **initial prescription** of orphan drugs,
 - an **expert network on rare diseases** to advise the national health insurance system in France.

Italian Network for Rare Diseases : legislation and organization

Domenica Taruscio

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<http://www.cnmr.iss.it>

**National Centre Rare Diseases
Istituto Superiore di Sanità
Italy**

RARE DISEASES : PUBLIC HEALTH INITIATIVES

Europe

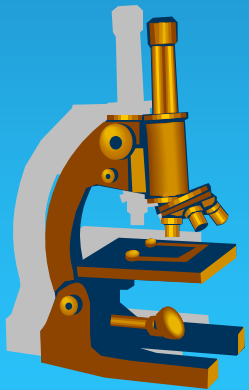
Italy



REGULATIONS ON RARE DISEASES IN ITALY



- 2 National Health Plans '98-00; 2003-05
- Regional Health Plans
- National Network for Rare Diseases (2001-)
- Agreement between the Ministry of Health and Regions (2002-)
- National Committee on RD
- Research Projects for RD
- Research Plans for Orphan Drugs (AIFA)



Italian National Health Plans 1998-2000; 2003-2005

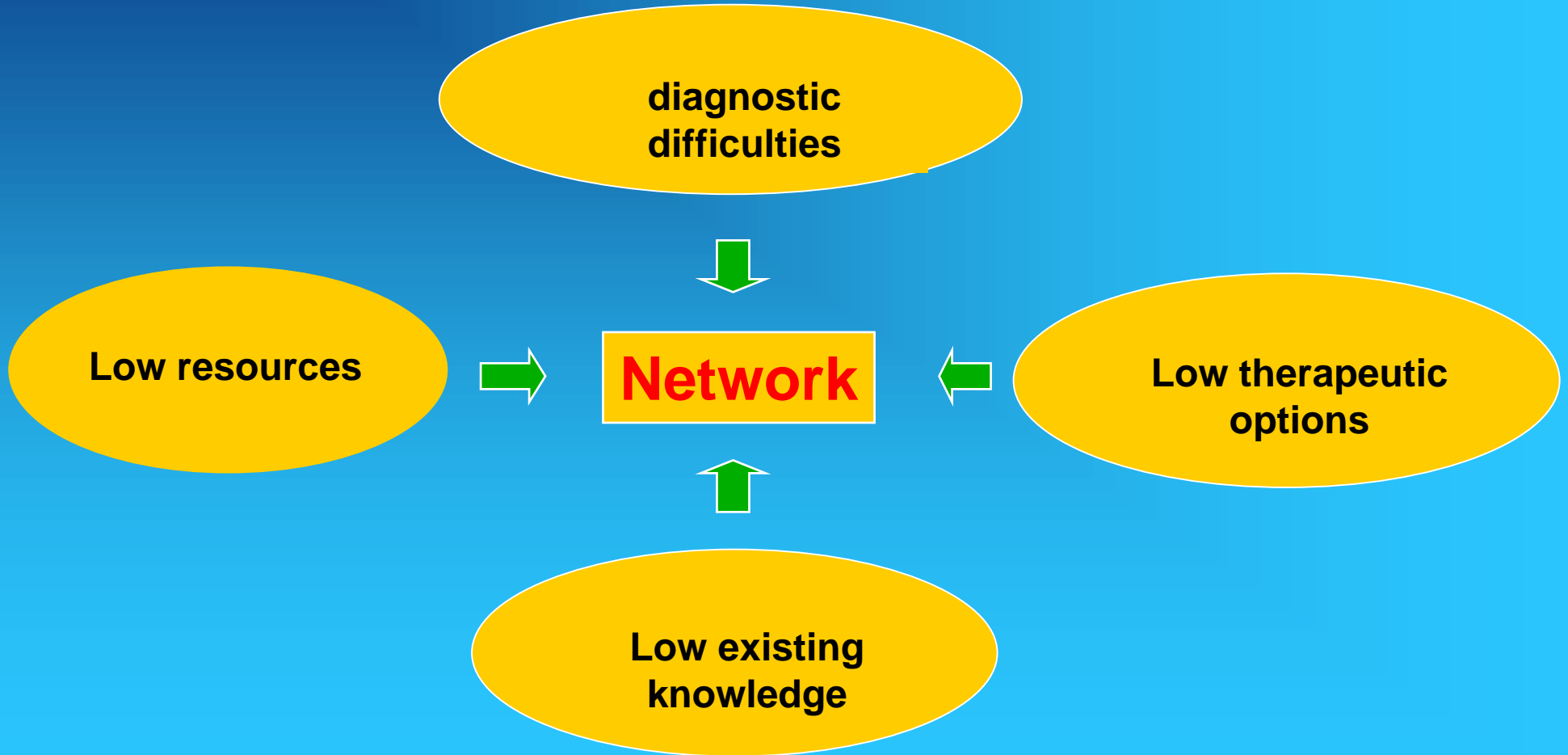
National Health Plans

underline the importance of:

- scientific research on rare diseases
- prevention activities
- appropriate and timely diagnosis
- treatment for patients with RD

TO IMPROVE COLLABORATION

FOR RARE DISEASES...



NATIONAL NETWORK FOR RARE DISEASES **(Governmental Decree 279/2001)**

It's a network for

**Prevention
Surveillance
Diagnosis
Treatment**

**National Registry Rare Diseases
(Istituto Superiore di Sanità)**

**about 500 Rare Diseases (284 specific RD+ 47 groups of RD):
health care services are provided at no charge to patients**

Rare diseases: criteria

- *rarity* - prevalence according to UE definition (<5 /10.000 inhabitants)
- *clinical seriousness of the RD*
- *degree of disability*
- *cost of treatment*

NATIONAL NETWORK FOR RARE DISEASES

set up in order to :

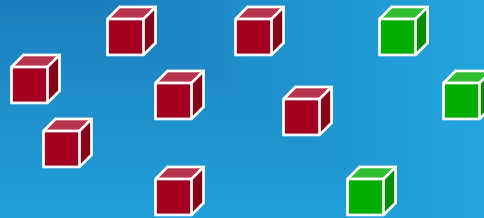
- **Implement prevention activities**
- **Develop epidemiological surveillance**
- **Implement both diagnosis and care intervention**
- **Improve health operators training**
- **Promote citizens information**

Network for health services and epidemiological flow

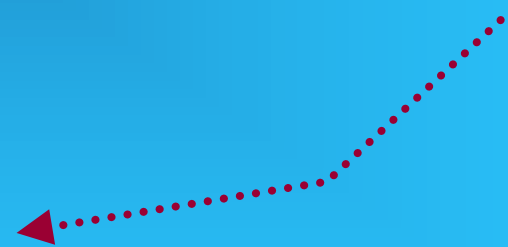
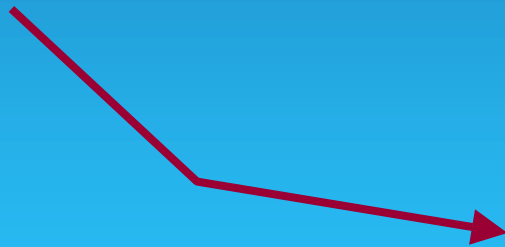
REGIONS



Regional Centre



Inter-regional
Coordination
Centre



National registry of rare diseases
Istituto Superiore di Sanità (Rome)

NATIONAL NETWORK FOR RARE DISEASES



National Registry of Rare Diseases

General objectives

- A) National and regional health planning**
- B) Surveillance of rare diseases**

NATIONAL REGISTRY OF RARE DISEASES

Specific objectives

To estimate incidence or/and prevalence

To define standartized diagnostic and therapeutic protocols

To improve collaboration among health care operators

Italian Regions (brown) which have identified Centres for diagnosis and treatment of rare diseases

Presidi individuati da Delibera di Giunta Regionale, ufficialmente comunicati dalle Regioni al Ministero della Salute e all'Istituto Superiore di Sanità (D.M.18 maggio 2001 n. 279)



CRITERIA

adopted by Regions to select Centres

- General settlement by the Decree (279/2001): documented specific experience in diagnostic or therapeutic activities and required health care facilities
- more specific: scientific publications /impact factor, collaboration with local health services, consulting to GPs, easy access to services
- uniform coverage of the territory

Who performed the selection ?

In most cases:

- *Ad hoc* Technical Organism (Technical-Scientific Committee)
- National Agencies for Regional Health Care Services (ARS/ARES)

HOW REGIONS PERFORMED THE SELECTION ?

- Every hospital declared its own experience by answering to a questionnaire.
- Regions verify the structures competences by processing activities data and analyzing the admission rates to the hospital care services.

ITALIAN REGIONAL NETWORKS FOR RARE DISEASES

Structures are selected according to their competences in :

- ❖ Both Health care and Diagnostic services
- ❖ Health care services mainly
- ❖ Exclusively diagnostic services
- ❖ Every single RD or groups of RDs
- ❖ All RDs or great categories

ACTIVITIES OF REGIONAL HOSPITALS / CENTRES

according Article 2 (Decree 279 / 2001):

- Behave in accordance with clinical protocols drawn up by Interregional / National Reference Centres**
- Collaborate with GPs and territorial health care/social Services**

ACTIVITIES OF INTERREGIONAL REFERENCES

CENTRES :

- **Maintaining local epidemiological registers and send the epidemiological flow to the National Registry of RD**
- **Sharing information with other Reference Centres and with international organisms**
- **Co-ordinating regional hospitals by means of clinical protocols, guidelines, etc.**
- **Supporting and guiding GPs and NHS physicians**
- **Training activities directed to health operators**
- **Providing information to patients'Associations**

Italian Constitution

Law N. 3 (Official Journal-G.U. N. 248, 24.10.2001 2001):

Health Care is matter on which Central Government and Regions share their competences:

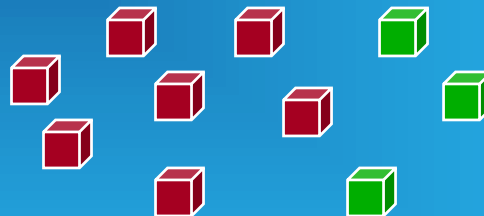
- Central Government states the main guiding principles by law;
- Regions define how health care services are delivered (number of services, number of health operators, etc.)
- Essential Health Care levels (LEA) are established by Central Government by laws and Regions are expected to comply with them.

Network for health services and epidemiological flow

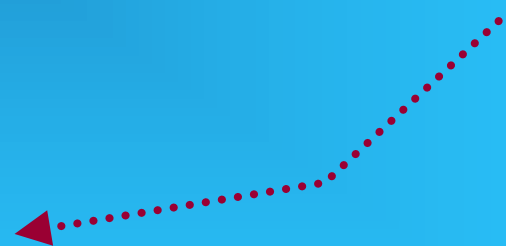
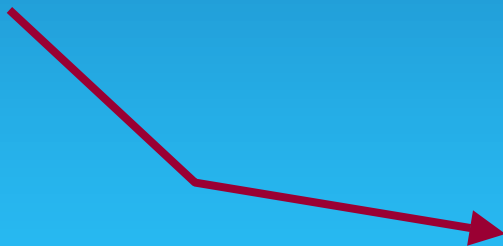
REGIONS



Regional Centre



Inter-regional
Coordination
Centre



National registry of rare diseases
Istituto Superiore di Sanità

Agreement between the Ministry of Health, Istituto Superiore di Sanità and all Regions (July 11, 2002)

- ✓ To co-ordinate the regional network activities
- ✓ To perform clinical protocols and guidelines
- ✓ To develop epidemiological surveillance
- ✓ To disseminate information on RD
- ✓ To collaborate with volunteers and non-government associations

CRITICAL ASPECTS

- The Network is not complete (three Regions are still working)
- Criteria used by Regions to identify Centres are not homogeneous (e.g. documented experience in diagnostic or therapeutic activities; number of patients; required health care facilities)
- Each Region has adopted a different model to organize the regional network, therefore there are differences in the management of RD patients.
- The interregional referral centers have been not identified yet.
- Epidemiological flow is not mandatory.

RESEARCH

**NATIONAL
REGISTRY
RARE DIS.**

**NETWORK
PEDIATRICS**

**E. Q. A.
GENETIC
TESTS**

**PATIENTS
ASSOCIATIONS**

NATIONAL CENTRE RARE DISEASES
<http://www.cnmr.iss.it>

ISTITUTO SUPERIORE DI SANITA'

INFORMATION

**ORPHAN
DRUGS-
EMEA**

**MEETINGS
COURSES**

NEPHIRD



RDTF meeting 3 June 2005

Notes on the English 'NSCAG' system for rare disorders

1. The national system in England for planning and organising specialised services for very rare disease is known as NSCAG (National specialist commissioning advisory group).
2. Services for a set of about 32 diseases or treatments are specially funded and monitored ('commissioned'). There is no global category of 'rare disease'. Each case is considered separately. The full list and further details are at:
<http://www.advisorybodies.doh.gov.uk/NSCAG/>

Criteria

3. Diseases with a prevalence of 1 per 50,000 or fewer are considered eligible. The national caseload for these diseases can probably be provided in 5 hospitals or fewer in England – hence the need for planning at national level. Note that this is much rarer than the prevalence limit for 'orphan drugs'.

4. Examples include

- the major organ transplants (heart, liver, lung and pancreas),
- very rare cancers such as chorioncarcinoma and retinoblastoma,
- genetic diseases such as severe combined immune deficiency
- and the extremely severe end of some more common problems such as intestinal failure and craniofacial anomaly.

Process

5. The practical steps we go through when we designate a service are as follows:

- a. Consultation – with the medical profession and with patient groups
- b. develop service standards – mostly structure (e.g. staffing) and process (e.g. response times)
- c. designation
- d. funding
- e. monitoring.

6. We use five basic sets of quality monitoring for our national services:

- Patient outcomes (e.g. survival);
- Benchmarks (from the literature);
- International peer review visits;
- Patient satisfaction surveys;

And because we have centralised the service geographically:

- Mapping of access rates from remote areas.

Problems and lessons

7. It is essential to specify the service with absolute clarity. 'Chorioncarcinoma' or 'severe combined immune deficiency' are completely clear cut. You've either got it or you haven't; and if you have got every clinician in England knows to refer the patient to the national centres. But categories such as 'intestinal failure' and 'craniofacial anomaly' are ambiguous. In their severest forms, these disorders are extremely difficult to treat and need the highest level of expertise combined with enormous experience. But where to draw the line between patients who should be referred to an expert centre and patients who can be treated locally?

8. For some services, particularly chronic disorders such as epidermolysis bullosa, we have not been able to agree outcome measures. It is good to ask clinicians very early in the process to specify how their expertise will benefit patient outcomes. Improvement in biomarkers or laboratory tests is not enough!

9. We also find it very difficult to obtain comparative data from the literature. We monitor outcomes on all patients seen i.e. a consecutive annual series of 100% of the caseload. (For some categories risk adjustment is needed. For others the patient group is homogeneous enough to allow monitoring of the entire group.) Literature reports typically provide only partial and selective reporting.



Instituto
de Salud
Carlos III

**Rare Diseases Task Force
Working Group on
Standards of Care
Meeting on European Centres of
Reference**

Paris, 3 June



Manuel Posada de la Paz
Coordinator

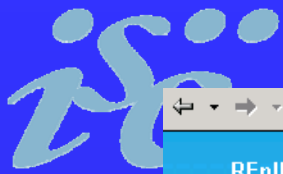
**REpIER (Rare Diseases
Epidemiological Research Network)**



Actions on Rare Diseases

- **Period 1999-2003**
 - Projects FIS (National Agency Health Research)
 - RETICS
 - Special Needs on Rare Diseases (IMSERSO)
 - CISAT-CISATER
 - CISATER-IIER
 - European Projects
- **Period 2004-2010**
 - National Rare Diseases Center (IMSERSO)
 - Research Networks
 - New perspectives on Rare Diseases





REpIER informa:

participantes para encontrar posibles vías de colaboración futuras en este ámbito.

Creación de un sistema de información de E.R. en Extremadura

La Junta de Extremadura acaba de publicar la orden por la que se regula la creación del registro de Enfermedades Raras. Esta

Enlaces

Sólo Miembros de la Red

REpIER

English Version

INFORMACIÓN

- Presentación
- Participantes
- Grupos de Trabajo
- Equipos Monográficos
- Actividades Científicas
- Código Buenas Prácticas REpIER
- Programa de Formación

RESULTADOS

- Lista de Enfermedades Raras
- Información Epidemiológica
- Registros
- Anomalías Congénitas
- GITER
- Tumores Malignos Raros
- Banco de Muestras

INERGEN

Red de estudio cooperativo en Retraso Mental de Origen Genético

R



Other Rare Diseases Research Networks

- **Mastocytosis (G03/007).**
- **Mitochondria diseases (G03/011).**
- **Retina Inherited Dystrophies (G03/018)**
- **Athaxia (G03/056).**
- **Fanconi Anaemia (G03/073).**
- **Congenital Deafness (G03/203).**
- **Genetic Research on Rare Psychiatric Diseases**

Consejería de Salud

APROXIMACION A LA SITUACION DE LAS ENFERMEDADES RARAS EN ANDALUCIA



**Red Epidemiológica
de Investigación de
Enfermedades Raras**



Reference Centres Policy

- **17 Health Care Systems**
- **17 Public Health Systems**
- **National Coordination (Special Law, 2004).**
 - MoH
 - Intersectorally Committee.
- **Specific budget**
- **Specialized units, centres and labs**
- **Designation (under discussions of procedures, diseases, costs, methods, etc)**



Red Epidemiológica de Investigación en Enfermedades Raras REPIER (G03/123)

Instituto de Investigación de Enfermedades Raras de Base Genética INERGEN (C03/05)



Red de Centros de Genética Clínica, Molecular RECGEN (C03/07)



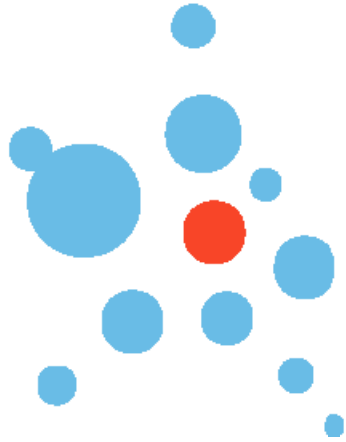
•Red de enfermedades metabólicas hereditarias REDEMETH (G03/054).



RETIC

•Red para el estudio cooperativo en retraso mental de origen genético GINMORGEN (G03/098).





Rare Disorders Denmark

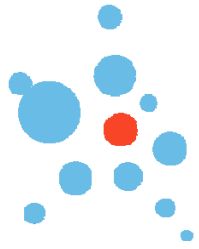
Centres of reference in Denmark

By

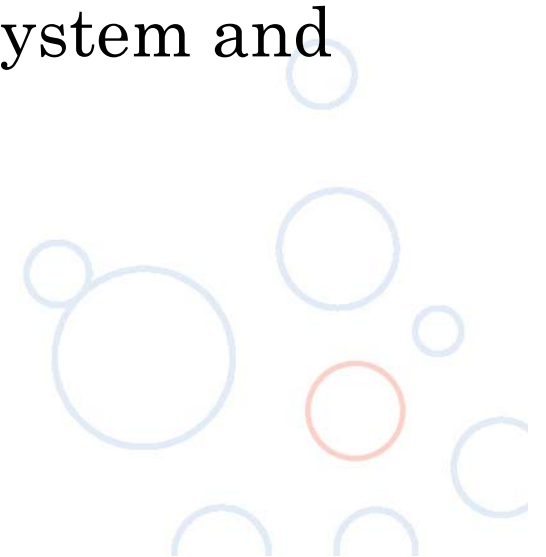
Dorthe Lysgaard

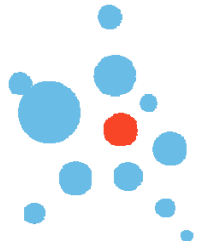
Chief Executive Officer

Rare Disorders Denmark
Frederiksholms Kanal 2, 3.
DK-1220 Copenhagen K



1. Introduction
2. History
3. Recommendations from the Danish National Board of Health
4. Facts on the Danish health care system and rare diseases in Denmark
5. What are the main issues today





History

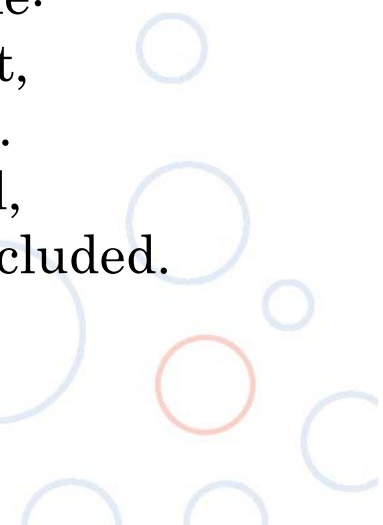
1994-1996:

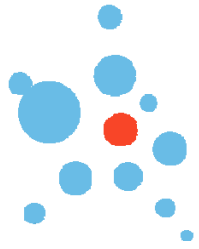
11 working groups were set up to establish state-of-the art treatment programs for 11 specific diseases to work as model programs

The state-of-the-art/reference programs include:

Best practice on diagnostics, treatment, monitoring, knowledge gathering and coordination.

Important: descriptions of social, psychological, educational and occupational problems also included.





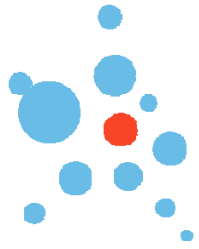
History (contd.)

1997:

Working group set up by the National Board of Health

Mandate: To make recommendations on the future organisation of diagnostics and treatment of rare diseases.



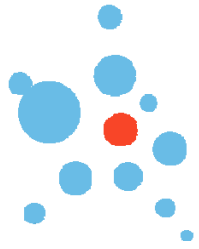


Recommendations

from the Danish National Board of Health

The report recommends

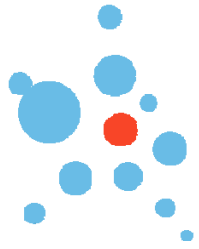
- that two centres for rare diseases are established: one in East Denmark and one in West Denmark
- that state-of-the art/reference programs are developed for the individual rare diseases or groups of rare diseases
- The following distribution of responsibility between centres of reference and regional/local hospitals:



Regional hospitals

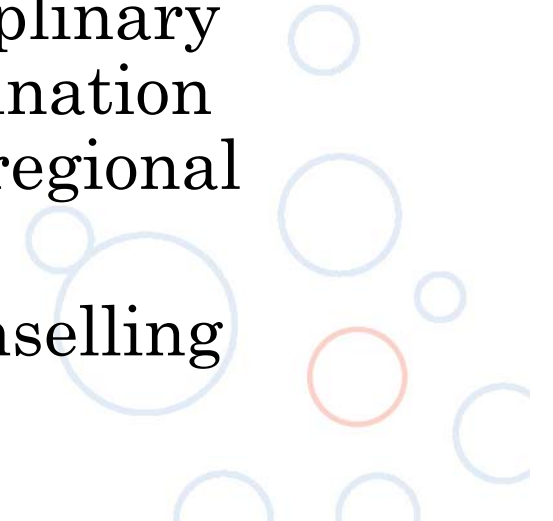
- Primary contact, preliminary diagnostics, referral to centre of reference
- Monitoring the patients (especially children) as far as the general growing up is concerned, including contact to the local social and educational authorities
- Carrying out the regular check-ups
- Acute problems
- Contact to the family GP

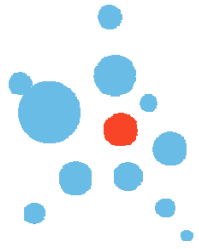




Centres of reference

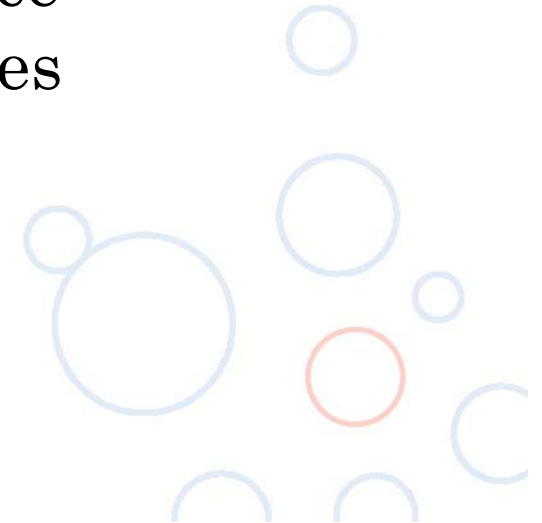
- Specialised diagnostics, treatment and monitoring
- Overall planning and monitoring of the patients treatment
- Coordination of the action taken by the various specialities in a multidisciplinary team function as well as the coordination between the central level and the regional level
- Counselling including genetic counselling

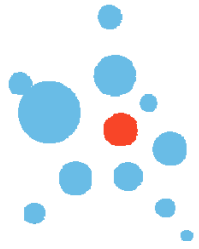




Centres of reference (contd.)

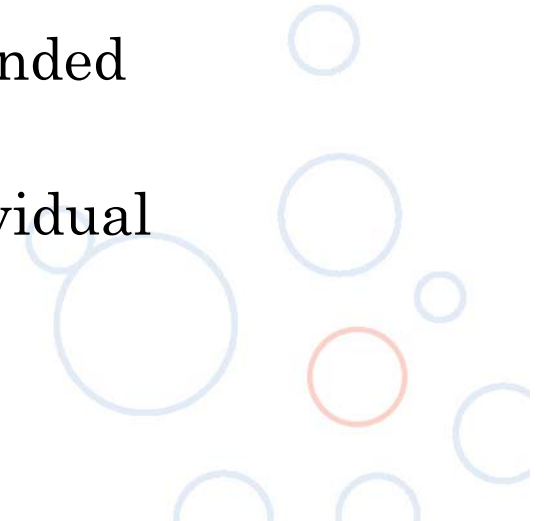
- Collection, registration and dissemination of knowledge on diagnostics and treatment
- Research and development, quality development, training
- Responsible for developing reference programs for the remaining diseases
- International cooperation

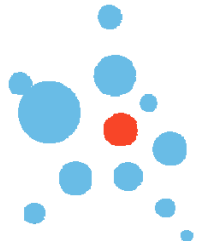




Important recommendations

- The responsibility for the overall treatment (diagnostics, treatment, contents and timing of check-ups etc.) should be clear and
- the responsibility for the *coordination* of the overall treatment of the individual patient should also be clear
- Agreements on cooperation are recommended between the central and regional level
- Action plans to be developed for the individual patients

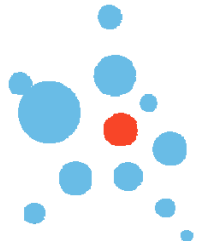




Facts on the Danish Health Care system and rare diseases in Denmark

- The total population of Denmark is 5 million people
- Health care in Denmark is free and financed through state and regional taxation
- All hospital services are run and totally financed by the 15 regional counties
- Denmark has 3 university hospitals
- Denmark has an estimated number of 25.000 patients with rare diseases
- Rare Disorders Denmark is an umbrella for 30 rare disease organisations



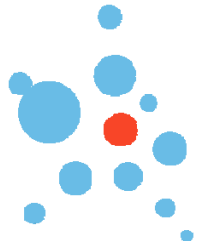


The situation today

Denmark has two centres of reference

- Center for rare diseases in Aarhus University Hospital
- The Clinic for rare disorders at the Copenhagen University Hospital

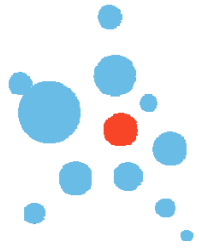




Center for rare diseases Aarhus University Hospital

- Part of the paediatric department
- 2 medical specialists, one nurse and 2 secretaries
- work based on disease specific or organ specific teams which include doctors from many other specialities
- 100 different diagnoses





Rare Disorders Denmark

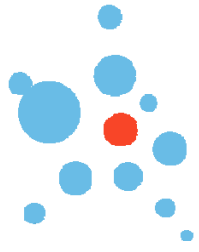
Centres of reference in Denmark

The Clinic for rare disorders Copenhagen University Hospital

- Part of the department for clinical genetics
- 2 medical specialists and 2 nurses
- 100 different diagnoses

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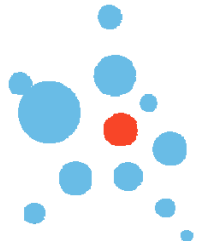




What are the main issues today?

In 2003 Rare Disorders Denmark carried out a survey among 900 people suffering from rare disorders. Patients from 24 organisations took part and the response rate was 71 per cent. It investigated the scope of health care offered to patients with rare disorders and their overall satisfaction with their course of treatment

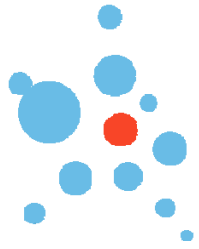




The overall conclusions are positive towards centres of reference:

- Patient satisfaction higher when treated at one of the two centres
- Individual action plans improve patient satisfaction
- Coordination and coherence extremely important
- To obtain coherence in the course of treatment patients need a personal coordinator

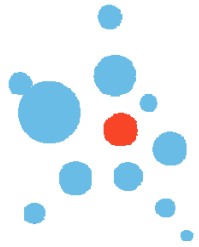




Recommendations not followed:

- Reference programs still not exist for the “remaining” diseases
- Agreements between centres and regional authorities do not exist
- No regional coordinators have been assigned
- Only a small percentage of the rare patients have an individual action plan





Questions to be raised?

- Are county hospitals reluctant to refer patients to centres (only 33% been to centres)
- When reference centres “keep” the patients to get the experience, does that compromise on other issues: dissemination of knowledge, research, international cooperation etc.
- Does the existence of reference centres lead to bad conditions for diagnostics?
- What is the correct balance of the responsibility between reference centres and regional specialist departments?