Presidency of the Council of Ministers

PERMANENT CONFERNCEE FOR RELATIONS BETWEEN THE STATE,
THE REGIONS AND THE AUTONOMOUS PROVINCES OF
TRENTO AND BOLZANO

Agreement pursuant to articles 2, para. 2, lett. b) and 4, para. 1 of Legislative Decree 28 August 1997, n. 281, between the Government, Regions and Autonomous Provinces of Trento and Bolzano on the document "National Plan for Rare Diseases (PNMR)".

Register of acts 140/CSR of 16 October 2014

THE PERMANENT CONFERENCE FOR RELATIONS BETWEN THE STATE, REGIONS AND AUTONOMOUS PROVINCES OF TRENTO AND BOLZANO

In today's session of 16 October 2014:

CONSIDERING Articles 2, para. 2, lett. b) and 4, para. 1 of Legislative Decree 28 August 1997, n. 281, assigning to this Conference the task of promoting and enacting agreements between the Government and the Regions, applying the principle of loyal collaboration, in order to coordinate the undertaking of the respective competences and undertake collaboration for activities of common interest;

CONSIDERING Legislative Decree 30 December 1992, n. 502 and subsequent amendments, which enacts the undertaking of programmes with close integration between hospital and territorial health and social care, with special reference to assistance for chronic pathologies with long duration;

CONSIDERING Art. 5 of Legislative Decree 29 April 1998, n. 124, which provides for the identification of the rare diseases giving entitlement to exemption from participation in the cost for the related healthcare services;

CONSIDERING Decree 18 May 2001, n. 279, and subsequent amendments, containing the "Regulations for setting up the national network for rare diseases and exemption from participation in the cost for the related healthcare services, pursuant to Art. 5, para. 1, lett. b), of Legislative Decree 29 April 1998, n. 124", which identifies the rare diseases giving entitlement to exemption from participation in the cost of the related healthcare services, provides for the setting up of the National Network for the prevention, monitoring, diagnosis and treatment of rare diseases, the activation of the National Register at the National Health Institute and other specific forms of protection in favour of the persons affected by a rare disease, with special regard to the availability of orphan drugs and the organization of the providing of care services;

CONSIDERING the Decree of the President of the Council of Ministers 29 November 2001, containing the: "Definition of the essential levels of care" and subsequent amendments and additions, published in the Official Gazette of 8 February 2002, n. 33;

CONSIDERING the Decree of President of the Republic 7 April 2006, containing the National Health Plan 2006-2008, published in the Ordinary Supplement of Official Gazette n. 139 of 17 June that establishes the objectives to reach in the area of rare diseases and the measures to undertake to enhance the protection of the persons affected, with special regard to diagnosis and treatment,

research, the improvement of the quality of life, the undertaking of programmes for information and the acquisition of specific drugs;

CONSIDERING its Act, register n. 103/CSR of 10 May 2007, approving the agreement on the recognition of Regional and/or Inter-Regional Centres of Coordination to favour the networking of the regional Centres for Rare Diseases and committing the Regions to set up Regional or Inter-Regional Registers and to provide data to the National Register of rare diseases;

CONSIDERING its Act, register n.82/CSR of 10 July 2014, approving the agreement on the new Pact for Health for the year 2014-2016;

CONSIDERING the letter received on 12 May 2014, disseminated on 13 May 2014, by which the Ministry of Health sent, in order to complete a specific agreement in State-Regions Conference, the document indicated above;

OBSERVING that at the technical meeting held on 20 May 2014, the Veneto Region, inter-regional coordinator for healthcare, handed over a document containing some observations on the second part of the text concerned and by note dated 22 May 2014, was distributed to the Administrations concerned;

CONSIDERING the note dated 6 August 2014, disseminated on 19 August 2014, by which the Veneto Region, Coordinator of the Health Commission, sent the version of the document concerned herein that takes into account the aforesaid observations of the Regions and the Autonomous Provinces, agreed in advance with the Ministry of Health and the AIFA;

CONSIDERING the letter dated 1 October 2014, disseminated on 8 October 2014, by which the Ministry of the Economy and Finance sent a document of observations on the document concerned herein;

CONSIDERING the letter of 9 October 2014, disseminated on 10 October 2014, by which the Ministry of Health sent the definitive version of the draft agreement concerned herein, taking into account the aforesaid observations of the Ministry of the Economy and Finance;

CONSIDERING the note dated 15 October 2014, by which the Veneto Region, inter-regional coordinator for healthcare, communicated its technical assent to the aforementioned measure;

HAVING ACQUIRED during today's session the assent of the Government and of the Presidents of the Regions and the Autonomous Provinces of Trento and Bolzano;

HEREBY APPROVES the agreement

between the Government, Regions and Autonomous Provinces of Trento and Bolzano, pursuant to articles 2, para. 2, lett. b) and 4, para. 1 of Legislative Decree 28 August 1997, n. 281, in the following terms:

Decision n. 1295/1999/EC of 29 April 1999 of the European Parliament and the Council, which adopted a Community plan of action for 1999-2003 on rare diseases with the aims of improving scientific knowledge of rare diseases and creating a European information network for the patients and their families, training

and updating of healthcare personnel to improve early diagnosis, strengthen international collaboration between volunteer organizations and professional organizations working in healthcare and support the monitoring of rare diseases in the Member States;
the Decision of the Commission 2004/192/EC of 25 February 2004 on *"Community action in the field of public health"* 2003-2008 which set up the *Rare Diseases Task Force (RDTF)* at the General Directorate for Health and Consumers of the European Union *(EU - DG Health and Consumer),* with the task of assisting the European Commission (EC) in the promotion of better strategies for the prevention, diagnosis and treatment of rare diseases, with special regard to the improvement of information on diagnosis, screening, treatment and treatment of the rare diseases, the promotion of networks of Centres for Expertise for the diagnosis and treatment of rare diseases, the promotion of monitoring and the availability of epidemiological data with high quality and comparable on the European level, the promotion of the development if systems for international classification and encoding of rare diseases, also in collaboration with the World Health Organization (WHO), and the promotion of the dissemination of best clinical practices to improve the quality of life of persons with rare diseases;
the Recommendation of the Council of the European Union of 8 June 2009 which called on the Member States to draft and adopt, preferably by 2013, in the context of their healthcare and social systems, national plans and strategies for rare diseases, in order to ensure that rare diseases are adequately encoded and traceable in all the healthcare information systems, promote research on rare diseases, identify Centres for Expertise in their own national territory by the end of 2013 and promote the participation of these centres in European networks, support the sharing, on the European level, of best practices in medical diagnosis and care, the training of personnel, the development of European orientation on diagnostic tests and screening, consult patients on policies in the sector of rare diseases, guarantee, in collaboration with the Commission, utilizing adequate mechanisms for funding and cooperation, the long term sustainability of the infrastructures created in the field of information, research and care for rare diseases;
EC Decision n. 2009/872/EC, 30 November 2009 for "Setting up the *European Union Committee of Experts on Rare Diseases* (EUCERD), to replace the RDTF" with the aim of assisting the EC in the drafting and implementation of Community actions in the sector of rare diseases, in collaboration with the Member States, the European authorities with jurisdiction in the area of research and public healthcare and the other entities operating in the sector;
Directive 2011/24/EU of the European Parliament and the Council of 9 March 2011, concerning the application of rights of patients in cross-border health care, containing specific provisions to actively favour cooperation between the States with regard to the diagnosis and treatment of rare diseases;
the *"Recommendations on Quality criteria for Expertise Centres for Rare Diseases in Member States. European Union Committee of Experts on Rare Diseases (EUCERD)"* of 24 October 2011;
the *"Recommendations on Rare diseases European Reference Networks (RD ERNS). European Union Committee of Experts on Rare Diseases (EUCERD)"* of 31 January 2013.
Legislative Decree 4 March 2014, n. 38, implementing Directive 2011/24/EU on cross-border healthcare, stating the areas of application of that Directive and setting up the National Contact Point;
the delegated Decision of the Commission (2014/286/EU), regarding the criteria and conditions to be fulfilled by the European Reference Networks and the healthcare providers that wish to adhere to a European reference network;
the Decision of execution of the Commission (2014/287/EU) laying down criteria for setting up and evaluation of European Reference Networks and their members and to facilitate the exchange of information and competences in relation to the setting up and evaluation of these networks;
Deeming it necessary to:

- contribute to the improvement of healthcare protection of persons with rare diseases, also

through optimization of the resources available;

- reduce the weight of the disease on the single individual and the social context;
- make the healthcare services more effective and efficient in terms of prevention and assistance, ensuring fair access and reducing social inequalities;
- organization on the national level of the initiatives and interventions in the field of rare diseases in order to further standardize the diagnostic-treatment process;
- affirm the need for a gradual transition towards an integrated system model, according to a "multi-centre" network, to highlight both the specialized role, and all the protagonists of primary care;
- identify the areas to implement and initiatives to adopt in the sectors of research, training and information;
- promote monitoring, enhancing the actions of the National Register and the Regional Registers;

IT IS HEREBY DECIDED
to approve the "National Plan for Rare Diseases" of which, Annex A to this act is an integral part. The Regions and the Autonomous Provinces of Trento and Bolzano hereby agree to implement the document with their own measures and implement its contents in their respective territorial areas, while retaining their autonomy in adopting the best organizational solutions in relations to their planning requirements.

This agreement shall be implemented within the limits of the human, instrumental and financial resources available under current legislation and in any case without further or higher charges on public finances. No fee, indemnity, attendance fee or expense reimbursement shall be provided for the members of the National Committee stated in Chapter 3 of the Plan.

The Secretary – Antonio Naddeo The President – Maria Carmela Lanzetta.

NATIONAL PLAN FOR RARE DISEASES 2013-2016

CONTENTS

Introduction

According to a definition used on the European level, rare diseases have an occurrence in the population of less than 5 cases for every 10,000 people. They are heterogeneous pathologies associated by similar care problems, requiring them to be faced globally and requiring a particular and specific protection, due to diagnostic difficulties, clinical seriousness, chronic duration, invalidating outcomes and the high cost of treatment. Rare diseases are a problem in public healthcare due to the numerical impact on the population. According to an estimate by the World Health Organization (WHO) the represent 10% of known human pathologies. It is estimated that 6-8% of the European population, totalling 27-36 million people, are affected by a rare disease. The WHO has calculated that there are about 6,000 treatment entities, but this is probably an underestimate; the European Union (EU) estimates these to number approximately 8,000, including the synonyms. In 2012 there were approximately 6,000 treatment entities listed by Orphanet, half of which can be correlated to the list of rare diseases already listed in Ministry Decree. 279/2001. If we exclude rare tumours, which have not been included in the list, most of the remaining forms have a very low occurrence. Reliable estimates on the occurrence of the total of rare disease patients refer to the list of diseases indicated in Ministry Decree 279/2001, leading us to believe that there are 5 sick persons every 1,000 residents and, among these, 1 out of 10 seem to be new cases (incidents). We can thus estimate that the occurrence of rare disease patients as a whole is 50 to 100% higher than the one estimated in the list in Ministry Decree n. 279/2001, i.e. from 7.5 to 10 per 1000 residents. On the basis of these estimates, there may be between 450,000 and 600,000 rare disease patients in Italy, of which only 300,000 having forms included in the current list attached to Ministry Decree n.279/2001. These discrepancies between estimates are justified by the fact that the effective number of rare diseases varies according to the accuracy of the diagnostic instruments and the evolution of the classifications in use. In particular, genetic analyses have shown the heterogeneous nature of many diseases, so that conditions not rare as such, if considered only on the level of their molecular mechanism, could be deemed rare (e.g. the most common form of genetic deafness affects approximately one person every 10,000). Genetic tests are thus producing a reclassification of many diseases, shifting many of them, clinically not rare, to the category of rare diseases. This is why the problem of rare diseases must be assessed also with reference to their clinical and functioning aspects.

Many rare diseases are complex, serious, degenerative and chronically invalidating; approximately one third of them reduce life expectancy by less than 5 years, while many others do not significantly affect life expectancy, if diagnosed in time and appropriately treated; other conditions, finally, they allow for a normal quality of life, also without treatment.

Rare diseases can affect physical and/or mental abilities, sense and behavioural capacities. The related disabilities limit educational, professional and social opportunities and, indirectly, can be a cause of discrimination.

Delay in the diagnosis of rare diseases depends on various factors, including the lack of adequate knowledge among physicians often connected with the extreme rarity of the disease, the presence clinical signs individually not diagnostic, the absence or the limited availability of diagnostic test, the fragmentation of the interventions, the shortfalls of the healthcare systems. As a result, many rare disease patients do not manage to obtain the exact definition of their pathology for their entire lives.

Furthermore, the aetiology of at least half of rare diseases is still unfortunately unknown. These problems, combined with the difficulty on the part of clinicians to communicate the diagnosis of diseases that are serious or fatal, are reflected in the delay in taking on responsibility and its efficacy, and the persons affected often have inappropriate treatments.

The frequent lack of effective etiological treatments does not imply that it is impossible to treat the persons affected by rare diseases. There are in fact numerous treatments for symptoms, support, rehabilitation, educative, substituting or supplementing functions, palliative treatment including some services not currently provided by the Italian National Health Service (SSN), which can considerably change the clinical outcome and life expectancy, the degree of autonomy and the quality of life of the persons affected and of their family members. Access to these treatments already available and their innovative aspects are key elements in care policies for rare disease patients.

1. European Context

The Council of the European Union has recommended the Member States to draft and implement appropriate plans or strategies for rare diseases or examine measures in the context of other public healthcare strategies, in order to guarantee to the persons affected access to high quality assistance from the diagnostic and treatment, and in particular:

a) draft and adopt a plan or strategy as soon as possible, preferably by the end of 2013, in order to orient and structure the pertinent interventions in the sector of rare diseases in the context of the healthcare and social system;
b) take action to integrate current and future initiatives at local, regional and national levels into their plans or strategies for a comprehensive approach;
c) define a limited number of priority interventions in the plans or strategies, developing aims and checking mechanisms;
d) acknowledge the development of orientations and recommendations for planning national interventions on rare diseases by the authorities having jurisdiction on the national level, in the context of the European project for the development of national plans for rare diseases (EUROPLAN www.europlanproject.eu), coordinated by the National Centre for Rare Diseases (CNMR) at the Italian National Health Institute and funded by the European Commission in 2008-2011 and 2012-2015 within the first Community Action Programme in the field of public healthcare.

1.1 Reference legislation

Rare diseases, given their special nature, have been identified by the European Union as one of the sectors of public healthcare in which collaboration between Member States is fundamental; therefore, rare diseases have been the subject of Community decisions, regulations and Recommendations aimed at providing incentives for regional and national initiatives and for transnational collaboration.

The main steps of the Community interventions in this area are summarized in the following interventions:

a) 1999 - Decision N. 1295/1999/EC of 29 April 1999 of the European Parliament and the Council, which adopted a Community plan of action 1999-2003 on rare diseases with the aim of:
   - improving scientific knowledge on rare diseases and creating a European information network for patients and their families;
   - training and updating healthcare personnel, to improve early diagnosis;
   - strengthening international collaboration between volunteer and professional organizations and involved in 'assistance;
   - supporting the monitoring of rare diseases in the Member States.
b) 2000 - Regulations of the European Parliament and the Council concerning orphan drugs (EC N. 141/2000). The regulation has set up a Community procedure for assigning the qualification of orphan drug, offering incentives for research, development and marketing of defined orphan drugs. Art. 4 of the regulation has set up, within the European Medicines Agency (EMA www.ema.europa.eu), the Committee for Orphan Drugs - *Committee on Orphan Medicinal Products* (COMP).
c) 2003-2008 - First Community Programme 2003-2008: recalled the added value of organizations of patients with rare diseases in creating and sharing knowledge in the different areas of rare diseases.
d) 2004 - Decision of the Commission 2004/192/EC of 25 February 2004 on *Community action in the field of public health 2003-2008:* set up the *Rare Diseases Task Force* (RDTF) at the General Directorate health and consumers of the European Union *(EU - DG Health and Consumers).* The RDTF, consisting of experts from the various Member States, representatives of the EMA and

patients' Associations, the persons in charge of research projects and public healthcare for rare diseases funded by the EC, had the task of assisting the European Commission (EC) in the promotion of the best strategies for the prevention, diagnosis and treatment of rare diseases, recognizing the added value from the coordination of the actions on a European scale. The specific aims included the improvement of information on the diagnosis, screening, and treatment of rare diseases; the promotion of networks of Centres of Expertise for the diagnosis and treatment of rare diseases; the promotion of monitoring and of the availability of high quality epidemiological data comparable on the European level; the promotion of the development of international classification and coding systems for rare diseases, also in collaboration with the World Health Organization (WHO) and the promotion of the dissemination of best clinical practices to improve the quality of life of persons with rare diseases.

e) 2008-2013 - The Community plan of action on rare diseases 2008-2013 has identified, among the main lines of action, the exchange of information by existing networks on rare diseases and the development of strategies to improve transnational cooperation and the coordination of the activities on the European level.

f) 2008 - Communication of the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions "Rare diseases: a challenge for Europe", 11 November 2008, set out the Community strategy to support the Member States in the diagnosis, treatments and treatment of European citizens affected by rare diseases, developing it in three main areas: improvement of recognition and visibility of rare diseases; support for plans or national strategies for rare diseases in Member Countries; reinforcement of cooperation and the Coordination for rare diseases on the European level.

g) 2009 - Recommendation of the Council of the European Union, 8 June 2009: invited the Member States to draft and adopt, in the context of their healthcare and social systems, national plans and strategies for rare diseases, preferably by 2013, on the basis of the orientation and recommendations drawn up by the European project EUROPLAN; ensure that the rare diseases are adequately coded and traceable in all the health information systems, in compliance with national procedures, encouraging their adequate recognition in the national care and reimbursement systems based on the International Classification of Diseases (ICD); providing incentives to research on rare diseases and promoting the participation of researchers in research projects on rare diseases funded at various levels, including the European level; identifying Centres of Expertise in their own countries by the end of 2013 and evaluating the possibility of promoting their creation; promote the participation of these Centres in European reference networks; supporting the sharing on the European level, of best practices in diagnosis and medical care, training of personnel, the development of European orientation on diagnostic tests and screening; consulting patients on policies in the sector of rare diseases, facilitating access by patients to updated information; promoting the activities undertaken by patients' organizations, including the awareness, training, the exchange of information and best practices, the building of networks and the involvement of more isolated patients; guaranteeing, in collaboration with the Commission, utilizing adequate mechanisms for funding and cooperation, the long term sustainability of the infrastructures created in the field of information, research and assistance for rare diseases.

h) 2010 – Decision of the EC n. 2009/872/EC, 30 November 2009: Setting up of the European Union Committee of Experts on Rare Diseases (EUCERD- http://www.eucerd.eu), replacing the RDTF. The aim of the Committee is to assist the EC in drafting and implementing Community actions in the sector of rare diseases, in collaboration with Member States, the European authorities having jurisdiction in research and public healthcare and the other parties operating in the sector.

i) 2014 - Decision delegated by the Commission (2014/286/EU) regarding the criteria and conditions to be satisfied by the European Reference Networks and healthcare providers that wish to join a European Reference Network
http://ec.europa.eu/health/ern/docs/ern_delegateddecision_20140310_it.pdf

j) 2014 - Decision for execution of the Commission (2014/287/EU) which sets forth criteria for setting up and evaluating the European Reference Networks and their members and to facilitate the exchange of information and competences in relation to the setting up and evaluation of these networks, http://ec.europa.eu/health/ern/docs/ern_implementingdecision_20140310_it.pdf

1.2 Centres of Expertise (CoE) and European Reference Networks (ERNs)

Due to the limited number of patients and the limited experience available, in order to guarantee the diagnosis and treatment of these diseases, the EC considers as indispensable the setting up of a European Reference Network for rare diseases, so that within this they may, when appropriate, the transfer and the exchange of experiences, the exchange of information and data, biological samples, X-ray images and other diagnostic elements, rather than moving the patients. The instruments that the EC intends to share most include the Registers and databases, guidelines and information, images transmitted via the web and training activities.

The Committee EUCERD has issued various Recommendations on the Centres of Expertise, the setting up of the European Reference Networks, the Registers, the indicators for the national plans and the added value of orphan drugs.

With regard to the setting up of networks and the identification of the facilities forming part of these, the basic documents are Recommendations on Quality criteria for Centres of Expertise for Rare Diseases in Member States of 24 October 2011 and the Recommendations on Rare diseases European Reference Networks (RD ERNS) of 31 January 2013.

According to the Recommendations of 2011, The Centres of Expertise for rare diseases are identified by the Member States as “expert” facilities for the diagnosis and treatment of patients with rare diseases in a defined geographical area, preferably national and, where necessary, international. They include or coordinate multidisciplinary competences, contribute to the drafting of diagnostic and treatment protocols, guidelines and best clinical practices and are connected with specialized laboratories and other facilities (e.g. for rehabilitation), participate in scientific research activities, contribute to the training of physicians, paramedics and non-medical professionals, provide information and collaborate with the patients' associations. They are connected with other national and European Centres of Expertise.

These Recommendations were implemented by the decisions of the Commission (2014/286/EU and 2014/287/EU) of 10 March 2014 on the European Reference Networks.

1.2.1. Criteria for designation and evaluation of the Centres of Expertise and European Reference Networks

The documents of the EUCERD and the acts of the Commission, Europe provides indications on the selection of the Centres of Expertise, suggesting some priority criteria, also defined on the basis of the Recommendations formulated by the patients ‘associations under the EUROPLAN project:

a) an adequate capacity of diagnosis, follow-up and admission of patients;
b) a significant volume of activity with respect to the occurrence of the disease;
c) the capacity to provide qualified opinions and to utilize guidelines for best clinical practices and conduct quality controls;
d) documented multidisciplinary approach;
e) advanced skills and documented experience with scientific publications;
f) awards, didactic and training activity;
g) significant contribution to scientific research;
h) close interaction with other Centres of Expertise, capacity to network on the national and international level;
i) close collaboration with the patients' associations;
j) periodical checking of maintenance of requisites.

1.2.2 Indications on setting up the European Reference Networks (ERNs)

The setting up of the European Reference Networks (ERNs) for diseases or groups will follow the designation of the Centres of Expertise on the national level, identified by the Member States according to the criteria already, on the basis of the specific situations of the various Countries/Regions.

The ERNs will preferably consist of services and facilities, rather than by groups of experts (EUCERD Recommendations to the European Commission and the Member States on European Reference Networks for Rare Diseases - 31 January 2013).

According to Community orientation, the Member States have the task of identifying the territory of jurisdiction for the experiences to be made available, defining the quality indicators to share with the other Member States and providing adequate information to professionals and healthcare personnel, to the public and patients' organizations, with regard to the conditions of access to the facilities of the ERNs.

On the European level, the categories of services and facilities necessary and the resources to share will be defined, together with the procedures for the sharing of competences and information, including the indications on best practices to disseminate to favour correct diagnosis and treatment.

The individual Reference Networks must adopt procedures for quality control and the entire system must be subjected to an evaluation able to estimate the strong and weak points e the strong, addressing the procedures to adopt for their improvement. This system can be connected with instruments for financial sustainability.

The documents for implementation of Directive 2011/24/EU, illustrated in the next paragraph, provide for the setting up of a body for the evaluation of the compliance with the defined criteria of the networks to be proposed by the Member States; quality evaluation will also regard the performance of the individual network and the maintenance of the requisites over time, with 3-year evaluation. The networks already set up can aggregate facilities to be proposed subsequently, both as associated facilities and as collaborating facilities.

1. 3. Cross-border healthcare

On 9 March 2011 the European Parliament and the Council of Europe formally adopted Directive 2011/24/EU on cross-border healthcare, clarifying the rights of the citizens and the possibility of going to other Member States for treatment. The application of this Directive, however, should not provide an encouragement to patients to receive treatment outside their country of affiliation beyond the necessary level.

The Member States were required to adopt the legislative, regulatory and administrative provisions necessary for compliance with the Directive by 25 October 2013. The Directive, originating from the need by the EU to harmonize the provisions of the European Court of Justice on the rights of citizens to receive treatment in another EU Member State, with full respect of the organizational autonomy of the individual States and national competences on healthcare services, clarifies responsibilities for the quality and safety of the care when several countries are involved, and aims to strengthen the collaboration between the Member States in various sectors, including the definition of reference centres for specialized care and treatment.[1]

[1]The Member States are required to set up one or more national contact points, to cooperate closely together and with the EC, facilitating the exchange of information and providing patients with all the information useful for making an informed decision.

The indications contained in the Directive, aimed at facilitating access to safe, high quality cross-border health care and to promote cooperation between the Member States, are issued, as explicitly stated in the same Directive, "in the full respect of the national competences on the organization and providing of healthcare."

When this healthcare is included among the services to which citizens are entitled in the Member State of affiliation, the costs of the treatment that the patients receive in another EU country are incurred by the country of affiliation in the form of reimbursement to the patient up to cost that the country of affiliation would have incurred; the Member States can introduce procedure for advance authorization of hospital admission or of treatment requiring the use of highly specialized and costly healthcare infrastructures, when there are planning requirements in order to ensure, in the territory of the Member State, the

With regard to the diagnosis and the treatment of rare diseases, the Directive specifies that the Commission actively supports cooperation between the States, specifying that, when a person affected or with a suspected diagnosis of rare diseases requests advance authorization, clinical evaluation can be made by experts in the sector. If the experts cannot be identified in the Member State of affiliation, or if the opinion of the experts is not conclusive, the Member State of affiliation can request a scientific opinion from a Member State.

According to the provisions of the Directive, the EU supports the Member States in the development of the European Reference Networks between healthcare providers and the centres of excellence present in the Member States, above all in the sector of rare diseases. The networks are based on the voluntary participation of their members, who contribute to the activities of the networks in accordance with the legislation of the Member State where they are situated. The networks are constantly open to new healthcare providers that intend to join, under condition that they satisfy the criteria and conditions adopted by the EC.

In the field of rare diseases, the EU supports the Member States, to inform the healthcare professionals on the instruments available in the EU, in particular on the Orphanet database, on the European Reference Networks and on the possibilities provided by Regulation (EU) n. 883/2004 for the transfer of patients affected by rare diseases to other Member States, for diagnosis and treatment not available in the Member State of affiliation.

The Directive provides for the reinforcement of cooperation between Member States through the use of e-health instruments and the development of a European network joining on a voluntary basis the national authorities having jurisdiction. Furthermore, it supports and facilitates cooperation and the exchange of scientific information between the Member States, in the context of a voluntary network connecting the national authorities or bodies in charge of the evaluation of the healthcare technologies designated by the Member States. The members of the network for the evaluation of healthcare technologies participate in and contribute to the activities of the network in accordance with the legislation of the Member State where they operate.

The Directive was implemented in our country with Legislative Decree 4 March 2014, n. 38, which defines the areas of application the European rule in the Republic of Italy and sets up the national contact point for cross-border healthcare at the Ministry of Health, save for the faculty of the regions and autonomous provinces to set up their own regional contact points to facilitate the transmission of the information to the national contact point.

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possibility of sufficient and permanent access to a balanced range of high quality care, or the willingness to guarantee the control of the costs and to avoid as far as possible any waste of financial, technical and human resources. Advance authorization can be requested, Furthermore, for healthcare involving a particular risk for the patient or for the population, or provided by a healthcare provider giving rise to serious and specific concerns for the quality or safety of the healthcare.

The Member State of affiliation can decide to reimburse other related costs, such as expenses for accommodation and travel, or any supplementary costs incurred due to one or more disability, by a patient who receives healthcare in another Member State, in accordance with national legislation and upon condition that these costs are documented. Legislative Decree n. 38 of 2014 attributes to the Ministry of Health the task of identifying, with its own decree, in agreement with the State-Regions Conference, the specific services to submit for authorization, save for the possibility for the regions and the autonomous provinces to identify further services, while respecting the conditions and principles set forth in the same decree, publishing them promptly on the websites and communicating them to the national contact point. Article 10 defines the procedure for the request and the issue of authorization.

Authorization can be denied when there is the risk of poor safety levels for the patient, when there are reasonable doubts as to the respect of quality and safety standards and compliance with validated guidelines. The Directive is not applied to long term care services for home assistance or by the assisted residential institutions and senior citizen residences.

2. NATIONAL CONTEXT

2.1. Introduction

The focus on rare diseases has developed in Italy starting from the 1990s and has increased in recent years, together with the awareness that, in a public healthcare context, these diseases share a number of problems and require specifically targeted policies.

The policies for the development of care for rare diseases, and the strategies, aims and actions illustrated in this Plan are mainly covered in previous regulatory provisions, which have identified rare diseases as a priority area in public healthcare and have confirmed the interest for this sector, according to lines of activities shared and agreed with the Regions.

The Plan therefore aims to create an overall framework and provide useful indications for facing the problem of rare diseases in an organic way, in the context of governance to undertake at the various institutional levels and the various areas of treatment, such as primary and palliative treatment, rehabilitation and home care.

Care for persons affected by rare diseases is mainly funded through the resources ordinarily allocated to the Italian National Health Service and distributed annually among the Regions, with a variable level of expense in the Regions also in relation to their budget resources.

For three years, starting from 2007, specific resources were allocated to activities for the planning and organization of care for this sector. In order to remove the healthcare imbalances between the various regions, Budget Law n. 296/2006 inserted rare diseases among the topics covered by co-funding of the regional projects implementing the National Health Plan (NHP), reserving to them a quota of 30 million euro to be assigned to the Regions by a Decree of the Minister of Health, after agreement with the Permanent Conference for relations between the State, Regions and Autonomous Provinces of Trento and Bolzano. A quota of the aforesaid fund, totalling 2.5 million euro for the same 3-year period 2007-2009, was reserved by the same Budget Law to national initiatives implemented by the Ministry of Health and was assigned to the National Health Institute (ISS). Ministry Decree 28 February 2009 defined the distribution of the fund to the Regions for the year 2007; for this year, the Regions shared a single project and the distribution was conducted on a per capita basis. For the years 2008 and 2009, the amounts of 4,482,008 and 4,984,727 euro were assigned respectively to the Regions that presented projects on rare diseases.

For the years 2010-2012, a non-additional quota (20 million euro/year) of the National Health Fund (NHF), divided among the Regions according to the criteria set by an agreement sanctioned by the Permanent Conference for relations between the State, Regions and Autonomous Provinces of Trento and Bolzano, was conditioned by the pursuit of aims of the NHP for the area of rare diseases.

For the year 2010, the constraint of 15 million euro was confirmed for interventions regarding Biological banks of human material obtained for treatment.

2.2. Essential assistance levels

The activities and services intended for the persons affected by rare diseases are an integral part of the Essential Assistance Levels (LEA) that the Italian National Health Service is required to guarantee to its patients, in relation to individual clinical conditions and for all the pathologies.

The LEA are provided to all the citizens through the regional systems, respecting the criteria of efficacy, quality and appropriateness of the treatments, as well as the ethical principles of fairness, universal access and solidarity. The Italian National Health Service must ensure, in all the sectors of treatment, quantity and above all quality standards in providing the services, in particular with regard to the instruments of clinical governance, the endowment of personnel and technology, accessibility and waiting time, respecting the principle of sustainability.

The choice between the various types of organization of services and the different types of activities must highlight the interventions which, while ensuring the result, guarantee an optimal use of the resources.

The measure defining the LEA is the Decree of the Presidency of the Council of Ministers of 29 November 2001, which quotes and confirms Ministry Decree 18 May 2001, n. 279 "Regulations for establishing rare diseases and exemption from participation in the cost of the relative healthcare services, pursuant to Article 5, para. 1, lett. b) of Legislative Decree 29 April 1998, n. 124". The Ministry Decree has an attached list of rare diseases for which exemption is provided, identified on the basis of the criteria indicated in the provision: limit of occurrence <5/10,000 people, established a European level as criteria of rarity, clinical seriousness, degree of invalidity and cost of the quota of participation deriving from the cost of the treatment.

Due to the variety and complexity of the clinical symptoms of rare diseases, the provision does not define in details the services subject to exemption, but provides for the ones in the list attached to the Ministry Decree the entitlement to exemption for all the services in the LEA, necessary to confirm the diagnosis, appropriate for the monitoring of the disease and for the prevention of further aggravation. The area of application of Ministry Decree n. 279/2001 does not regard drug treatment or prosthesis and additional treatment, which are governed by other specific provisions, also for exempted persons. Nevertheless, many of the Regions where the economic and financial condition allows for the introduction of further levels of assistance have independently provided for the free issue of level C drugs and other products not classified as drugs, to persons citizens affected by rare diseases and resident in their territory.

The correlation of rules on rare diseases with the LEA implies that the legal instrument and the procedure for updating are those defined by the Law for the modification of the essential levels, i.e. a decree of the President of the Council of Ministers, in agreement with the Minister of the Economy and Finance and with the State-Regions Conference. At the time of the updating of the Essential assistance levels, special attention must be dedicated to the care needs of the persons affected by rare diseases in order to safeguard the principle of fairness between the citizens and to ensure a greater homogeneity in the availability of treatments between the various Regions.

Currently, rare tumours are in mostly excluded from the list of rare diseases attached to Ministry Decree n.279/2001: nevertheless this situation must be reassessed, also in the light of the results of testing under way, in order to organizational models and treatment processes between the existing networks, as occurs in the other European countries.

2.3. Organization

2.3.1 National Network for Rare Diseases

The general framework of the national care network dedicated to rare diseases (279/2001) is a strong point of the system.

The Ministry Decree n. 279 of 2001 has had the merit of introducing in the healthcare system principles of the protection of persons with rare disease that are wholly innovative, also in the European context of the those years:

1. Focus on the need to create a network for care and admission of patients with a rare disease;
2. Recognition of rights and specific benefits to the persons with rare diseases;
3. Attributing to the Regions the task of identifying, with legislation, the facilities of the network where rare disease patients can find specific diagnostic and treatment skills;
4. Providing a national and local monitoring system.

Starting from the end of 2001, regional networks for assistance to rare disease patients have been planned and implemented by the Regions on the basis of various methodologies while respecting the criteria indicated in Ministry Decree 279/2001. These networks, which over the years have undergone revisions and reorganizations, have been gradually extended throughout the country and currently forms the National Network for Rare Diseases (State-Region agreement 2007).

The network for rare diseases consists of all the facilities and services of the regional systems, which in an integrated manner with each one in relation to the specific competences and functions, to develop preventive actions, implement the monitoring actions, improve interventions

for diagnosis and treatment, and promote information and training.

The model desired, coherent with the spirit and the founding principles of the National Health Service, of which the national network for rare diseases is an integral part, aims to guarantee the undertaking of highly specialized functions and deriving from specific competences, as well as general treatment functions throughout the country. The desired organization is based on the management, coordinated on a regional and inter-regional level, of the responses to the specific needs of the patients by the individual facilities.

The main areas of the National Network for Rare Diseases are the accredited facilities, hospital preferably, specifically identified by the Regions among those having documented experience in the diagnosis and treatment of specific rare diseases or groups of rare diseases, as well as the suitable availability of support facilities and complementary services, for example for the management of emergencies and for biochemical, genetic and molecular diagnosis (art. 2, par. 2, Ministry Decree n. 279/2001). The providing of support can also be guaranteed by the functional connection between the facilities and/or services, as is the case of the Medical Genetic Centres, an integral part of the network for rare diseases. The facilities of the network are connected in a diversified manner on the basis of the different regional healthcare organizations, to the hospital and local services nearest to the places of residence of the patients. These connections, though experienced as being strategic for the effective admission for the persons with rare disease, currently suffer from lack of standardized implementation, and there are still drawbacks in many areas. The facilities included in the network operate according to agreed clinical protocols and collaborate with the local services and the family physicians for admission to and management of the treatment. The facilities of the network must respect the new requisites set forth in the Recommendations of the European Union, in such a way as to be able to undertake the actions of the Centres of Expertise and be entitled to participate in the ERNs.

In relation to developments on the European level and the experience already acquired in Italy, the revision of regional networks should identify centres of competence which are also functional units, consisting of one or more organizational/operational units with the management of the diagnostic path aimed at identifying the disease as early as possible, and with the definition of the overall healthcare and social path for the person affected by the rare disease.

In order to effectively undertake the latter task, the Centres of Expertise must be inserted in the regional care network. In the process of ongoing evaluation of the quality of assistance in these facilities, the Regions can acquire the opinion of the Patients' Associations and propose programmes for external quality evaluation with external audits, according to models already applied in various European Countries.

For the coordination of the facilities within each Region, under the agreement between the State and the Regions of 10 May 2007, when compatible with the regional organizational layout, there is the recognition of regional and/or inter-regional Centres of Coordination to favour networking. The Centres of Coordination must ensure the exchange of information and documentation regarding rare diseases with the other regional and inter-regional Centres and with the other international bodies having jurisdiction; the coordination of the facilities of the network; consultancy and support to the physicians of the Italian National Health Service; the collaboration for training activities for healthcare personnel and volunteers and prevention initiatives; information to the public and associations of the patients and their family members. Furthermore, the Centres of Coordination must guarantee the functional connection with the individual facilities of the network for rare diseases, collecting the requests of the physicians and/or patients and addressing the patients to the facilities of the network. In order to undertake these tasks, the Centres of Coordination must ensure the presence of an autonomous facilities, able to support the activity of collection and sorting of the requests, with dedicated personnel and telephone lines; the insertion of the research in an information network; the availability of communication and operational networks through adequate functional connections between the healthcare and social services of the Local Health Agencies and facilities of the network for the admission of patients and families and to guarantee the continuity of treatments and healthcare education. Finally, the Centres of Coordination must be a major reference point for the patients' Associations and their family members.

Over time, agreements have been made between the Regions to foster the exchange of experiences and planning solutions used. This has led to the definition of larger inter-regional areas within which the gradual partial standardization of treatments proposed has been conducted.

In order to further support and implement the common strategy of cooperation and sharing of knowledge, inter-regional coordination can be undertaken for all the diseases individual diseases and/or groups of diseases requiring the same clinical and diagnostic skills, through specific agreements between the Regions, aimed at regulating the exchange and sharing of diagnostic and treatment paths in the qualified or expert facilities identified by the same Regions (facilities).

Further regional agreements must detail the processes of interrelation between the individual facilities for the management of rare diseases, in particular the less frequent ones (ultra-rare), according to an agreed arrangement competences and responsibilities, including the procedures for involvement and collaboration of the Associations of patients and their family members. In practice, "alliances and coalitions" must be set up between the Regions, at least for the rarest and most complex diseases from the diagnostic and treatment point of view. For specific pathologies with special characteristics, ultra-rare or of particular complexity, or for the management of specific stages of care, the facilities identified by the Regions can utilize the skills of highly specialized centres abroad, also by the use of remote medicine and remote consultation, in compliance with the provisions of European Directive of 9 March 2011 regarding cross-border health care.

For the same pathologies with very low occurrence (<1 person affected per million residents), the above-mentioned agreement already provides for the identification of national facilities dedicated to diagnosis and treatment, defining the criteria for their identification:

A. documented diagnostic, clinical and care experience;
B. structural and functional resources certified at the time of identification of the regional or supra-regional facilities;
C. insertion of the formal regional and/or supra-regional networks for the care of rare diseases;
D. diagnostic and treatment protocols or algorithms defining the treatment paths and documenting the adoption of functional organizational procedures in the management of care for patients with rare diseases (multidisciplinary approach to the patient, integration with local services and the general physician or paediatrician freely chosen for all the services that can be performed at eh place nearest to the patient's home or at home, with remote follow-up activities).

2.3.2 National system for surveillance and monitoring: the National Register of Rare Diseases (RNMR), regional and inter-regional registers and the information flow

In order to contribute to national and regional planning of interventions aimed at the protection of persons with rare diseases and their monitoring, starting from 2001 a system for monitoring rare diseases, area-based, was set up in Italy using regional and inter-regional population registers referring to a single National Register which, through the national flow, aims to obtain estimates of occurrence of rare diseases and evaluation of the impact of the phenomenon as a whole.

The National Register of Rare Diseases (RNMR) was set up at the ISS (art. 3 Ministry Decree n. 279/2001) and was subsequently implemented by the State-Regions Agreements of 2002 and 2007.

Under the agreement of 10 May 2007 between the State, Regions and Autonomous Provinces of Trento and Bolzano, the Regions agreed to set up the regional or inter-regional registers, to endow them with the necessary resources and provide data to the RNMR by a data flow, according to a variable number (dataset) defined by the agreement, containing information regarding the patient enrolment database and the disease itself.

The national surveillance and monitoring system includes the facilities, identified formally by the regions and enabled for the registration of the cases diagnosed and the admission of the patients. The facilities send the data collected to the regional or inter-regional registers which, after a validation process, send the minimum dataset to the RNMR.

At the Italian National Health Institute (ISS) a multidisciplinary working group regarding the RNMR acquires the data, makes appropriate quality controls and conducts the analyses.

The regional/inter-regional registers, set up since 2001 in the various Regions in different times and in different ways, differ by the type of organization, the information collected and for the aims attributed to them by the regional/provincial administrations. In particular, some of them have mainly epidemiological purposes and support to regional planning, as well as compliance with the information requirements of the Regions with respect to the RNMR; others are structured to undertake tasks to support the care activities and to coordinate the admission of the persons with rare diseases, collecting and making available the information to the services and personnel involved from time to time in undertaking the diagnostic and treatment interventions forming part of the individual assistance paths. When the monitoring system allows the recognition of the right to exemption for the persons with rare diseases, in the presence of a diagnosis formulated by a facility of the network, the register is immediately filled with the insertion in the monitoring system of all the patients present and known in a given geographical area.

Epidemiological data is extracted from the clinical and assistance information to support the regional planning, control and monitoring activities, as well as the elements of the dataset to provide data to the national information flow towards the RNMR.

The sharing the processes and projects has led to the creation of inter-regional conventions and agreements, forming inter-regional areas in Italy for the monitoring of rare diseases, the first one consisting of Piedmont and Valle d'Aosta, the second of Veneto, Autonomous Provinces of Trento and Bolzano, Friuli Venezia Giulia, Emilia Romagna, Liguria, Puglia and Campania, Umbria and Sardinia. In 2011, the ISS published the first Report on "National, regional and inter-regional registers of rare diseases" (ISTISAN Report 11/20) illustrating the activities of the RNMR and the regional/inter-regional registers.

The analysis of the data showed some important critical factors above all regarding the completeness and updating of the dataset and the methodology for processing the data, also related to the complexity of the subject involved.

2.3.3 Instruments for coordination: the Joint Board at the Secretariat of the State-Regions Conference and the Inter-regional Board

The need for the coordination of the regional activities, which was immediately necessary after the implementation of Constitutional Law n. 3/2001, was met by various agreements signed at the State-Regions Conference.

After the agreement State-Regions and public administrations of 2002, already mentioned previously, a permanent joint Board between Regions and branches of the public administration, Ministry and ISS was set up at the Secretariat of the State-Regions Conference to coordinate the actions undertaken in Italy in favour of rare disease patients. In 2006 the Health Commission, the coordination of the regional councillors in branches of the public administration, set up a permanent technical Board consisting only of representatives of the Regions and branches of the public administration. The Board currently has the task of exchanging experiences and practices, sharing organizational and planning solutions and defining the processing of the technical documents submitted for approval by the Commission for Health, expressing the point of view of the Regions on topics regarding the care and monitoring of rare diseases. During the years of its activity, the Board created or contributed to undertake in collaboration with the Ministry and the ISS, many initiatives, such as the proposal of updating the list of rare diseases in Ministry Decree 279/2001, the regional and inter-regional governance document of the network for assistance for rare disease patients, the agreement between the State, Regions and branches of the public administration of 2007, the policy document of the Regions on draft law on rare diseases currently under discussion in both houses of Parliament, the list of drugs and para-pharmaceuticals usable for rare disease patients as off label or imported from abroad, partially reimbursable by the Italian Medicines Agency (AIFA), the agreement on neuromuscular pathologies, Congenital Haemorrhagic Diseases (CHD) and vegetative states.

The most important process, currently under way, is the continuous networking between the various local situations on the operational strategies activated to guarantee assistance for rare disease patients within the existing healthcare services. This networking has allowed a gradual standardization of solutions, in relation to the selection of pre-accredited bodies and the protocols used, so that the monitoring and information systems feeding the so-called local registers are brought into compliance with the protocols.

Another significant result of this work are the inter-regional agreements, which have allowed for the gradual creation and development of large inter-regional areas using common information systems, protocols, and accredited networks.

2.3.4. National Centre for Rare Diseases (CNMR)

Since the late 1990s, the Italian National Health Institute (ISS) contributed to achieving the aims of research and public healthcare on rare diseases, employing human and structural resources distributed in the various facilities of the organization. In order to improve the efficiency of the activities, the Decree of the President of the ISS 26 June 2008 (G.U. 7 July 2008) set up, as an internal body, the National Centre for Rare Diseases (CNMR) with the scope of "research, consultancy and documentation on rare diseases and orphan drugs aimed at prevention, treatment and monitoring".

The RNMR is run by the CNMR, that coordinates the national information flow on rare diseases and the network of regional and inter-regional registers of congenital malformation. On the basis of its institutional scope, the CNMR promotes, coordinates and conducts research projects and collaborates regularly with the national (Ministry of Health and other Ministries, AIFA, Higher Health Council, AGENAS) and international institutions (European Commission; EMA-COMP; EFSA; IRDiRC) involved in the activities regarding rare diseases and orphan drugs and with the patients' associations (www.iss.it/cnmr).

In particular, the CNMR conducts scientific and experimental research activities and in public healthcare; checking (national quality programme for genetic tests); drafting of guidelines for the clinical management of patients in the context of the national system guidelines; promotion of studies, research and actions of public healthcare in prevention (primary, secondary and tertiary) such as the coordination of the Italian Folic Acid Network; training of healthcare professionals (courses, summer schools*)* and patients and family members (parent training; self/mutual help); information to personnel, patients, family members by the National Helpline for Rare Diseases (TVMR), the website and the ISS bulletin "Malattie rare e farmaci orfani" (Rare Diseases and Orphan Drugs).

2.3.5 Coding

Many rare diseases are hard to detect and trace in the healthcare systems due to the difficulties in classification and coding, both due to the inadequacy of the systems currently in use, and to the factors related to the nature of rare diseases (heterogeneity of the pathologies, low diagnostic accuracy, presence of numerous synonyms, acronyms and groups of pathologies).

In general, the processes of converting the diagnosis of a disease into codes are a difficult operation since the medical terminology used is different from that in the currently used classification for rare diseases, and the impact of the problems regarding coding is even greater. Inappropriate or incorrect diagnoses lead to inappropriate coding and classifications; inappropriate coding can significantly influence the statistics, which are based by definition on a small number of cases. The improvement of the coding and classification of rare diseases is a priority goal on the national and international level because the correct coding and classification is fundamental to ensure the traceability of the cases in health information systems, for example, in the hospital release forms in order to produce the epidemiological registers or to conduct statistical analysis for purposes of healthcare planning, and for research purposes. The accuracy of the flows is a major information source on treatment needs, is a significant source for the production of statistics of the morbidity data, and the efficacy and quality of the healthcare systems and is therefore an indispensable tool for adopting appropriate and effective measures in public healthcare.

The European Commission is strongly oriented to assuming the classification defined by the Orphacode system as a reference for the diagnosis and coding of rare diseases and to integrate this coding into current information flows.

2.3.6. Pathology registers and biobanks

Patient registers and databases are key instruments for clinical research on rare diseases, to improve the admission of patients, plan their health and assess their social, economic and quality of life impact. They allow for combination of the data until sufficiently large samples have been achieved to undertake clinical and epidemiological studies, evaluate the possibility of planning and implementing clinical trials, favour the enrolment of patients and measure the impact of the new interventions.

In Italy in the past 10 years there has been a focus on the development of regional and inter-regional population registers forming the source of the Italian National Register for the ISS. There are a number of pathology registers, sometimes local and not totally recorded, as well as a number of registers of patients treated with orphan drugs, each dedicate to a specific commercial product.

The problem of the sustainability of a number growing of pathology and drug registers also exists on the European level, where trials are under way for the creation of a shared platform useful for the exchange of a core of information common to all the registers dedicated to rare diseases. Focal points include the numerous problems connected with quality and completeness of the data recorded, the different methodologies followed, the procedures for storage and use of the information and consequently the ethical implications of some of these datasets.

The Registers of patients treated with orphan drugs also have a specific function, since they allow us to evaluate the appropriateness and efficacy of the treatment and the eventual collateral effect, taking into account that the authorizations for marketing are usually issued when the evidence is still limited, though already convincing.

The gradual development of the population registers, which improve information provided by clinical cases and avoiding the distortion of the information derived from the data collected on smaller parts of the population, will probably lead in the future as already happened for other groups of non-rare diseases to a re-evaluation of the role and functions of the pathology registers.

Biobanks are services dedicated to the collection and conservation of human biological material, aimed at diagnosis, studies on biodiversity and research. The EU considers the biobanks as non-profit organizations, which should be recognized by the pertinent health authorities of the Member States, to guarantee the treatment, storage and distribution of the biological material obtained by the diagnostic or treatment interventions, donated for a research project and conserved for subsequent use, donated for a transplant and then not used, coming from deceased persons subjected to autopsy.

The biobanks are characterized by the type of material collected (blood, healthy and pathological tissue, cell lines, DNA, gametes etc.) and by their activities: biobanks aimed at scientific research and diagnosis and those aimed at treatment and transplants.

The genetic biobanks collect and conserve biological samples to be utilized for research on genetic diseases or to define the genetic basis of common diseases, associable to personal, family member and clinical data of the persons from whom the material stored originates. The aim of these biobanks is to favour research dedicated to the identification of the causes of hereditary diseases; to foster the collection of biological material coming from persons with genomic characteristics useful for understanding the biological basis of common diseases and the hereditary factors conditioning susceptibility; making samples available that are useful for the study of genomic characteristics that condition response to drugs; centralizing the collection of samples of genetic material coming from persons affected by genetic diseases, for in vitro studies; to offer a service to favour the growth of research and communication and exchange between researchers.

At the present time there is no list of the other collections of biological material present in Italy, most of which were set up before the drafting of the national and international guidelines that have since governed the sector. Many of these collections of biological material have been organized at research centre and regard samples coming from persons with rare diseases.

The *Telethon Network of Genetic Biobanks (TNGB)* was founded in 2008 by 7 genetic biobanks supported by the Telethon Foundation, in order to collect, preserve and make available to the scientific community biological samples and related clinical data, coming from individuals affected by genetic diseases, their family members and controls consisting of healthy individuals. Currently, 10 biobanks take part in the network. The coordination of the activities of the biobanks takes place by a centralized computer system facilitating the consultation and access to samples, to increment synergies and offer researchers an effective service responding to the highest quality standards, according to strict ethical principles and in compliance with Italian law and international recommendations. The TNGB is managed by the Network Board (NB), the decision-making body consisting of an elected Coordinator and the Directors of the associated biobanks, supported by an Advisory board (AB).

The website www.biobanknetwork.org provides the catalogue of the samples collected all the biobanks included in the network. On the website, anyone can verify the availability of biological samples for a given genetic disease and request them for research purposes, and the website also shows scientific results obtained thanks to the samples made available.

Italy participates (www.bbmri-eric.it) in the European research centre Biobanking and Biomolecular Resources Research infrastructure (BBMRI: www.bbmri.eu) which aims to ensure safe access to biological resources and guarantee appropriate management in order to improve the health of European citizens.

2.4 Diagnostic and treatment path

The treatment path for persons affected by rare diseases starts from a suspected diagnosis made by a hospital physician or a professional operating in the local health service. The general medicine physician or chosen paediatrician usually send the patient to a specialist of the Italian National Health Service in charge of starting up the path in the context of the Italian National Health Service. The patients themselves or their family members showing signs and symptoms are often the first to turn to healthcare facilities and start up special diagnostic procedures. The first formulation of the suspected diagnosis is a critical element on the path, since it affects the possibility of prompt treatment and consequently, the progress of the disease. In order to reduce the time between the appearance of the first symptoms and the diagnosis of rare diseases, all the actions aimed at training and updating of the professionals operating in this complex system of services are important. For sake of brevity this can be defined as a reference system, including their insertion in the compulsory training programmes drawn up by the Regions. There must also be incentives to the instruments and infrastructures able to guide and orient all the physicians towards the suspicion of rare diseases. When there is a suspected diagnosis, the physician must immediately send the patient to a facility of the network formally identified by the Region for the specific disease or for the group of rare diseases to which the suspected pathology belong. It is up to the accredited facilities to guarantee the diagnostic process of rare diseases without costs for the patient, for the procedure conducted in day hospitals. If the diagnostic procedure requires services that can be provided only in operational units not included among the facilities of the network, the latter facilities must ensure the execution of such services at other facilities of the Italian National Health Service. In particular, when testing can be made directly on a biological sample, the facilities must provide for the taking of the sample, send the sample and guarantee undertaking of the analysis. When the diagnostic confirmation requires the conducting of genetic tests on the family members of the person concerned, these tests must also be conducted free of charge. In any case, the diagnostic procedure must be organized in such a way as to guarantee the better quality and completeness with the least discomfort for the patient and his family.

To this end, agreements between the Regions and facilities of the network must be promoted with incentives, in order to allow forms of remote consultancy, also through computer tools for sharing medical documentation. To this end, the Regions can implement agreements and adopt, also on a trial basis, procedures to allow the consultation services to have specific charging.

All the diagnostic tests must be conducted according to the criteria, supported by scientific evidence, of appropriateness and efficacy, essential requirements and safety. Tests for which the diagnostic value is still undergoing scientific research are not included among those provided by the Italian National Health Service. In any case, they can be proposed only in the context of a research project approved by an Ethical Committee, after the signature of the informed consent form by the patient or his tutors.

If at the end of the diagnostic process the presence of a rare disease included in the list of Ministry Decree 279/2001 is confirmed, the specialist in the facility must draw up the certificate of rare disease and issue it to the patient as soon as possible. The pertinent Local Health Authorities for the patient holding the certification issued by a facility of the network specifically identified for the pathology involved, will issue the certification of exemption corresponding to the disease certified.

Once the disease diagnosis is issued, it is still the task of the facility of the network to define the current and estimated damage profile in the patient and his functional potential. The second part of the diagnostic picture is essential to allow the subsequent drafting of the treatment plan, which must take into account the specific treatment needs identified on the basis of the individual characteristics of the person, and thus not defined solely on the basis of the standard paradigm of the disease. All of the previous indications also apply to this stage of more in-depth diagnosis. On the basis of the disease diagnosis and the profile of the treatment requirements, the facility will formulate the individual treatment plan which can include the supply, free of charge, of all the services included in the national LEA or on further levels eventually guaranteed on the regional level (drugs, dietary products, facilities, auxiliary items, prostheses, rehabilitation treatments, planned surgery etc.) considered by the specialists of the facility to be necessary for the admission of the patient, according to principles, based on scientific evidence, of appropriateness, indispensability, lack of any substitutes and economic convenience. The Plan must be formulated according to the procedures provided for by the Region where the facilities are located.

The services indicated in the Plan and included in the national or regional LEA, must be guaranteed by the pertinent Local Health Authorities of the patient and provided either directly by their own services or by regional or inter-regional assistance network, wholly paid for by the Regional Health Service. To this end, the Regions must indicate the organizational procedures implemented to guarantee this right of the patient. Furthermore, any inter-regional initiatives would be welcome to define, also through formal decisions, the treatment protocols and paths organized and guaranteed for every type of assistance requirement in rare diseases, including aspects such as the treatment of symptoms, intensive and extensive rehabilitation, social insertion (school and work), palliative treatments and integrated home care.

The paths defined by every Region must identify the protagonists, connections and available care, as well as clarify the plans with overall responsibility. These paths will then contain the individual care plans drawn up by the facility assisting the individual patient, on the basis of his care requirement profile. The individual care plans and the application of the paths and protocols must be based on the principle of compliance-based appropriateness and take into account the specific clinical condition if the individual patient.

The care plan must be periodically updated by the facility of the network, also on the basis of the clinical progress of the disease and the response to the treatments under way. The actions contained in the treatment plan must be preferably implemented by the hospitals and the local services near to the place of residence of the person with the rare disease. It is therefore essential to have a connection between the pertinent facility and the hospital and local healthcare services of the Local Health Authorities in the place of residence, which must include the transfer and sharing of the clinical documentation essential for correctly implementing the measures planned and to monitor their result, also through remote supervision and consultancy and, in exceptional cases, also by a personal consultancy. Various Regions have had experiences with the mobility of the specialized physicians of the Local Health Authorities of the place of residence who have had access to the facilities of the network.

The aim was to refine the skills needed for adequate care at the peripheral hospitals of the Local Health Authorities or at home with regard to especially complex patients. In this case, too, the observations made in relation to the diagnosis procedure shall apply.

In the case of rare diseases appearing during the paediatric age and allowing survival in the adult age, there must be a careful management of the transition phase, in such a way as to ensure the continuity of care during the next life phase of the patient. This transition must be specifically planned in the above-mentioned treatment paths and can utilize organizational and management innovations that facilitate the joint work of the specialists belonging to various operational units and a facilities. As for the terminal phases of the clinical development there must be a specific connection with the networks for palliative treatments. If the ill person needs constant and significant assistance is treated for long periods of time in the family, there must be plans for short relief admissions to non-hospital facilities, specifically qualified for this type of assistance. Similarly, in the cases requiring continuous assistance that cannot be guaranteed at the patient's home due to problems related to the family members concerned or by the decision of the patient or his tutor, Assistance must be guaranteed in residential facilities qualified for the specific care requested.

2.5 Instruments for treatment innovation: orphan drugs and Law n. 648/1996

2.5.1 European regulatory context

As already stated previously (para 1.1), European policy regarding orphan drugs began in 2000 with the adoption of the Regulations of the European Parliament and the Council of the EU concerning orphan drugs (EC n. 141/2000), which set up a Community procedure for assignment of the qualification of orphan drugs and governs the offer of incentives for research, development and marketing of the orphan drugs defined in this way. Art. 4 of the regulation provides the European Medicines Agency (EMA www.ema.europa.eu), the Committee on Orphan Medicinal Products (COMP) with the task of assigning the designation of orphan drug on a centralized level.

In 2008, the Pharmaceutical Forum between the 27 Member States focused on the need to facilitate the exchange of information and knowledge among Member States and the European authorities to contribute to improving the evaluations and decisions in order to guarantee fair and prompt access to orphan drugs for all the rare diseases.

In 2010 the EC conducted the study on Clinical Added Value of Orphan Medicinal Products (CAVOMP) aimed at verifying the feasibility of the mechanism for the exchange of knowledge among the various stakeholders involved in the process of evaluation of the orphan drugs. The study, published in 2011, highlighted the importance of the initial discussion between the parties and advance exchange of scientific information between the EMA - European Network for Health Technology Assessment (EunetHTA) and the sponsors in the process of evaluating the significant benefit of a drug in the stage of orphan designation. The Mechanism of Coordinated Access to Orphan Medicinal Products (MOCA) is a project in the access platform to orphan drugs of the EU General Directorate of Enterprises and Industry, aimed at identifying common and alternative paths between the Member States to facilitate sustainable access to orphan drugs.

The AIFA, together the agencies of 9 other Member States, was appointed to coordinate a mechanism of harmonized investments to improve the sharing of knowledge and responsibilities.

2.5.2 Rules for providing orphan and innovative drugs in the Italian National Health Service

The number of orphan drugs authorized by the European Medicines Agency (EMA) as at 31.12.2013 totalled 67. Of the present orphan drugs, 54 were marketed in Italy on that date. In particular, of the remaining 13 products not marketed in Italy, 2 were being negotiated, while for the last 11, the manufacturers had not yet applied for negotiation of the price of the drug and its reimbursement status. Decree Law 21 June 2013 n. 69 implemented, with amendments, by Law 9 August 2013 n. 98, introduced a special procedure for the classification of the orphan drugs, setting a maximum 100 day period within which the AIFA evaluates the application. Furthermore, Italy has a post-marketing monitoring of some orphan drugs, i.e. those that have obtained reimbursement status subject to a monitoring register managed by the AIFA. The AIFA, in particular, collects information regarding the post-marketing phase for some recent drugs.

Law n. 648/1996 allows for the issue by the Italian National Health Service, of innovative drugs on sale other States, but not in Italy, when no valid alternative treatment is available; drugs not yet authorized but subject to clinical testing; drugs used for a treatment indication other than the one authorized (off-label use). This possibility is limited to the active principles and the uses indicated in an attached list updated by the AIFA Technical and Scientific Committee. The updating is conducted taking into account the applications to the AIFA by bodies, institutions, clinicians and patients' associations.

Law n. 94/1998 governs the prescription of a legally marketed drug but for an off-label use, for a patient that the physician believes cannot be treated with other drugs already approved for that treatment indication or type of administering, as long as this use is known and in compliance with works appearing in scientific publications accredited in the international field. Subsequently, Law n. 296/2006, Art. 1, para. 796, lett. z) limited this use, allowing it only in the context of the trials and prohibiting when the prescription of these drugs "takes on a widespread and systematic character and becomes, outside of the conditions for the authorization for marketing, as a treatment alternative aimed at patients with pathologies for which there are authorized drugs with the specific indication for treatment".

Ministry Decree 8 May 2003 (for so-called "compassionate" use), allows the use of a drug without marketing authorization but in an advanced phase of clinical testing, for patients in case no valid treatment alternative is available. The drug is supplied free of charge by the producing company.

Recently, Decree-Law 13 September 2012, n. 158, implemented with amendments by Law 8 November 2012, n. 189, containing "urgent provisions to promote the development of Italy by a higher level of protection for health", established that access to innovative drugs shall take place on the basis of the provisions already present in agreement n. 197/CSR, approved in the Permanent Conference for relations between the State, Regions and Autonomous Provinces of Trento and Bolzano of 18 November 2010.
Furthermore, Art. 12 of the aforesaid Law states that the pharmaceutical companies can apply for the price and reimbursement only after obtaining authorization for marketing, while for orphan drugs in particular it is also possible to submit the application for the price and reimbursement before the publication of the Community decision in the European Official Gazette, i.e. as soon as the positive opinion of the CHMP of the EMA as to the quality, safety and efficacy of the drug to be marketed has been issued. This will allow an acceleration of the availability of the orphan drugs to the patients.
The same Law states that drugs that are marketed and for which negotiation on reimbursement status has not yet started can be included in a specific category C (nn), guaranteeing its immediate availability on the market.

In order to prevent the drug from remaining in Class C (nn) without any negotiation of the price and reimbursement status with the AIFA, Decree Law 69/2013 was issued, implemented by Law 98/2013), establishing that once the class C (nn) is obtained the class C (nn), the pharmaceutical companies must apply to the AIFA within 30 days for the price and reimbursement.

In case of failure to make such application within 30 days from the issue of authorization for marketing, the AIFA requests the company holding the marketing authorization to apply for the classification and reimbursement status in the subsequent 30 days. The same law states that the negotiation procedure must be concluded within 100 days from the date of application. Since the applications made often lack the necessary documentation for the evaluation of the drug, the AIFA has to ask the companies for further details, which inevitably lengthens the time of the procedure.

Furthermore, Stability Law 2013 (Law n. 147/2013) provides for mechanisms for economic protection for the owners of orphan drugs. If the hospital expenditure ceiling is exceeded on the national level, the AIFA, in applying compensation charges to the pharmaceutical companies, excludes the owners of orphan drugs and spreads the liability of this excess expenditure over all the other pharmaceutical companies.

Under this regulation, the AIFA board of directors has approved the list of the orphan drugs which as at 31.12.2013 were entitled to the economic benefits described above.

In drawing up this list, the AIFA board of directors considers:

- the drugs qualified as orphan drugs pursuant to EC Regulation 141/2000 and in having authorization for marketing in Italy, as well as the assignment of the reimbursement class covered by the Italian National Health Service
- the drugs qualified as orphan drugs pursuant to EC Regulation 141/2000 which have concluded the advantageous 10-year period of market exclusive
- the drugs included in Circular EMA/7381/01 (so-called orphan-like), i.*e.* drugs with the same characteristics as the drugs qualified as orphan and which were authorized previously under Regulation (EC) 141/2000, upon proposal by the pharmaceutical companies, other drugs with the same characteristics as the orphan-like products and included in the Orphanet register.

A total of 99 drugs are marketed for the treatment of 141 diseases. Sixty-two drugs used for the treatment of 82 diseases have obtained authorization for marketing in Europe and the orphan designation, while another 44 drugs, lacking the orphan designation, are marketed for 74 diseases. In the general sense, the greatest availability of drugs regards, in increasing order, the rare diseases of interest in the from the oncological, neurological, haematological, metabolic, dermatological and endocrinological point of view.

The Stabilimento Chimico Farmaceutico Militare (SCFM – Military Chemical Pharmaceutical Factory) in Florence, a production facility of the Agenzia Industrie Difesa (Technical Industrial Area) supervised by the Ministry of Defence, guarantees upon request by the ISS and the AIFA, the production of the drugs for the treatment of rare or infrequent pathologies, and not produced by major pharmaceutical industries because they are unprofitable (e.g. D-Penicillamine, Cholestiramine and Ketoconazole), and Galenic products for which preparation by the individual hospital pharmacies or regional facilities is difficult or impossible due to the variability and the lack of continuity of human and technological resources available, and because it is hard to obtain small amounts of the active principle on the international market. The intervention of the Stabilimento has also solved emergency situations caused by the sudden lack of availability of essential drugs on the market.

Despite the progress made in the last decade, there are still some critical elements in the availability, supply and access to drugs and products, partly due to regulatory constraints and general law with a negative impact on the treatments planned for the persons with rare disease.

2.5.3 Other treatments for persons with a rare disease

The sector of orphan drugs is just one area, still not very large, of research for the treatment of rare diseases, and utilises of non-pharmacological tools including surgical treatment and transplants, cellular treatments, prostheses, rehabilitation and robotics. These are sectors promising major results to the benefit of rare disease patients, and where research must undertake significant investments.

For many rare diseases, there is currently no likelihood of etiological treatment (congenital and complex malformations), but there is possible treatment by the replacement or supplementing of the individual's functions or abilities, or of organs or apparatuses damaged or dysfunctional due to the disease. Over time, treatments for support and contrast to the symptoms have acquired increasing value for guaranteeing the survival and quality of life of the persons with rare disease. Interesting developments and applications are already partly available thanks to the use of nanotechnologies, such as those ones used in some new generation prostheses. Also specific facilities, such as recently available medications, allow for a more favourable outcome of the pathology with respect to its natural history. The updating of the EALs will take into account some innovative treatments in order to guarantee a more constant and standard availability. Considering that some of these treatments, concentrated in some centres, are especially expensive, it will be necessary to try new forms of remuneration for compensating the costs incurred by the facilities providing such treatments.

2.6 The Associations

The role of the patients' associations was fundamental, also in our country, for encouraging targeted policies, research and interventions in healthcare. Much progress in the field of rare diseases, on the various institutional levels, is due to the activities of these organizations, which have allowed civil society to acquire an awareness of the peculiar nature of these diseases and the problems they involve. The work of the Associations has also helped change the relationships between the institutions (central, regional and local) and the community of the patients, removing many of the existing barriers.

The patient is entitled to orient the choices on his own disease or condition, on the form of treatment and the path to follow, and this has a positive effect on the success of the treatment. Furthermore, it has been shown that the reinforcement of support groups leads to greater appropriateness in the use of services and the improvement of the efficiency of the treatment providers. The increase of awareness and of the patient's capacity for self-determination (empowerment), the strong point for chronic diseases considered as a whole, is indispensable for rare diseases, which besides being chronic involve a variety of needs related to the difficult of their treatment and the fact that their rarity requires coordinated efforts to improve knowledge and assistance.

Besides the need to share the difficulties and problems and the desire by patients to get their rights recognized and receive protection, we can add the special value of the work undertaken by the Associations for rare diseases which, starting from the sharing of experiences, can provide knowledge which though not medical is nonetheless useful in correctly facing the disease. In Italy, starting from 1998, the discussion about the fundamental topics regarding rare diseases has advanced considerable, opening up to patients' organizations also with regard to the technical and scientific aspects; in the sector of rare diseases, the patients and their organizations have actually reached an advanced level of empowerment, representing a model for other groups of pathologies.

It is thus up to healthcare personnel and physicians to promote a constructive and collaborative relationship with the patients, enhancing their information and supporting solidarity and community-based attitudes. On the other hand, participation in decision-making processes by the patients' organizations requires a strong civic attitude and capacity to act in favour of the community, which is not helped by the fragmentation of representation.

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Today, on the national and international level, there are well-structured patients' organizations having as their primary focus individual diseases or groups of related diseases, and operating in the interest of all the persons affected by rare diseases.
The Orphanet database has listed 1673 individual associations federated in the European Organisation for Rare Diseases (EURORDIS), founded in 1997, which conducts activities and initiatives in the common interest of all the rare disease patients. The UNIAMO (www.uniamo.org) federation grouping together about a hundred Associations, represent Italy in the EURORDIS.

The Associations, besides undertaking a complex role with participation in the collection of funds to be targeted to research, also collaborate in public healthcare programmes, study projects, the enrolment of patients in clinical studies, as well as producing information material on the diseases, the treatments available and the clinical networks and expert facilities, given their collaboration with clinicians, healthcare personnel and the institutions. Many joint activities of this type, in specific sectors, have allowed for the creation of collaborative networks with specialists and with the facilities, initially on clinical and scientific problems for starting up research activities and then for the creation of care networks.

In Europe, participation in government bodies is guaranteed to the COMP, set up by the EC with the task of evaluating the applications for the designation of orphan drugs, for the Rare Diseases Task Force, set up in 2004 and for EUCERD, starting from 2010.

An example of the collaboration set up between the Associations, the Ministry, the Regions, the ISS, the scientific societies and professional organizations was the planning and holding of a national conference to prepare the definition of this National Plan for rare diseases, within the EUROPLAN project.

Among the associations in Italy, about a hundred have been federated since 1999 in the UNIAMO, an association for social promotion; its website illustrates the projects in which the Federation collaborates on the national and international level, through EURORDIS. Since 2010 numerous Associations have been federated in the “Consulta nazionale delle malattie rare” (National Council for Rare Diseases) and since 2012 some have been federated in the Movimento Italiano Malati Rari (MIR - Italian Movement of Rare Patients). Among the projects funded on the central level, some regard the empowerment of the patient, the creation of a website managed by the associations to orient the patients and their families in the choices and actions of daily life, the definition of quality criteria of the network facilities and the corresponding indicators. Thanks to an agreement with the national federations of physicians for general medicine and the freely chosen paediatricians (Italian Federation of Physicians in general medicine and Italian Physicians of Paediatricians) and the scientific societies (SIGLI, SIMG, SIP, SIMGEPED), the UNIAMO Federation has conducted training activities on rare diseases in several Regions, with the collaboration of the Region and Farmindustria. With an agreement between UNIAMO and Telethon, monitoring has been conducted on the activities of the Associations in order to provide and support, also economic for research, and with the initial setting up of a national biobank of the biological material of persons affected by rare diseases.

Between 2006 and 2007 the Ministry of Health set up the “Consulta nazionale delle malattie rare” as an elective representative organ of all the Associations, Federation and Forums of rare diseases, in order to strengthen the relations between the central institutions in charge of planning of interventions on rare diseases, and the protection organizations involved both to orient patients and their family members within the Italian National Health Service, and to help identify the priorities of healthcare policies. The logistic and technical support for setting up and operating the National Board was assigned to the CNMR of the ISS. The National Council for RDs has faced some topics deemed a priorities: the simplification of the procedure for ascertaining invalidity, integrated and complex admission and the continuity of the assistance, the reinforcement of the network of centres for rare diseases in Italy, investments in research, the training of physicians in general medicine and the reduction of the time for access to initial diagnosis, the right to treatment for all the rare disease patients (from diagnosis to rehabilitation). The documents produced on these topics were made available on the website of the National Council for RDs. The National Council for RDs presently exists legally as a private body, but continues the work undertaken previously.

2.7. Research

Research, both clinical and basic, is the main instrument of increasing knowledge on rare diseases. Although not conducted on a homogeneous basis in Europe, the volume of research, considered as a whole, remains low compared to the high number of the diseases and their variety. It is therefore necessary to start up initiatives able to attract the interests of researchers and industry in research on rare diseases.

This need nevertheless contrasts with the small number of experts, the limited dedicated resources and the lack of concern for this type of research, which individually has a low social impact. Furthermore, it represents a small, niche market for industry, and basic research is thus often left to the universities. Consequently, it is necessary to overcome a number of “bottlenecks”, starting from the low numbers of patients, which requires the promotion of collaborative studies on the national and international level, and the need to develop alternative clinical plans, applicable to a low number of patients; according to the place, the limited availability of highly technological platforms and the need to invest continuously in innovation. Then there is the issue of the positions due to the clinical features of rare diseases, usually heterogeneous, often not adequately documented as to phenotype, with a natural history which in many cases is little known or unknown and, more in general, the lack of interest in clinical research.

On the other hand, thanks to technological acceleration and progress deriving from the so-called genetic revolutions the expectations of the International Rare Diseases Research Consortium (IRDiRC) are promising and no longer unrealistic. Its goal is to develop 200 new treatments for rare diseases and diagnostic tests for most of them by 2020.

Research on rare diseases, at the present time, has three main sources of funding.

a) National: the AIFA funds independent research with the contribution of 5% of the promotional expenses, paid by the pharmaceutical companies as stated by the Law setting up the AIFA (Law n. 326/2003). The fund is allocated to the undertaking of research on the use of drugs and in particular of comparative clinical trials between drugs, aimed at demonstrating their added treatment value, as well as the trials on orphan drugs and rare diseases. Every year, a tender announcement is issued to the facilities of the Italian National Health Service, research institutes, universities and non-profit associations non-profit on the topics considerate as having priority. There are other dedicated funds, some dedicated to initiatives regarding pharmaceutical products and others issued through tender announcements issued by the Associations and private or non-profit foundations. "E-Rare" is a programme inserted in European projects FP6 and FP7, which propose the improvement of cooperation and coordination of the research activities undertaken on the national or regional level in the Member States and in the associated States, through the creation of research networks. Italy has participated in the first tender announcement together with 5 other countries and in the second tender together with 9 others;
b) European: starting from 1990, Europe has identified rare diseases as one of the priority areas of research in the EU Framework Programmes for Research and Technological Development (FP); in the FP5, FP6 and FP7 programmes dedicated to rare diseases. Italy has coordinated 17 projects and participated in 97 projects (data updated to November 2010);
c) International: the IRDiRC, created in 2011, aims to favour international collaboration in research on rare diseases. This Consortium has been joined by the EC and the US National Institutes of Health, as well as numerous countries, including Italy. In order to achieve the ambitious projects of the Consortium, the first thing is to enhance clinical activity, to make homogeneous data and samples available, with the promotion of translational pre-clinical and clinical research, with streamlining of the ethical and regulatory procedures.

2.7.1. European research

The EC (8 June 2009) has identified research on rare diseases as a priority. On the other hand the sector is known to be a driving force for innovation, not only in the field of biology and genetics, but also in the biotechnology and pharmaceutical industries. Currently, approximately 20% of all innovative products authorized in Europe for marketing are developed for rare diseases. The EC has thus issued to Member States a series of Recommendations identifying as priorities the identification of the research in progress and of the resources dedicate to research on rare diseases; the coordination of the activities on the regional and national level; the identification of the needs and priorities of basic, clinical, translational and social research and on how to promote it; interdisciplinary collaboration; participation in national and community research projects; insertion in plans and national strategies of resources dedicated to the promotion of research on rare diseases; the promotion of research with other countries, to favour the exchange of information and the sharing of knowledge.
As of March 2013, the Orphanet database contained 4,690 research projects, conducted in 27 countries, regarding over 2,177 rare diseases, included 512 basic research projects on genetic studies, mutation analysis, gene expression profiles, genotype-phenotype correlations, functional in vitro, functional studies, animal models and studies on human physiopathology. This important basic research activity is justified by the considerable impact that these studies could also on common diseases, which in the case of rare diseases, often provide reference models for understanding them (we can cite the examples of some Mendelian pathologies such as inherited hypercholesterolemia, Alzheimer's and Parkinson's, which have driven the development of drugs for the treatment of the respective common diseases). Another 480 projects regarded pre-clinical trials (development of drugs and medical devices, gene therapy and cell therapy); 676 clinical research projects (observational and epidemiological studies); 450 research projects on diagnosis and biological markers relevant for clinical laboratories; 169 projects on public healthcare and socio-economic research.
The number of these studies is undoubtedly under-represented in the Orphanet database, since many data, above all industrial, are not easily accessible. Despite these limits, a 2011 analysis of RD Platform identified 581 orphan designations potentially useful for the treatment of 343 rare diseases, which affect over 8 million European citizens. The study also identified 666 clinical trials in progress, focused on 312 rare diseases.

2.7.2. National research

Because of the complexity of the problems involved in rare diseases, all the areas require new knowledge: epidemiological, clinical, basic research and regarding treatment and the improvement of the quality of life and the social services, in order to respond to the needs of the patients.
On the other hand, the capacity of Italian researchers to produce competitive scientific results concerning rare diseases is confirmed by the number of publications and the value provided by the bibliographical indicators. This result seems all the more significant when correlated to the limited availability of dedicated funds. According to a studio by CERM (2009) Italy contributes to over 10% of all the scientific publications on the subject. Our country thus has a good aptitude and tradition for research on rare diseases, and a specific point of strength in the capacity, consolidated over time, to create a national and international network.
In 2011 Orphanet-Italy recorded 654 research projects on rare diseases, including 143 studies dedicated to the identification of disease genes or their mutational analysis, 71 regarding genotype-phenotype correlations, 117 in vitro functional studies, 73 animal models of human diseases, 79 studies on human physiopathology, 40 on preclinical gene treatment, 18 on cell treatment, 14 aimed at the development of drugs or vaccines, 34 on the development of diagnostic protocols or for the identification of biomarkers and 36 observational clinical studies. Furthermore, 110 clinical trials, 80 Registers and 42 networks have been listed.
One aspect of the research, long critical in our country, but now being solved, regards the inadequacy of the instruments for the monitoring and evaluation of the results obtained above all when the research was funded through public funding; starting from the 1990s, were merit-based evaluation systems demanding more scientific rigour were introduced, while previously being not very widespread or not used at all.

Another critical area regards the resources allocated to research on rare diseases, which were often issued on an irregular basis and in many cases failed to provide access to funding in the time stated in the announcements. In Italy there has de facto been no centralized system for correlating the funding and the results of research and a function for the evaluation of the efficiency and efficacy of the public research and innovation programmes. To this end, forms of collaboration should be developed between the Agenzia nazionale di valutazione del sistema universitario e della ricerca (ANVUR – National Agency for evaluation of the university and research system) and the Italian National Health Service to identify and monitor the research activities directly or indirectly relevant for the rare diseases.

Ministry Decree 15 July 1997 requires the sponsor to ensure third party liability for risks deriving from testing on persons taking part in the tests, assigning to the Ethics Committee the monitoring of the existence of suitable insurance coverage. Subsequently, Ministry Decree 14 July 2009 defined the minimum requisites for the insurance policies for protecting the persons participating in clinical trials of the drugs, establishing that the insurance policy must guarantee specific coverage of compensation of damage caused to persons by the experimental activity for the entire period of trials, to cover the third party liability of the experimenting party and promoter, without excluding damage involuntarily caused by something that is accidental and/or attributable to negligence, imprudence or lack of skill, as long as the damage has occurred in the periods indicated in the said decree.

2.8 Training

Training is a crucial aspect in the field of rare diseases.

The growth and professional updating of the healthcare personnel are essential requisites that must be ensured through permanent training.

In Italy, both basic and specialized training is mainly undertaken by the Universities, which manage the university courses and specialization courses; the Regions can guarantee further training. Vocational updating (not only ECM - Continuing Medical Education) for healthcare personnel is organized on the national and regional level (Ministry of Health, ISS, Regions and category associations).

An important area of training interventions involves physicians in general medicine and freely chosen paediatricians, forming the first contact point of the patient with the Italian National Health Service. Their competences are critical in correctly addressing the patient to the specialist in charge of preparing the suspected diagnosis on the basis of which the patient can have free of charge access to the diagnostic services in the national network of facilities. It is therefore necessary to specifically train the physicians in general medicine/freely chosen paediatricians and the specialists in the interpretation of complex symptoms of rare diseases and in the formulation of the suspected diagnosis, to avoid delays in diagnosis and admission.

Updating, or continuing training, is the tool to support the strategic choices of the healthcare organizations and is aimed at implementing and integrating the knowledge provided by basic and specialized training plans: knowledge, skills and abilities on the specific clinical aspects, the coding systems, progress in research, organizational models, the governance of healthcare systems, management, effective communication (currently critical with respect to persons with rare diseases and their families), the multidisciplinary factor and integration of health and social assistance aspects. The correct information to users, their satisfaction, the quality of the services, the results obtained in clinical and social terms, as well as the ratio between the costs and the results must form a significant of the aims to achieve and of the measurements and comparative evaluations between the different local situations.

Rare diseases are studied in pre- and post-graduate university curriculum in various Italian universities. Specific courses are already conducted in degree courses for Medicine, in the training programme of some specialization schools and in the post-graduate diploma courses.

While respecting the autonomy of the universities, this training should be more widespread in the basic and specialized and other training initiatives, classroom and remote. Various training initiatives for rare diseases have been started by the CNMR of the ISS and in particular, by the Regions, the healthcare authorities, regional coordinators and scientific societies, also in collaboration.

The contents of these activities are closely correlated to the organization and availability of services and interventions locally present: relevant topics thus include the procedures for access to the assistance networks dedicated to the management of rare disease patients, the paths defined for the admission of these persons, the treatments available and the procedures of access to them The activities have been undertaken frequently according to the procedures of compulsory education, and addressed to physicians in general medicine, freely chosen paediatricians, hospital and specialist physicians, pharmacists and healthcare technicians, actively in involving the associations for patients and their family members. Furthermore, there have also been courses for training of personnel dedicated to the management of information systems reserved to the admission of persons affected by rare disease.

The Associations and Federations of patients' associations also organize training activities aimed both at patients and professionals. Of these we can recall the experience of "Knowing to Treat", a training programme for physicians in general medicine and freely chosen paediatricians on the aggregations of clinical signs and symptoms to facilitate the suspicion of rare diseases.

2.9. Information **Introduction**

The persons affected by rare diseases and their family members often find it difficult to obtain information of interest to them which has easily identifiable quality. Similarly, healthcare professionals can find to hard to obtain such information also due to the lack of guidelines. In some cases, the information is based on data derived from the observation of only a few patients on the world level, so that no physician can be considered to be an expert. In general, but above all in these cases, the testimonials of the patients are of particular importance, and contribute to the dissemination and development, together with the physicians and other personnel, of knowledge on the needs as a whole (not only healthcare, but also social) of the persons affected. Furthermore, the information on experiences, shared by the persons with the same difficulties, can be useful in order to find solutions to the problems of everyday life and can orient operators towards actions for change and simplification of access to services and treatments.

In this context, information that is validated, updated and easily accessible, and only on the medical aspects of rare diseases, is of great value. Today, dissemination via web is one of the most effective instruments for reaching this goal. Many institutions, not only on the central level, provide validated information through their websites and make available dedicated telephone lines to support and assist patients and their family members.

There follow some of the main validated instruments presently available on the European and national level.

2.9.1. European information sources

The database of the rare diseases and orphan drugs website Orphanet (www.orpha.net), founded and managed by the *Institut National de la Santé et de la Recherche Medicale* (INSERM) in France, is supplied with data provided by the institutes collaborating in the single individual countries. Orphanet is cited as the European reference website for rare diseases and orphan drugs of some EC documents *(Rare Diseases: Europe's Challenge,* 11 November 2008;

Recommendations of the Council on Rare Diseases, 8 June 2009), not only as a source of data on the current situation of rare diseases in the EU, but also as a key element of national strategies on these diseases.

The actions of Orphanet Europe, started in 2001, join the resources made available by the EC for the maintenance of the website activities, with the resources of the Member States which in 2010 identified the national reference bodies of the project. Orphanet - Italy is currently coordinated by Bambino Gesù Children's Hospital - IRCCS.

The website orphasdata.org, created to guarantee the dissemination of the Orphanet nomenclature for rare diseases and to maximize the use of the information collected on the Centres of Expertise, allows direct access to an extract, updated monthly, of the information contained in Orphanet, regarding an inventory of rare diseases, with cross-references with the OMIM catalogue, with ICD-10 and with the recognition of the genes present in HGNC, OMIM, UniProtKB and Genatlas; a classification of rare diseases developed by Orphanet, based on data published by the experts; epidemiological data on rare diseases in Europe, derived from literature (occurrence, average age at appearance, average age at the time of death); a list of signs and symptoms associated with the diseases and their frequency.

Upon request, access is available to other information: the list of orphan drugs, cross-referenced with the diseases, including their stage of development, the orphan designation of the EMA, authorization for sale in Europe; the compendium of over 3,000 rare diseases (in six languages, including Italian); the connection with other websites providing information on specific rare diseases; a list of specialized services and reference centres, diagnostic laboratories, diagnostic tests, research projects, clinical trials, patient registers, registers of mutations, the associations of rare disease patients in the countries of the Orphanet network.

A new project, still being developed, connected with the database, is "Orphanet – urgencies", a series of practical guidelines, validated by the experts and scientific societies, aimed at the personnel who accept patients with rare disease in emergency situations.

The approximately 20,000 users from over 200 countries who daily enter the Orphanet website are 50% formed by healthcare professionals and approximately 25% by patients or their family members.

The aim of the joint European action is to enhance, update and adapt the Orphanet database in the 37 States participating in the network, in particular improving the current level of information on the network of services regarding rare diseases, developing new instruments and services and expanding the number of languages of the database and the documents accessible through Orphanet.

Orphanews Europe is an electronic newsletter of the EUCERD, published online every 15 days starting from 2005 and sent free of charge to over 15,000 stakeholders. Each issue number of the newsletter contains news and points of view on rare diseases and orphan drugs in Europe, subdivided into various sections: an editorial, news from the EUCERD, news on EC policies, other international news, a focus on the projects funded by the EU, news on rare diseases, genetic disease, basic research, clinical research, research on public healthcare, orphan drugs, funding and job opportunities, news from the Associations, new publications and the calendar of the upcoming planned events.

The newsletter is produced in English and is intended to reach all the sectors research sectors on rare diseases and orphan drugs, guaranteeing updating of all the stakeholders on the most significant developments and on new initiatives in this area. Since December 2011, the Italian language edition of the newsletter has been available.

2.9.2 Italian information sources

The website of Ministry of Health (http://www.salute.gov.it/malattieRare/malattieRare.jsp) contains the list of the diseases exempt from participation in the cost of the healthcare services pursuant to of Ministry Decree n. 279/2001, the reference legislation, news in the sector with the relative links and an archive.

The ISS website (www.iss.it/cnmr) provides information on rare diseases, the national network for rare diseases, patients' associations, the activities of the National Centre for Rare Diseases (CNMR), the projects implemented and the services provided.

The website (Italian and English) is aimed at healthcare professionals, institutions, patients' associations, information media and the public in the broad sense. It is structured on two levels: a central one of general interest and some satellite websites with in-depth information on specific projects or topics.

The central part of the website is subdivided into 15 sections, which provide updated information on legislative references on the Italian and European level, exemption entitlement and the list of rare diseases exempted from payment of healthcare fee, the network of facilities of the national network for rare diseases subdivided by regions and with the charters for creation, on the rights of disabled persons, and the CNMR national and international projects and activities. The part dedicated to patients' associations contains a database of the Associations present in Italy (currently over 300) and abroad, and a service for "Contact search" aimed at persons with rare diseases and/or their family members who do not have an association to refer to on the national level and wish to share their experience with others who face the same situation. A FAQ section contains the most frequently asked questions to the CNMR, while the sections "Highlights and Appointments" provide information on events, courses, conferences and workshops on rare diseases organized by the Centre and other institutions. The thematic areas are more in-depth websites dedicated to particular topics or projects of the CNMR: orphan drugs, guidelines, narrative medicine, the Italian network for folic acid promotion, genetic tests and European projects coordinated by the CNMR, for example, EUROPLAN (www.europlanproiect.eu), EPIRARE (www.epirare.eu) and *Rare Best Practices* (www.rarebestpractices.eu). The Registers section illustrates the activities of the RNMR, the National Register of orphan drugs and the regional and inter-regional registers of congenital malformations. The National Helpline for Rare Diseases (TVMR), set up in 2008 and managed by a multidisciplinary team of researchers (psychologists, sociologists and physicians), with clinical and epidemiological and psychological-social, legislative and relational skills, provides information on rare diseases, orphan drugs, the national network and facilities, and the activities of the CNMR. Furthermore, the TVMR (collaborates with the regional Centres of Coordination and their information points and with numerous stakeholders (mainly patients' associations) and forms part of the network European telephone lines dedicated to rare diseases monitored by EUCERD.

The Supplement of the Italian National Health Institute Bulletin "Malattie Rare e farmaci orfani" is a periodical edited by the CNMR, available in both printed and electronic format. Each issue has an editorial and focus, as well as updates on scientific research, the RNMR and narrative medicine, with life stories written by the patients, their family members and healthcare and social assistance personnel, as well as on projects in the sector and international experiences. There are sections dedicated to the scientific events (courses, conferences and congresses) and to the Associations.

The websites of the Regions, the public administrations and the local health authorities. The Regions, the public administrations and local health authorities have websites dedicated to persons affected by rare diseases. The regional and provincial websites described the organization of the regional network with information on legislation, rights, procedures for access, the services that can be provided and eventual integrations to the regional or provincial LEA and on contacts for direct access to the accredited facilities and/or information regional and provincial information centres. some Regions and Autonomous Provinces have organized dedicated helplines (one of which is part of the network of European Helpline for Rare Diseases, monitored by EUCERD), where the patients and professionals have support to find responses to specific problems (for example access to treatments). The information centres, based on the regional network, can provide responses to persons and put services in contact, favouring the integration and continuity of treatments.

Information on the Associations, Federations and Foundations

Most of the websites of the Patients' Associations and their Federations make available scientific information on the diseases of interest, news about the reference centres for diagnosis and treatment, the services they offer to their members and the procedures for getting into contact with other patients.

The Telethon Foundation makes available information on research funded by the Foundation from 1991 to the present, as well as the titles of the projects for which Telethon has provided funds, their content, the names of the researchers, their addresses and institutions. Furthermore, in 2004 Telethon activated a helpline for patients and physicians, providing information on genetic diseases and useful references for the diagnosis and for the admission of patients and updated news on studies under way.

2.10. Prevention

2.10.1. Primary prevention

The implementation of primary prevention strategies is directly related to progress in scientific knowledge about individual diseases, their risk factors and protective factors. Many rare diseases have an uncertain etiopathogenesis, but it is estimated that 80% of them are genetically based and 20% with a multi-factor or acquired origin. Without specific knowledge on the correlations and the figures of occurrence, it is difficult if not impossible, to prevent the risks of disease. Nevertheless, it is admitted that some important groups of rare diseases, like some congenital malformations, originate from complex interactions between genes and the environment, including exposure to some risk factors (for example, environmental and food contaminants, and occupational exposure) and specific lifestyles (for example, alcohol and tobacco abuse, inappropriate diet). Therefore, in agreement with the items highlighted by the National Prevention Plan 2010-2012 for most of the diseases, it is fundamental, when the premises are present, primary prevention interventions must be conducted for rare diseases by removing and containing risk factors, with particular reference to and focus on the most exposed and vulnerable persons. for the specific malformations for which there is a causal relationship with exposure to infective agents, toxic factors and drugs, primary prevention must be implemented in the pre-conceptional and peri-conception period.

The measures for public healthcare consist in the promotion of correct lifestyles to avoid exposure to teratogenic and genotoxic substances(drugs, environmental/occupational xenobiotics etc.), the consumption of alcohol and tobacco, with incentives for a correct diet for women of a fertile age, as well as the appropriate use of folic acid to reduce the risk of occurrence of congenital defects sensitive to folic acid (e.g. Spina bifida).

The various actions specific measures on risk factors should be integrated in a coherent strategy for the primary prevention of congenital malformations, through the correct of drugs, aware of lifestyles, the protection of food products and the work environment etc. In this regard, the EUROCAT (www.eurocat-network.eu) and EUROPLAN (www.europlanproject.eu) projects have developed an overall Recommendations Plan on *"PRIMARY PREVENTION OF CONGENITAL ANOMALIES. Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases",* designed for policy makers, healthcare personnel and women. (www.eucerd.eu).

In order to pursue effective interventions for primary prevention, it is indispensable to make considerable investments aimed at closing gaps in knowledge and promoting activities of studio and research aimed at the understanding of etiopathogenic mechanisms and causal factors in pathology, in order to identify the rare diseases for which effective measures of primary prevention can be implemented. In this context, and with these aims, the RNMR, once it is able to collect the relevant data, can form a valid instrument for knowledge, also able to highlight the causal factors of disease, improve the prevention system and estimate the long term efficacy.

Prevention in the preconception phase, from the clinical point of view, involves a health check-up for the couple, above all for the first pregnancy, which should be conducted from three to five months before planning the pregnancy, by physicians in general medicine in collaboration with the gynaecologist and with obstetrician of the consultancy centre. On the basis of Ministry Decree 10 September 1998, instrument, lab and other specialized diagnostic services, necessary to ascertain any genetic defects and prescribed to the couple by the specialist if the reproductive or family anamnesis shows risk conditions for the foetus, are free of charge to the patient. The pre-conception health check-up as an occasion to perform an anamnesis to prevent reproduction risks as stated in the above-mentioned EUROCAT 2013 document.

The aim is also to implement customized interventions aimed at encouraging the lifestyles necessary for the natural proceeding of the pregnancy.

Genetic consultancy can have an important role in the primary prevention of genetic diseases. this prevention can be addressed by genetic consultancy in couples who have a family member diagnosed as having that pathology or, in general, in consanguineous couples, at risks for recessive autosomal diseases.

2.10.2. Secondary prevention and early diagnosis

One of the main difficulties generally encountered by the persons affected by a rare diseases is that it is impossible to get a prompt diagnosis, ideally as early as the pre-clinical and pre-symptomatic phase. The adoption of treatments in the initial phase of the disease can in many cases considerably improve the health of the patients and the quality of their life.

Diagnosis in the phase without or with few symptoms can be sought when it is an effective advantage for the individual, since are interventions are available for to modify the natural history of the disease, or because the patient wishes to know the reproduction risks. Even if today we can diagnose numerous rare diseases with biological tests (biochemical, genetic, etc.) and eventually morphological tests (echograph diagnosis), allowing prenatal diagnosis, early diagnosis and cascade screening on family members potentially at risk, though interventions effective for the admission of the patients are not always available.

Considering the high frequency of genetic-type rare diseases deriving from a new mutation or segregated in the family, primary prevention measures can be planned, and above all there can be dissemination to the population of information on the potential risk factors.

Screening programmes, not only neonatal, must take into account updated knowledge updated and scientific evidence available.

The European project *"Evaluation of population newborn screening practices for rare disorders in Member States of the European Union",* coordinated by the CNMR-ISS and funded by the European Commission (http://ec.europa.eu/health/rare_diseases/screening/index_en.htm) has highlighted the criteria to develop and start up screening programmes focused on relevance for the newborn (REF).

Starting from above-mentioned project, EUCERD has drafted two documents, available on the website www.eucerd.eu.

Therefore, the new tests must be made available for the diseases that are a serious problem for public healthcare and personal health, in cases where the natural history of the disease is known and where there are appropriate and effective treatments which, if started early, are beneficial for the persons affected.

On the national level the project "Extended neonatal screening: proposal a national operational model to reduce inequality in access to healthcare services in the various Regions" is now under way. It is coordinated by National Centre for Rare Diseases (National Health Institute - Istituto Superiore di Sanità) and funded by the Ministry of Health (CCM). The project, after completion of a survey on the situation in the various regional, aims to explore strategies for the development and application of an extended national neonatal screening programme responding to criteria of homogeneity, coherence, efficacy and transferability in the various regional contexts.

The introduction of new tests in screening programmes, also neonatal, should thus be preceded by an accurate evaluation of the scientific aspects and of the ethical and social implications, the consensus among physicians, paediatricians, epidemiologists, the scientific societies, the associations for patients and their family members, as well as the evaluation of an Ethical Committee. This also applied for metabolic rare diseases, detectable in neonatal diagnosis, and caused by metabolic alterations for which there are diagnostic techniques for identifying numerous pathologies at the same time. There is still under an international debate on the advantage of extended neonatal screening to various types of metabolic rare diseases for which there are treatments with documented efficacy available. The attitude of the European countries in this regard is not homogeneous but tends to be oriented to prudence.

In this regard we can recall that that according to Law 27 December 2013, n. 147, Art. 1, par. 229, within the limit of five million Euros, neonatal screening for the early diagnosis of hereditary metabolic pathologies is to be undertaken, also on a trial basis, in the bases where treatment, pharmacological or dietary, shows scientific evidence as to the therapeutic efficacy or where there is scientific evidence that an early diagnosis at neonatal age involves an advantage in terms of access a treatments in an advanced testing stage, also dietary. The Ministry of Health is currently preparing the provision for the definition of the list of pathologies. In order to favour the maximum uniformity of application throughout Italian territory of neonatal early diagnosis and the identification of optimal user sections proportional to the birth-rate index, the Law has established a Centre for coordination of neonatal screening at the Agenzia nazionale per i servizi sanitari regionali (Age.Na.S. - National Agency for Regional Healthcare Services).

While in the case of the diseases covered by “traditional” neonatal screening the diagnosis and assistance paths have been consolidated, guidelines for treatment paths for newborns affected by the diseases covered by the extended screening and the essential requisites of the facilities conducting such activities are not presently available on the national level,. The trials promoted by the law will help to bridge these gaps. The inter-regional committee has drafted a document highlighting the critical points and minimum requisites to consider in planning the treatment and assistance paths for the newborns selected as affected by the neonatal screening programmes.

Considering the number of tests that must be developed and validated, an exchange of competences on the international level must be promoted to facilitate the choices that each country will then adopt independently, in compliance with European legislation.

The neonatal screening programmes with greatest impact and supported by substantial scientific evidence of efficacy include those for congenital deafness and for some sight defects including congenital cataract.

Pre-symptomatic genetic tests are applied to the persons belonging to families exhibiting genetic diseases with late emergence. The persons rated positive to testing will to develop the disease at a certain time of their life (in the case of complete penetration mutations), or have a high probability of development it (in the case of the diseases with incomplete penetration). The adoption of appropriate lifestyles and the undertaking of clinical and instrumental testing can influence the age of occurrence of some of these diseases and prevent the occurrence of some complications (third level prevention).

2.10.3 Prenatal diagnosis

In Italy, prenatal diagnosis started in the 1970s and has recorded constant and considerable development. Access free of charge to prenatal diagnosis in the Italian National Health Service facilities is governed by Ministry Decree 10 September 1998, which indicated the criteria for the identification of pregnancies with higher procreation risks with respect to the general population. Most prenatal diagnoses at the facilities of the Italian National Health Service are conducted for the identification of foetuses with chromosomal anomalies using cytogenetic tests conducted in the 1st or 2nd quarter of the pregnancy (chorionic villi or amniocytes). Molecular genetic tests, above all in the 1st quarter of gestation, are used in the identification of foetuses affected by genetic diseases in specific pregnancies where the procreation risk is known a priori. Genetic consultancy must always precede the conducting of prenatal tests.

The genetic tests are accompanied by instrumental analysis, especially echography, conducted in virtually all pregnancies and relevant in the early diagnosis of a number of congenital defects including some susceptible to correction at birth. The morphological echography of the foetus, widely used throughout Italy, must comply with adequate quality levels according to the expectations of the couple about the health of the newborn. Furthermore, a broad category of pregnancies is monitored (1st and 2nd quarter of gestation) with biochemical analysis of maternal serum in association with the echographic screening.

These tests, used in a non-homogeneous manner in various regions, do not provide a diagnosis but rather indicate the probability of foetal chromosomal pathology with a relatively high margin of accuracy.

Molecular tests have recently been developed based on the analysis of foetal DNA found in the maternal blood (around the 10th week), thus allowing non-invasive screening of the major chromosomal aneuploids. In Italy, these tests are still used on an experimental basis in very few facilities of the Italian National Health Service. The sensitivity of the test is very high, but the diagnostic certainty is currently obtained only by performing the cytogenetic test on the chorionic villi or amniocytes

3. Aims of the Plan, the actions and the monitoring

The main aim of the Plan is the development of an integrated, global medium term strategy on rare diseases for Italy, focused on the treatment needs of the individuals and their family and defined with the involvement of all the stakeholders, taking into account the experiences already accrued and in the context of European indications.

In order to ensure the governance of the system, a National Committee should be set up, with the participation of all the parties involved (the Ministry of Health and the other Ministries concerned, the Regions, AIFA, ISS, Age.Na.S. and the patients' associations), with the task of laying down the strategic lines to implement in the sectors of diagnosis and' assistance, research, social protection and promotion, training, information and system information, to indicate the priorities of use of resources dedicated to rare diseases and to undertake monitoring activities.

Furthermore, we believe that the Permanent Committee for the checking of the effective providing of the lea stated in the State-Regions agreement of 23 March 2005, should add to the actions to be monitored the interventions to implement this National Plan, taking into account the timing and gradual progression necessary to implement the actions involved in the various regional situations.

There follow the actions to be implemented and the basic instruments to be adopted in the specific areas.

3.1 Network

The implementation and qualification of the national network must proceed in the context of planning agreed between the Regions, in compliance with the general national guidelines, in relation to the occurrence of the individual diseases and groups of diseases, taking into account the evaluations regarding the activities of the individual facilities/facilities of the Italian National Health Service and their experience documented through case histories and the data on scientific activity and production.

In order to guarantee that the network is effective in achieving the overall admission of patients with rare diseases on a multidisciplinary basis, organizational tools can be used, such as specific agreements between the Regions, aimed at setting up "alliances/coalitions" at least for the rarest and most complex diseases from the diagnostic and treatment point of view. The inter-regional agreements can define the procedures for relations between the individual facilities, in particular for the management of the least frequent (ultra rare) rare diseases, according to an agreed system of competences and responsibilities, including the procedures of involvement and collaboration of the associations of the patients and their family members.

Besides guaranteeing that assistance to patients with rare diseases is provided in competent, qualified facilities, this planning must minimize the differences in the providing of services and their accessibility in the various Regions, in any case enhancing the transfer to local services, when possible.

The facilities identified and monitored should receive adequate instrumental and human resources, also considering their capacity of attraction, in order to guarantee their activity over time. The activation of multidisciplinary teams is recommended, when possible in the same facility of the network, through adequate procedures for funding and incentives.

To this end the following actions must be implemented:

- pursue the identification of the facilities of the network for rare diseases by the use of criteria that are, as far as possible, objective, common and agreed, in compliance with the requisites set forth in the European recommendations. These facilities must have a large cohort of users, significant volumes of activity and appropriate performance, develop clinical research, have formal links with the rest of the local network and maintain records of the clinical history of the patient also in the transition from the paediatric age and the adult age. They must undertake the tasks planned for the European Centres of Expertise and be qualified to become part of the ERNs.
- enhance the existing networks by supporting the functional connection between the facilities themselves and with the other facilities and services involved for the admission of patients, in order to guarantee the continuity of assistance;
- undertake the periodical evaluation of the facilities, on the basis of activity and result indicators, as well as patient satisfaction, also with the participation of the Associations and by external auditing procedures with the model already implemented in various EU countries;
- facilitate cooperation agreements between the Regions to create inter-regional areas for assistance intervention, increasingly homogeneous and integrated;
- utilize technological solutions to support the sharing of clinical information (e.g. telemedicine,

teleconsultancy), to reduce the need to move the patients and make available the skills and experience of the reference centres in the locations where the patient lives;

- provide for trials and implementation of new administrative instruments to pay out and guarantee the adequate remuneration of the teleconsultancy services of the reference centres;
- ensure that the dissemination of innovative treatment practices for rare disease patients is always in a context of safety and proved efficacy, for the protection of the patients;
- utilize in an integrated manner regional centres (including the regional registers which have the function of support to assistance) and national monitoring information centres (including the RNMR) as knowledge elements for the orientation of government policies and action and the evaluation of the system;
- develop assistance programmes able to guarantee transition from the paediatric age to the adult age. To this end, the Regions must identify the appropriate procedures to ensure the exchange of information and the sharing of clinical and assistance protocols between the paediatric facilities and the facilities for adults, to accompany the patients and reduce their difficulties; further strengthen the instruments for coordination and integration of the actions already stated by the agreements between the State and the Regions, in a supra-regional context, to minimize the differences in the offer of services and their accessibility between the various Regions and, above all, to allow the patients to be correctly addressed towards the appropriate facilities;
- Incentives to networking between the facilities sharing procedures, prospects and knowledge.

Indicators for monitoring

Indicators are identified in order to measure:

- the functioning of the network in relation to the coverage and capacity of attraction of facilities for the diagnosis of diseases or groups of diseases;
- the availability of functional connections of facilities between them and with the other facilities and services involved in the admission of patients

3.2 National system for surveillance and monitoring: National Disease Register Rare, regional and inter-regional registers and information flow

The regional or inter-regional registers and the National Register of rare diseases must improve the coverage and efficiency of the collection of epidemiological data, to fulfil their institutional tasks. To this end, adopt all necessary measures will have to be adopted to improve the quality of information and to make analyses useful to support the interventions in public healthcare
and improve clinical practice. In particular, it is necessary to standardize the procedures, the contents and the expiry of data collection in the regional/inter-regional registers to the RNMR and the analyses of the data contained in the RNMR at the ISS.
While awaiting the updating of the list of rare diseases, the National Register and regional and inter-regional registers can amplify the collection of the data contained in the minimum data set already agreed, and eventually extend the survey to other diseases, including rare tumours.
This is also in harmony with what is happening in the rest of Europe; this can also take place through the setting up of a database designed to collect epidemiological data of rare diseases being included, and therefore not yet contained in the RNMR, in compliance with regulations in force regarding protection of personal data.
Finally, we must consider the "Core Recommendations on rare disease patient registration and data collection" developed and adopted by EUCERD (www.eucerd.eu).
We can also survey the pathology registers, evaluating their quality, compliance with legislation in force, economic sustainability and opportunities for maintenance.

Indicators for the monitoring

- coverage of the regional and inter-regional surveys and of the completeness and quality of the data sent to the RNMR;

- completeness, quality and reliability of the drafting of the RNMR data in relation to the panel of indicators agreed with the Regions, the public administrations and the Ministry of Health.

3.3 Nomenclature and coding

In order to ensure that rare diseases are traceable in the Italian information system based on the ICD, it will be necessary to:

- unify and standardize the coding of the diseases;
- plan and test the adoption in Italy of the procedures for coding of rare diseases used on the European level *(Orphacode),* in addition to the ICD in some current flows.

Indicators for monitoring

Are identified indicators to measure:

- trials in the use of the Orphacode in some current healthcare data flows and in some regions or Autonomous Provinces.

3.4 Diagnostic, treatment and assistance path

The following actions must be guaranteed:

- implementing all the actions aimed at reducing the diagnostic delay, by interventions and instruments designed to guide and orient physicians towards suspicion of rare diseases;
- if the diagnostic path requires procedures that can be conducted only in operational units not included in the facilities of the network, the treatment facility shall ensure the conducting of the indispensable tests, also at other facilities of the Italian National Health Service, where the diagnosis can be ascertained and confirmed;
- guaranteeing that all diagnostic tests are conducted according to criteria supported by scientific evidence, appropriateness and efficacy, indispensability and safety;
- focusing on and implementation of actions able to allow the admission of persons with diagnosis of a disease according to paths defined and described in the assistance networks (places, procedures, resources and timing);
- defining, also through formal resolutions, preferably agreed on the inter-regional level, of protocols based on guidelines and international scientific evidence and with treatment paths organized, guaranteed and defined in relation to the profile of patient treatment needs;
- disseminating and sharing the diagnostic and treatment protocols drawn up by the Regions for individual diseases and/or groups of diseases so that they can be adopted as uniformly as possible on the national level, in compliance with the essential assistance levels and organizational and logistic characteristics of each Region and Autonomous Province;
- updating LEA with particular focus on the treatment needs of the rare disease patients;
- promote trials and the dissemination of treatments, also innovative, able to replace of compensate functions lost or abilities harmed due to rare diseases of treatments for support and countering of symptoms related to a rare disease;
- avoiding any form of discrimination of access to treatments effective for the persons with rare diseases or with disabilities deriving from rare diseases;
- guaranteeing that the interventions included in the treatment plan are preferably conducted by the hospitals or local and district services near to the place of residence of the persons with rare diseases, focusing on the use of home treatments;
- guaranteeing the coordination of the multidisciplinary interventions for the cases requiring this, with continuous assistance on the hospital and local level;
- favouring access by specialists and professionals of the pertinent Local Health Authorities to the network facilities, also in other Regions, to update the skills necessary

- to adequately follow their patients;
- managing the transition phase of the patient from the paediatric to the adult age, in such a way as to ensure assistance continuity;
- defining actions on the national level and performing actions on the regional level in order to make it possible to provide pharmacological and other treatments in the school environment;
- providing, when possible, for short relief admissions to non-hospital residential facilities;
- for the rare diseases requiring intensive care, guaranteeing support to the family and/or those perform treatments and participating in the implementation of the assistance plan (caregivers);
- testing the integration procedures between the existing networks concerned with rare forms of various pathologies, including tumours, in order to achieve agreed organizational models and procedures for monitoring and action, as takes place in the other European countries.

Indicators for monitoring

Indicators are identified to measure:

- updating of the list of rare diseases attached to Ministry Decree n. 279/2001;
- updating the LEA with special regard to the treatment needs of rare disease patients.

3.5 Associations/Empowerment

The decision-making processes to define the interventions, the planning of services and their evaluation must utilize the set of knowledge and skills derived from experience, the patients and their family members.

The following actions must be guaranteed:

- providing incentives to the creation of a collaborative relationship aimed at the participation of patients in the decision-making processes, encouraging their information and training and supporting solidarity and community-based attitudes;
- in the assistance path, the inclusion of the patients and/or their family members in all the decisions regarding them must be ensure by the use of a comprehensible and shared language, and the systematic identification of the needs through the involvement of the patients and their family members;
- focusing on the respect of the right to education and training, work and social participation;
- the participation of patients' organizations in the decision-making processes must take place according to the principle of representativeness.
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Indicators for monitoring

Indicators are identified to measure:

- the formal participation of the representatives of patients' associations in national and regional planning activities regarding rare diseases.

3.6. Research

In order to promote studies able to respond to the health needs of persons with rare diseases, research on rare diseases on the clinical, biomedical, public healthcare and social level must be identifiable and traceable. In order to reach the aim of enhancing and supporting these research activities, the following measures must be adopted:

- concentrating resources dedicated to research on rare diseases with priority on the least developed areas (clinical, public healthcare and social-healthcare) and addressed to the needs of patients, on aims shared by the Centres of Expertise and scientific excellence;
- promote multidisciplinary research, favouring national aggregations able to created a critical mass that can facilitate participation in international consortiums;
- concentrating resources preferably on institutions that have demonstrated capacity and competence in research;
- building a system for the traceability of research on rare diseases and subsequent evaluation of the results obtained;
- developing and enhancing the instruments to support research and clinical activity for rare diseases (EMB, guidelines, protocols, epidemiology of small numbers etc.)
- developing strategies to disseminate the results and transfer them to clinical practice;
- providing for certain and targeted functioning for research, reserving part of the funds provided on the central and regional level;
- adopting procedures to ensure that funding is issued on a continuous basis and in compliance with the timing stated in the tender announcements;
- promoting the transfer of research results from the places of clinical testing to treatment facilities;
- simplifying procedure and providing the support necessary for increased phase I trials in Italy (both on the patient and on healthy volunteers);
- promoting, also with the help of the Associations and through scientific coordination between the Regions, synergies for groups of pathologies, to coordinate the activities and case studies;
- promoting the development of a collaborative model between the main protagonists of research on rare diseases: patients, physicians, researchers, enterprises, public institutions and the private companies funding research, with the creation of consortiums including the private companies;
- identifying the priorities for basic, clinical, translational and social research and promote interdisciplinary cooperative approaches favouring the participation of Italian researchers in research projects funded at all levels, including the European level, and facilitate, in collaboration with the EC, the development of cooperation with non-EU countries active in the sector, also with regard to the exchange of information and the sharing of skills;
- promoting and funding research projects also focused on innovative and complex non-pharmacological treatments (prostheses, robotic, transplants, rehabilitation etc.) which can significantly determine the quality of the individual's life.

Indicators for monitoring

Indicators are identified to measure:

- the number of new research projects on rare diseases funded by the Ministry and Regions, AIFA, ISS, AG.e.N.A.S;
- the adoption of procedures for collaboration with ANVUR for information regarding the specific area of rare diseases.

3.7. Training

The training targets are professionals, patients and their Associations, the persons in assistance (caregivers, family members, volunteers). The various training initiatives should be coordinated on all the levels of the system (Local Health Authorities, Hospital Authorities, research institutes, universities and specialization schools) and for all healthcare social-healthcare personnel, through the priority interventions identified in this paragraph.

There must be a particular focus on the training plans targeting physicians in general medicine and freely chosen paediatricians, so that they can:

1) correctly direct the patients to the specialist of the Italian National Health Service able to formulate the suspected diagnosis in the shortest time possible and orient them to the specific facility of the network for rare diseases able to guarantee the diagnosis of the disease;
2) contribute actively to the admission of the patient.

Appropriate methodologies must likewise be used, and teacher training must be supported in the specific sectors of rare diseases.

The training should be extended to the development of instruments and methods designed to support the development of guidelines for the clinical management of patients and to guarantee the dissemination and implementation of the existing guidelines also available on the international level.

3.7.1 Professionals

- **Basic training:** degree courses in Medicine and all the healthcare professions should provide for knowledge about the specific aspects of admission of patients with rare diseases, with reference to the organizational models of the healthcare system in our country and the socio-healthcare dimension of rare diseases.

- **Specialized training:** in 2nd level training (specialization schools and master's degrees), the topic of rare diseases must be integrated in the specific contents of each course in order to acquire knowledge on rare diseases coming within the sphere of interest.

- **Specific training** in General Medicine must provide for a focus on rare diseases with the covering and extension of the topics already introduced in the basic degree course.

- **Continuing training**: the topic of rare diseases must be inserted in the national and regional continuing courses and in the healthcare authority training programmes; on the local level locale it is desirable to create systems for the evaluation of the efficacy of continuing training to modify the treatment practices of professionals (activating evaluation systems for the quality and efficacy of training, with result indicators).

3.7.2 Patients, caregivers, family members, volunteers

There must be specific training programmes for "patients" and their Associations, ordered by groups of pathologies, treatment needs and practices and involving decision-making processes. The regional or inter-regional assistance networks and the national training agencies and institutes have the task of planning actions to provide individual patients and their family members with knowledge

and competences for the management of their condition. Examples of actions are the self-help groups, parent training, parent to parent, etc.
The persons involved in assistance to patients must be trained to skilfully undertake their role, through specific training plans developed and conducted by the Expertise Centres and the local services. In these training projects there is a particular supporting role for the users' associations. Examples of interventions can also include instruments suited for remote training.

Indicators for monitoring

Indicators are identified to measure:
- the number of continuing training courses, including the courses accredited on European level, dedicated to rare diseases (under continuing training activities)

3.8 Information

There should be action to guarantee the enhancement and support to the maximum dissemination of the institutional information sources currently available (websites, national, regional and local local telephones and information points), promoting their use by all the stakeholders and with the participation of patients in the planning phase of the measures to provide information on rare diseases:

- each information source must provide for the training of personnel assigned to provide the information and adopt systems of verification and checking of the quality of the information provided.

Indicators for monitoring

Indicators are identified to measure:
- the number of institutional help lines existing on the national level

3.9 Prevention

3.9.1 Primary prevention

It is necessary to promote and enhance the following interventions:

- always making available preconception counselling for couples in the fertile age who are planning a pregnancy, and monitoring in pregnancy;
- implementing programmes to provide incentives to the adoption of correct lifestyles (including a correct diet and the appropriate taking of folic acid); •
- evaluating the consequences of cascade screening in terms of health;
- favouring genetic consultancy, when required;
- undertaking national study and research activities on the causal factors (major or minor) of rare diseases and on the factors that can contribute to their pathogenesis, by fostering their development or accelerating their progression (risk factors and/or conditions);
- collaborating in the international debate to define which rare diseases can benefit from primary prevention measures;
- operating, in accordance with the provisions of the provisions of the National Prevention Plan 2010-2012, regarding the "Prevention of pathologies from exposure to chemical, physical and biological agents" (par. 3.3.b) and with the indications provided by the document "*PRIMARY PREVENTION OF CONGENITAL ANOMALIES. Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases*" regarding primary prevention of congenital malformations developed by EUROCAT and EUROPLAN (www.eucerd.eu).

3.9.2 Secondary prevention

- The priority aim in this area is the improvement of early diagnosis (clinical, clinical-genetic and neonatal) of rare diseases, provided in the Italian National Health Service. To this end, the following is recommended:
- implementing operational models for screening programmes for rare diseases, including population screening in the neonatal age, based on scientific evidence, criteria of fair access, ethical aspects, availability of treatment with proven efficacy;
- for the rare genetic diseases (cluster at risk), making available genetic consultancy to the family members of the persons affected;
- activating the procedures for the diagnosis of stillborns when necessary for the definition of risks of recurrence;
- promoting the informed consent to the undertaking of the screening tests and the communication of the results, also if negative;
- ensuring the definitive implementation of the agreement between the Government, Regions and Autonomous Provinces of Trento and Bolzano regarding guidelines for the activities of medical genetics (Act n. 241/CSR of 26 November 2009). In particular, promoting and adopting diagnostic and assistance paths in accordance with guidelines scientifically validated and oriented to guaranteeing the appropriateness and quality of the services, and calling for an adequate pre- and post-test genetic consultancy and comprehensive and exhaustive information to the patients and family members; defining the best geographical distribution, the characteristics of the accredited facilities and their adequate organizational layout, in order to concentrate the case studies with facilities and personnel who can guarantee an adequate volume of activities associated with a constant updating of knowledge and technology; adopting, when not already provided for in the pertinent regional regulations, accreditation procedures for the facilities providing medical genetic services (laboratories and clinical facilities) which provide specific criteria, including the participation in external quality audits and certification mechanisms;
- strengthening the training of the physicians in general medicine and freely chosen paediatricians on the aggregations of clinical signs and symptoms able to determine the suspicion of rare diseases, facilitating and accelerating the transfer of the patient with a suspected diagnosis to the specialized clinical services of the national network for rare diseases.

3.9.3 Prenatal diagnosis

The priority aim of prenatal diagnosis is the early recognition of foetuses affected by rare diseases and to address the parents to facilities qualified for the treatment of the mother and the newborn with the use of treatments that can change the natural history of the disease (secondary prevention). A major goal of prenatal diagnosis is also to guarantee the right to responsible maternity and paternity and the consequent aware choices.

The following actions are planned:

- guaranteeing access to prenatal diagnosis for couples appropriately identified on the basis of higher risks with respect to the general population;
- undertaking a prenatal morphological test in specifically accredited facilities and by professionals having special qualifications;
- developing the regional initiatives for accreditation and certification of facilities and genetics laboratories dealing with prenatal diagnosis.

Indicators for monitoring

Indicators are identified to measure:

- the increase of diagnosis at birth of diseases for which treatment is available, to be selected on the basis of single code ICD9-CM and traceable by hospital release form flows.

3.10 Drugs

The aims of the Plan are the reduction of waiting times for the availability and effective use of the drugs to be used for the treatment of rare pathologies.
The following actions are required:

- simplifying and standardizing the procedures for prescription, procurement, issuing and administration of treatments;
- favouring the continuous discussion and collaboration between the Technical Inter-Regional Board for Rare Diseases and AIFA for maintaining the list of Law n. 648/1996 and for the management and access to the AIFA fund for orphan drugs (Law n. 326/2003) and the procedures for monitoring innovative products;
- enhancing and highlighting the role of the Stabilimento Chimico Farmaceutico Militare (SCFM) to ensure the availability of drugs and other treatments for rare diseases, at a low cost.

Indicators for monitoring

Indicators are identified to measure:

- the number of the orphan drugs authorized in on the European level and available in Italy
- the number of the drugs introduced in the list attached to Law n. 648/1996.

3.11 Economic sustainability

This Plan is not supported by the allocation of specific resources, considering the ordinary funding procedures in the Italian National Health Service, as well as the difficult and continuing economic crisis.

The assistance to persons affected by rare diseases is mainly funded by the resources ordinarily allocated to the Italian National Health Service and distributed annually between the Regions. The resources actually allocated to the assistance of rare diseases vary in the different Regions, also in relation to the budget resources. The safeguarding of the principle of fairness between citizens and the greater homogeneity in the availability of treatments between the various Regions must be pursued through an updating of the LEA with a particular focus on the assistance requirements for rare diseases.

The processes of checking prescription appropriateness, which must be implemented by the Regions through the agreement on and definition of the diagnostic, treatment and assistance path, will free resources that must be partly reinvested in appropriate assistance to persons with a rare disease.

During the 3-year period of validity of this Plan, management and administrative trials will be favoured in order to evaluate the feasibility of remuneration procedures that will take into account the complexity of managing assistance in rare diseases in the hospital and geographical setting. Tariffs regarding specific services of telemedicine and teleconsultation must also be tested.

In order to support the actions for planning, orientation of services, training and monitoring, changes, also legislative, may be evaluated to the current system of funding, and which will involve the reserved allocation of NHF quotas to the rare disease care system.