ÜNIAMO
Federazione Italiana Malattie Rare

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MonitoRare

VIII Report on the situation of people living with a rare disease in Italy

EXECUTIVE SUMMARY

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Executive summary

The last 2 and a half years have been characterized by the serious epidemiological emergency from Covid-19 that, especially at peak times in the different waves, but not only that, has strongly influenced the daily life of the entire population and the functioning of the health system clearly oriented to give timely responses to the pandemic.

The field of rare diseases has therefore been physiologically affected by some slowdowns, but there have been, even in this complex period, some steps forward: the picture of the national rare disease network according to the EUCERD indicators indicates a marked progress, linked, mainly, to the adoption of **Law 10 November 2021, n. 175 "Provisions for the treatment of rare diseases and for the support of research and production of orphan medicinal products"** - which provides for: 1) the establishment of the **National Committee for Rare Diseases** with the involvement of the most representative organisations of people with rare diseases at national level; 2) the approval of a **National Plan for Rare Diseases** at three-yearly intervals; 3) specific **measures to support research on rare diseases and the development of orphan medicinal products** and 4) a **solidarity fund to support the care and assistance to rare disease patients.** The aim of the standard is to protect the right to health of persons with rare diseases by means of measures aimed at ensuring:

- uniform provision of services and medicinal products, including orphans, throughout the country;
- coordination, regular updating of levels of care and the list of rare diseases;
- coordination, reorganization and strengthening of the national network for rare diseases established by the regulation referred to in the decree of the Minister of Health of 18 May 2001, n. 279 including the centres that are part of the European Reference Networks (ERNs), for prevention, surveillance, diagnosis and treatment of rare diseases;
- support for research.

A further boost to international political action on rare diseases came from another important measure of late 2021: the **first resolution in favour of people with rare disease issued on 16 December 2021 by the UN**, during the 76 session of the General Assembly. A historic resolution that puts rare diseases on the agenda and, therefore, between the actions and priorities of the United Nations. The resolution commits all 193 Member States to take measures to ensure greater integration and social inclusion for people with a rare disease. In Europe, this will result in the hoped-for development of a European action plan for rare diseases, which has already been brought to the attention of the European Commission.

At the national level, a signal of attention to the world of rare diseases also came from the **National Recovery and Resilience Plan**, which provides, for the period 2023-2026, specific **support measures for rare disease research** (EUR 50 million, whose call for proposals was published in the spring) and **on rare cancers** (EUR 50 million) as well as major investments for

projects on the so called. “after us” and for the independent life of people with disabilities. (500.5 million).

To date, unfortunately, it must be stressed that **none of the implementing measures has yet been defined, the implementation of which was planned in the first 6 months of entry into force of Law No. 175/2021** (on 12 December 2021).

To date, moreover, **the update of the “ENBS panel” (Extended New-born Screening)** has not been carried out either, despite the positive opinion on the introduction of SMA (spinal muscular atrophy) was handed over by the Working Group to the Ministry over a year ago. Without forgetting that the forecast of enlargement of newborn screening panel extended to neuromuscular diseases of genetic origin, severe congenital immunodeficiencies and lysosomal storage diseases date from the end of 2018. (Law no. 145 of 30 December 2018). A sign of hope on this topic comes from the many Regions that are today implementing and/or experimenting with neonatal screening for other diseases not included in the current panel.

Despite these limitations, the national ENBS (Extended Newborn Screening) programme remains a flagship of the Italian rare disease network in the European Union: Internationally, our country is second only to the United States for the number of rare diseases subject to newborn screening. Other strengths of the national rare disease network in the international comparison are represented a) by the organizational model of regional rare disease networks, in accordance with national policy, and the excellence of several centres of competence confirmed also by the results of the second call for participation in the European Reference Networks whose results were made official in November 2021; b) the accessibility of the medicinal products also through the different paths defined over time; c) the surveillance and monitoring system implemented on a regional/interregional and national basis and d) the existence of several institutional help-lines of reference for rare diseases. On the other hand, the critical aspect identified, namely the absence of funding specifically dedicated to the implementation of the NPRD, remains (ID 18): paragraph 4 of art. 9 of Law no. 175/2021 affirms that from the implementation of the aforementioned article - which contains the forecast of both the NPRD on a three-year basis and the reorganization of the national network for rare diseases divided into regional and interregional networks - no new or greater burdens must be borne by the finance public.

For the more specific aspects, this year too, there are numerous food for thought that emerge from reading of the “MonitoRare” report and which lend themselves well to subsequent in-depth studies. In these first pages, we grapple with the arduous task of trying to effectively synthesize the picture of this eighth edition of the report with the sole intention of offering to the reflection some elements that, more than others, assume a strategic role for the future of the assistance to people with rare disease (PLWRD) and their families internationally, nationally and locally.

Some examples of the strengths of the rare disease system in Italy that the eight edition of Monitor Confirmation are:

- **Access to therapies**
  - **8 million doses of orphan medicinal products were delivered in 2020,** which represent **only 0.03% of total pharmaceutical use**;
  - **expenditure on orphan medicinal products in 2020 amounted to € 1,393 million,** with an **incidence of 6.0% on total pharmaceutical expenditure;**
  - **the number of orphan medicinal products for rare diseases included in the list of Law No. 648/1996 has increased from 27 in 2012 to 38 in 2021** (there were only 13 in 2012);
  - **the number of people with a rare disease who have benefited from the AIFA fund** (referred to in Law 326/2003, Art. 48) drops in **2021 to 1,010,** after witnessing an exponential increase in previous years, **from 20 people in 2016 to 1,361 in 2020;**
  - 8 of the 14 Advanced Therapy Medicinal Product (ATMP) with European approval (data updated at the end of 2021), are currently reimbursed in Italy, while 3 AMTP are being evaluated - one concluded the evaluation phase of the Committee on Prices and Reimbursement and pending publication in the OJ, 2 being evaluated by the Committee on Prices and Reimbursement (in Europe we are second only to Germany and England which reimburse 10);

- **access to information**
  - **16 Regions/PPAA** have an **institutional information system specifically dedicated to rare diseases:** over 11, 200 PLWRD with which they came into contact in 2021, to which must be added the more than 3,700 PLWRD come into contact with the Rare Diseases Helpline of the National Centre for Rare Diseases of the National Institute for Health (CNMR-ISS):

- **the training**
  - The number of CME courses dedicated to rare diseases reached 49 in 2021 (45 in 2020); there was a **significant increase in CME training events carried out ONLINE (32 in total compared to 6 in 2019)** which partially compensated for the impossibility of carrying out training activities in the presence due to the Covid-19 pandemic;

- **newborn screening and clinical laboratories**
  - At the end of 2021, the **extended newborn screening programme is active in all Regions/Autonomous Provinces.** There is also a growing homogenisation of the number of diseases included in the screening panels at regional level;
  - the Prime Ministerial Decree (DPCM) of 12 January 2017 "Definition and updating of essential levels of assistance" in art. 38 guarantees all newborns the services necessary for the early diagnosis of congenital deafness and congenital cataract. **At the end of 2021, neonatal audiological screening was active throughout the country. Similarly, neonatal**

ophthalmological screening is active throughout the country with the sole exception of one Region where it is being implemented;

- **constant growth in the last five years of the number of rare diseases tested in the Italian clinical laboratories** considered in the Orphanet database, which, given the substantial stability of the number of laboratories, **increase by 1,200 units in the space of 5 years:** from 1,503 in 2017 to 2,779 in 2021.

- **the quality and coverage of surveillance systems**

  - **the coverage of rare disease regional registries (RDRR) increases:** the estimated **prevalence on the population** of persons included in RDRR at 31.12.2021 rises to **0.75% (0.89% in children under 18)** from 0.30% of the first edition of the Report monitor in 2015;

  - **the data contained in the RDRRs relate to all rare diseases referred to in Annex 7 of the DPCM 12.01.2017: based on the over 414,000 PLWRD recorded in the RDRRs at the end of 2021 (+ 37,000 units compared to the previous year) the most present group is that of diseases of the central and peripheral nervous system (15.7%), followed by the group of congenital malformations, chromosomopathies and genetic syndromes (14.2%), then diseases of the blood and hematopoietic organs (12.7%)**; all the other groups of pathologies have a percentage weight of less than 10% on the total. on the total less than 10%;

  - **the differences in age are very significant: in children / young people over 38% of rare diseases are attributable to the group of "Congenital malformations, chromosomopathies and genetic syndromes",** whose percentage weight is reduced to less than 9% in adults for which the modal class, on the other hand, is the group **of "Diseases of the central and peripheral nervous system" (just under 18%);**

  - **1 person with a rare disease out of 5 of those included in the RDRR is under 18 years of age;**

  - the phenomenon of health mobility is relevant: the estimate of mobility on RDRR data is 17% in the total population and reaches over 25% in minors;

  - based on the data **currently** included in the RDRRs, **the number of people with rare disease** exempt in our country should reach over **600,000** units with an estimated prevalence of 1.08% of the population;

  - according to the most recent studies[1], the prevalence of rare diseases would be between 3.5% and 5.9% of the population worldwide: the total number of people with rare disease in Italy would consequently be between 2, 1 and 3.5 million people, a figure far higher than that of exempt PLWRD only.

[1]Stéphanie Nguengang Wakap, Deborah M. Lambert, Annie Olry, Charlotte Rodwell, Charlotte Gueydan, Valérie Lanneau, Daniel Murphy, Yann Le Cam, Ana Rath "Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database", European Journal of Human Genetics, 16 September 2019.

- research

  - **the weight of authorized rare disease clinical trials on the total number of clinical trials is increasing: from 25.5%** in **2017** to **31.8% in 2021** (up by 32.1% in 2019). The number of authorized clinical trials on rare diseases has increased to 260 in 2021 (195 in 2020);
  - in 2021 **clinical trials on rare diseases** in **Phase I and II reach the threshold of 50%** of the total (49.2%);
  - a slight increase in the **weight of active substances of a biological/bio-technological nature** representing 31.1% **of the total number of clinical trials on rare diseases** compared to the previous year (28.7% in 2020). More widespread, in clinical trials on rare diseases, the ATMP (1.9% vs. 1.1%), although decreasing compared to previous years;
  - the trend of reducing the presence of Italian research **groups in rare disease projects included in the Orphanet platform** continues: **7.6% in 2021** (compared to 19.9% in 2016);
  - **492 the current research projects on rare diseases carried out by the Scientific Institute for Research, Hospitalization and Healthcare (IRCCS,** which according to the prevision of the NPRR should be subject of a re-organization) **in 2021 (13.6%** of the total, up from the previous year) **for a value of almost 16.8 million euros;**
  - **11 million euro (19.2%** of the total) the resources of **targeted health research invested** by IRCCS on rare disease projects (a stable figure compared to the previous year but a sharp increase compared to 2019);
  - the number of participating centres, the number of people involved and the number of diagnoses perfected by the various programs implemented for undiagnosed diseases increase.

- **the quality of centres of competence**

- There are **223 reference centres for rare diseases** identified by Regions/PPAA (3.7 per 1 million inhabitants); 83 of these are part of at least one ERN (66 until the end of 2021);
- **Italy remains first in the number of health care providers (HCPs) members of the ERNs even after the call for enlargement** whose results were announced at the end of 2021: 333 out of about 1,500 (more 1 out of 5 as before) and Italian HCPs are present in all ERNs except one (only France, Holland and Belgium are present in all 24 erns). The median figure for the presence of Italian HCPs in ERNs is 12 (it was 6 at the end of 2020);
- with regard to **cross-border healthcare, Italy is characterized by a much higher level of active mobility** (incoming patients, about 8,290 per year in the period 2016-2020) **compared to passive mobility** (outgoing patients, about 180 per year in the period considered);
- during 2020, another 17 **Therapeutic Diagnostic Care Pathways** (PDTAs) were approved by Regions/PAs, bringing the total number to over **320 PDTAs** defined at the end of 2021;

- **the active participation of people with rare diseases and their organisation representatives**
- the number of **Italian associations of people with rare disease** rises to **670** (1.4 per 100,000 inhabitants);
- **14 Regions/PPAA** provide for the **presence of representatives of associations of rare disease patients in regional participation bodies on rare diseases;**
- **3 representatives of people with rare disease are members of the "Newborn Screening Coordination Centre"** provided for in art. 3 of Law No. 167 of 19 August 2016 "Provisions on newborn diagnostic tests required for the prevention and treatment of inherited metabolic diseases";
- **a representative of PLWRD is member of the national coordination centre of the territorial ethics committees** provided for by Law no. 3 of 11 January 2018 *"Delegation to the Government for clinical trials of medicinal products and provisions for the reorganization of the health professions and for the health management of the Ministry of Health";*
- **a representative of PLWRD has been identified as a member of the Newborn Screening Working Group.**

It should also be noted that, at the end of 2021, **16 Regions / PPAAs have included the issue of rare diseases within the general health planning tools** (in force or in the process of being approved in 2021) or that have defined a Regional Plan for Rare Diseases.

The other side of the coin is represented by the criticalities, some of which mentioned above, that persist, such as **the territorial inequalities in access to health, social and social services**, of which some exemplifications:

- the lack of homogeneity in the geographical distribution of the Italian hospitals participating in the ERNs: 7 Regions/PPAA do not have any ERNs participating centres and 2/3 of the hospitals participating in at least one ERN are located in the northern regions. This is not irrelevant also in view of the prospect of 'integration of the centres participating in the ERNs (centers of "excellence" according to L. 175/2021) in the national network rare diseases;
- the difficulty in accessing care as evidenced by the data on the health migration of minors with rare disease exempt highlighted by the RDRR and which is also exemplified by the fact that of the 159 patients treated with ATMP CAR-T in 2020, more than half (n = 83; 52.2%) were in the Lombardy Region;
- the still incomplete activation of the extended newborn screening referred to in Law No. 167/2016 and the failure to update the panel of pathologies to be included;

- the lack of definition of the Diagnostic Therapeutic Care Paths of people with rare disease in some territories and the diversity of the models adopted for the definition;
- the still partial coverage of the entire exempted population of people with rare disease from some of the Regional Rare Disease Registries.

Three years after the establishment of the **working group for the elaboration of the Second National Plan for Rare Diseases** - in which the representation of the community of people with rare disease has also been foreseen, recognizing this fundamental role of advocacy to UNIAMO - the technical text was delivered in May to the Ministry of Health. To date, however, - **regardless of what UNIAMO has done in recent years through the report MonitoRare -** lacks **an assessment of the PNMR 2013-2016 that should have been the starting point of the new Plan.**

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