MonitoRare 2025 – Executive Summary

Once again this year, the MonitoRare report provides numerous points for reflection and, as usual, for further, more detailed analysis. In these first few pages, we attempt the arduous task of summarising this eleventh edition of the report with the sole intention of offering all stakeholders in the rare disease field some elements that, more than others, currently play a strategic role in the future of care for people living with rare diseases (PLWRDs) and their families at international, national and local level. Some examples of the strengths of the rare disease system in Italy, as confirmed by the eleventh edition of MonitoRare, are:

Drug accessibility

- as of 31 December 2023, out of a total of 155 orphan medicinal products authorised by the EMA, **146 were available in Italy** (+ 94.2%, from the previous year);
- in 2023, **14.9 million doses of orphan medicinal products** were dispensed (3.5 million more than the previous year), representing just **0.05% of total pharmaceutical consumption;**
- **expenditure on orphan medicinal products in 2023 amounted to €2,231.5 million, accounting for 8.5% of total pharmaceutical expenditure**; €1,096 million was spent on orphan medicinal products that meet the innovation requirement;
- **the number of medicinal products for rare diseases included in the list of Law No. 648/1996 grew from 31 in 2018 to 68 in 2024** (there were just 13 in 2012);
- **the number of people with rare diseases who benefited from the AIFA fund** (referred to in Law 326/2003, Art. 48) continues the decline that began in 2021, following changes to the eligibility criteria, reaching 92 in 2024, after seeing an exponential increase in previous years, from 20 people in 2016 to 424 in 2020;
- in 2024, **3,503 people with rare diseases were treated in one of the 28 active compassionate use programmes**, of which 16 (for a total of 1,000 patients; + 490 compared to 2023) involved medicines that received orphan designation from the COMP and 12 medicines intended for rare diseases but not designated as orphan medicinal products (for a total of 2,503 patients; + 749 compared to 2023);
- **12 of the 27 Advanced Therapy Medicinal Products (ATMPs) with European approval are currently reimbursed in Italy**, 4 ATMPs are currently being evaluated by AIFA, and 2 have not been granted reimbursement. Total national expenditure on ATMPs grew in 2023 to €121.4 million (+41.6% compared to 2022);

Access to information

- **17 regions/PPAAs have an institutional information system specifically dedicated to rare diseases**: almost 11,400 PLWRD come into contact in 2024, in addition to the more than 2,400 PLWRDs who contacted the Rare Diseases Helpline of the National Centre for Rare Diseases of the National Health Institute (CNMR-ISS);
- over 37 million visits and over 7 million pages viewed in the last year on the website www.malattierare.gov (almost double the number compared to 2022);

Training

- The number of CME courses dedicated to rare diseases stands at 76 in 2024 (18 of which feature a UNIAMO representative among the speakers), a trend that is continuing to grow. There has been a positive return to **face-to-face training**.

Diagnosis, newborn screening and clinical laboratories

- since the end of 2023, **the extended newborn screening -ENBS- programme has been fully operational in all regions/autonomous provinces**, and the homogenisation of hereditary metabolic diseases included in regional screening panels pursuant to Law 167/2016 can be considered achieved. Furthermore, more than half of the regions/autonomous provinces have expanded the panel of diseases often as part of experimental projects.
- from 2022, the ENBS programme has reached the total coverage of the population.
- article 38 of the Prime Ministerial Decree of 12 January 2017, "Definition and updating of essential levels of care", guarantees all newborns the services necessary for the early diagnosis of congenital deafness and congenital cataracts. **At the end of 2024, neonatal audiological and ophthalmological screenings are active throughout the country.**
- the **€1 million funding for the "Next-Generation Sequencing Test Fund" for the diagnosis of rare diseases** has also been confirmed for 2025.

The quality and coverage of surveillance systems

- according to the most recent studies, the prevalence of rare diseases is estimated to be between 3.5% and 5.9% of the global population: **the total number of people with rare diseases in Italy would therefore be between 2.1 and 3.5 million, a figure far higher than that of PLWRDs who benefit from the exemption** In Italy, since 2001, with the approval of Ministerial Decree no. 279/2001, people affected by rare diseases have the right to exemption from the ticket only if their pathology is included i**n the list drawn up by the Ministry of Health** which also includes groups of diseases.;
- **the coverage of regional rare disease registries (RRMR) is increasing: almost 500,000 people with rare diseases** as of 31 December 2023 and were included in the RRMRs of their region of residence (+30,000 compared to the previous year);
- the estimated **prevalence** in the **population** of people with rare diseases as of 31 December 2023 and included in the RRMRs rises to 0.84% (0.94% in children under 18) from 0.30% in the first edition of the MonitoRare Report in 2015;
- **the phenomenon of healthcare mobility is significant**: the estimate of mobility between regions based on RRMR data is **18% of the total population** and reaches **24% in minors**;
- **the estimate** (including the phenomenon of mobility) **of the number of people with rare diseases who are exempt and alive at the end of 2023 is between 585,000 and 738,000. The estimate for minors is between 103,500 and 127,000;**

- **the data contained in the RRMRs relate to all rare diseases listed in Annex 7 of the Prime Ministerial Decree of 12 January 2017**. The most common group is **"Diseases of the central and peripheral nervous system" with 15.2%, followed by "Congenital malformations, chromosomal abnormalities and genetic syndromes"** with 14.1% and "**Diseases of the blood and blood-forming organs**" with 13.6%. All other groups of diseases account for less than 10% of the total;
- **there are significant differences by age: in children/adolescents, 40% of rare diseases are attributable to the group "Congenital malformations, chromosomal abnormalities and genetic syndromes"**, whose percentage weight is reduced to 9.1% in adults, for whom the modal class,that is, which has the highest frequency, is, instead, the group "**Diseases of the central and peripheral nervous system**";
- **just under 1 in 6 people with rare diseases included in the RRMRs are under 18 years of age, while about 1 in 3 are over 60 years of age**;

Research

- After the growth observed until 2021, **the reduction in authorised clinical trials on rare diseases as a percentage of total clinical trials continues (163 in 2024, equal to 27.1% of the total).**
- Even in 2024, although to a lesser extent than in previous years, **Phase I and II clinical trials on rare diseases exceed the 50% threshold** (50.9% in 2024) and, in particular, there has been a marked **increase in the percentage of Phase I clinical trials (almost 1 in 5) over the last 3 years**.
- The distribution of clinical trials on rare diseases by type of medicine confirms the **prevalence of chemical active ingredients** (52.4% of the total, in line with 55.8% of all clinical trials in 2024).
- There are **42 out of 51** (1 more than the previous year) **biobanks participating in the BBMRI network, which collect samples of rare diseases throughout the country**:
  - 22,159 samples were collected during the last year (+ 6,326 compared to the previous year);
  - 2,624 samples were distributed during the year (+554 compared to the previous year);
- In June 2025, the **Italian Medicines Agency – AIFA, launched a new call for independent research, with a budget of €17.8 million, entirely dedicated to rare diseases**. The resources come from an increase of 2% in the so-called AIFA Fund, which consists of a contribution of the promotional expenses incurred annually by pharmaceutical companies, as provided for by Law No. 175/2021;

Reference centres

- There are **262 reference centres for rare diseases** identified by Regions/PPAA (4.4 per 1 million inhabitants); **78 of these centres are part of at least one ERN** (there were 66 until the end of 2021).
- with regard to **cross-border healthcare**, **Italy is characterised by a significantly higher level of active mobility - a figure that is set to increase again in 2023 with 1,250 incoming patients compared to passive mobility (outgoing patients, 236 in 2023);**

- During 2024, a further **19 Diagnostic Therapeutic Care Pathways** (PDTA) were approved by the Regions/PPAA, bringing the total number to **over 346 PDTA** defined at the end of 2024.

The active participation of people with rare diseases and their association representatives

- **17 regions/PPAAs** that declare the inclusion of **representatives of associations of people with rare diseases in regional participatory bodies on rare diseases**;
- **3 representatives of people with rare diseases are members of the "Coordination Centre for Newborn Screening"** provided for in Article 3 of Law No. 167 of 19 August 2016 "Provisions on mandatory newborn diagnostic tests for the prevention and treatment of hereditary metabolic diseases";
- **1 representative of people with rare diseases is a member of the national coordination centre of regional ethics committees** provided for by *Law No. 3 of 11 January 2018, "Delegation to the Government on clinical trials of medicinal products and provisions for the reorganisation of the health professions and for the health management of the Ministry of Health";*
- **1 representative of people with rare diseases has been identified among the members of the ENBS(Extended newborn screening) Working Group** provided for by the Decree of the Ministry of Health of 17 September 2020;
- **2 representatives of people with rare diseases (UNIAMO FIMR and EURORDIS) have been identified among the members of the National Committee for Rare Diseases** as provided for in Article 8 of Law 175/2021;
- **Since July 2023, UNIAMO has also been among the permanent guests of the National Observatory on the Condition of Persons with Disabilities**. Finally, in autumn 2023, a representative of **UNIAMO was called upon to join the "Technical Committee for the analysis and definition of useful elements for a state law on family caregivers"**;
- The 2025 budget law established the **RUAS - Single Register of Health Associations** under the aegis of the Ministry of Health and AIFA "in order to enhance, in the public interest, the contribution, expertise and impact of patient associations, groups of patient associations and their federations";
- **The Ministry of Health will be required to include a representative of the associations registered in the RUAS within the bodies set up at the Ministry itself**, such as committees, working groups, observatories and working groups, based on the specific subject matter and active institutional processes. **AIFA will have to proceed in a similar manner for decision-making processes on drugs** identified by the Scientific and Economic Commission.

Also noteworthy:

- **the entry into force on 30 December 2024 of the new fee schedule for specialist outpatient services and prosthetic assistance**, already provided for in the Prime Ministerial Decree updating the Essential Levels of Care (LEA) of 2017 but still frozen at 1996 and 1999 respectively;
- the fact that, at the end of 2024, **17 regions/PPAAs have included rare diseases in their general health planning tools** (in force or pending approval in 2024) or have defined a Regional Rare Diseases Plan.

The other side of the coin is represented by the critical issues that persist, such as the **long implementation time of measures relating to people with rare diseases**. In this regard, it is sufficient to recall the following:

- **the panel of diseases subject to neonatal screening has not yet been updated, rendering Law No. 145 of 30 December 2018**, which provided for the extension of neonatal screening to genetic neuromuscular diseases, severe congenital immunodeficiencies and lysosomal storage diseases, effectively "ineffective". In April 2025, the Ministry of Health presented the draft Decree of the President of the Council of Ministers containing the **new update of the Essential Levels of Care (LEA) and providing for the extension of the neonatal screening programme to cover eight additional diseases**.
- **To date, most of the implementing provisions of the specific measures provided for by Law No. 175/2021** - such as those related to incentives for the development of orphan medicinal pproducts and the solidarity fund to support the care and assistance of people with rare diseases - have not yet been approved.

Furthermore, there are still significant regional disparities in access to healthcare, social-healthcare and social services, as exemplified by:

- the heterogeneity in the geographical distribution of Italian hospitals participating in ERNs: 7 regions/PPAAs have no reference centres participating in ERNs, and 61.5% (n= 48) of hospitals participating in at least one ERN are located in northern regions. This is a significant issue, particularly in light of the document reorganising the National Rare Diseases Network and the potential role within it of the so-called "centres of excellence" (the reference centres participating in the ERNs);
- the difficulty of accessing diagnosis and treatment, as evidenced by data on **healthcare mobility**, especially for minors with rare diseases, as highlighted by the RRMRs;
- **the differences in the geographical distribution of healthcare facilities authorised to administer ATMPs** (0.8 centres per 1 million inhabitants in the southern regions vs. 1.2 in the north);
- the lack of definition of Diagnostic-Therapeutic-Care Pathways for people with rare diseases in some areas and the diversity of models adopted for their definition;
- **the still partial coverage of the entire population of people with rare diseases with co-payment exemption** (as for the above mentioned list) **from some of the Regional Registries of Rare Diseases**.

In addition to these aspects, there are two other elements that need to be carefully evaluated, related to the economic sustainability of the system. The **capacity of the Fund for Innovative Medicines**, recently subject to intervention with the 2025 budget law, has been sufficient so far, but with **the arrival of new treatments expected in the coming years, it could reach its maximum limit, creating serious difficulties in accessing certain medicines**. We must also take into account the "return" effect linked to the expiry of innovation, which will mean that many ATMPs will have to be reimbursed under ordinary LEA (Essential Levels of Care) directly by the dispensing centres/regions. Other high-cost treatments, not necessarily innovative, have begun the approval process.

If not adequately included in the planning, this could already have an impact in the near future (and in some cases there are already signs of this) on budgets and economic sustainability: this seriously jeopardises access to treatments that have proven to be of enormous clinical benefit for people with rare and ultra-rare diseases.

The approval of the **National Plan for Rare Diseases 2023-2026** on 24 May 2023 represents, on the one hand, an **important milestone** (also because of the much greater attention paid to the issue of treatments, pharmacological and non-pharmacological), long awaited by the PLWRD community, but at the same time represents a **new starting point** for other important objectives - 77 in total - to be achieved through the implementation of the planned actions (n=115).

To date, **all Regions/PPAAs have formally adopted the "National Plan for Rare Diseases 2023-2026" and the document for the "Reorganisation of the national network for rare diseases".** On the other hand, **19 regions out of 20, have already identified regional coordination centres, reference centres and centres of excellence for rare diseases** in accordance with the contents of the document on the reorganisation of the national rare diseases network. To date, only the Autonomous Provinces of Bolzano and Trento are still formally missing.

Finally, to date, 15 (out of the 16 entitled to) regions have already formally committed the resources allocated for 2023 (€25 million) for the implementation of the "National Plan for Rare Diseases 2023-2026" and the "Reorganisation of the National Network for Rare Diseases": only the Veneto Region is missing from the list, although it should be noted that four other regions – Calabria, Campania, Puglia and Sicily – have so far only formally committed the amount in their regional budgets without yet approving the act of operational allocation of resources.

At the time of writing this report, therefore, **approximately two-thirds of the resources made available for 2023 to support the implementation of the PNMR 2023-2026 have been formally allocated**.

An examination of the first measures to commit resources for the implementation of the NPRD 2023-2026 already reveals some critical issues related to the fragmentation observed in the distribution of resources and the dispersion of resources across multiple objectives (generally not even clearly specified), which makes it difficult, if not impossible, to assess the effectiveness and impact of the use of resources. **The experience of some regions**, such as Emilia-Romagna and Lombardy, **is worth highlighting, as they have not only identified specific objectives for the allocation of resources but have also already established the relevant evaluation indicators.**

Two years after its approval, the NPRD 2023-2026 is still in its infancy, but the actions taken by the regions/Autonomous Provinces to implement the NPRD and identify the centres are, in fact, a precursor to its full implementation: now everyone's commitment is needed to put the numerous and complex provisions contained in the Plan into practice.