

EDITORIAL

The long journey of people with rare diseases: from darkness to the UN Resolution 2021

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Rare diseases (RD) occur globally, affecting 6-8% of the population worldwide; they include 6000-8000 different conditions of either genetic (80%) or multifactorial (20%) origin. RD may involve any organ or system, often are multisystemic, arising at any age, mainly during infancy and childhood. RD are defined by the European Union (EU) as life-threatening or chronically debilitating diseases, with low prevalence (not more than 5 persons per 10 000) [1]. Their rarity, numerosity and heterogeneity pose a major hurdle to timely diagnosis and to provisions of appropriate care to patients.

Individual RD are known since ancient times and are part of history of medicine and culture, for example the achondroplasia of the Egyptian god Bes [2] or neurofibromatosis depicted in works of Hellenistic art [3].

However, only few decades ago RD have been recognised as public health issue as a whole, with specific features. US started in 1983 with the Orphan Drug Act and the EU in 2000 with the European Commission's (EC) Orphan Medicinal Products regulations to incentivize research, development and marketing of new treatments. Similar legislative mandates exist in many Countries worldwide [4].

Tackling RD goes beyond the development of treatments. Severe knowledge gaps still exist on many conditions, due to the combined effects of low prevalence, scarce awareness and weak commitment by funding bodies and enterprises. Hence, uncertainties often burden the evidence basis for action [5], from prevention to treatment and social inclusion. Diagnosis and care require multidisciplinary expertise: prompt diagnosis is crucial for reducing the severity of outcomes, including morbidity and early mortality. Moreover, undiagnosed conditions are estimated to affect around 10%-30% RD patients.

These specific characteristics require special solutions in both healthcare and research. RD-tailored public health plans or strategies should include, e.g., primary prevention actions to reduce risk factors, newborn screening programmes and medical management. Besides, patients and their families often experience

stigma, discrimination, and lack of active participation and visibility in society.

Several initiatives have been implemented at EU level as well as in many Countries, within as well as outside the EU. In particular, the EU, recognizing that combined efforts are needed to address the above challenges, has singled out RD as a unique domain for European added value. In 2017, the EC launched 24 European Reference Networks (ERN) encompassing all RD groups. ERN are virtual networks connecting healthcare professionals and centres of expertise in different countries to share knowledge and resources. They aim to tackle complex or rare diseases and conditions that require high competences. ERN allow experts to discuss patients' diagnosis and care, with their consent, via an online IT platform, the Clinical Patient Management System. Hence, knowledge travels instead of patients.

At Member States level, Italy recognized RD as a public health challenge since 2001, establishing the National Network for RD for their prevention, surveillance, diagnosis and treatment. The National Network is articulated in regional networks with Centres of expertise; it includes the National Registry for RD, a pivotal scientific tool for collecting and analysing epidemiologic and clinical patients' data, at the National Centre for Rare Diseases (NCRD) of the Istituto Superiore di Sanità (ISS). The ISS, is the technical and scientific body of the Italian National Health Service; its mission includes promotion and protection of public health through activities carried out on several groups of diseases, including RD (www.iss.it/en/web/guest/home).

The NCRD formally established in 2008 at the ISS is the national and international reference point for RD, its activity includes scientific research, prevention, surveillance of RD and monitoring of the National Network through the National Register. NCRD activities span from scientific research through to patients' empowerment. Accordingly, priority topics encompass translational research, including undiagnosed RD,

promoting high-quality diagnosis and care, training of health care professionals, providing information on relevant services, promoting empowerment of patients and their social inclusion, health humanities, as well as the proactive contribution to European and international programmes and networks on RD (www.iss.it/web/iss-en/rare-diseases).

In November 2021 the Italian Parliament approved an innovative law on RD [6]. The law's objectives include: uniformity of RD patients care across the Country; educational, social and work inclusion; strengthening the activities of the NCRD and the National network, including ERN Centres; coordination of actions, and incentives to research. Research is vital to reduce the main knowledge gaps on RD, and beyond. Already in 1657, William Harvey highlighted "...; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease" [7].

The long journey of people with RD made recently an important leap forward. On December 2021 the United Nations (UN), during the 76th session of the General Assembly, recalling the *Universal Declaration of Human Rights* and the *Convention on the Rights of Persons with Disabilities*, adopted the first Resolution – "Addressing the Challenges of Persons Living with a Rare Disease and their Families" – which recognizes the need to promote and protect the human rights of all persons, including the estimated 300 million persons living with a RD worldwide, many of whom are children, by ensuring equal opportunities to achieve their optimal potential development and to fully, equally and meaningfully participate in society [8].

Importantly, the Resolution was promoted by patients' organizations such as Rare Diseases International in partnership with EURORDIS and NGO Committee for Rare Diseases. The Resolution places RD at the top of the agenda of the UN Secretary General, identifying five main objectives: 1) to encourage social

inclusion and participation of people with RD and their families, taking into account major equality issues such as gender and poverty; 2) ensure equal and universal access to quality health services; 3) promote national and international strategies and actions; 4) integrate RD among the programs and priorities of the UN agencies; 5) publish periodic reports to monitor progress in the implementation of the Resolution itself.

The UN Resolution is a form of "soft law" binding on the UN secretariat and the UN budget and programs. The Resolution therefore serves as a basis for further integration of RD into the UN agenda, actions and priorities. The motto *Leave no one behind* is at the core of the UN Agenda 2030 Sustainable Development Goals (SDGs), and it fits for persons living with a RD. For instance, for children with RD, discrimination may strike very early in life with access to education, while in adulthood it may be difficult to find, maintain or return to work or to pursue lifelong learning, relevant to SDGs 4 ("quality education") and 8 ("decent work and economic growth"). Women are disproportionately discriminated in society, either as patients or as mothers of RD patients (SDG5 "Gender inequality"). Families with a member living with a RD are at greater risk of impoverishment, as they have more expenses and less income (SDG1 "No poverty").

In conclusion, the impact of going through life with a RD goes beyond health issues, and involves the whole family, affecting the place, role and perspectives in society.

The Resolution becomes a reference point to support the RD community at national and international levels. A major point is encouraging the development of national strategies and international collaborations to address the challenges and barriers faced by patients and their families.

Conflict of interest statement

The Author declares that there are no conflicts of interest.

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