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RARE DISEASES

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PRESENTATION

Giovanna Cenacchi

A rare disease, also known as an orphan disease, is a condition that affects a small percentage of the global population. At the European level, a disease or condition is defined as "rare" when it affects fewer than 1 in 2,000 individuals. Over 6,000 rare diseases have been identified, 80% of which are of genetic origin and accompany the affected person throughout their life; even if symptoms may not be present at birth, they are chronic and often reduce life expectancy. In addition to the psychosocial and economic, diagnostic and therapeutic challenges common to other more numerically represented diseases, rare diseases also involve a number of distinct features that group them in a field of their own and which, for patients and specialized healthcare workers, make them difficult to deal with and relegate them to an entirely separate chapter of medicine. Rare diseases are, in fact, bearers of loneliness, discrimination and chronicity. These specific characteristics have led to a scarce presence of specialized and competent doctors and researchers interested in deepening the scientific knowledge that supports – and initiates – research on innovative and personalized therapeutic treatments and orphan drugs; there is also little knowledge of the natural history of these diseases, which leads to uncertainty of prognosis. Finally, taking into account the genetic component opens up the much

broader chapter of generativity, inviting an ethical and bioethical point of view as well, which touches upon the very definition of a human being and thus adds another layer of complexity to the picture. Almost all genetic diseases are rare diseases. However, not all rare diseases have a genetic origin; for example, there are very rare infectious diseases, as well as autoimmune diseases and rare carcinomas. The cause of many rare diseases is still unknown today.

These diseases are characterized by a wide diversity of disorders and symptoms, which vary not only from disease to disease, but also from patient to patient with the same condition. Even fairly common symptoms can hide the presence of a rare disease, leading to an incorrect diagnosis. Rare diseases not only affect patients, but involve their families, friends, caregivers and society as a whole. For most of these diseases, effective treatment is not yet available, but numerous appropriate treatments can improve quality of life and prolong it. In some cases, substantial progress has been made, showing that we must not surrender but, on the contrary, pursue and intensify the work of research and social solidarity. Rare diseases still often go untreated and for this reason are also called "orphan diseases", also because there is no incentive to invest significant resources into what will be a very limited market. This book is the result of the commitment by experts in the field and describes in a usable way the various challenges inherent in this group of pathologies, albeit at a highly scientific level, that concern a limited number of patients requiring a multidisciplinary, ethical-social and economic health intervention of great impact. Moreover, these pathologies deserve to be brought to the attention of the public so that they are aware and educated about the challenges faced by all affected. The organization of the book therefore brings together different disciplinary approaches, as is particularly evident in the specific and diversifying language usage ranging from the humanities to the social to scientific disciplines, in order to obtain a work that is the comprehensive and multi-faceted read which this important subject matter necessarily requires.

CHAPTER I

RARE DISEASES AND WHO THEY AFFECT

Rocco Maurizio Zagari, Franco Bazzoli

A rare disease is a pathological condition that affects a relatively small number of people. Rare diseases are very heterogeneous, both in the etiopathogenesis (the study of the causes of a disease and their mechanism of action), and in the involvement of organs and systems of the human organism. Rare diseases can affect physical and/or mental abilities, and sensory and behavioural abilities (Taruscio, Cerbo *et al.* 1999). These are complex, often serious, degenerative, chronically invalidating pathologies; about a third of them reduce life expectancy to less than 5 years, while many others do not significantly affect life span if they are diagnosed early and treated appropriately. Finally, some conditions allow one to carry on a normal life even in the absence of treatment (Salerno *et al.* 2005).

Rare diseases represent a group of pathologies transversal to all the nosological classification systems currently in use. The defining criterion, in fact, is neither etiological nor topographical, but epidemiological, and in fact somewhat arbitrary: a disease that is rare today may not be rare tomorrow and vice versa. For example, when AIDS was first discovered it was considered a rare disease because it was not widespread. Afterwards, with the improvement of the diagnosis and the development of drugs that, though effective in reducing mortality, were not able to eliminate the virus, the number of patients grew dramatically, and today, AIDS is

no longer a rare disease (Field, Boat *et al.* 2010). If a non-curative treatment can make a rare disease "common", then conversely, an effective prevention can make a common pathology "rare". This is, for example, the case of many childhood infections that were once common, such as mumps and rubella, and that thanks to vaccinations have now become rare; the opposition of parents to vaccinating their children could however reverse this situation.
All this should have discouraged the classification of the rare diseases group, which instead however is motivated by some clinical and care characteristics that are common to the individual pathologies, such as the diagnostic difficulty, the poor therapeutic options, the chronic course and often disabling outcomes (Stoller 2018).

Definition of rare disease

There are several terminologies to indicate a rare disease, including orphan disease, neglected disease, and specialized disease. The term orphan disease derives, for example, from the name of the drugs used for the treatment of rare diseases, which are called "orphan drugs" since under normal market conditions they would not be marketed, as they are unprofitable for their poor use in clinical practice. However, the term "rare disease" is the most used worldwide for the desire to clearly and formally distinguish rare diseases from common diseases (Richter *et al.* 2015).
The definition of rare disease is generally based on the low prevalence of the disease in the general population; the incidence is an epidemiological criterion seldom used, if not only for the definition of rare tumours (Richter *et al.* 2015). The prevalence, i.e. the proportion of sick individuals over a given period of time, rather than the incidence, which indicates the percentage of new sick individuals per year, more appropriately reflects how frequent a disease is, and is also an easy measure to evaluate the spread of a disease in population subgroups.

Currently, there is no universal definition of rare disease, since there is no international prevalence limit accepted by all countries to define a rare disease; this, however, would not even be appropriate considering the demographic, political and financial differences that exist between countries. Thus the definition of rare disease varies in different states, and a disease defined as rare in one state may not be rare in another. The prevalence limits set by regulatory authorities to define a rare disease vary from 0.5 cases per 10,000 people in Korea to 7.6 cases per 10,000 people in China (Richter *et al.* 2015). In 1999, a European Union law established the definition of rare disease to be adopted in Europe: a disease with a prevalence of no more than 5 cases per 10,000 people (Regulation EC, 2000). In reality, the regulatory authorities of some countries, such as the United States, Australia and Japan, unlike the European community, have not explicitly specified a prevalence limit, but have indicated what the maximum number of people affected must be in order to define a disease as "rare". For example, in the United States, a disease is considered rare if it affects less than 200,000 people, which based on the population estimate means less than 6.5 out of 10,000 people, while in Japan a disease must affect less than 50,000 people, that is, less than 4 people out of 10,000 (Liu *et al.* 2010).

Public or private bodies and associations can adopt different prevalence limits to define a rare disease, even within the same country. It has been observed that private bodies and associations, such as companies that activate health insurance, indicate lower prevalence limits than public associations or patient associations (Richter *et al.* 2015). This clearly reflects the different needs and competences of the different types of entities or associations; when it comes to defining a rare disease, the main interest of private bodies, addressed to the costs related to the treatment of the disease, is certainly not the same as for patient associations, whose main objective is to have easy access to effective treatments and cures. This would explain why private entities or associations tend to give a more stringent definition of rare disease than other organizations.

How many rare diseases are there and how many people do they affect?

The epidemiology of rare diseases is still poorly understood today. There are numerous types of rare diseases, some of which have not been named yet; it is not clear what the total number of people affected by rare diseases is, nor their exact prevalence and incidence, both individually and overall, in different countries (Auvin *et al.* 2018). To date, there is a lack of prevalence and incidence studies in the general population; there are many problems in the identification and coding of rare diseases, as well as in the collection of data from patients affected by them (Rodwell, Aymé *et al.* 2015). For example, most rare diseases have so far been excluded from the International Classification of Diseases (ICD), with consequent problems in their identification in health systems and in obtaining information on the corresponding morbidity and mortality. However, the coding problem will be partially solved by the new ICD-11 Classification, presented by the World Health Organization in June 2018 and coming into force from January 1, 2022, in which about 5,000 rare diseases have been included, each of which will have a specific ICD-11 code (WHO, 2018). Rare diseases are also not easily identifiable in health systems due to factors that belong to their very nature, such as the heterogeneity of the pathologies, the poor accuracy of the diagnostic tests available today, and the presence of numerous synonyms, acronyms, and groups of pathologies.

To improve our knowledge on the epidemiology of rare diseases, the European Commission of Rare Diseases Experts (EUCERD, European Union Committee of Experts on Rare Diseases), replaced in 2014 by the Group of Experts of the European Commission of Rare Diseases (CEG-RD, European Commission Expert Group on Rare Diseases), recommended the establishment at the national and international level of registries and databases for rare diseases (EUCERD Core Recommendations on Rare Disease Patient Registration and Data Collection) (Rodwell, Aymé 2014). There are currently 753 rare disease registries in Europe (69 European,

69 international, 535 national and 80 regional); almost all of the registers concern diseases for which there is a medical treatment in development, or already on the market, and therefore they also collect information on the efficacy and tolerability of orphan drugs, such as the Rare Disease Registries in Europe (Orphanet 2019b). Most of the registries are located in academic institutions and are integrated into the national health system, while others are managed by pharmaceutical companies or patient associations. The European Platform for Rare Disease Registries (EPIRARE) recently evaluated the possibility of creating a European platform for the registration of patients with rare diseases, similar to the Global Rare Diseases Registry (GRDR, subsequently called RaDaR, the Rare Diseases Registry Program) of the National Institute of Health in the United States (Rodwell, Aymé *et al.* 2014).

Currently, the most important source of information on the epidemiology of rare diseases in Europe and worldwide is Orphanet, the reference portal of the European Union, founded in 1997 in France by the *Institut National de la Santé et de la Recherche Medical*. Orphanet provides an updated list of known rare diseases twice a year, and a global estimate or, when not available, an estimate at the European level, of the prevalence, incidence or number of cases for each disease. For the collection of data, Orphanet uses various sources of information, such as disease registers, national and international health authorities and bodies, bibliographic searches on electronic databases (e.g. MEDLINE®), and expert reports. Therefore, the epidemiological data provided by Orphanet cited here are only estimates, and not correct data.

According to the latest Orphanet report, the 2017 Activity Report, there are 6,151 rare diseases worldwide, a number that, according to the World Health Organization, could possibly reach 7,000 or 8,000 (Orphanet 2018). These numbers are clearly destined to grow with the advance of knowledge and, in particular, with advances in diagnostics and genetic research. According to Orphanet data, most rare diseases are "extremely" rare, since they affect only a few people or a few families, while the

others affect hundreds or even thousands of people. Currently, the most frequent rare diseases in the world seem to be Down Syndrome, neural tube closure anomalies, labio/cleft palate, endocrine gland tumours and cutaneous Lupus Erythematosus (Orphanet 202019a). The total number of rare disease patients has been estimated to be around 27-36 million in Europe and 25 million in the United States, with a prevalence in the general population of 6-8% (Field, Boat 2010).
Rare diseases, individually infrequent by definition, when considered all together represent a common condition that affects tens of millions of people around the world. These numbers mean that rare diseases represent an important public health problem today.

Reporting rare diseases in the western world: the case of Italy

In 2001, the National Institute of Health in Italy, the *Istituto Superiore di Sanità*, identified 495 rare diseases, for which the exemption from payment of the co-pay fee (known as the "ticket") was activated (Ministerial Decree 279/2001). Since then, more than 100 diseases have been added to the list (Ministerial Decree 15/2017). In addition, in 2001, a national system for the surveillance and monitoring of rare diseases was established in Italy through the National Register of Rare Diseases of the Istituto Superiore di Sanità, the regional and interregional registers, and the health units specialized in the diagnosis and treatment of rare diseases, identified by individual regions. The National Rare Disease Registry periodically receives the data of patients suffering from rare diseases from the 20 regional registries existing in Italy, which in turn receive them from the Health Presidia at the time of the co-pay fee exemption certification (National Plan for Rare Diseases 2013-2016 of 2014). The portal of the National Centre for Rare Diseases (see some reference links) provides information on rare diseases and on the national network of rare diseases in Italy.
Unfortunately, the regional registers, and therefore also the National

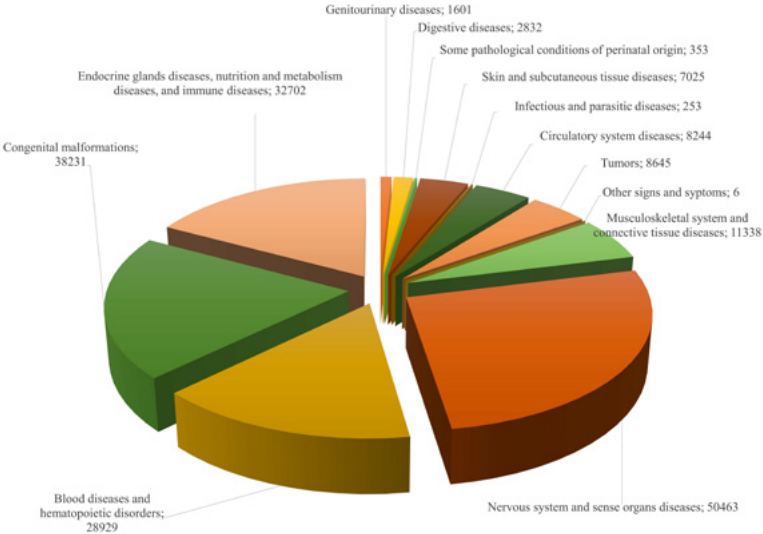

Fig. 1. Rare diseases in Italy, stratified by disease groups, as of 31/12/2014. Reproduced image courtesy of the Istituto Superiore di Sanità, Rome, taken from *Rapporti ISTISAN* 17/8, p. 23 (Taruscio 2017). © Higher Institute of Health 2017.

Rare Disease Register, monitor only ticket-free rare diseases, and not rare diseases as a whole. Furthermore, the regional registers currently cover just over half of the Italian population (Taruscio *et al.* 2017).

In 2017, the regional registers reported the presence in Italy of 236,460 cases of rare diseases out of a population of 44,622,658 inhabitants, with an average prevalence of 0.53%; projecting the prevalence of 0.53% to the entire Italian population of 60,589,445, it is possible to estimate a number of people with rare diseases in Italy of 321,124; to this estimate, we must add about 20% of people with rare disease who resort to centres outside the region, thus reaching 385,348 cases. Since, as previously mentioned, the regional registers report only ticket-exempt diseases, it is assumed that the total number of people with rare diseases in Italy may be 50-100%

higher than the estimation, and therefore might lie between 578,000 and 770,000 cases, meaning 7.5-10 people out of 1,000 residents, with a prevalence ranging from 0.95% to 1.27%; of these patients, around 160,000 would be children or adolescents (Astolfo, Porchia 2018).
According to the data of the 3rd Report of the National Registry of Rare Diseases, the most frequent rare diseases in Italy are diseases of the nervous system and sense organs, congenital malformations and diseases of the endocrine glands, and nutritional, metabolic, and immune disorders (Fig. 1) (Taruscio *et al.* 2017). These diseases represent about 80% of the rare diseases reported in Italy.

Who is affected by rare diseases?

Most rare diseases are genetic diseases; other diseases are caused by environmental factors, such as bacterial or viral infections, toxins, chemicals, radiation, or by autoimmune reactions (Field *et al.* 2010). Rare diseases can affect anyone, at any age; however, the exact demographic distribution of rare diseases is not well known (Field, Boat 2010). Although rare diseases are very often genetic, in Italy the majority of those affected are adults, while only about 25% of the subjects with rare diseases are children or adolescents (Astolfo, Porchia 2018). In other words, only 1 in 4 individuals with a rare disease are under the age of 18, while 3 out of 4 are adults. This is an interesting fact because in the common perception, partly influenced by news from the mass media, rare diseases are largely associated with children and adolescents. Additionally, in Italy, the most frequent rare diseases in adults are those of the nervous system and sense organs and of the blood and hematopoietic organs, while in children and adolescents congenital malformations and diseases of the endocrine glands as well as nutritional diseases, metabolism and immune disorders are more frequent (Astolfo, Porchia 2018). As for sex, rare diseases in Italy seem to affect males and females similarly, although there seems to be a slightly higher prevalence of women (52.4%) than men (47.6%) (Astolfo, Porchia 2018).

Conclusions

Rare diseases are extremely heterogeneous diseases, the defining criterion of which is neither etiological or topographical, but epidemiological. A disease is defined as "rare" when it has a low prevalence, but the prevalence limits vary from country to country, so there is no universal definition of a rare disease. Therefore, a disease defined as "rare" in one country may not be rare in another, just as a disease that is rare today may not be rare tomorrow and vice versa. Although the epidemiology of rare diseases is not well known, we know that there are thousands of rare diseases which, collectively, are not so rare, since they affect tens of millions of people around the world. There is no doubt that, due to their large number, rare diseases today represent a real public health problem. It is certainly necessary to improve the identification, coding and data collection tools regarding rare diseases, and the coverage of the population by national registers, in order to have more precise estimates on epidemiology, i.e. on the number of people affected, and on the prevalence, incidence and demographic distribution of rare diseases, in Italy and worldwide.

CHAPTER II

WHY IS A DISEASE RARE?

Laura Mazzanti, Emanuela Scarano, Annamaria Perri
with the contribution of Federica Tamburrino, M.D., Ph.D.

Rare diseases now constitute a public health problem, due to their numerical impact on the population. In Italy, greater attention has been focused on rare diseases since the beginning of the 1990s. The Ministry of Health approved the National Rare Disease Plan 2013-2016 on October 16, 2014. Rarity leads to scarce availability of scientific knowledge and difficulties in obtaining an appropriate diagnosis, with long periods of latency between the onset of the disease, obtaining an appropriate diagnosis, and receiving adequate treatment, which often negatively affect the prognosis of the condition. If we then consider that some ultra-rare diseases affect individual family units, these diagnostic difficulties become even more evident.

Approximately 25% of the diseases affect pediatric patients (under 14 years of age), 28% in the Emilia-Romagna region. In children, the rare diseases that occur most frequently are congenital malformations (45%), in fact, congenital rare diseases with developmental defects represent a less numerous, but extremely important group from a clinical-diagnostic point of view. The annex to the Ministerial Decree 279/2001 listed 290 forms, however, following the new Decree of the President of the Council of Ministers (Prime Ministerial Decree) of 12 January 2017 and the related update of the Essential Assistance Levels (LEA), the number was increased

to 350. We then have diseases of the endocrine glands, followed by diseases of the metabolism and the immune system (20%). This is an estimate which is significantly lower than the 50-60% of pediatric cases, calculated internationally. For adult patients, however, the highest frequencies concern diseases of the nervous system, diseases of the sense organs (29%), pathologies of the blood and hematopoietic organs (18%).

Rare disease patients

People with rare diseases, especially children, are exposed to the great suffering and challenges of growing up with a rare disease (condition), involving the whole family context: parents, siblings, and relatives. All children and their families live a twofold painful experience, characterized, on the one hand, by the pathological condition that requires frequent clinical visits, and sometimes even invasive procedures and, on the other hand, by a condition of loneliness, linked to the scarcity of available scientific knowledge. It is very difficult to accept a rare disease and it is essential to learn to live with it. Many rare diseases are complex, serious, degenerative, chronically disabling: about a third lower life expectancy to less than 5 years; many, however, do not significantly affect lifespan if they are diagnosed promptly and treated appropriately; others allow people to live a normal life, even without treatment.

Diagnosis and diagnostic difficulties

Rare diseases are characterized by their large number and by the numerous symptoms that vary not only from condition to condition, but also from patient to patient, even with the same disease. Due to their low prevalence and their specificity, diagnosing rare diseases requires experience in rare conditions and a good knowledge of normal variants. The inadequacy of scientific knowledge prevents patients, in the majority of cases, from obtaining effective treatments and care. Rare diseases

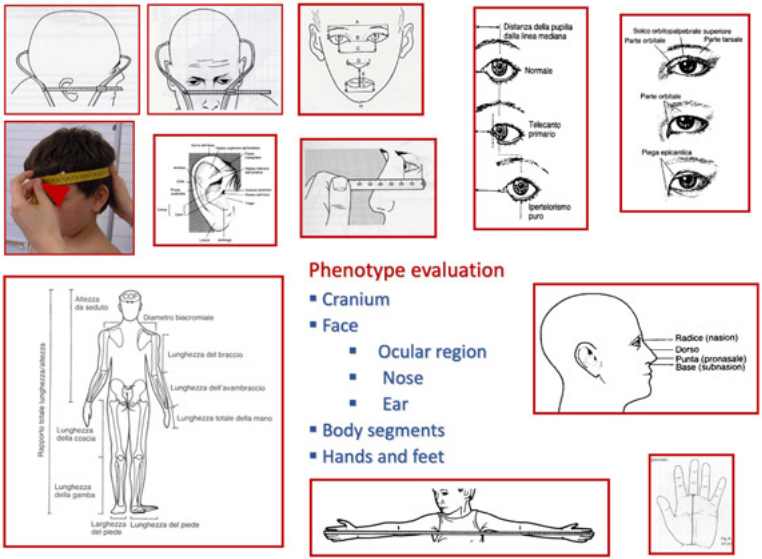

Fig. 2. Analysis of the external phenotype: evaluation of dysmorphic signs and body proportions.

very often affect various organs and have complex and often multi-systemic clinical pictures, which require the coordinated intervention of numerous specialists, thus a global multi-disciplinary approach, with very complex diagnostic and follow-up pathways (Douzgou *et al*. 2014; Vasudevan, Suri 2017); 40-50% of conditions still remain without a diagnosis today. On the basis of the foregoing, the importance of an early and precise diagnosis emerges in subjects with indicative or suggestive phenotypic aspects. Early diagnosis and an adequate follow-up to prevent any complications related to the syndromic condition are even more important when dealing with subjects of developmental age.

The diagnosis of rare diseases requires specific multidisciplinary skills aimed at recognizing, following and treating the various anomalies

detected in the individual, and carrying out accurate family screening (Hall 1993). The analysis of the phenotype to detect major or minor anomalies is a science called Dysmorphology. It is primarily a visual specialty and the ability to be an accurate observer is obtained over time, by developing a sense of dimension, proportion, position, and symmetry (Fig. 2) (Hunter 2002). We now have new diagnostic tools, such as Next-Generation Sequencing (NGS), which facilitate large-scale diagnosis, allowing for the evaluation of many genes in a single analysis (Hennekam, Biesecker 2012; Nambot, *et al.* 2018). On the other hand, even with the use of these powerful diagnostic methods, the evaluation of the phenotype and the genetic-clinical evaluation remain essential. Biology is very complex, the phenotypes of subjects with rare diseases are caused by a combination of the actions of multiple genes, epigenetic influences, and the environment. Here the essential role of physicians with expertise in rare diseases and clinical geneticists comes into play, as they must hone their diagnostic skills by switching from the pre-NGS-test to the post-NGS-test differential diagnosis modes (Robin 2018). In the era of genomic medicine, the integration of the hypotheses of experienced syndromologists and NGS techniques will be very productive in terms of translational research and clinical activity.

Expertise of medical personnel in the diagnosis of rare diseases

It is essential to have medical experts in the field of diagnostics with adequate training and who also carry out research. In fact, research, both clinical and basic, plays an important role and is recognized as an instrument of choice for increasing knowledge on rare diseases, contributing to the progress of medical research in general, while also having a huge impact on common diseases. In fact, rare diseases act both as an experimental model to increase knowledge on the physiology of growth and development processes, and as a "laboratory" for new health policies.

Continuing medical education

Training represents a crucial aspect in the field of rare diseases. The growth and professional assessment of healthcare workers is an essential requirement, which must be ensured through continuing medical education. Basic and specialist training is undertaken at the university level, through university courses and graduate school programs; professional updating is then organized at national and regional levels. Specific courses are offered in the degree courses in Medicine, in the training program of some specialization schools and in post-graduate degrees, yet it is desirable that this training be more common in programs, both basic and specialised, as stated by the Ministry of Health in the National Rare Disease Plan 2013-2016 (Ministry of Health 2014).

Networks for rare diseases

Rare diseases, due to their characteristics of multi-organ complexity and rarity, require the establishment of competent points of reference for both patients and general practitioners, and the specialists who do not have an in-depth knowledge of rare diseases. In the management of activities involving a high degree of specialization, such as rare diseases, specific and combined interventions are necessary in order to prevent morbidity and improve the quality of life of those affected. It goes without saying that interregional and international networks are therefore indispensable.

At the national level. In 2001 the Ministerial Decree n. 279 had listed the diseases and rare disease groups, each identified by a specific code, for which the right to exemption from participation in the cost for the related health care services, included in the LEA, was recognized, with the identification of accredited centers for the diagnosis and treatment of rare diseases by the Regions. As already specified, the recent Prime Ministerial Decree of January 2017 defined the new LEAs by extending the list of rare diseases.

The Emilia-Romagna Region has applied the Hub & Spoke network model, identifying highly specialized centers in the field of rare diseases, in which clinical cases and expertise are concentrated and connected by the network. Their collaboration leads to the definition of shared diagnostic-therapeutic pathways, in order to offer diagnostics and, subsequently, homogeneous healthcare to patients. Therefore, various networks have been set up dedicated to single pathologies or groups of pathologies (Emilia-Romagna Region, Regional Council Resolution of 19 September 2017, no. 1351).

At the international level. The need to offer people with rare diseases the most up to date knowledge and the most reliable information, in order to improve their medical assistance and quality of life, led the European Commission, in 2016, to launch a call for the development of European Reference Networks for Rare Diseases (ERN, European Reference Network) between member states. ERNs are networks of centers of expertise providing healthcare, with an organization that goes beyond the borders of the individual state. The collaboration between the member states of the European Union can, in fact, provide valuable support for sharing expertise, ensuring the exchange of knowledge between medical professionals. The Italian Ministry of Health joined the call and Italy was granted approval to participate in 23 of the 24 European Reference Networks, in which 63 hospitals and 187 units are involved, as full members.
In this regard, the centers of expertise for rare diseases or Health Care Providers (HCP) of the University of Bologna that received recognition as ERN were: the Rizzoli Orthopedic Institute of Bologna (included in BOND, the European Reference Network on Bone Disorders, and in EURACAN, the European Reference Network on congenital and hereditary anomalies), the S. Orsola University Hospital of Bologna (ENDO, the European Reference Network on endocrine conditions; EURACAN; ITHACA, the European Reference Network on congenital malforma-

tions and rare intellectual disabilities; LUNG, the European Reference Network on respiratory diseases; SKIN, the European Reference Network on skin disorders) and IRCCS, Institute of Neurological Sciences (EIPCARE, the European Reference Network on epilepsy; EURACAN).

Organization of centers of expertise (HCP) for rare diseases

To guarantee patients an adequate diagnostic pathway and ongoing care, with a defined pathway for follow-up, the centers experienced in rare diseases have competent and dedicated staff, and are required to implement a multidisciplinary care network. The diagnostic and therapeutic protocols prepared for single diseases and/or groups of diseases must be adopted as uniformly as possible, both nationally and internationally. The transition phase of the patient from pediatric age to adulthood must also be managed, in order to ensure continuity of care.

An example is the Pediatric Rare Diseases Center of Sant'Orsola, University Hospital in Bologna, Italy, which is recognized as a Regional Hub (Emilia-Romagna Region, Regional Council Resolution of 19 December 2011, n. 1897). The center has formalized a permanent multidisciplinary team of specialists, to share and optimize a network of multidisciplinary interventions, connected and coordinated for both the diagnosis and follow-up of patients, in order to manage the complex problems of subjects with rare diseases, creating an individualized clinical project (Figs. 3, 4, 5). A clinic for undiagnosed rare diseases with developmental defects was also set up, in which experts in clinical syndromology, neonatologists, developmental pediatricians, clinical geneticists and any additional specialists from the multidisciplinary care network are present at the same time, to activate all the expertise of the hospital and apply the new molecular genetics technologies, in order identify ultra-rare conditions.

The multidisciplinary team includes the role of the clinical psychologist, as highly specialized psychological support is needed for these young patients and their families to promote a better quality of life, alleviate the

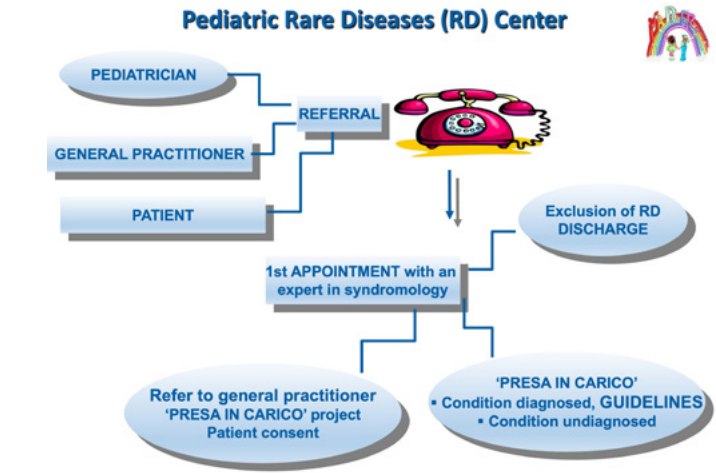

Fig. 3. Functioning of a Center for rare diseases in developmental age.

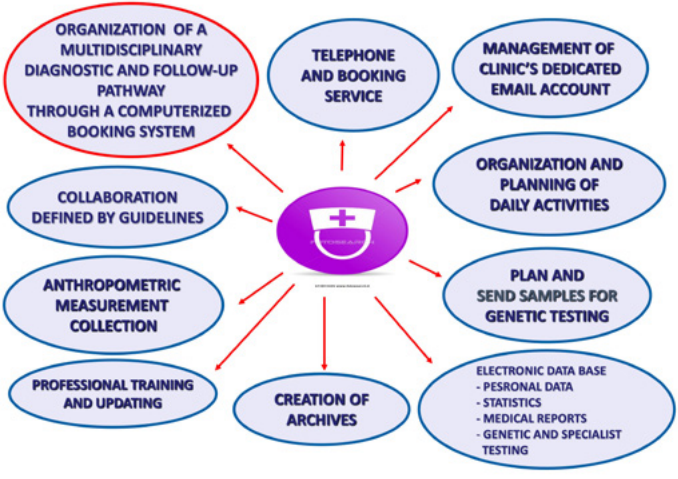

Fig. 4. Organization, by qualified staff, of the activities related to the diagnostic pathways and follow-up of a child with a suspected rare disease.

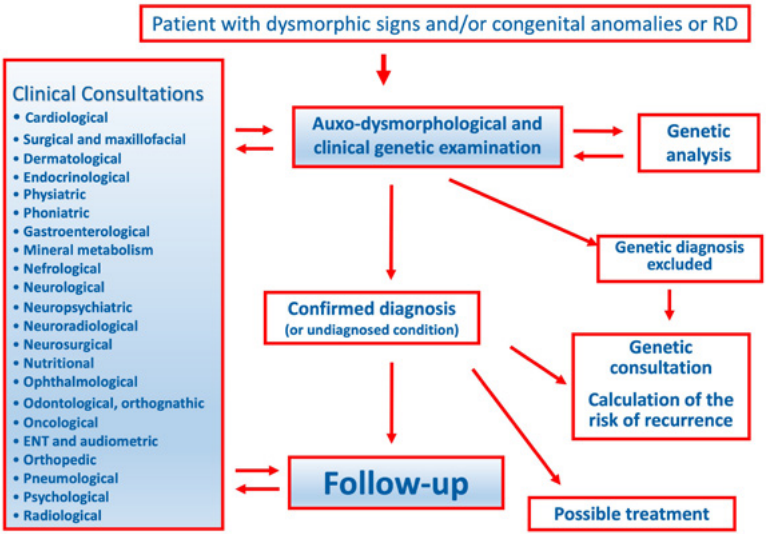

Fig. 5. Diagnostic and follow-up pathway of a child with a suspected rare disease.

burden on family and promote the social inclusion of children. The need for qualified psychological support is recognized in the international literature and in the most recent guidelines.

Volunteer associations

Volunteer associations are essential for centers that follow patients with rare diseases, since they bring the patient's requests to the attention of the general population, in order to reduce their sense of loneliness, and can contribute to raising funds both for welfare purposes, where the public fail to cover needs, and to promote research.

Therapy and rare diseases

Successful etiological therapies are often lacking, but this does not imply that treating people with rare diseases is impossible. In fact, there are numerous symptomatic, supportive, rehabilitative, educational, replacement or supplementary functions, and palliative treatments, including some services currently not provided by the National Health Service, which can significantly change the clinical course and life expectancy, the degree of autonomy and quality of life of affected people and their families. Access to these already available treatments and their innovative aspects constitute key elements in the healthcare policies aimed at patients with rare diseases.

CHAPTER III

THE DIAGNOSIS: GENETIC TESTING

Pamela Magini, Giovanna Cenacchi, Marco Seri

Mendelian genetic diseases are rare clinical conditions caused by a defect in the genome, and are classified as chromosomal disorders, due to either alterations in the number or structure of chromosomes, or gene disorders, when caused by DNA mutations that alter the sequence of genes and, consequently, the structure or function of encoded proteins. Common diseases, whose pathogenesis involves the interaction between genetic susceptibility factors and environmental risk factors, are defined as multifactorial or complex.

Thanks to the completion of the Human Genome Project in the early 2000s and the development of ever more advanced technologies, knowledge on genetic diseases has progressed very rapidly, allowing research in the field of medical genetics to determine the role of specific genes in over 6,000 different diseases (Lander *et al*. 2001; Venter *et al*. 2001; International Human Genome Sequencing Consortium 2004; OMIM portal, see some reference links).

The information deriving from the identification of the altered gene, in a specific genetic disorder, has two important clinical applications: therapy and diagnosis. This information can promote the elucidation of the pathogenetic mechanism, responsible for the onset of the disease and the identification of possible targets for specific therapies. To date,

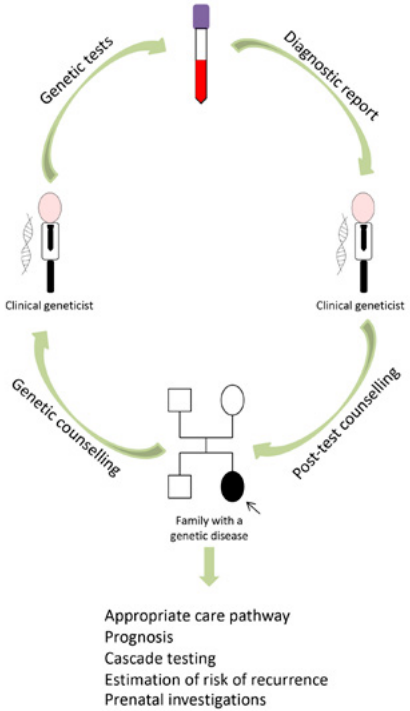

Fig. 6. When a specialist doctor (pediatrician, child neuropsychiatrist, neurologist, etc.) suspects a genetic disorder, he or she generally refers the patient to a clinical geneticist, who provides a physical examination and collects anamnestic data and family history. Based on the data collected during the examination, the clinical geneticist may decide to start a genetic test to confirm a diagnostic hypothesis, explaining the purpose, potential and limitations of the test to the patient or their guardians and collecting informed consent for its execution. After the genetic investigation, the laboratory sends the report to the geneticist who communicates the result to the patient/guardians, during a post-test genetics counselling, together with all the implications for the clinical management of the patient and his/her family.

however, "curable" genetic diseases are a small percentage, and the most relevant medical application of the knowledge gained from genetic research is diagnosis. In fact, genetic tests are essential for the molecular confirmation of a diagnostic hypothesis based on clinical information, allowing the definition of risk of recurrence, prognosis of the disease, clinical surveillance and possible personalized therapies (ACMG Board of Directors 2015).

Given the importance of the identification of the molecular defect in patients with rare diseases, the use of genetic tests in medical practice has increased exponentially, especially in recent years.

The commonly accepted definition of genetic testing is "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes" (Holtzman 1999).
Genetic tests have some peculiarities compared to other laboratory tests. Firstly, their results can have impact not only on the person who has undergone the test, but also on family members. This is why, in common practice, a genetic test must be included within a specific diagnostic path and must be supported by genetic counseling, which gives patients specific indications about its sensitivity and its purposes (Fig. 6).
On the basis of their purposes and the type of disease investigated, genetic tests are classified into diagnostic, presymptomatic, predictive or prenatal (McPherson 2006). Some tests are aimed at evaluating genetic susceptibility for complex diseases, but they often have a limited clinical impact.

Diagnostic tests

Diagnostic tests allow to establish a diagnosis, or to confirm a suspected pathological condition based on clinical evaluation. With a definite genetic diagnosis, the mode of inheritance of the disease can be determined and thus more appropriate genetic counseling, with specific recurrence risks, can be offered. They can be carried out throughout a person's life, but also in the prenatal period. Sometimes the outcome of a diagnostic test also allows to evaluate the prognosis of the disease under examination, if the correlation between genotype and phenotype has been characterized thoroughly, so that certain genotypes have been attributed to clinical pictures with well-defined degrees of severity and clinical courses. For example, in most trinucleotide repeat neurological diseases, due to the expansion of specific trinucleotide repetitive elements, the age of onset and the severity of the symptoms are correlated with the number of triplets (Paulson 2018). Furthermore, in some cases, molecular diagnosis can also provide useful information regarding the choice of the most effective therapeutic

treatment. For example, the early identification of mutations in the *SLC2A1* gene and the timely administration of a ketogenic diet greatly improve the neurological outcome in children suffering from encephalopathy related to *GLUT1* deficiency (Wang *et al.* 2002).

Presymptomatic tests

Genetic diseases not present at birth but later in life, even in old age, are defined as late-onset. These disorders generally show an autosomal dominant inheritance pattern (due to mutations in one of the two alleles of genes located on chromosomes 1-22, called autosomes) and raise a relevant issue in the diagnostic process. In fact, through the presymptomatic test, the causative mutation previously identified in an affected individual, representing the index case, can be searched for and found in asymptomatic relatives who will inevitably develop the disease throughout their life.
The presymptomatic test is performed without limitations on minors, when the diagnosis can decrease morbidity and/or mortality, thanks to the availability of secondary prevention strategies or adequate therapies. Conversely, the presymptomatic genetic test is limited to adults when results cannot lead to an improved clinical management, as it happens in most cases. People identified as presymptomatic are usually assisted by a multidisciplinary team composed by geneticists, psychologists and appropriate specialists.
However, there are no *a priori* preclusions for performing the presymptomatic test. The supportive medical assistance will help the patient to understand if results might provide useful information in making choices on certain important aspects of life (maternity/paternity, work, etc.) or, conversely, they could be a great burden to bear, negatively affecting life, when disease symptoms are not yet present. Many diseases, for which presymptomatic tests are available, are neurological. The most classic example is Huntington's disease (Quaid 2017).

Predictive tests

The onset of a relatively small group of tumors, called hereditary cancers, such as hereditary breast and ovarian cancer or Lynch syndrome (predisposition to develop non-polyposis colon cancer), is due to mutations of single genes (Garber, Offit 2005). However, in the vast majority of cases, a hereditary alteration in a gene associated with cancer represents only one of the potential factors involved in the development of the disease and is associated with a greater predisposition to the disease. A critical point is therefore the evaluation of the predictive value of the genetic test.

Predictive tests are particularly important, since the possible identification of healthy subjects with a high genetic risk of cancer involves the need to decide whether to take preventive measures. However, the approach to prevention is very complex, as the availability of effective measures varies greatly depending on the type of disease.

Prenatal tests

During gestation, genetic tests can be used to identify genetic disorders affecting the product of conception. Some tests are carried out without specific indications (in particular chromosome analysis in the case of advanced maternal age, when women have a relatively high risk of pregnancies with chromosomal abnormalities), others focus on the specific genetic disease present in the family (mainly when parents are heterozygous carriers of recessive genetic conditions, or in the case of a mother carrying a X-linked defect).

Some examples are: cytogenetic analysis to detect chromosomal anomalies (for example, the identification of trisomy 21 in Down syndrome), sequence analysis of the *CFTR* gene in fetuses at risk of cystic fibrosis, the identification of trinucleotide repeat expansions in the *FMR1* gene in fetuses conceived by a woman carrying a premutation.

New technologies applied to medical genetics

Over the years, the continuous development of new technologies for DNA analysis has greatly increased the sensitivity and the rapidity in the identification of both numerical/structural anomalies of the chromosomes, and alterations of gene sequences, as shown in Figure 7. This technological progress has allowed the identification of an increasing number of genes with a role in the pathogenesis of genetic diseases, leading to a significant improvement in the diagnosis within the field of medical genetics (Boycott *et al.* 2013; Durmaz *et al.* 2015).

The analysis of the karyotype (classical cytogenetics) allows the detection of large chromosomal anomalies (> 5-10 Mb) through the observation under the light microscope of the entire diploid set of chromosomes (two copies of each chromosome, one paternal and one maternal) of an individual. This was the main diagnostic test from the 1950s to the 1980s, until molecular cytogenetic techniques, such as FISH (Fluorescence In Situ Hybridization), were subsequently developed. By using a fluorescent DNA probe, complementary to the genomic region of interest, FISH is able to detect possible deletions or duplications (Copy Number Variants, CNVs) in the patient's chromosomes, with higher resolution compared to karyotype analysis (about 100 kb).

The real turning point came at the beginning of the third millennium, thanks to the aCGH (array-based Comparative Genomic Hybridization) technology, in which the patient's DNA and a reference DNA, labeled with different fluorochromes, compete for the hybridization to oligonucleotides (short nucleotide sequences) complementary to the whole genome (DNA contained in an organism, human in this case), and spotted on a slide. After hybridization, the slide is scanned by lasers, to detect the fluorescence signals, calculate their ratios (patient DNA/reference DNA for each oligonucleotide) and determine the corresponding number of copies, with a high resolution for the identification of CNVs along the whole genome (10-100 kb) and with a few days (3-4) of analysis (Pinkel *et al.* 1998;

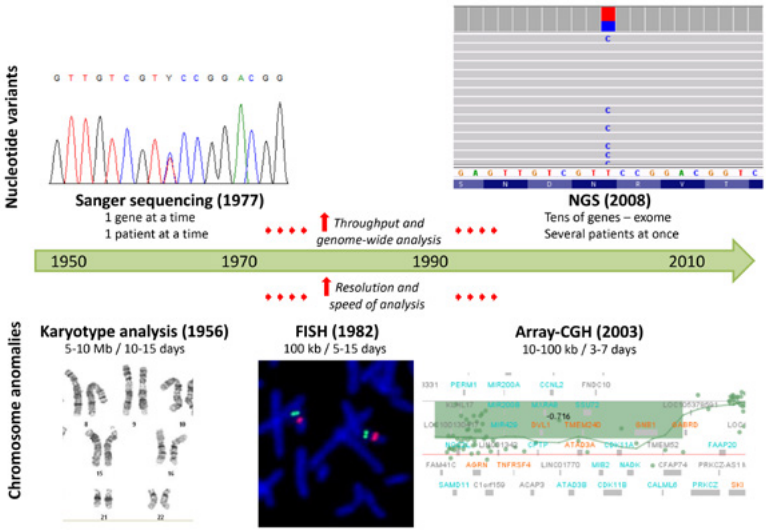

Fig. 7. The main cytogenetic and molecular cytogenetic techniques are illustrated in the lower panel, in temporal order of development (karyotype analysis, FISH, Array-CGH), with their contribution to improved resolution and speed of analysis. The upper panel shows the techniques used for the identification of sequence variants: Sanger sequencing, which has been the reference method for about 30 years, and Next Generation Sequencing, which has greatly increased the analysis capacity, allowing parallel sequencing of multiple genes (up to the entire exome or genome) and multiple patients.

Albertson, Pinkel 2003). To date, aCGH is considered the first-tier test for genetic diagnosis in patients suffering mainly from isolated or syndromic intellectual disability, and is frequently applied also in the prenatal period with specific indications, for example when ultrasound anomalies are detected, or for the definition of anomalies identified by karyotype analysis (Park *et al.* 2011).

Sequencing technologies for the analysis of the nucleotide sequence of genes underwent an even faster development (Heather, Chain 2016).

From the second half of the 1970s until a few years ago, the Sanger method was the gold standard sequencing technique, widely used in laboratories. Based on capillary electrophoresis separation of nucleotide fragments, amplified from patient's DNA and modified through the incorporation of di-deoxyribonucleotides, defined as chain terminators, the Sanger method allows the analysis of the sequence of single disease-genes and the identification of anomalies (nucleotide substitutions, deletions, insertions) with a limited throughput (only one gene at a time). For this reason, the diagnostic process was almost prohibitive, especially for disorders with high genetic heterogeneity, in which several genes are involved. Often, after months of waiting, few genes are sequenced and the genetic cause is not identified.

The development and clinical application of Next Generation Sequencing (NGS) technologies in the first decade of the 2000s, have greatly improved the diagnosis of genetic diseases, both in terms of efficiency and efficacy. These technologies allow the sequencing of multiple genes simultaneously, decreasing significantly the time and costs of the diagnostic process, and offering the patients the concrete possibility of identifying the genetic defect underlying their disease (Jamuar, Tan 2015).

From the analysis of small panels of genes in disorders with well-characterized molecular bases (e.g. chromatinopathies, rasopathies, hereditary spastic paraparesis), the application of NGS has been moved on the sequencing of all known disease-genes (Clinical Exome), which are about 4,000, or even of all the genes included in the human genome (Whole Exome Sequencing, WES) (Xue *et al.* 2015).

Target differences between the two mentioned platforms, Clinical Exome and WES, give them different potentialities. Since the finding of pathogenic mutations in known disease-genes, analysed by both platforms, has diagnostic value, both the clinical exome and WES can be used as genetic tests. On the other hand, only WES can identify sequence variants with possible clinical significance in genes not yet associated with genetic diseases, thus allowing to improve knowledge in the field of medical genetics,

and to outline new genotype-phenotype associations to be included in the clinical diagnostic pathways.

Considering that each individual has tens of thousands of nucleotide variants that have no clinical consequences, analysing all the genes included in the genome in a patient with a genetic disease, and identifying the causative mutation, require a considerable interpretative effort. To facilitate the identification process, various strategies have been implemented, including the simultaneous analysis of parents and the consultation of public databases that collect benign and pathogenic human genetic variants (for example: gnomAD, dbSNP and ClinVar; see some reference links). An additional difficulty concerns the need to demonstrate that the variant, identified in a gene not associated to diseases, is actually responsible for the clinical picture observed in the patient under examination. The effect of the variant on the structure/function of the protein encoded by the altered gene, on cell morphology/homeostasis, or on the development/functionality of organs and organisms can be investigated through *in vitro* and *in vivo* functional studies. The sharing of anonymized genetic and clinical data with other laboratories, through dedicated online platforms (for example, GeneMatcher), allows in some cases to identify unrelated individuals with similar phenotypes and variants in the same gene, providing further evidence to support a role of that gene in the pathogenesis of the disease (Quintáns *et al.* 2014).

Conclusions

Genetic tests are an essential component of the diagnostic process of people suffering from genetic disorders. Although its therapeutic impact is still limited, the identification of the pathogenic mutation is very important for the clinical management of patients and their families, especially if it is rapid. The use of new technologies, in addition to improving the sensitivity for the identification of CNVs and sequence variants, has considerably shortened the time required for the execution of genetic

tests, thus increasing the clinical utility of molecular diagnosis in the context of medical genetics.
In the near future, new sequencing techniques, able to sequence long fragments (long-reads, about 10 kb) suitable for the identification of structural chromosome alterations and CNVs, will probably replace classical cytogenetics and aCGH, and will be combined with NGS (short-read sequencing, up to 150 bp) to offer patients the concrete possibility of arriving at a definitive diagnosis in a short time, undergoing only two tests investigating the entire spectrum of possible genetic and chromosomal alterations.

CHAPTER IV

THE BEFORE AND AFTER

Maura Foresti

"Rare" is a word full of implications when combined with "disease"; it brings with it a range of issues, such as isolation, loneliness, discrimination, chronicity, shortage of competent professionals and scientific knowledge, uncertainty of prognosis and orphan drugs. If we add the genetic component, the implications also run towards generativity and reach the very definition of human being, touching on themes of considerable complexity.

Thus we can understand how communicating the diagnosis of a rare disease to a carrier, or to their parents if they are children, is a moment universally recognized by doctors as difficult. In clinical experience, we often find in patient reports that even years later the communication of a rare genetic condition can take on various traumatic characteristics. The many clinical testimonies collected could be well summarized as follows: there is a before and an after.

The scientific literature of the last decades has been very interested in the topic (Starke *et al.* 2002; Liao *et al.* 2009), highlighting the highly stressogenic and psychopathogenic potential of receiving such delicate information, capable, capable of capsizing one's world and life expectations for the future: it is documented that such an experience can cause various psychopathologies from post-traumatic stress disorder to anxiety-depressive disorders.

Beyond the many useful indications that can be found in the literature (summarized in the form of a list in the next paragraphs) on how to communicate this type of information, it is important to clarify that it is not possible for this information to be painless. Therefore, it is absolutely necessary that the communicator anticipates accepting the natural reaction of pain, giving space and time to the people who receive it in order to integrate it into their mindset and planning. However, the experience of the human being learning such a truth about him or herself or about a child is sometimes pain of devastating proportions. We need to meet this pain head-on in order to fully understand its challenge. Sometimes even operators try to defend themselves from this encounter, for the completely unfounded fear of being overwhelmed. It is, in fact, a matter of handling a "highly toxic" material, as the scientific literature on burnout has clearly highlighted.

From this premise that it is not possible to communicate this type of information without causing intense pain, it follows that the goal of diagnostic communication should not merely be passing on the information, but offering the people who receive such information the necessary support to be able to integrate it, and achieve a new state of balance. In short, if we know we must inflict a necessary injury, we will have to be careful to avoid possible "infections" and complications, not to feel like bad healthcare workers and not to become targets of intense negative feelings that are difficult to bear.

Here then are the general conditions that the literature has come to describe to achieve adequate communication, that is, communication capable of preserving the health of all the actors involved (Fig. 8).

The communication should:

- take place in a dedicated place, reserved for this activity and, above all, it should be transmitted without haste and with adequate time provided;
- be given to the interested party together with a relative or, in the case of minors, to the parents together;

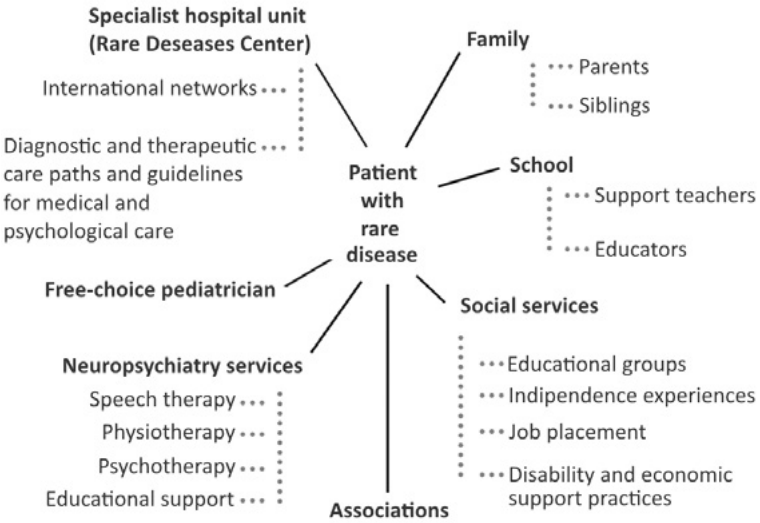

Fig. 8. The network for taking care of the patient with rare disease.

- be accompanied by the scheduling of at least one further explanatory meeting, within a short time;
- provide psychological support/consultation;
- provide a contact number to refer to from then on for information on the condition that has been diagnosed;
- be accompanied by offering information brochures, contacts with other carriers and/or with associations of patients or parents;
- be provided with the collected input shared by a multidisciplinary team and a network of professionals.

Furthermore, in the case of minors, the communication should set in motion an "internal debate" between parents on how to commu-

nicate with the child about the diagnosis as they grow and develop. In this regard, in fact, there is some literature on the difficulties of parents in communicating to their children their chronic conditions, with far-reaching consequences for the way in which the future adult will manage and elaborate his or her own clinical condition (Sutton *et al.* 2006; Suzigan *et al.* 2004). With regard to this last point, often the advice or intervention of a psychologist, an expert in the developmental age and rare diseases, is necessary.
Two phases of life pose specific challenges that require further precautions: the prenatal phase and adolescence.

Prenatal diagnosis

Many studies have tried to highlight the serious threats implicit in prenatal diagnostics stemming from two factors: The first is connected to the fact that pregnancy is a moment of great delicacy for the psyche of a future mother, who is trying to prepare herself, both in practice and through fantasies about the unborn child, to welcome a new human being with whom a relationship already exists. The second relates to the fact that the relationship between the infant and its caregivers is a foundation for the development of every human being. In fact, in taking care of the newborn, adults will carry out the crucial functions of imprinting, activating and conducting all its mental development (Camaioni, Di Blasio 2007).
In the prenatal phase, fantasies take on a much greater power than in other stages of life. In this phase, the words spoken by doctors are powerful as they affect these parental fantasies about the unborn child: in clinical psychological practice it is a daily occurrence to receive testimony about how the information received is indelible and, unfortunately, also easily misunderstood.
Countless studies, starting from the Second World War, have highlighted the crucial importance of early care experiences, as well as the importance

of adults' expectations and fantasies that attribute meaning to the experience of the newborn (Winnicott 1970). That is why a meeting should always be provided to communicate the outcome, positive or negative, of a prenatal diagnosis: the mere fact of being contacted by phone already translates into a negative communication, bringing hours or days of nameless anguish. Thus couples who undergo such diagnostic procedures should be prepared psychologically, giving them an opportunity for preventive health protection in which they can reflect on their parenting adventure and their willingness to receive non-positive news from the diagnostic procedure itself. This is why, finally, in the event of a prenatal diagnosis of rare disease, it is always necessary to offer the parental couple, after consulting with the geneticist, counselling with paediatricians who are specialists in the condition and with an expert psychologist.

Diagnosis in adolescence

Another critical moment that requires special attention is adolescence. It is a phase of development that in recent decades has attracted a lot of attention from society (keeping in mind that adolescence did not exist as a category until the beginning of the last century) and psychological science. The pubertal phase that characterizes its beginning – second in importance only to the stages of embryonic and perinatal development – is the era of human development characterized by the most significant transformations that concern the body (biological maturation), the mind (cognitive development) and behaviour (relationships and social values). The discovery of a rare disease, at this stage of development, can be much more difficult to accept and can trigger very complex reactions to contain and elaborate the information (Sawyer *et al.* 2003). The intervention of an expert psychologist in the developmental age is often necessary and must include the adolescent as the main interlocutor although the family context must also be considered, even if in most cases this remains separate from the individual patient treatment.

Diagnosis process

The most common defences against negative news are well-known to doctors, who face daily difficult diagnostic communications: disbelief (requests to repeat tests to be sure they are not a mistake), cognitive confusion and denial (some time after the communication, the patient claims that he or she has not been informed of a part or all that was actually communicated to them, or has misunderstood crucial parts of the communication) or escape (patients put aside the diagnosis, do not access the proposed follow-up, forget to book prescribed exams, do not talk to anyone about the diagnosis received). These defences prevent the healthy course of processing the communication from taking place. This process foresees that, by going through the pain brought by the negative truth, we will get to integrate it into our world of knowledge and to welcome the treatments and resources proposed. It is these defences that also explain the frequent isolation of many families and many rare patients.

The course of processing the diagnosis is activated slowly after communication and requires a variable time; it is necessary to check that it starts correctly and, in the case of rare conditions of developmental age, it must be monitored over time (D'Alberton 2018).

First of all, as anticipated, it is necessary to plan at least a second meeting after a diagnostic communication in order to be able to ascertain that a processing has started adequately. If this has not happened, the necessary specific psychological interventions must be put in place (psychological counselling, discussion groups led by a psychotherapist, targeted psychotherapy courses). Therefore, if the process has started correctly and the pain of the news is contained, it will not be necessary to arrange other interventions; if, however, the people who received the news are suffering acutely, it will be necessary to offer them a path of some talks that unfold over time and that accompany them in containing and thinking through that great pain that they cannot manage to tame. In short, we can say that when the communicated rare condition heavily impacts the quality

of life or future expectations, when anxious or depressive symptoms occur, when a teenager shows an angry or withdrawn reaction, or abandons his or her vital plans, it is necessary to intervene with appropriate psychotherapeutic tools; when the pain of a parental couple risks damaging the relational developmental, because it produces a dysfunctional interaction with the child, a specific intervention must be offered that reactivates the mother/father-child relationship (the so-called participatory consultation, see Vallino 2009); when feelings of guilt or shame damage the relational life of a person with a rare disease (or of his or her family in the case of minors) some psychological interviews must be offered to address these psychopathogenic feelings and appropriately provide contacts with associations, group meetings conducted by a professional, or mutual help, which can make them feel less alone, unique and at fault.
Since the acceptance of certain painful truths is a great challenge for every human, we can conclude that the diagnostic communication of a rare disease should be understood as a multidisciplinary process – involving doctors, psychologists and associations – rather than as a punctual event that ends in a mere communicative transfer of information, and should take into account the particularities of the diagnosed condition, the context and the moment of development or life of the subject, preparing specific pathways for pathology and for the delicate stages of development described above.

CHAPTER V

GROWING UP WITH A RARE DISEASE

Maura Foresti

In the previous chapter we discussed how challenging the experience of learning to be carriers of a rare disease is. Even when it is possible to process this news, and integrate it into one's own world of thoughts and planning, having a rare disease – which, for certain genetic conditions, brings elements of human rarity into one's life as a whole – is a very strong experience that does not remain confined in the body, but which can seriously impact the quality of life of the carrier and their family members, with important reverberations also on the life contexts of the subject and on an entire community that wants to take care of the health of its members. For this reason, the cure of rare diseases requires, over time, various appropriate medical, psychological and social interventions in order to contain their psychopathogenic potential (Rebecchi 2018). However, like many painful experiences in human life, rare disease also contains positive potential.

In this chapter, we will first try to describe the main areas of life that can be affected by a rare childhood-onset disease and possible treatment interventions; we then discuss the potential value of rare diseases for a human community.

The effects on the foundational relation of human mental development

This point has already been covered in part in the previous chapter (see Prenatal Diagnosis, Chapter IV). Here it is important to add that a newborn child carrying a rare disease may not have the synchronic capacity, typical of a healthy newborn, to enter into the early relationship with the caregivers; it could also have adults who are much more anxious, when not pained and injured, and therefore have difficulty playing the role of partner in the foundational relationship of human development. In other words, this is a very disadvantageous situation, in terms of the attachment relationship as well (Bowlby 1958). Often, in this phase, couples report the painful experience of desperate solitude, of uncertainty about the future of the child, of wandering among specialists without a guide, of a growing feeling of anxiety and inadequacy towards a "difficult" or distressed child, in any case rare or different, for which nobody knows how to intervene. In this phase it is necessary to provide for an early and competent psychological intervention that monitors the relationship and attachment, which can indicate to the parents the skills of the child beyond the impairment, offering them alternative ways to synchronize with their rare newborn, and that can coordinate useful or necessary rehabilitation interventions: physiotherapy, speech therapy, psychotherapy or other specific interventions. To avoid these chilling experiences, careful coordination is needed between hospital care and territorial assistance, between the specialized centre for the rare condition, the paediatrician of free choice and the neuropsychiatry service of the territory of residence, and sometimes social services and institutions or schools. In other words, a network, a community must be present to take charge of the child and his or her parents. From the scientific point of view, however, it is necessary that the appropriate guidelines for each rare disease are prepared as soon as possible from the point of view of the knowledge achieved.

Psychological consequences of early hospitalization

Sometimes rare diseases can involve surgery or long hospitalizations in the paediatric age. In general, in the case of prolonged hospitalizations at the early stages of life, special attention is needed to try to contain the harmful effects both on the development of the child and on the early relationship.
Early and/or prolonged experiences of hospitalization, especially if surgical, in fact risk the sense of continuity and security as well as the basic trust necessary for building one's identity. The limitation of the development of autonomy, linked to the reduced possibility of movement, the alteration of daily rhythms, the lack of usual social and family relationships, and the lack of positive stimuli, could further slow down the child's psychomotor development (Robertson 1958). Psychological intervention at this stage will be mainly aimed at supporting parents, observing the attachment process and emotional development of the child, and offering timely interventions to support these fundamental processes despite hospitalization (Sarajarvi *et al.* 2006).

Communication needs for individuals with rare diseases

The strategies used by each child to cope with the same disease are different and depend on various factors: the child's temperament and personality, the stage of development, whether there is a need for surgery, hospitalization, or therapies, the different past experiences, the family and social environment in which it is embedded, the type of disease, and the circumstances and life changes imposed by the disease itself. Because of this complexity, care interventions should be tailor-made for each child and his or her family.
From the early days of life, a child is a subject centre of will and sensations, inserted in a relationship of very close dependence on adults. Because of this duplicity of the infantile condition, it is important for

attention to be directed to multiple aspects: both towards the family and caregivers as well as towards the child and his/her living environment. At all times of the treatment the operators must cultivate an attitude that aims to make the child, even when very small, aware of their reactions to the disease, and also of the reactions of their reference adults (parents' fear, pain and sadness can be misunderstood by the child as a negativity that disappoints loved ones); furthermore, when the child is placed in school settings, it is important to help them understand the possible reactions of their companions (for example, some children may, even if in many cases erroneously, fear getting sick by attending a sick child) and help parents communicate effectively with the teaching staff to better welcome the child and their reflections of the hospitalization experience when re-entering the school context (some children tell the experiences of hospitalization to adults and classmates, or express them through games that may also have an aggressive background, creating strong emotions in their peers, which it is good for adults to know how to mediate and welcome).

After seven years of age, cognitive development gradually allows the child to understand diseases and therapies; therefore it is necessary during the medical examinations to share with the child the main information and awareness aspects in order to enable the child to understand and begin to manage his or her condition independently; it is, in fact, potentially very harmful for a small human being's sense of self and identity to hear adults talk about them without being helped to understand what is said about them. Thus when parents ask to hide some aspects of the disease from their children, it is not good to contradict them, but it is necessary at least to offer them psychological advice that can help them reflect on the meaning and possible consequences of their choice. The quantity and quality of the information transmitted to the patient and family (diagnosis, prognosis, treatment) and the ways in which it is transmitted are fundamental, since they play a crucial role in the process of acceptance and adaptation to chronic disease.

The impact on caregivers

Even those who, professionally, take care of people with rare diseases find themselves in daily contact with strong requests for support and emotional help that can make them feel submerged and helpless, which creates a high risk of burnout: for this reason it is it is necessary to offer information and support to the staff as well. To avoid feelings of helplessness in carers, in addition to good psychological support, a good care network is necessary which the operator can feel part of. In this regard, the patient associations present in the area are essential, and in synergy with the carers can play a fundamental role for both patients and operators.

Family dynamics, from parents to siblings

The experience of a child sick with a rare disease has a profound impact on family dynamics. When a couple is expecting a child, it can be the fruit of different choices, or even be experienced as imposed by fate, but it always represents, in the human symbolic imagination, the fruit of the union of the parents. For this reason, the fact that a child is sick, or a carrier of a rare genetic condition, is full of meaning with a negative potential for the parents. It can be thought that the disease is a kind of punishment: parents often confess strong and frequent guilt feelings in these life stories. Parents can also experience illness as a great injustice and become overwhelmed with powerful feelings of envy, or inferiority, towards those couples who have given birth to healthy children; one may think that they their union was unfortunate, and that this disease is the confirmation or revelation of one's defective nature. Moreover, if an unborn child is normally a source of joyful anticipation for a future full of promise, a sick child becomes an anguished potential of a future of disability, lack of autonomy, limitations imposed on the child and their parents, as well as a lifelong commitment for

parents to bear along with a formidable source of anguish about the time that parents call "after us". And this is how that experience of becoming parents, which in itself represents a challenge for the couple, becomes a test full of dangers when a child is born with a rare disease. It is not easy, in fact, to challenge the sense of pathological guilt, the feeling of generative failure and this looming sense of "after us". In this phase, professional and specialist help is necessary in most cases. The Italian National Institute of Statistics, ISTAT, reported that the incidence of minor relationship problems or even the breakdown of the relationship is much greater in the case of the birth of a child suffering from a rare disease.

The presence in a family of a child with a rare disease, which necessarily requires a great deal of parental commitment and which worries them differently than a so-called "healthy" child, has a powerful impact on fraternal dynamics. Healthy siblings often have an incidence of psychopathological and conduct disorders much higher than the normal population. It is frequently a way to attract attention, the communication of a discomfort related to feeling healthy next to a sick sibling and, therefore, a feeling of guilt compared to a sibling for whom there are intense feelings of jealousy for the attentions that the sibling receives from their parents, even if it is considered more unfortunate; it is the communication of a guilt-related discomfort over the aggressive feelings that having a sick sibling can generate. These are some of the most complex and powerful psychological dynamics. This unease of the so-called "healthy" siblings, if caught early and treated by competent professionals, can be resolved; in contrast, if ignored, it can degenerate throughout life even in serious psychopathologies. A psychological intervention to support these families should always provide for a careful observation of family dynamics, supporting parents in explaining and reading the complex emotional intertwining of their children's sibling relationships.

The transition to the adult therapeutic world

In light of what has been said so far, it is useful to mention another complex aspect of the care of the rare sick child: the transition from care centres dedicated to children to adult services. It is clear from the above that the care of a rare sick child requires specialist centres with periodic follow-up and staff capable of becoming reference figures for patients and their families. Here the transition to adult care services is a crucial moment in the life of a rare disease patient; for this reason it should not be a mechanical transfer from childhood to adult services, but a carefully planned process, aimed at responding to the medical-assistance, psychosocial, educational and vocational needs of adolescents and young adults with chronic conditions (Wright *et al.* 2018). For patients, transitioning to adult services means, in fact, enduring a new separation, interrupting another significant relationship, which is a relationship of care and also deeply emotional, to start a new unknown. For this reason, getting to know the new staff and the functioning of the adult services, and being aware of a collaboration between the two services, can help increase the sense of personal security during the transition phase. In order to plan the transition, it is useful to introduce this concept in advance to patients, right from adolescence, and to make contact with the adult team before the patient moves to the new centre, avoiding implementing it in times of particular patient stress.

Autonomy and extra-family life: from school to work placement

Finally, the issue of autonomy and relationships outside the family environment with the broader world is very important. Rare diseases differ greatly from one another in the impact on the life of the carrier. Some situations prevent one from reaching basic autonomies such as dressing and eating, and impact cognitive skills in various ways; others, on the

other hand, only affect physical autonomies, or only cognitive skills. It is often difficult to predict at an early age the degree of impairment that will accompany a condition. It is a matter of following the subject and his or her parents in trying to develop the potential of mutual autonomy to the maximum. This requires exploring with parents their assessments, which could sometimes prove limiting for the child in achieving some possible autonomies, or which in other cases could lead to highly conflicting relationship dynamics; to avoid this it is necessary to support parents in finding solutions that can at least alleviate the burden associated with the child's lack of autonomy.

Another major theme is, in fact, that of relationships outside the family: the literature indicates that a rare disease patient risks a more withdrawn and modest social life. This is variously due to the different conditions the patient might have, the objective limitations, the prejudices spread in society and, finally, also to feelings of dysthymia of the bearer subject, which can also lead to dysfunctional ways of relating to others. This area of the life of a rare disease patient can frequently require the intervention of specialists to support their good social, scholastic and working integration. It would be extremely important to immediately support a good relationship with peers. The inclusion in school and in the world of work are fundamental stages in the development of every human being and, in the case of a rare disease, the involvement of the school requires specific attention that varies from condition to condition. We have no way here to address this issue with the importance it deserves. The same could be said about job placement.

However, it is important to highlight here how the social inclusion of a rare patient derives, fundamentally, from the ideas that a community has about rare disease and disabilities in general (Zani, Cicognani 2000). Here is our brief reflection on the positive potential of rare diseases in a human society. The degree of civilization of a human culture is assessed by historians on the basis of several parameters, including the care of their sick. A society that pursues a value of perfection and

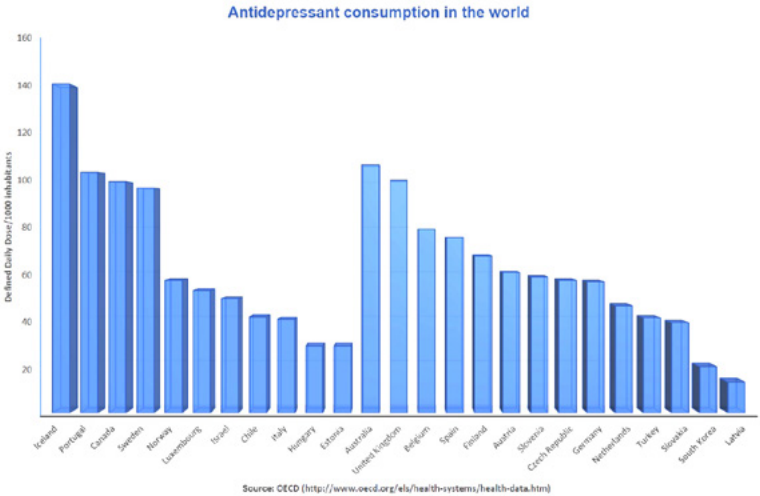

Fig. 9. The graph illustrates the consumption of antidepressants in some countries of the world, in the years 2016 and 2017. Image based on data extracted from OECD (2019), N06A - Antidepressant, Pharmaceutical Market, OECD.Stat, https://stats.oecd.org/viewhtml.aspx?datasetcode=HEALTH_PHMC&lang=en#, accessed on April 23, 2020. © OECD.

success with too much absolutism risks falling into the violence that characterizes the myths of racial perfection, which have been seen in human history on several occasions. The encounter with the disease, with the fragility of human biology, on the other hand, allows us to recognize the limits of our nature and to recover the values of mutual care and respect for human value, regardless of any other possible consideration, thus inviting us to cultivate the values of collaboration and the virtues of prudence and reflexivity, which our time is increasingly confining in favour of the search for adrenaline-fueled experiences and competitiveness (Mancuso, Boncinelli 2008).

I believe that having the opportunity to know and observe (as operators,

but not only) the daily experience of the carriers of a rare disease and their caregivers can be a continuous starting point for reflection and analysis of our era which, despite the extraordinary material well-being achieved, expresses great psychological distress, as evidenced by the data relating to the consumption of antidepressant drugs (Fig. 9) and psychoactive substances worldwide.

CHAPTER VI

WHAT IS THE COST BURDEN OF RARE DISEASES?

Marianna Cavazza

When faced with the question "What is the financial burden of rare diseases?", one may wonder what the differences are for this specific area compared to the care load and volume of resources absorbed by the most common diseases. Indeed, a significant lower frequency of cases of these pathologies entails an equally substantial greater effort, not only in terms of knowledge, but also of time and resources. A study conducted between the USA and Great Britain in 2013 (Hendriksz 2013) showed that, aside from any innovative pharmacological treatments, not always present in all rare diseases, there is actually a substantial increase in costs in the daily treatment of patients with rare diseases: in the case of Great Britain, an average of £ 7,000 more per year per patient was estimated. In particular, it was found that not only the diagnosis takes an average of five or six years, due to the two or three failures that frequently characterize this phase, but that even single specialist visits are always longer compared to the other more common pathologies. Another aspect to consider is the number of clinicians on average involved in taking care of these patients. In the UK there are on average eight clinicians, a much greater number than for those patients suffering for example from rheumatoid arthritis or from cardiovascular diseases (Hendriksz 2013).

Despite this evidence, attention to the cost incurred by patients with rare diseases, their families and health systems has only grown in recent years. A search with the keywords "rare disease" and "cost" recently carried out on PubMed, one of the main search engines of medical science, revealed that more than 70% of the 244 results have been published in the last six years. The interest first focused mainly on the drugs available for the treatment of these pathologies, their cost and the methods of access to the market, foregrounding the role and burden that the paying third party invests in such situations (Zamora *et al.* 2019). This is of course a crucial aspect, especially when a new drug therapy is identified for a disease once untreatable; however, on the other hand, it is not the only element to be considered to address the cost dimension in the rare diseases. Thanks perhaps also to the increase in life expectancy recorded for some rare diseases (Franchini, Mannucci 2017; Janssen *et al.* 2014), in recent years we have begun to overcome this limited perspective and have started to not only consider the financial burden sustained by third-party payers, but widened the analysis to patients, their families and the society as large.

This broadening of perspective has, in turn, led to greater attention to the impact of the resources engaged in the treatment and assistance of people with rare diseases, not only in terms of clinical results, but also in the patient's quality of life and that of their caregivers. Finally, it should be emphasized that this perspective is also present in a document of recommendations by the Group of Experts on Rare Diseases of the European Commission (CEGRD 2016), which highlights the need to consider and address the needs of social assistance, and in the management of daily life required by many patients with rare diseases. In this contribution, we review the approaches and tools that have accompanied the above-mentioned evolution of the cost analysis of rare diseases, and the results obtained so far.

Approaches and tools for analysing the costs of rare diseases

In general, the estimation of costs in healthcare requires careful attention to two key aspects of the analysis, and this is even more true for rare diseases, as we will see. On the one hand, it is necessary to carefully evaluate the perspective that is adopted in identifying the costs to be estimated; on the other hand, it is necessary to interpret the result obtained, considering whether the resources consumed, and the related costs incurred, have or have not produced the expected result in terms of improving the patient's health and/or level of quality of life.

Regarding the first aspect of "perspective", in this context we refer to the point of view of the "proprietor" of the resources used, or to which these resources are attributable: if we consider, for example, a treatment that requires a phase of hospital and territorial assistance, a survey of costs in the perspective of the hospital includes resources exclusively attributable to the latter, such as hospital medical and health personnel, beds, and drugs administered during hospitalization. The same applies if the prospect of territorial assistance is adopted. It is therefore the perspective of the National Health Service (SSN) or Regional (SSR) – that is, of the paying third party – that is adopted to reconstruct all the phases of a treatment and the relative assistance provided by the different sections of the public health system, in addition to the related resources used by the latter. This approach excludes resources not attributable to the NHS, such as, for example, any travel costs incurred by the patient, the purchase of goods and services not covered by the NHS, or even the informal assistance provided by the family members or by other non-professional people, always not attributable to the NHS. These items will, however, be included when the patient's perspective is adopted. Finally, we must consider the perspective of the society. I make reference to the society in terms of community which allows us to understand the resources committed by the NHS and individual patients, but also the "burden" of the so-called loss of produc-

tivity that the community faces in terms of any disability pensions for patients, and/or early retirement and with a lower tax contribution capacity by both the patients themselves and the family members who provide informal assistance (Drummond 2010).

It is clear how the perspective adopted, in the context of a cost survey, has a decisive impact on the final result, and how the choice is linked to a series of elements such as the object and purpose of the analysis, the information sources that can be used and the resources available to carry out the analysis itself.

In the case of rare diseases, the most effective perspective is that of society, since most of these are diseases that entail high treatment costs, with repercussions on the public as the paying third-party, and/or highly invalidating with high burdens both for the family in terms of assistance and for society with respect to the loss of productivity (López-Bastida 2016). For example, a pathology such as haemophilia is generally characterized by the prescription of particularly expensive drugs (90% of direct healthcare costs) and could lead to greater focus on the perspective of the paying third-party, although the increase in life expectancy is also increasing attention on other resources and related costs (Kodra *et al.* 2014). On the other hand, in the case of a patient suffering from a highly disabling pathology such as Duchenne, the consumption of drugs is irrelevant and health services are very reduced, as opposed to the care load generally provided by the patient's family (Cavazza *et al.* 2016) (see Figs. 10 and 11). Given this context, the field of rare diseases increasingly uses a new interpretation of a traditional cost and benefit analysis tool, such as the cost of disease (Cost of Illness, COI) (López-Bastida 2016). It allows us, in fact, to provide an exhaustive description of the social burden on the community, identifying all the actors actually involved, highlighting the predominant cost items (for example, drugs or informal assistance) and analysing the origin of any cost variability attributable to the different contexts and organizational structures (Tarricone 2006).

		TOTAL		ADULT		CHILDREN	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Direct health care costs							
Drugs	€	107.728,30	95.866,80	100.649,80	96.513,22	130.649,40	92.257,03
Tests	€	52,89	160,56	61,91	182,30	23,67	30,45
Specialistic visits	€	880,17	1.556,10	995,99	1.747,58	505,14	479,63
Primary care	€	600,65	1.582,75	786,15	1.772,65	–	–
Acute hospitalization	€	448,72	1.510,65	587,29	1.707,27	–	–
Devices	€	54,46	137,38	59,51	139,51	38,10	132,20
Healthcare transportation	€	3,51	21,32	4,59	24,34	–	–
Subtotal	€	**109.768,70**	96.164,64	**103.145,24**	103.145,24	**131.216,30**	92.400,97
Direct costs of formal and informal non-health care							
Social services	€	158,72	535,39	191,26	601,42	53,33	185,08
Informal care	€	4.959,92	22.419,95	2.961,57	21.092,40	11.430,80	20.629,49
Main non-professional caregivers	€	4.534,76	20.153,44	2.961,57	21.092,40	9.628,92	16.157,54
Other non-professional caregivers	€	425,16	2.266,51	-	-	1.801,88	4.471,95
No healthcare transportation	€	104,43	231,59	132,24	258,96	14,40	14,52
Subtotal	€	**5.223,08**	20.815,10	**3.285,07**	21.237,26	**11.498,54**	18.475,38
Total direct costs (direct health and direct non-health costs)	€	**114.991,78**		**106.430,31**		**142.714,84**	
Indirect costs							
Loss of labour productivity patients (sick leave and early retirement)	€	1.748,56	4.495,55	2.288,55	5.028,93	–	–
Loss of labour productivity carers (sick leave and early retirement)	€	991,38	5.904,85	31,46	259,42	4.099,70	11.828,46
Subtotal	€	2.739,94	7.241,01	2.320,01	5.132,52	4.099,70	11.828,46
Total costs	€	**117.731,72**	**98.013,37**	**108.750,30**	**96.133,36**	**146.814,60**	**100.733,90**

Fig. 10. The distribution, expressed in absolute values, of the average direct medical costs, direct non-medical and indirect costs, calculated per adult patient, per minor patient and for the total of adult patients and minors with haemophilia, in Italy in 2012. The NHS perspective refers to the direct costs item while the organization's perspective also includes direct non-healthcare costs and indirect costs. The Table has been adapted from the original, reproduced with the permission of *Blood Transfusion*, 12 (suppl. 3), p. S571. © 2014 *Blood Transfusion*.

		TOTAL		ADULT		CHILDREN	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Direct health care costs							
Drugs	€	321	224	249	222	343	222
Tests	€	219	181	157	114	238	194
Specialistic visits	€	1.863	2.329	1.358	2.133	2.023	2.381
Acute hospitalization	€	708	911	674	935	719	910
Health material	€	6.612	9.636	18.111	10.781	2.953	5.546
Healthcare transportation	€	23	132	53	217	13	90
Subtotal	€	9.744	10.002	20.601	1.123	6.289	6.583
Direct costs of formal non-health care							
Professional carer	€	75	703	–	–	99	807
No healthcare transportation	€	150	202	52	125	181	213
Social services	€	655	1.902	1.865	3.272	270	930
Subtotal	€	880	2.807	1.917	3.397	550	1.950
Direct costs of informal non-health care							
Main non-professional caregivers	€	18.518	18.012	23.806	19.182	16.835	17.439
Other non-professional caregivers	€	12.120	16.441	16.053	16.963	10.869	16.202
Totale parziale	€	30.638	34.453	39.859	36.144	27.704	33.641
Direct non-healthcare costs	€	31.518	32.408	41.776	33.691	28.254	31.552
Total direct costs (direct health and direct non-health costs)	€	41.262	36.049	62.378	37.315	345	332
Indirect costs							
Loss of labour productivity carers (sick leave)	€	285	2.659	1.181	5.412	–	–
Loss of labour productivity carers (early retirement)	€	–	–	–	–	–	–
Subtotal	€	285	1.330	1.181	2.706	–	–
Total costs	€	**41.547**	**35.811**	**63.559**	**36.672**	**34.543**	**33.182**

Fig. 11. The distribution, expressed in absolute values, of the average direct healthcare costs, direct non-healthcare costs and indirect costs, calculated per adult, underage patient and for the total population considered with Duchenne muscular dystrophy, in Italy in 2012. The high values of the standard deviation indicate a wide dispersion in the distribution of costs among the population considered. The NHS perspective refers to the direct health costs item, while the organization's outlook also includes direct non-healthcare costs and indirect costs. The table has been adapted from the original, reproduced with the permission of Springer Nature Customer Service Center GmbH: Springer Nature, *The European Journal of Health Economics*, from the article "Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe", by Marianna Cavazza *et al.* © 2016.

The second key element, namely interpreting the results obtained from the cost analysis, is based on the assumption that examining the monetary value of the resources on average consumed for the treatment and assistance of a patient suffering from a given pathology certainly provides important indications, but only tells part of the story. In fact, the next step, to fully represent the actual value of the costs incurred, is the comparison of the latter with the results of the services for which the valued resources were used (Drummond 2010). In this perspective, the main tool to be used in the field of rare diseases is quality of life in relation to the state of health (Health-Related Quality of Life, HRQoL) (López-Bastida 2016). This is a "reinterpretation" by the medical science community of the notion of quality of life, further elaborated by social sciences and psychology: specifically, among the various determinants of quality of life, only health and related aspects are considered. This approach, therefore, allows us to remain within the perimeter of the medical mission and to examine the aspects of daily life that can actually be modified by medical interventions. Therefore, the HRQoL provides indications, based on the patient's perception and their objective functional capacities, about the level of physical, mental and social well-being attributable to their state of health (Ierardi *et al.* 2010). These surveys can be carried out using a wide range of pathology-specific or general scales; among which one of the most widely used is the EQ-5D family of scales together with Zarit Burden interview instead used to assess the impact of informal assistance on the quality of life of caregivers.

Results

A large-scale application of these approaches and tools was provided by the Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe (BURQoL-RD) project, promoted from 2010 by DG SANCO of the European Commission, to detect the social burden of ten rare diseases (cystic fibrosis, Prader-Willi syndrome,

haemophilia, Duchenne muscular dystrophy, epidermolysis bullosa, fragile X syndrome, scleroderma, mucopolysaccharidosis, juvenile idiopathic arthritis and histiocytosis) in eight countries of the European Union (Bulgaria, France, Germany, Hungary, Italy, Spain and Great Britain). The approach based on the cost of the disease revealed, within each pathology, a strong variability in terms of costs, attributable to the different institutional and non-institutional organizational structures, to the different components of formal and informal assistance provided, as well as to the different level of accessibility to drugs. Equally variable is the HRQoL of patients and their possible caregivers, also following the different volume of resources deployed by health institutions and society (López-Bastida 2016).

Some analyses carried out side by side with the BURQoL project have confirmed that, in general, a greater consumption of resources, and therefore a higher cost, translates into higher HRQoL levels. A more specific examination of this report was therefore carried out with respect to the Italian population of haemophiliac patients, always enrolled in the context of the BURQoL project (Kodra *et al.* 2014). It was observed that an increase of one point on the measurement scale of the HRQoL, using the EQ-5D and EQ-VAS tools, entails a decrease in the costs of the disease (€ 217 per year) if we exclude the cost of medication. Although the latter represent the most significant cost item for this pathology, the result must be read in the context of the increase in life expectancy of haemophiliac patients in recent decades. In fact, a further analysis of the relationship between the trend of costs, always excluding drugs, and age indicates that the trend is the same as that of the healthy population, with an increase in the first years of life (0-4 years) followed by a steady decrease in subsequent years, up to 46 years of age, when costs start to rise again.

Conclusions

Returning to the initial question regarding the financial burden of rare diseases, the answer is that they generally cost more than other more common chronic diseases, as evidenced by the above data (Hendriksz 2013). The question becomes, therefore, how much more do they cost and the answer – always feared by policy-makers and typical of complex situations – is: it depends. It depends, of course, on the pathology and resources it requires, as well as on institutional and non-institutional organizational structures, and so on. What certainly combine these pathologies is, however, the complexity of monitoring and managing them. Hence we need to take on the perspective of society to be able to take into account all the actors involved and the resources actually consumed. Finally, it is important to continue to deepen the analysis of the relationship between the costs incurred and HRQoL, since it is probably the best way to answer the question of how much rare diseases actually cost.

CHAPTER VII

FOR AN EPISTEMOLOGY AND ETHICS OF THE SINGLE CASE

Raffaella Campaner, Silvia Zullo

This contribution aims to provide some insight on rare diseases, addressed from the point of view of epistemology and bioethics. These are two distinct views, but in clear relationship with each other, which we believe can bring out relevant aspects inherent in our ways of dealing with rare diseases, both in biomedical research and in the clinic.

Models and single cases

The EURORDIS-Rare Diseases Europe portal, an international non-governmental organization representing patients suffering from 894 rare diseases, states that rare diseases, also known as an orphan disease, are diseases that affect a small percentage of the population. "The European Union considers, a disease as rare when it affects less than 1 in 2,000 citizens […] Rare diseases are characterised by a wide diversity of symptoms and signs that vary not only from disease to disease but also from patient to patient suffering from the same disease". In what respects does this "variety" constitute something peculiar and impact on the elaboration and use of medical knowledge?

Indeed, science aims to identify regular patterns in phenomena, and to design models representing them effectively. Models are elaborated

through abstraction and idealization procedures, providing frameworks in which the pathology is represented in its ideal features. The doctor's task will be to establish the correct relationships between the general model and the individual patient, who never presents all and only the elements figuring in the model. The ability to correctly grasp these relationships is important in the definition of a disciplinary area: "Grasping the peculiar features of a discipline amounts to, among other things, shedding light on the distinctive relationship, by nature or degree, it draws between these two aspects: single facts and general models" (Gabbani 2013, p. 15).

Various views address this issue, directly questioning the relationship between biomedical research and clinical practice, along various axes. From a purely theoretical and principle point of view, are there reasons to privilege portions of knowledge that can be generalized or, at least, widely applicable, over information referring only to the individual case – and therefore, in a medical context, to prefer knowledge on "typical" conditions to research on rare ones? In an epistemological perspective, the role of forms of general knowledge is debated. Empirical knowledge starts from the observation of individual cases and "there may well be a regularity corresponding to each singular fact, but the regularity does not constitute the truth of the singular claim, nor is it necessary for its confirmation. […] Regularities have no privileged position. Singular claims can be established just as reliably" (Cartwright 2000, pp. 47-48). Furthermore, that phenomena are governed by regularity is an assumption, and can be disputed. Indeed, the world could prove to be dominated by variations, rather than repetitions, by disorder rather than order (Dupré 1993; Cartwright 1999). The belief that forms of general knowledge, capable of progressively unifying an increasing number of cases, necessarily provide a better understanding of the world, and are therefore preferable, cannot be taken for granted.

In a framework that questions the relationship between general models and single cases, what role is attributed to rare diseases? Are these prob-

lematic cases to be marginalized – for epistemological and/or pragmatic reasons – or can they count as epistemological resources? On the one hand, diseases occurring with particularly low frequency tend to be conceived as puzzling; on the other hand, at least two aspects foster further reflections. A phenomenon which happens to be widely discussed in the international literature is so-called *disease mongering*, i.e. the "promotion" to the status of "disease" of a condition that is widespread in a given population, thus making it the object of treatment (see, for example, Wolinsky 2005, p. 612). Paradoxically, we are thus in a situation where research is struggling to find new and specific treatments for a few patients, actually affected by rare diseases, and, at the same time, diseases are "invented" through the re-categorization of routine conditions as pathological conditions. The broader underlying issue is the definition of "normality", from which the pathological emerges by difference: what notion of normality – natural/functional, statistical, conventional – do we assume? Who is entitled to set its thresholds?

Another interesting element is given by the extensive medical literature on case studies, focused on problems emerging "in situations where diagnosis would be difficult or particularly tricky, and describe uncommon or even 'unique' clinical occurrences. […] Single cases […] capture exceptions or highly unusual manifestations of health and disease" (Ankeny 2017, pp. 310-311), where there is often "an element of surprise" (Jenicek 2001, p. 83). The space dedicated to case studies – including the creation, for example, of the Journal of Medical Case Reports in 2007 – testifies to the recognition of their epistemic role: case studies are individual cases not simply in a numerical sense, but insofar as they introduce some novelty on a descriptive/explanatory/therapeutic level, and it is for this reason that they are regarded as worth considering. The epistemic process characterizing the dynamics of the construction of knowledge between the general level and the single case will then be iterative. The description of an actual single case is to be related to the extensive knowledge which has already been acquired, progressively

abstracting from some characteristics to highlight similarities with what is already known. In turn, general knowledge can be confirmed or, vice versa, corrected and perfected, in light of the peculiarities of the individual case (see Ankeny 2006). Single cases stimulate new cognitive processes, encourage new discoveries, bring to the fore anomalies and limits of the accepted theories, and impel to create new approaches. Rare cases can thus play an important role not in a statistical sense, in the development of some average or standard framework, but as a comparison and control for the models accepted by the scientific community at a given time. The individual suffering from a rare disease is relevant not because her condition exemplifies at least some regularities, typical of the human body and its functioning (which it certainly does), but because of her distinctive, non-typical features. At the same time, it should not be excluded *a priori* that even the peculiar characteristics may have, in the end, a supra-individual scope and provide cognitive contents which can prove to be relevant also on a large scale.

Concluding our epistemological reflections, let us raise the following question: in what respects can (and, at least in part, must) medicine be a science of the individual? Certainly not by virtue of any alleged disciplinary inexperience, but due to the high variability of its objects of investigation, i.e. diseased subjects. If a medicine "of the individual", including also individuals with a rare pathology, may encounter difficulties, it is important to acknowledge the full range of its possible impacts on the methodology of scientific research, the contents of the clinicians' training, and, as we will see in the following section ethical dilemmas. If awareness of the uniqueness, actually, of every patient is growing – thanks to, for example, to the progress of cancer research – rare diseases strongly remind us how differences are crucial from an epistemological standpoint. Diversity has to do "with both health and disease, that is, human beings are different both when they are healthy and when they are sick" (Gabbani 2013, p. 37). In other words, the status of "being an individual" is not a provisional, but a permanent one. The patient is

not an "undifferentiated being", and both medical research and clinical practice cannot but acknowledge it. Medical doctors are therefore asked to act "by interpreting cases in light of rules, revising the rules in light of cases" (Montgomery 1991, p. 47) they are faced with – including, and perhaps above all, cases of rare diseases.

Bioethical issues

Rare diseases, considered from a bioethical perspective, raise moral dilemmas and complex problems of social, distributive and allocative justice that can be traced back to, in summary, to three main issues (Barrera, Galindo 2010). The first question relates to an empirical framework that highlights the unbalance between the needs of patients with rare diseases and their satisfaction (unmet needs) that is, between the number of people with rare diseases and the truly effective treatments available. Here the most relevant moral dilemmas concern the "difficult choices", that is the access to the administration of not only experimental but also not validated therapies, the so-called "compassionate use" of drugs and treatments, which represent the only available alternative, thus highlighting the need for an effective, transparent and therefore ethical approach to therapies.

The second aspect concerns the issues of social, distributive and allocative justice, therefore the procedures and criteria of sustainability, as regards the distribution and access to public health resources. Since it is impossible to guarantee everything to everyone, in principle one should at least consider the moral imperative of guaranteeing "everything that is effective for all those who need it", as each and every patient has the right to be treated equally. On this side, there are many issues to be solved, which affect new drugs and innovative therapies as regards clinical development, the ethics of experimentation and market access (Juth 2017). The third question concerns the non-negligibility of the rights-based approach in health policy choices. Here, in fact, there is the need

for a governance that, at national and international levels, is structured according to ethical criteria and legal instruments aimed at guaranteeing the right to health for all, through measures and guidelines of principle in line with the Declarations of Human Rights (UN 2007) and with our Constitutional Charter (principles of equality, solidarity, dignity and development of the person).

Regarding the first question, the main ethical issues concern the freedom and right of access to therapies which, although not yet authorized, have at least entered the trial phase and for which clinical trial results are available. In fact, in most cases, orphan drugs are available, or rather, drugs for orphan diseases that are rare diseases, which, due to the high testing costs, see pharmaceutical companies usually reluctant to develop them according to normal market conditions. On the other hand, when available, treatments and drugs for the treatment of rare diseases are very expensive even if their efficacy and safety in many cases are not documented. For these reasons the so-called "orphan" interventions are often discouraged compared to the more conventional ones which, although limited in efficacy, nevertheless apply to larger patient populations. The QALY (Quality-Adjusted Life-Year) is the most used model to establish the value of a drug and is used to measure the patient's quality of life in reference to a treatment (Fig. 12) (Williams 1996). The cost of a therapy, in relation to the QALY, represents a cost-effective measure to establish the convenience of a treatment compared to others; however, the value generated by QALY is purely statistical and is based on an overall calculation, which does not take into account the specific conditions of each patient interested in the treatment. This has clear ethical implications that affect the adoption of a mainly economic and utilitarian logic based on the sole criterion of cost-effectiveness analysis. In fact, the adoption of an utilitarian logic would not ensure the right balance with fundamental bioethical principles, namely the principle of charity, oriented to always act for the good of the patient, and the principle of justice, oriented to the protection of equity in health (Beauchamp, Childress 1999).

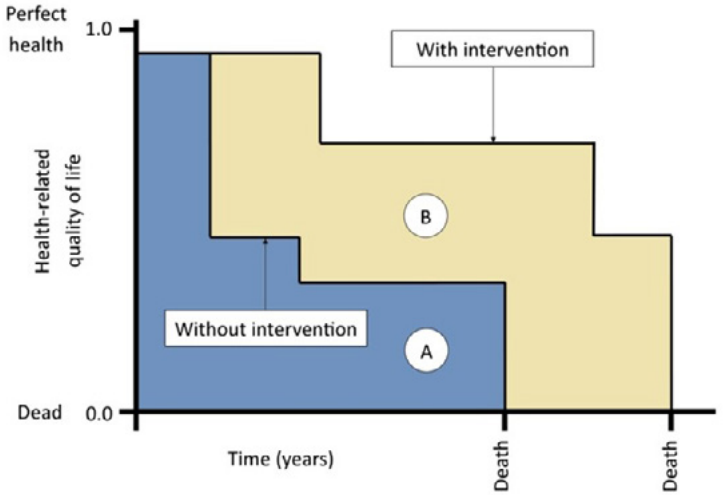

Fig. 12. The image illustrates the change in the level of quality of life, in relation to the state of health, comparing two different paths: with intervention actions (A) an elongation is observed in life expectancy, compared to a path without intervention (B). Image taken and adapted from Wikimedia.org. under CC BY-SA 4.0 license. Author: Chris Sampson.

Such principles aim at focusing on the health of individuals and not only on the maximization of general well-being. If we move towards the adoption of an ethics that goes beyond the economic data and the utilitarian perspective, we cannot separate the cost-effectiveness measures from a more specific attention, for people suffering from rare diseases, and from a joint commitment to the promotion of their state of health, in accordance with the aforementioned bioethical principles of care.

Regarding the second question, the issues of social justice in this area intersect the ethical requirement of health equity and the concept of the highest attainable standard of health. These are two aspects that may affect the possibility to take decisions on the issues of distributive

and allocative justice by assigning everyone the same share of resources. This is a tension that, in the field of health, requires to take into account the different natural and social distribution of diseases and psychophysical deficits, therefore the different degrees of intervention, to ensure that each person enjoys the highest level of health attainable. This is particularly evident where the research and development of therapeutically effective drugs for rare diseases are still debated in the public health system, since they would require a sizable investment that can be perceived as contrasting with the interests and the right to treatment of all other citizens, affected by non-rare pathologies (Rai 2002). Here it is useful to underline, in relation to the epistemological framework illustrated in this chapter, that the contrast between rare diseases and common diseases has gradually become more nuanced, in public and medical-scientific representations. In this regard, it has been demonstrated how certain orphan drugs constitute a therapeutic potential also for non-rare diseases, highlighting the usefulness of rare diseases for understanding common diseases (Stolk *et al.* 2006; Wästfelt *et al.* 2006). These issues lead us to consider the last aspect about the relevance of the rights-based approach (Daniels 1998): it must be said, in fact, that patients with rare diseases have the same right to treatment that is exercised by other patients with non-rare diseases, a right which, in this case, is expressed both as a "right to effective treatments" and as a "right to hope" in the development of new possible treatments, thanks to the progress of pharmacological research. The two rights above are enshrined in the Preamble to the Constitution of the World Health Organization, according to which "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being" (Callahan 1973).

In conclusion, rare diseases represent a public health priority recognized, at least formally, within a European and international regulatory framework, in which the governments of the EU countries are engaged. However, the rare disease field still poses an ethical, political and social

challenge, where scientific research and clinical practice increasingly need to involve not only patients, doctors, researchers, but also different stakeholders, including companies, legislators, politicians and health professionals, in order to make scientific knowledge and clinical practices accessible to patients and families, through transparent and inclusive processes, such as national and international networks (Mikami, Sturdy 2017).

SOME REFERENCE LINKS

Ambulatorio delle Malattie Rare Congenito-Malformative Non Diagnosticate:
https://www.aosp.bo.it/content/ambulatorio-malattie-rare

Centro Nazionale Malattie Rare:
http://old.iss.it/cnmr/

ClinVar:
https://www.ncbi.nlm.nih.gov/clinvar/

EUCERD:
http://www.eucerd.eu/

European Joint Programme on Rare Diseases (EJP RD):
https://www.ejprarediseases.org/

European Platform on Rare Disease Registration (EU RD Platform):
https://eu-rd-platform.jrc.ec.europa.eu/_en

European Reference Networks:
https://ec.europa.eu/health/ern_it

EuroQol (EQ-5D):
https://euroqol.org/

EURORDIS – Rare Diseases Europe:
https://www.eurordis.org/it

GeneMatcher:
https://www.genematcher.org/

Genome Aggregation Database (gnomAD):
https://gnomad.broadinstitute.org/

IRdiRC – International Rare Diseases Research Consortium:
https://www.irdirc.org

MEDLINE®:
https://www.nlm.nih.gov/bsd/medline.html

National Library of Medicine:
https://www.nlm.nih.gov/

Online Mendelian Inheritance In Man® (OMIM):
https://www.omim.org/

Orphanet:
https://www.orpha.net/consor/cgi-bin/index.php

PubMed:
https://www.ncbi.nlm.nih.gov/pubmed

https://pubmed.ncbi.nlm.nih.gov/

Rare Diseases Registry Program (RaDaR):
https://rarediseases.info.nih.gov/radar

Reti di riferimento europee – ERN:
http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=4935&area=Malattie%20rare&menu=vuoto

Single Nucleotide Polymorphism Database (dbSNP):
https://www.ncbi.nlm.nih.gov/snp/

Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe (BURQoL-RD):
https://www.eurordis.org/content/burqol-rd-project

UNIAMO – Federazione delle Associazioni di Persone con Malattie Rare d'Italia:
http://www.uniamo.org/

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Are rare diseases really rare? There are more than 6,000 "orphan diseases", 80% of which are gene-related, leading to chronicity, discrimination and loneliness. However, there are numerous support networks capable of taking care of patients and their caregivers, from diagnosis to identification of the most suitable therapies, thanks to the expertise of experts and specialized centers in Italy and in Europe. This book is an introductory tool to orient oneself, understand and begin to move around in the complex and constantly evolving panorama of rare diseases.

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