

RARE DISEASES AND GENETIC DISCRIMINATION

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SUMMARY:

Rare diseases are characterised by their low prevalence (less than 1/2,000) and their heterogeneity. They affect both children and adults anywhere in the world. From the medical perspective, rare diseases are characterised by the large number and broad diversity of disorders and symptoms that vary not only from disease to disease, but also within the same disease.

Main characteristics of rare diseases include:

- Rare diseases are often chronic, progressive, degenerative, and often life-threatening
- Rare diseases are disabling: the quality of life of patients is often compromised by the lack or loss of autonomy
- High level of pain and suffering for the patient and his/her family
- No existing effective cure
- There are between 6000 and 8000 rare diseases
- 75% of rare diseases affect children
- 30% of rare disease patients die before the age of 5
- 80% of rare diseases have identified genetic origins.

Other rare diseases are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative.

Beyond the diversity of the diseases, rare disease patients and their families are confronted with the same wide range of difficulties arising directly from the rarity of these pathologies. The period between the emergence of the first symptoms and the appropriate diagnosis involves unacceptable and highly risky delays, as well as wrong diagnosis leading to inaccurate treatments. Living with a rare disease has implications in all areas of life, whether school, choice of future work, leisure time with friends, or affective life. It may lead to stigmatisation, isolation, exclusion from social community, discrimination for insurance subscription (health insurance, travel insurance, mortgage), and often reduced professional opportunities.

Innovative treatments are often unevenly available in the EU because of delays in price determination and/or reimbursement decision, lack of experience of the treating physicians (not enough physicians involved in rare diseases clinical trials), and the absence of treatment consensus recommendations.

It is fundamental to realise that rare diseases can affect any family at any time. It is not just “something terrible that happens to other people”. It is a very cruel reality that can happen to anyone, either when having a child or in the course

of one’s own life.

In fact, the terminology “rare diseases” only highlights the characteristic of rarity of the complex and heterogeneous mosaic of an estimated 7,000 life-threatening and heavily debilitating conditions.

The rare diseases for which a simple and effective preventive treatment is available are being screened for, as part of public health policy. But this is not enough, and it is essential for public authorities to consider rare diseases as a Public Health priority and take action to concretely support patients and families affected by rare diseases.

As underlined in the Background Paper on Orphan Diseases for the World Health Organisation Report on Priority Medicines for Europe and the World, “despite the growing public awareness of rare diseases in the last one or two decades, there are still many gaps in knowledge related to the development of treatment for rare diseases. Policymakers have to realise that rare diseases are a crucial health issue for about 30 million people in the EU”.

A good medication for rare disease patients is a medication that is both available in the country where they live and affordable. If one of these two factors is missing, the drug is of little use.

Personalized medicine however is an emerging term for a medical philosophy that uses a person’s individual clinical, genetic, genomic, and environmental information to tailor a treatment plan that will maximize efficacy and safety for that individual. While the technology offers much promise, it also is also challenged by some ethical and social questions in both its clinical application and in its research enterprise. Questions about privacy, safety, phenotypical expression, drug interactions, and genetic vs. social group identities will challenge clinical pharmacogenetics.

Key words: Rare disease, Orphan drug, health policy, policy makers, professional care, diagnosis

A rare disease is a disease that occurs infrequently or rarely in the general population. In order to be considered as rare, each specific disease cannot affect more than a limited number of people out of the whole population, defined in Europe as less than 1 in 2,000 citizens. Rare diseases are characterised by a broad diversity of disorders and symptoms that vary not only from disease to disease but also from patient

to patient suffering from the same disease. Relatively common symptoms can hide underlying rare diseases, leading to misdiagnosis.

From the medical perspective, rare diseases are characterised by the large number and broad diversity of disorders and symptoms that vary not only from disease to disease, but also within the same disease. The same condition can have very different clinical manifestations from one person affected to the other. For many disorders, there is a broad diversity of subtypes of the same disease. It is estimated that between 5.000 and 7.000 distinct rare diseases exist today, affecting patients in their physical capabilities, their mental abilities, in their behaviour and sensorial capacities. Many disabilities can coexist for a given person, and this is defined as a polyhandicap.

Rare diseases also differ widely in terms of severity, but in average the life expectancy of rare disease patients is significantly reduced. The impact on life expectancy varies greatly from one disease to the other; some cause death at birth, many are degenerative or life threatening, whilst others are compatible with a normal life if diagnosed in time and properly managed and/or treated.

80% of rare diseases have identified genetic origins, involving one or several genes or chromosomal abnormalities. They can be inherited or derived from de novo gene mutation or from a chromosomal abnormality. They concern between 3% and 4% of births. Other rare diseases are caused by infections (bacterial or viral), or allergies, or are due to degenerative, proliferative or teratogenic (chemicals, radiations, etc) causes. Some rare diseases are also caused by a combination of genetic and environmental factors.

There is also great diversity in the age at which the first symptoms occur. Symptoms of many rare diseases appear at birth or in childhood, including Infantile Spinal Muscular Atrophy, Neurofibromatosis, Osteogenesis Imperfecta, ect. In some cases, the first symptoms of the disease, such as Neurofibromatosis, may occur in childhood, but this does not prevent much heavier symptoms to occur at a later stage of life. Other rare diseases, such as Huntington disease, Spinocerebellar Ataxias and thyroid cancer are specific to adulthood.

Despite this great diversity, rare diseases have some major common traits. The main characteristics including:

- Lack of access to correct diagnosis
- Delay in diagnosis
- Lack of quality information on the disease
- Lack of scientific knowledge of the disease
- Heavy social consequences for patients
- Lack of appropriate quality healthcare
- Inequities and difficulties in access to treatment and

care

Because rare disease patients are a minority, there is a lack of public awareness. These diseases do not represent a public health priority, and little research is performed. The market

is so narrow for each disease that the pharmaceutical industry is reticent to invest in research and to develop treatments for rare diseases.

Patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients. The European union, had adopted Regulation¹ 141/2000 on orphan medicinal products. The purpose of this Regulation is to lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products.

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of rare diseases. These drugs are called “orphan” because, under normal market conditions, it is not cost-effective for the pharmaceutical industry to develop and market products intended for only a small number of patients suffering from rare conditions. The drugs developed for this unprofitable market would not be financially viable for the patent-holding manufacturer. For drug companies, the cost of bringing an orphan medicinal product to the market would not be recovered by the expected sales of the product. For this reason, governments and rare disease patient organisations have emphasised the need for economic incentives to encourage drug companies to develop and market medicines intended for the “orphaned” rare disease patients.

A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and

b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Experience in the United States of America and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered.

Advances in deciphering the human genome have brought hope to millions of people suffering from genetic

¹ Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, (OJ L 18, 22.1.2000, p. 1–5.)

diseases, many of which are rare and disabling. However with this renewed hope comes the risk of using genetic information to discriminate against those who have a genetic condition, risk or predisposition.

The US has taken an important decision to explicitly ban this type of discrimination with the recently enacted Genetic Information Anti Discrimination Act (GINA). GINA forbids insurance companies to ask for genetic tests to be performed or to access existing results in order to set premiums or determine eligibility of enrolment. Employers are also prohibited from using genetic information in hiring, firing or promoting employees. The legislation, initiated by the National Organisation for Rare Disorders (NORD), which was under discussion for 13 years, was finally enacted thanks to the relentless advocacy efforts of patient groups such as Genetic Alliance, who managed to convince a large number of senators to back the bill.

GINA not only protects the privacy of each individual but it also encourages them to seek tests which could help diagnose their condition or extend their life expectancy without fear of misuse or discrimination. It will also have a positive effect on research since fear of discrimination will no longer dissuade large numbers of people from participating in clinical trial, speeding up the research and development process for targeted drugs and treatments. This is especially worrying when applied in the workplace and by insurance companies.

In Europe similar but uneven steps are being taken in this direction. The Committee of Ministers of the Council of Europe has adopted an Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes. The purpose of the document is to set legal rules to protect fundamental human rights with regards to the latest advances in genetic testing.

The Protocol addresses the protection of private life and access to information collected through genetic testing. Although, the Protocol does not specifically address genetic testing for employment and insurance purposes, it speaks undoubtedly against any kind of discrimination based on genetic testing by linking all justification of genetic testing to health purposes. In this way, only a direct medical benefit could be cited as justification for the performance of a predictive genetic test.

Although the European Council's Convention and its Protocols are important because they represent an official standard at the European level and serves as a guidelines for Member States, its major weakness is that it is non-binding and not all countries adhere to it. Some countries have not ratified the Convention because they fear it might restrict research possibilities. Moreover, they have not passed specific anti-discrimination legislation.

For example, there are currently no laws banning insurance companies from accessing genetic tests in the UK. However, insurers and the government have agreed on a voluntary five-year ban, which has been extended until 2014. Similar moratoria are in place in Germany and the Netherlands. Under the UK voluntary ban, nobody has to disclose genetic

test results to insurers unless they are buying a policy which will pay out more than J500,000 on life insurance or J300,000 on critical illness insurance, and provided that the test is approved by the Genetics and Insurance Committee. One such test is the one for Huntington Disease, a rare neurological monogenetic disease, which has a high predictability rate.

At the other end of the spectrum are countries like France where insurance companies cannot ask for a test or use information provided by such a test and it is a criminal offence to attempt to obtain or supply test results for any other purpose than medical or scientific purposes. Similar legislation exists in Spain where insurance companies are not allowed to carry out genetic tests on their customers, nor make genetic diagnosis a condition for issuing a policy.

Overall, the rules regarding genetic testing in Europe vary from country to country, and safeguards against discrimination by the insurance industry are less explicit than in the US. The explanation might lie in the differences in health protection systems. Whilst in the US the cost of insurance is carried mostly by employers (mutuality based) in most European countries the burden of insurance is spread out throughout society (solidarity based).

Families and health care workers frequently complain about the extreme difficulty in taking the necessary administrative steps required to receive social benefits. Major and arbitrary disparities exist between countries - and even between regions within the same country - in the allocation of financial aid, income support and reimbursement of medical costs. Usually in Europe, treatment costs incurred are often higher than they are for other diseases because of the rarity of the disease and the limited number of specialised centres. In most cases, a significant proportion of these expenses is born exclusively by the families, thereby generating an additional inequality between rich rare disease patients and poor rare disease patients. Travel costs to specialised centres are high in terms of time off work and financial cost.

In a family where a child has a rare disease, most often one of the parents either completely stops or significantly reduces work remunerated outside home. As a consequence, while expenses increase dramatically, incomes is considerably reduced. In the case of an adult rare disease patient who is well enough to be able to work, the work hours must be adapted to allow for medical visits and appropriate care. In terms of logistics, much remains to be done to ensure real equality between a disabled and a healthy citizen.

For some rare diseases, such as fragile X syndrome and cystic fibrosis, treatment protocols and defined medical, social and educational programmes exist in certain countries, as well as more or less well-targeted screening programmes.

The European Commission has launched a public consultation in view of modernising rules on the transparency of Member States' decisions regarding the pricing and reimbursement of medicines. The consultation invites all interested parties to share their views on the review of Council

Directive 89/105/EEC². The objective of the consultation, which continues from 28.03.2011 to 25.05.2011 is to seek the views of interested parties to determine how the existing EU rules on the transparency of pricing and reimbursement procedures for medicines may be modernised. At present, the Transparency Directive applies exclusively to medicinal products. The consultation also aims to assess its relevance to the medical devices sector.

Within this context of raising awareness of rare diseases in Europe, the European Commission launched Eurobarometer survey – published on 28 February 2011. According to this survey, Europeans have a relatively accurate understanding of what rare diseases are but detailed knowledge and awareness remain low. 63% of Europeans correctly define rare diseases as diseases affecting a limited number of people and requiring very specific care. However, some misconceptions exist with 14% who believe that these are conditions which nobody can do anything about or that nobody cares about.

Almost one in six European citizens is personally affected (17%) or through knowing somebody who is suffering from a rare disease (13%). However, 40% of Europeans have never heard of anyone who suffers from a rare disease.

Almost all agree that national health authorities should provide specific support to people suffering from rare diseases (96%) and fully reimburse their medication even if it is very expensive (93%). There is widespread support for policy initiatives aiming at increasing cooperation at European level, granting full access to care for patients in other Member States and introducing national strategies for rare diseases.

An overwhelming majority of respondents in every Member State – in many cases 90% or more – supports resource allocation to various actions which tackle rare diseases in various areas, such as strengthening research cooperation, easing access to drugs and laboratory tests and giving support to families and patient organisations.

An overwhelming majority of Europeans support the idea that national health authorities should give specific support to people suffering from rare diseases and that they should fully reimburse the cost of medication developed to treat such patients. However, the European public is divided on whether

rare diseases should be made a priority at national level when considering other major health issues which exist.

Almost all (96%) agree that people suffering from a rare disease need specific support from national health authorities. More than nine in ten Europeans (93%) agree with the statement that the cost of developing drugs to treat people suffering from rare diseases should be fully reimbursed by the national health care system even if they are expensive. Nearly two-thirds (64%) totally agree with the statement.

An overwhelming majority (95%) of Europeans agree that there should be more European cooperation in order to help the limited number of people suffering from rare diseases more efficiently. The same proportion believe that people suffering from a rare disease should have the right to access appropriate care in another EU Member State. In addition, nine in ten citizens (90%) agree that every EU Member State should have a National Plan or Strategy on rare diseases.

The European Commission and the national health authorities of the EU Member States have adopted several initiatives to help people suffering from rare diseases. When asked whether such support is justified, the European public express their strong agreement. Over 90% of respondents consider that it is justified to allocate resources to each of the actions in the areas of research, access to treatment, communication and patient support.

The majority of respondents in every Member State with the exception of Portugal find it totally justified to allocate resources to provide additional support for families with a member suffering a rare disease. Respondents in Cyprus, Spain Greece, Malta, Slovenia and Bulgaria are particularly supportive in this respect. A small minority in each country find allocating resources to support families unjustified, the highest level of opposition (7%) being seen in Austria and in Sweden.

Among the European public there is a widespread willingness to improve the treatment of rare diseases. However this willingness is instinctive and empathetic rather than based on actual knowledge. Future policy needs to be accompanied by education and awareness-building to increase the general recognition and visibility of rare diseases which in terms of real knowledge is very low amongst the general public.

² Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ L 40, 11.2.1989, p. 8–11)

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