Clinical genetics and public policies: how should rare diseases be managed?

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ABSTRACT

The implementation of a specific policy for rare diseases in the Brazilian Unified Health System presents challenges in terms of its rationale. Recognizing the importance of rarity in the context of public health means understanding genetics as one of the dimensions of disease and accepting that Brazil is undergoing a period of transition in health indicators. Although most rare diseases lack pharmacological treatment and genetic counseling constitutes the best strategy for their prevention, the cost of "orphan drugs" and their consequent lack of cost-effectiveness are still claimed as hurdles to the implementation of public policies in this field. Epidemiological aspects should not be used as isolated criteria for prioritization in public policies.

Keywords: Medical genetics; orphan drugs; rare diseases; Brazil

Over the last two decades, Brazil has become an emerging international economy, as part of the so-called BRIC (Brazil, Russia, India and China) countries, which are all deemed to be at a similar stage of newly advanced economic development. This economic change has made possible several improvements in health conditions in Brazil, leading to a scenario of epidemiological transition. This has been reflected in improved maternal-child health indicators, with a significant impact on infant and perinatal mortality, which decreased by 47% from 1990 to 2007[1]. However, under-five mortality due to congenital disorders, which affect 3 to 5% of the population and can lead to lifelong disabilities[2], remained unchanged, contributing to approximately 5 deaths per 1,000. As a result, congenital disorders have become the second leading cause of infant mortality, surpassed only by perinatal causes[1].

The total birth prevalence of serious genetic congenital disorders in Brazil was estimated by the March of Dimes to be 57.2 per 1,000 live births[3]. It is also likely that perinatal causes of death include undiagnosed congenital disorders, such as cardiac defects, chromosomal disorders, and inborn errors of metabolism[3].

In 2000, the World Health Organization (WHO) proposed that interventions for prevention and control of genetic disorders and congenital malformations should be added to the primary health care (PHC) framework[4]. This recommendation is justified by ample evidence in support of the argument that genetic factors are associated with all human diseases except for trauma[5]. Most human diseases are the result of an interaction between genetic and environmental factors. According to the traditional classification of genetic disorders, several highly prevalent conditions (such

as high blood pressure, autoimmune diseases, and hypercholesterolemia) are multifactorial (i.e., the genes involved in their etiology are many, they have different relative weights in determination of the phenotype, and interact among themselves and with the environment to generate the disease phenotype). Rare genetic diseases are those in which the genetic component plays an unquestionably greater role in phenotype genesis than the environmental component. In these conditions, development of the altered phenotype is usually the result of mutations in a single gene located in the nucleus (monogenic diseases, such as the hereditary breast–ovarian cancer syndrome caused by *BRCA1* gene mutations) or in the mitochondria (mitochondrial DNA diseases, such as certain types of diabetes), or of mutations in the number or structure of chromosomes (chromosomal diseases, such as Turner syndrome, in which 45,X is the most common karyotype) (Table 1). Where there is a genetic component, there is the possibility of prevention by genetic counseling. (For instance, a woman at risk of carrying a known pathogenic *BRCA1* mutation could undergo genetic testing and limit her risk of developing ovarian cancer — if the test is positive — by undergoing prophylactic oophorectomy if she so desires.) Where there is an environmental factor at play, there is the possibility of prevention by means of combined genetic counseling and interventions targeting the environmental factor

(as in phenylketonuria, a monogenic disorder in which the disease phenotype can be prevented by early prescription and lifelong maintenance of a low-phenylalanine diet). Genetic counseling is a cornerstone of clinical genetics and includes a variety of elements or stages, namely: diagnostic and clinical aspects; documentation of family and pedigree information; recognition of inheritance patterns and risk estimation; communication and empathy with those seen; information on available options and further measures; support in decision making and for decisions made[6]. A growing number of studies are evaluating the cost-effectiveness of genetic counseling, particularly in the field of oncogenetics[7-10].

This narrative review seeks to discuss, from the perspective of the authors (two medical geneticists practicing in different fields, a physician specializing in pharmacology and health technology assessment, and a prosecutor specializing in human rights), the current panorama of public policies and pharmaceutical assistance for genetic diseases in Brazil.

MEDICAL GENETICS IN THE BRAZILIAN HEALTH SYSTEM

In Brazil, medical practice in genetics is fairly recent. The first medical residency program in medical genetics was established in 1977, at Hospital das

Table 1: Genetic disorders: a comparison between multifactorial and monogenic diseases

	Multifactorial diseases	Monogenic diseases
Prevalence	Common	Rare
Number of genes involved in phenotype genesis	Many	One (other genes, known as modifiers, influence phenotype severity)
Age at diagnosis	- Prenatal/perinatal: congenital malformations (congenital heart disease, congenital hip dislocation, etc.). - Adulthood: diabetes, most cancers, Alzheimer's disease, etc	- Prenatal/perinatal/childhood: dysmorphic syndromes, inborn errors of metabolism* - Adulthood: Huntington's disease, spinocerebellar ataxias, etc.
Risk of recurrence	Higher than the population-wide rate, but lower than in monogenic diseases	- Autosomal dominant: 50% (if one parent is also affected) - Autosomal recessive: 25% (both parents are considered obligatory heterozygotes); - X-linked recessive: 50% in male children of heterozygous mothers
Genetic testing for diagnosis	Not usually recommended	Feasible
Genetic counseling indicated	Yes	Yes

*Dysmorphic syndromes are genetic diseases associated with typical facial features and/or malformations (e.g., Down syndrome). Inborn errors of metabolism are genetic diseases associated with reduced activity of a specific enzyme; patients are born without any phenotypic features and later develop the condition, usually of a neurological nature, sometimes due to dietary exposures (e.g., phenylketonuria).

Clínicas de Ribeirão Preto (University of São Paulo). The Brazilian Society of Clinical Genetics (Sociedade Brasileira de Genética Clínica) was established in 1986[11]. Later, it was renamed the Brazilian Society of Medical Genetics (Sociedade Brasileira de Genética Médica, SBGM), which currently grants board certification in Medical Genetics[12].

Over the last three decades, there were several initiatives to include genetics in the Brazilian public health system. In 1989, a "National Policy for People with Disabilities" was created, aiming to provide a network that would ensure access to treatment and rehabilitation. Some basic genetic tests, such as karyotyping, were offered within the framework of this policy. However, genetic counseling or consultations with a medical geneticist were not covered[13].

In 2001, the National Neonatal Screening Program ("Teste do Pezinho") was implemented, including the following diseases to be progressively screened in all Brazilian newborns: phenylketonuria (PKU), congenital hypothyroidism (phase I), sickle cell disease and other hemoglobinopathies (phase II), and cystic fibrosis (phase III). In 2012, screening for biotinidase deficiency and congenital adrenal hyperplasia were included in the program (phase IV)[14].

Family associations and charity organizations, such as the APAEs (Associação de Pais e Amigos dos Excepcionais)[13], have also played a role in providing assistance for disabled children. These associations also exerted significant pressure on government entities to help move policies forward in the Brazilian Unified Health System (SUS).

Despite the close relationship between clinical genetics and management of birth defects, less than 30% of the total demand is currently met by existing genetic services[2]. Most clinical genetics centers and care services are integrated with university and referral hospitals, and are predominantly concentrated in the South and Southeast regions of Brazil[12].

In 2009, the Brazilian Ministry of Health enacted a decree creating a "National Policy for Comprehensive Care in Clinical Genetics at SUS" (Política Nacional de Atenção Integral em Genética Clinica no SUS)[15], taking into consideration regional inequities in clinical genetics in the country. The policy also designated the strategies for action that must be taken into account in its regulation. The linchpin of healthcare in clinical genetics would be genetic counseling, which should be guaranteed to any individual or family who may require it[12]. However, no supplementary ordinance, which would be essential for the organization and regulation of this policy, was published afterwards. At least, the need for organized action in the area of medical genetics and birth defects in Brazil was acknowledged.

From 2009, the Brazilian Genetic Alliance, several patients' and parents' organizations, and the Brazilian Society of Medical Genetics tried to pressure the Ministry of Health into implementing this special policy. These efforts culminated with the creation of a Working Group at the Ministry of Health, which brought together patients' and parents' associations, medical geneticists, and SUS managers to devise detailed policy documents and ordinances for the care of individuals affected by rare diseases.

THE NATIONAL POLICY FOR COMPREHENSIVE CARE OF RARE DISEASES IN THE BRAZILIAN UNIFIED HEALTH SYSTEM (SISTEMA ÚNICO DE SAÚDE - SUS)

According to WHO, rare diseases are defined as those having a prevalence of up to 65 per 100,000 populations[16]; this is the criterion adopted in Brazil. As the population of Brazil is approximately 190,000,000[17], the number of people affected by a rare disease is expected to exceed 13 million. The total number of rare diseases ranges from 5,000 to 8,000, according to different estimates. Around 80% of these conditions are of a genetic etiology, and even the remaining 20% considered "non-genetic" (environmental, inflammatory, autoimmune, and infectious) frequently have genetic susceptibility involved in its pathogenesis (i.e., they are multifactorial)[18].

In February 2014, the "National Policy for Comprehensive care of People affected by Rare Diseases within the SUS" was enacted[19]. SUS, or the Unified Health System in English, is the Brazilian publicly funded health system, built on the principles of universality (it may be used by anyone, even by non-Brazilians), comprehensiveness (it covers preventive and curative care, at all levels of complexity), and provision of free care at the point of delivery.

This "National Policy for Comprehensive care of People affected by Rare Diseases within the SUS" has two main axes: 1) genetic diseases and 2) non-genetic diseases.

The genetic axis was further subdivided into three subgroups for specific attention:
a) Congenital anomalies and late-onset genetic diseases: 2% to 3% of all liveborn infants

exhibit a congenital anomaly. In Brazil, this is the second leading cause of infant mortality, and accounts for one-third of pediatric hospitalizations. Around 60,000 new cases are expected to occur each year[12].

b) Intellectual disability caused by rare disease: Intellectual disabilities can be caused by genetic factors as well as by environmental exposures, and are often by both. Learning disabilities are observed in almost 15% of the world population[20], but only 1 to 2% of cases are severe and attributable to a underlying rare disorder[21].

c) Inborn errors of metabolism: The prevalence of these conditions is estimated at 1 in 1,000 to 1 in 2,500 births. In Brazil, an estimated 3,000 new cases occur each year[22].

The policy mandates comprehensive patient care, including diagnosis, genetic counseling, and treatment, which can include rehabilitation, supportive therapy (physical therapy, occupational therapy, speech therapy, pedagogical and psychological support), and dietary or pharmacological measures when such treatments exist. The services are expected to interact as a network within the overall model of the Brazilian SUS.

DRUGS FOR RARE DISEASES (ORPHAN AND ULTRA-ORPHAN DRUGS) AND THEIR PARTICULARITIES

The premises that rarity (i.e., a small number of patients) would be associated with low profits and that the pharmaceutical industry would lack interest in developing medicines for these conditions was always associated with the so-called "orphan drugs", as drugs for rare diseases have classically been known. Two concepts are thus considered jointly for attribution of orphan drug status: one epidemiological (prevalence or incidence of the disease within a population) and one economic (presumed non-profitability of the drug destined for treatment of the disease).

To face this challenge, in the 1980s and 1990s, several governments began developing specific legislation and policies to encourage research and development of drugs to treat rare diseases[23]. The United States pioneered these initiatives. In 1982, the U.S. Food and Drug Administration (FDA) created a specific sector for orphan drugs, which was followed in 1983 by the enactment of the Orphan Drug Act by Congress (*http://oig.hhs. gov/oei/reports/oei-09-00-00380.pdf*). The U.S.

legislation was followed by others approved by Japan (1993) — (*The Pharmaceutical Affair Law 145-10 August 1960 – Revised in 1993*), Australia (1997) — (*Therapeutic Goods Regulations 1990. Statutory Rules 1990. No. 394*), and the European Union (1999) — (*Regulation (EC) No. 141/2000 of the European Parliament and Council of 16 December 1999*). Currently, according to the WHO, specific legislation also exists in Taiwan and Singapore. Canada has no specific legislation for orphan drugs, but has some policies in place, such as fast-track review for registration (*Michols, D.M. Report on orphan drug policy for Canada. Health Canada.1997*). In Brazil, there is no specific legislation directed to orphan drugs, but we believe that the development of such a policy will be a natural consequence of implementation of the National Policy for Comprehensive Care of People Affected by Rare Diseases. It bears stressing that "orphan drugs" does not mean drugs for neglected diseases (such as malaria), i.e., diseases that are highly prevalent in certain geographic areas, particularly in underdeveloped nations. It also bears stressing that most rare diseases have no specific treatment available (e.g., therapies targeting the cause of the disease and its direct biochemical consequences), but can be managed by symptomatic measures (e.g., analgesia, physical therapy, etc.). Nevertheless, the efficacy and the safety of both specific interventions and symptomatic treatment for rare diseases are usually not based on high-quality evidence, which increases uncertainty in the related decision-making processes.

Incentives for orphan drug development vary across different countries and regions. The U.S. Orphan Drug Act created special lines of government funding for research, differentiated taxes for drug licensing, faster evaluation and approval, and a period of marketing exclusivity (*http://oig.hhs.gov/oei/reports/oei-09-00-00380. pdf*). The EU legislation also offers special taxes, fast-track review for registration, a period of market exclusivity, and the possibility of scientific consultation during the research phase (*Regulation (EC) No. 141/2000 of the European Parliament and Council of 16 December 1999)*. The results of these policies can be considered successful in terms of discovery and approval of new drugs. According to Franco[24], in the U.S. alone, the number of orphan drugs approved from enactment of the Orphan Drug Act in 1983 to 2011 was 403, versus only 10 products which could have been

classified as orphan drugs licensed before this law. However, fast-track review enables marketing authorization of drugs with less evidence of efficacy and safety than that usually required for approval of drugs destined to treat highly prevalent diseases. Therefore, this increased number of drug approvals may not be reflected by significant improvements in patient quality of life. At least two reasons for acceptance of low-quality evidence in this field should be highlighted: 1) for rare diseases, there are usually no treatment alternatives available, unlike for prevalent conditions; and 2) due to the small number of cases and the chronic nature of most rare diseases, there is an intrinsic difficulty in conducting comparative studies with relevant clinical outcomes, such as mortality.

Unfortunately, while approval of orphan drugs is proceeding space, access to these drugs is not improving at a similar rate. The costs associated with orphan products are a major obstacle[25]. They are usually very high, creating a new paradox: treatments are available for many conditions, but many patients cannot afford them (*Ultra orphan drugs for lysosomal storage disorders. A guideline comparison and survey of international current practice. http://www.webarchive.org.uk/ukwa/target/136020276*). Even in countries with mechanisms to fund procurement of these drugs fully or partially, the sustainability of these programs and of the health system itself in view of such high costs is an essential question.

In the UK, the National Institute for Health and Clinical Excellence (NICE) is responsible for reviewing all new health technologies that may be adopted by the National Health System (NHS). NICE applies health technology assessment tools to make its recommendations. In 2007, NICE researchers evaluated enzyme replacement therapy (ERT) with recombinant agalsidase for Fabry disease (26). Fabry disease is an X-linked disorder caused by deficient activity of alpha-galactosidase A, which causes acroparesthesia and kidney, heart, and brain disorders, mainly in adults, and is associated with early mortality (usually due to kidney failure). According to the NICE study, ERT for this condition was not cost-effective (for a review of the efficacy and safety of ERT in Fabry disease, see Alegra et al.)[27], and to be considered acceptable (using a threshold of £30,000 per QALY), the price of the enzyme would have to be reduced more than sevenfold. To provide some high-cost orphan drugs to its citizens, the UK chose to create a different funding strategy,

known as Patients Access Schemes (PAS), based on an agreement between manufacturers and the UK government[28].

As for the NICE conclusion regarding ERT in Fabry disease, many authors currently consider classical econometrics and health technology assessment methodologies inappropriate for the evaluation of rare diseases and their treatments. These authors believe findings will always indicate a net deficit for society in view of the high running costs and the type of assessment employed[29].

Once again using Fabry disease as an example, the Canadian agency (CEDOC) originally did not recommend the incorporation of ERT for this disease (ERT was not considered cost-effective and its results on clinical outcomes were unclear); however, some provincial governments maintained schemes to fund these drugs, leading to unequal drug access across the country. In 2006–2007, a pioneering cost-sharing program, the Canadian Fabry Disease Initiative (http://www.cihr-irsc.gc.ca), was implemented in the country. This program is a partnership between the manufacturers of the available recombinant enzymes for Fabry disease (agalsidase alfa and beta, respectively), the Canadian federal government, and provincial governments; this solution not only allowed sharing and rationalization of treatment costs but was also designed to collect data on treatment effectiveness, disease progression, and comparability of the two enzymes available on the market. In Brazil, both agalsidase alfa and beta have been approved by ANVISA, but are not available through the SUS. However, many Brazilian patients are receiving ERT due to judicial decisions[30].

Alternative funding solutions associated with strict criteria for patient inclusion, treatment, and follow-up are among the viable options for countries that decide to provide these treatment options to its citizens. Otherwise, none of these treatments would be sustainable in the long term.

DRUGS FOR RARE DISEASES IN THE BRAZILIAN UNIFIED HEALTH SYSTEM (SUS)

Many medicines are provided free of charge within the SUS. These drugs are grouped into two programs, or components. The first component follows the WHO concept of essential medicines, and thus focuses on highly prevalent diseases (e.g., diabetes and hypertension) and low-cost drugs. The second component, known as the Specialized Pharmaceutical Assistance Program (Componente

Especializado da Assistência Farmacêutica, CEAF), covers more expensive drugs, medicines used for second-line treatment or refractory disease, and more infrequent conditions[31]. The lists of medicines covered by each component are periodically reviewed.

The medicines included in the CEAF list are organized into three different subgroups. The first subgroup is funded entirely by the federal government, and includes the more costly drugs. The second subgroup is funded exclusively by state governments. Finally, in the third subgroup, costs are shared among the federal, state, and municipal governments. Currently, the CEAF includes 194 drugs in 383 different pharmaceutical forms (http://portalsaude.saude.gov.br/images/pdf/2014/abril/16/Tabela-de-situa---es-cl--nicas-CEAF-abril-2014.pdf).

The diseases for which drug treatment is available through the CEAF also have clinical protocols and practice guidelines (Protocolos Clínicos e Diretrizes Terapêuticas, PCDT) for their care published by the Brazilian Ministry of Health. These protocols establish inclusion criteria for patients, follow-up procedures, therapeutic options, failure criteria, and treatment goals.

As mentioned before, despite the absence of a specific policy for orphan drugs in the SUS, some drugs for genetic diseases are accessible to citizens in Brazil and are included in the CEAF program[32]. Examples include imiglucerase, velaglucerase alfa, taliglucerase alfa, and miglustat for Gaucher disease and the nutritional formula for phenylketonuria (http://portalsaude.saude.gov.br/images/pdf/2014/abril/16/Tabela-de-situa---es-cl--nicas-CEAF-abril-2014.pdf). Additionally, a specific program is available to fund pamidronate for patients with osteogenesis Imperfecta.

This topic, and its association with the judicialization of access to health in Brazil, are the main research area of our group. As a counterpoint to the cost-effectiveness argument for non-investment in rare diseases in health systems, we have advanced arguments based on human rights and on the principle of human dignity, as have other authors[33]. Regarding the judicialization of access to orphan drugs, our data suggest that failures in pharmaceutical assistance, and not merely a lack of incorporation of high-cost medicines into the SUS, are among the causes of this phenomenon[29,34,35]. One example is phenylketonuria. Although treatment for this condition is included in the CEAF, approximately 20% of patients in Rio Grande do Sul, the southernmost state of Brazil, obtain access to this treatment via judicial means[35].

Another pervasive issue in the debate on regulation of rare-disease pharmaceutical assistance in Brazil is the classification as "foods" versus as "drugs" of some substances used in the treatment of rare diseases (such as uncooked cornstarch for the management of hepatic glycogen storage diseases), with all the implications — such as approval and funding requirements — that this difference in classification entails[36].

DISCUSSION

There is no easy answer or easy road when it comes to discussing management of rare diseases. The main obstacles are discussed below.

For many rare diseases, the available information is inadequate. The need for knowledge improvement, especially in epidemiology, natural history of disease, and potential peculiarities of Brazilian patients, cannot be overstated. Adequate knowledge of these aspects is essential for the development of appropriate care policies that cover diagnosis, follow-up, and treatment.

Health professionals frequently lack appropriate training to diagnose and adequately treat these diseases. Investments in technical training and awareness are essential to change this scenario. A more efficient diagnostic network, investment in equipment, collaborative work, and data sharing are the solution to overcome these difficulties.

Policies directed at providing access to orphan drugs for rare diseases are still either unclear in Brazil. Medicines for some rare diseases (such as osteogenesis imperfecta) are provided through specific programs, whereas others (such as imiglucerase, velaglucerase alfa, taliglucerase alfa, and miglustat for Gaucher disease) are provided through the so-called special component of pharmaceutical assistance. Finally, many rare diseases have no available treatment in the country and are not included in any assistance programs. Patients with some of these diseases receive treatment only after recourse to the courts[33].

Also worthy of note is the absence of any defined policy on procedures for incorporation of new health technologies in the field of rare diseases. The lack of established, reproducible, and transparent technical criteria to guide the incorporation process for rare disorders contributes to an unequal relationship between citizens and health system managers. This, in turn, ultimately facilitates the lobbying efforts of interest groups and

associations — sometimes led by the oft-unclear interests of pharmaceutical companies. In this context, the establishment of CONITEC (Comissão Nacional de Incorporação de Tecnologias, the National Committee for Technology Incorporation) in 2011 by means of Law no. 12,401 on therapeutic assistance and health technology incorporation within the framework of the SUS[37], was a notable advance. However, CONITEC uses classical criteria to make decisions regarding new technologies — namely, evidence-based analysis and comparative economic assessment of costs and benefits in relation to existing technologies — and does not distinguish between rare and prevalent diseases.

Since the majority of orphan drugs are very costly, their affordability is a major issue for the government, for patients, and for society as a whole. Treatment with orphan products will never be deemed cost-effective. To change estimates of cost-effectiveness, the benefits of treatment would have to be immeasurably greater and the costs of treatment much lower than they actually are. In view of these aspects, a reflection on the need for new models of health technology assessment and incorporation — models capable of ensuring equity among different individuals — is in order. This is not an easy issue to address, but it should be a priority if any advancement is to be achieved in this area. Furthermore, the extent to which arguments based on cost-effectiveness can hinder incorporation of new health technologies must be evaluated. As the right to health is enshrined in the Federal Constitution of Brazil[38], it occupies a higher plane of normative hierarchy than sub-constitutional norms mandating cost-effectiveness studies.

Options for funding of these technologies should be considered and encouraged. These include the establishment of public-private partnerships that enable cost-sharing; partnerships between academia and industry in an attempt to decrease the costs of technology development; so-called conditional reimbursement, in which reimbursement is conditioned to treatment response; and cost-sharing schemes in which all stakeholders are involved. In this sense, the public-private partnership recently established between the Brazilian government and one of the manufacturers of treatment for Gaucher disease is worthy of note.

Another aspect to be considered is the need to encourage and invest in research and development of therapeutic alternatives that may provide superior clinical responses as compared with current drugs. As the evidence used to support prescription of orphan drugs is often of low quality, it is important that the Brazilian Ministry of Health develop programs for patient monitoring and follow-up so as to construct a more robust evidence base on the actual benefits of these medicines. One option for such monitoring is the creation of nationwide registries sponsored by the government and not by the pharmaceutical industry.

Perhaps the greatest challenge in the field of rare diseases is the establishment of models and processes for health technology assessment that cover both technical and ethical aspects and are capable of ascertaining the real therapeutic benefit of orphan drugs. This is an especially pressing concern in view of the need to set priorities in health. Issues of resource allocation necessarily entail consideration of ethical aspects, particularly of the so-called ethics of scarce resources, which propose criteria for allocation of such resources pursuant to the principle of equity. This principle demands that the differences between persons and situations be taken into account. Therefore, countries that choose to provide access to these technologies will be faced with the daily challenge of sustaining their strategies, because regardless of the funding or reimbursement scheme adopted, there will always be a monetary deficit. Conversely, countries that choose not to provide such therapies will be forced to admit that they do not treat their citizens equitably, as treatments will be affordable and available to persons affected by highly prevalent diseases but infeasible for others affected by rarer conditions.

Studies on societal preferences regarding resource allocation for rare diseases have been conducted, with divergent results[39,40]. Decision frameworks have also been proposed; Pinxten et al.[41], for instance, support the proposal of budgetary insulation of a guaranteed — but limited — share of resources dedicated to the development and supply of orphan drugs. Once a budget has been insulated, rare diseases that constitute "rational priorities" could be chosen, according to these authors, on the basis of the following criteria: 1) disease severity; 2) evidence that health improves with treatment; and 3) life-threatening nature of the disease. In addition to this fair allocation, the authors suggest a second track of resource allocation which should be organized at random, so as to cover all patients with a rare disease. However, such a proposal would violate the SUS principles. The establishment of an insulated budget for rare diseases would create

inequality between patients with rare diseases (resources for treatment of whom would be limited) and other users of the System (whose treatment resources are limited only by the general budget). Regarding criteria for the development and provision of medicines for rare diseases, we believe the use of evidence criteria "adapted to rare diseases" is both possible and advisable within the SUS, insofar as cost-effectiveness criteria are of limited applicability in these conditions for the reasons described above. The use of disease severity and risk of death as criteria to determine access to treatment could violate the principles of universality (as it would leave some patients untreated if resources are not sufficient for all) and comprehensiveness (which ensures access to all at all levels of complexity).

CONCLUSIONS

The complexity of the issue of allocation of resources for orphan diseases and drugs imposes a pressing need for integrated approaches that combine aspects of (bio) ethics, law, the health sciences, and economics. With the implementation of the National Policy for Comprehensive Care of Rare Diseases, Brazil has made one of its first leaps forward in this respect. We hope that Brazilian society will shape its own model for dealing with orphan drugs, respecting its own preferences and the guiding principles of a new model for health technology assessment that acknowledges the many peculiarities of rare diseases.

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