

A compilation of national plans, policies and government actions for rare diseases in 23 countries

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Summary Previous studies have focused on the comparison of specific laws among multiple countries and regions; for example, laws related to facilitating treatments with orphan drugs or laws seeking to address the multiple needs of patients with rare diseases. The purpose of this scoping review is to examine and compare published reports on national plans, policies and legislation related to all rare diseases in different countries. We also examine strategies or programs that countries may have for these diseases. Articles were obtained from journals and books published between January 1, 2000, through December 15, 2017. Reports from the grey literature (documents issued by government and private organizations) were included if they were available on the internet. The databases used were Google and Google Scholar, PubMed, and the websites of Orphanet and the National Organization for Rare Disorders (NORD). We obtained information on 23 countries. Among these countries, the way in which rare diseases were defined varied from having similar definitions to no definition. Multinational programs supported by common or similar laws are likely to have a greater impact on rare diseases than single country programs.

Keywords: Rare disease legislation, program, strategy

1. Introduction

In the United States (US), a rare disease is one affecting fewer than 200,000 individuals at a given time. Despite their individual low frequencies, the large number of rare diseases (estimated between 6,000 and 8,000) makes them collectively common (1,2). Worldwide, rare diseases affect approximately 400 million people (3). About 80% of these diseases have a genetic origin and their severity ranges from minor to life threatening (3,4). Because of their genetic or congenital origin, numerous rare diseases have a serious impact on health starting at birth or early childhood and represent a major challenge for patients, caregivers, physicians, healthcare providers, and society in general. The financial impact

of rare diseases is also significant (3,5,6). For instance, the medical expenses for adults with spina bifida could be three to six times as high as that for adults without the disease (7). In 2014, the average annual cost in the US for orphan drugs developed for rare diseases was \$137,782 per patient (8). This financial impact noticeably increases the overall cost of managing a rare disease for which orphan drugs are prescribed. Furthermore, the quality of life for patients with a rare disease may decline with age (6). A Swedish study showed that, in a ten-year period, the proportion of individuals with adult forms of muscular dystrophy able to walk without assistive devices decreased from 91% to 52% (9). The age range of this group was 16 to 65 years (9).

Rare diseases also affect physicians and the healthcare system in general. The scarcity of knowledge, guidelines, and training on rare diseases makes the diagnosis and management of these diseases difficult (3,5). For example, a survey conducted among caregivers of patients with a rare disease in the US and the United Kingdom (UK) found that these patients had often received a misdiagnosis from multiple physicians. It was not until approximately three years after the first misdiagnosis that patients with a rare disease received a

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correct diagnosis (6). This delay in diagnosis adds to the costs of the disease incurred by patients, their caregivers, and the healthcare system. Further, patients with a rare disease may not only need to see multiple physicians to get a correct diagnosis, they may also need care from multiple practitioners. This can also present a challenge. A majority of physicians in the US (76%) and in the UK (88%) reported having difficulties coordinating care with other providers who are managing the same patient with a rare condition (6).

In addition to the challenges of accurately diagnosing rare diseases and assessing the impact these diseases have on patients and their caregivers, there is the challenge of how to reach a patient population that is few in number and widely scattered geographically. The typical public health approach, designed for diseases that are either common or tend to cluster, might not be relevant for rare diseases. Hence, a frequently used strategy to support public health approaches aimed at reducing the burden of rare diseases is by government action; for example, the US has used this approach extensively: in 1983 the US Congress passed the Orphan Drug Act, its first major federal statute dedicated to rare diseases. This law encouraged the production of orphan drugs (drugs developed to treat rare diseases) by providing financial incentives to pharmaceutical industries to offset the potential losses of marketing drugs to such a small market (10). Further, in 2001, the US Congress passed the "Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001" (MD CARE Act) (11), which promoted surveillance and research, improved screening techniques, fostered collaboration among muscular dystrophy centers, and stimulated the development of educational programs for all types of muscular dystrophy. Research that resulted from the MD CARE Act included early detection, diagnosis, prevention, and treatment for muscular dystrophy (12).

Finally, a government may create laws aimed at reducing the occurrence of rare diseases that have a preventable cause, such as neural tube defects (NTDs). In 1998, a regulation issued by the US Food and Drug Administration (FDA) went into effect that mandated the addition of folic acid to cereal grain products labeled as enriched in the US (13). The objective of this regulation was to provide women with an avenue for increasing dietary intake of folic acid, which can help prevent NTDs. As a result of this regulation, just over 1,300 more babies were born without a NTD each year from 1999 through 2011 (14). To date, mandatory folic acid fortification of grain cereals now exist in 86 countries (15).

The use of legal means to benefit patients with rare diseases has also been underway in the European Union (EU). The academic literature shows the EU has created a unified approach toward the management of rare diseases through the use of regulations, directives,

recommendations, and communications (16-21). This approach seeks to make rare diseases more visible by identifying and coding them; by encouraging the development of national plans to ensure equal access to health care for people with rare diseases; and by promoting regional support to activities such as research, financial incentives, screening, and orphan drug development.

In sum, the literature demonstrates that law-based interventions aimed at rare diseases in the US and Europe have encouraged the production of orphan drugs, accommodated health care systems to the needs of patients with rare diseases, and promoted research to prevent and ameliorate the impact of these diseases on affected individuals and populations. The purpose of this study is a scoping review exploring the academic literature for the past 18 years, searching for publications in English that refer to national plans, policies and legislation on rare diseases from countries around the world. This review also includes strategies or programs for rare diseases from these countries. As a result, we will compile similarities and differences reported in the literature among law-based national approaches that focus on rare diseases.

2. Literature Search Strategy

First, we searched repositories of biomedical literature for articles and book chapters describing national plans, policies or laws for rare diseases in general. Second, we complemented the previous search by searching the same repositories for countries with specific strategies or programs for rare diseases that were national or multi-national in scope. Third, we searched the grey literature for reports about any of the items searched in the previous two steps. Our search was limited to publications and documents in English, or in other languages with complete abstracts in English, that were published from January 1, 2000 through December 15, 2017. In our search we used only keywords in English and we collected three types of documents: 1) all in English; 2) with a complete abstract in English but the rest of the document in another language; and 3) websites in English. The search engines we used were Google or Google Scholar, PubMed, Orphanet, and the database of the National Organization for Rare Disorders (NORD). The search terms, alone or combined, included "rare disorder," "rare disease," "national plan," "legislation," "policy," "strategy," and "program." We then examined abstracts, book chapters, websites, and reports resulting from the searches to assess their relevance to our objectives. We retrieved a document for inclusion in the study only if it described a plan, policy, legislation, strategy, or program for rare diseases at a national or multi-national scale. We excluded from this review documents that appeared to be duplicates, that had no publication date; that reported unpublished results

or personal communications, and conference abstracts. Figure 1 shows the flow diagram of our search. Finally, we organized the results of our review by country within large geographic regions and highlighted the characteristics of the national approaches to rare diseases that we found in the literature.

3. Results

Our exploratory search yielded 19,179 potentially relevant publications for the period under study. After applying the selection criteria (Figure 1), 56 publications qualified for our compilation: 37 from scholarly journals, 17 from the grey literature, and two books. The publications originated from four regions or their combinations as follows: 8 from Canada and the US, 19 from Europe, 13 from Asia-Pacific, 4 from Latin America, and 12 from multi-country regions (Figure 2).

Regarding these combined regions, two publications included Europe and Latin America, nine included Canada, the US, Europe and the Asia-Pacific region, and two included Canada, the US and Europe. Tables 1-4 present the rare disease definitions, plans, legislation, programs, and strategies by region and country. Of note, since the term *rare* refers to diseases of very low frequency in a population, the definitions of this term are based on the prevalence rather than the attributes of a disease. According to the literature, some countries use total number of cases in a population as a threshold to define a rare disease, while other countries use proportions.

3.1. Canada and the US

Table 1 reports the results for Canada and the US. Unlike the US, Canada defines rare diseases by the

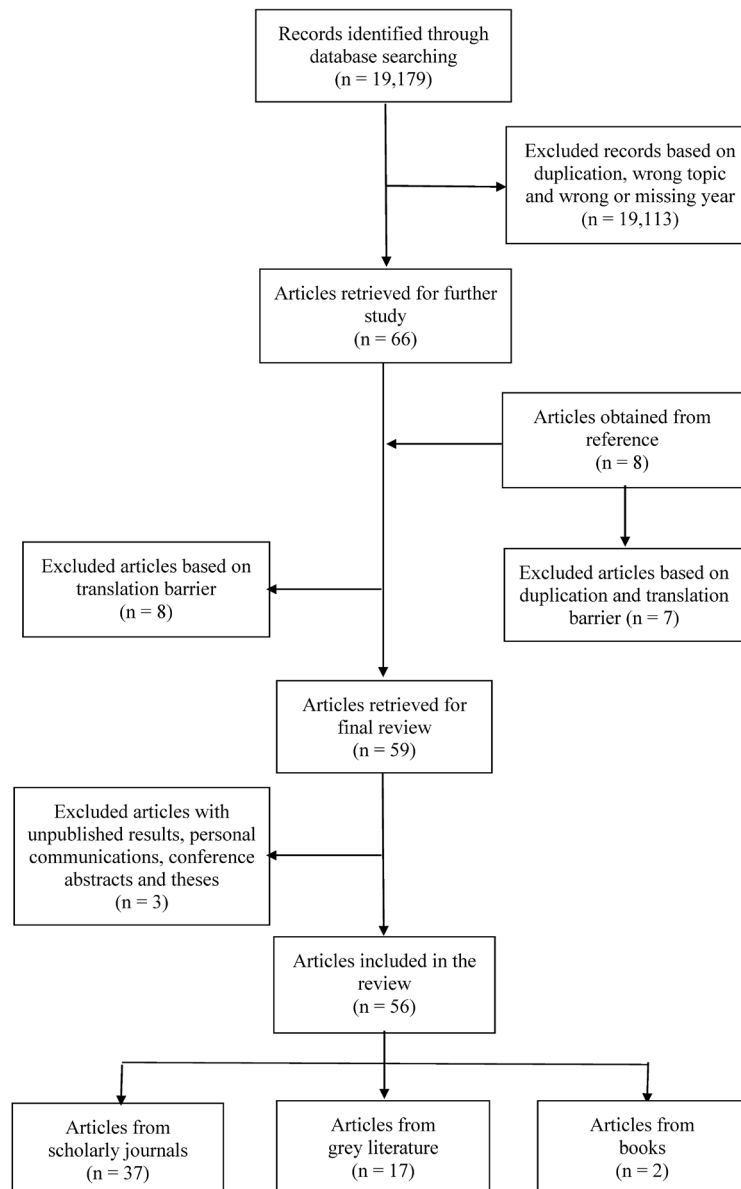


Figure 1. Flow diagram of the search strategy.

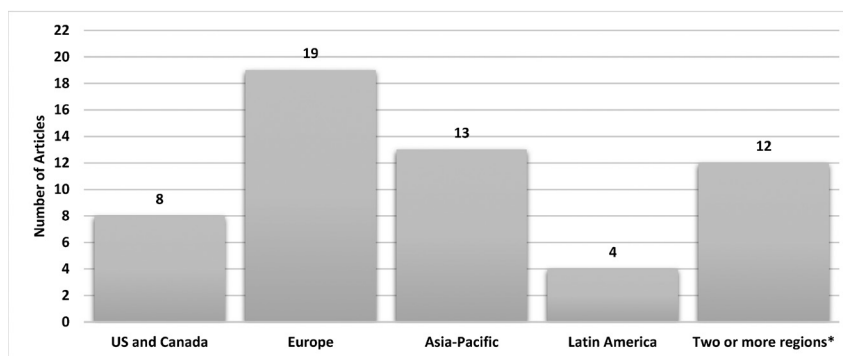


Figure 2. Number of rare disease articles from different countries, by region.*indicates that the documents described a plan, policy, legislation, strategy, or program for multiple regions.

Table 1. Rare disease plans, legislation, programs or strategies in Canada and the United States

Country	Definition of rare disease	National Plan	Legislation	Program or Strategy	Highlights
Canada (1,2,10,22,23,25)	Fewer than 5 cases per 10,000 people (draft)	No	No	Yes	<i>Health Canada's Special Access Program:</i> Provides access to several orphan drugs for patients with rare diseases. <i>Orphan Drug Framework:</i> Promises to increase lifecycle of orphan drugs, work with other countries with an established orphan drug framework, and to improve access to orphan drugs and facilitate research. <i>The Canadian Organization for Rare Disorders (CORD) 5 Strategic Goals for Canada's Rare Disease Strategy:</i> Detection and prevention, timely, equitable and evidence-informed care, community support, access to promising therapies and research.
United States (1-3,5,8,10,25,35,39,49-57)	Fewer than 200,000 cases	No	Yes	Yes	<i>Orphan Drug Act (1983):</i> Regulatory fee waivers, 50% tax credit in clinical expenditure, grants for clinical research, development of medical devices and medical food, protocol assistance, accelerated review if indication permits, and 7 year market exclusivity. <i>Rare Disease Act (2002):</i> Established the Office of Rare Diseases. Increased federal funding for the development of treatments for rare diseases. <i>National Institute of Health Research Programs:</i> Translational research on rare diseases and emphasis on diagnostics and interventions (e.g.: Genetic and Rare Disease Information Center).

proportion of cases in a population (22). The reports that we found indicate that Canada has no national plan or specific legislation on rare diseases (10,22), the Minister of Health put forward a draft for an orphan drug regulatory framework in 2012 (22,23). According to a previous report, this framework would rely on existing Canadian laws that regulate health products and food, including the regulation of labelling and packaging, clinical trials, and manufacturing and marketing of these products; however, this framework has yet to be implemented (24). Also, the Canadian Organization for Rare Disorders (CORD) has provided five strategic goals for a Canadian Rare Disease Strategy (23).

About 35 years ago, the US passed its first major law on orphan drugs, known as the Orphan Drug Act, aimed at stimulating the production of medicines for rare diseases by offering pharmaceutical companies research grants, tax credits, fee waivers, and a seven-year market exclusivity for approved medications (10). Other pieces of legislation in the US include the Rare

Disease Act, which established the Office of Rare Diseases at the National Institutes of Health (NIH) (10) and legislation for single rare disease entities, such as the MD Care Act (11).

3.2. Europe

For Europe, our exploratory search resulted in a handful of publications from the subset of countries that form the EU. Multiple articles, spanning a number of years, demonstrate that Europe has an integrated, multi-country approach to rare diseases (Table 2). The publications found report that all 28 countries in this union have a common definition of rare disease, based on the proportion of cases in the population, and their rare disease activities operate under multinational legislation called the Orphan Medicinal Product Regulation (EC) No. 141/2000. This regulation seeks to stimulate research and to promote the development of orphan drugs to treat patients with rare diseases (17-20). Europe also has developed the European Project

Table 2. Rare disease plans, legislation, programs or strategies in Europe

Within Europe, the European Union (EU) has adopted a common definition of a rare disease (Fewer than 5 cases per 10,000 people) and has a common legislation [Regulation (EC) No. 141/2000 (1999): Regulatory fees reduced or waived, access to centralized procedures, and protocol assistance. Member states implemented measures to encourage the development of orphan medicinal products. Tax credits are managed by member states. Market exclusivity for 10 years; 6 years if drug criteria not met.] Each member state has additional legislation (1-5,8,10,18-21,39,51,57,59,60).

Country	National Plan	Legislation	Program or Strategy	Highlights
Bulgaria (1,16,17,25-27,66)	Yes	Yes	Yes	<i>National Plan (2009-2013)</i> : To deliver prevention, diagnostics, treatment and rehabilitation to rare disease patients.
France (1,3,16,17,25-28,53,61)	Yes	Yes	Yes	<i>First National Plan (2005-2008)</i> : To increase knowledge on the epidemiology of rare diseases, recognize the specificity of rare diseases, develop information on rare diseases for patients, healthcare professionals and the general public, train healthcare professionals for better identification of this disease, organize screening and access to diagnostic tests, continue efforts in favor of orphan drugs, meet the specific requirements for social services for patients with rare diseases, promote research on rare disease, and develop national and European partnership. <i>Second National Plan (2011-2014)</i> : Increase quality of patient care with the use of reference centers and telemedicine, develop research on rare disease such as translational clinics and therapeutic research, and increase European and global cooperation
Germany (1,16,17,25-27,63)	Yes	Yes	Yes	<i>"Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen" (NAMSE)</i> : There were 52 policy proposals for action. Action fields for these proposals include care/centers/networks, research, diagnostics, information management, patient orientation, registries, and implementation and future development.
Greece (1,16,17)	Yes	Yes	Yes	<i>National Plan (2008-2012)</i> : Includes early diagnosis, medical treatment, prevention, research, education, and partnership and co-operation strategies.
Italy (1,16,17,26-28,58,64)	Yes (Draft)	Yes	Yes	<i>Ministerial Decree n. 279/2001</i> : Provides a price exemption for care on certain rare diseases; contemplates setting up a network of centers for rare disease patients identified through their experience, activities and services for these patients. The decree also contains regulations for a national registry.
Portugal (1,16,17,26,27)	Yes	Yes	Yes	<i>National Plan (2008-2015)</i> : To determine the needs of rare disease patients and their families and to improve the quality and equity of healthcare services.
Spain (1,16,17,26,27,65)	Yes	Yes	Yes	<i>National Plan (2010)</i> : Includes information on rare disease (resources, registers and coding plus classification), prevention and early detection, healthcare, therapies, integrated health and social care, research and training. Centers of expertise provide services and focus on the needs of rare disease patients. Reference centers promise access to healthcare for these patients.
United Kingdom (UK) (1,17,25-28,62)	Yes (Plan approved for 4 UK states)	Yes	Yes	<i>UK strategy for rare disease</i> : Examines patients and their families. Includes empowering rare disease patients, identifying and preventing these diseases (screening and carrier testing), diagnosis and early intervention, coordination of care (specialist centers) and research. Strategy will continue to work with other countries with rare disease.

for Rare Disease National Plan (EUROPLAN) to facilitate the creation of national plans in the region (3,16,19-21,25). These plans are defined as official public health strategies accepted by a government with explicit priorities, actions, a timetable and a budget (16). Research on rare diseases in Europe is supported by The Seventh Framework Program (FP7), which is a program that funds medium- to large-sized collaborative research projects (19,20,25). In addition, free, short-term access to orphan products is accomplished through Compassionate Use Programs (CUPs) in Member States (26-28), with some exceptions such as Greece (26,27). For the period of our search, eight countries from the EU issued publications related to their national plans, legislation, and programs or strategies for rare diseases. These results are summarized in Table 2.

3.3. Asia-Pacific

Our search found documents that show evidence of legislative activity on rare diseases in seven countries of the Asia-Pacific region (Table 3). In the articles reviewed, the definition of a rare disease varies widely among these countries. Only Singapore and South Korea share a definition. Six of the countries are reported to have legislation addressing rare diseases, yet none appear to have a national plan for these diseases. All seven countries were shown to have programs or strategies aimed at rare diseases. Our review found that Australia has at least two regulatory programs, derived from healthcare laws enacted by the parliament: the Orphan Drug Program, which provides financial and marketing incentives for drug makers

Table 3. Rare disease plans, legislation, programs or strategies in Asia-Pacific Countries

Country	Definition of rare disease	National Plan	Legislation	Program or Strategy	Highlights
Australia (1-3,10,29,32, 35,39,51)	Fewer than 2,000 cases.	No	Yes	Yes	<i>Orphan Drug Program (1998)</i> : Regulatory fee waivers, no grants or tax credits, protocol assistance, and priority review. 5 year market exclusivity.
China (1,25,30-32, 35,71)	Prevalence lower than 1/500,000 (disorder) or incidence lower than 1/10,000 (newborns). Definition not agreed by patient organizations.	No	No	Yes	<i>China pilot project</i> : to provide and use guidelines, create registries and encourage molecular testing for rare diseases. This project seeks to build relationships with collaborative networks, clinicians and patient organizations. <i>"Rare Disease Clinical Cohort Study"</i> : Research program will establish the unified National Registry System of China in 2020 and large cohort study will examine classification, diagnosis, treatment and prognosis for rare diseases.
Japan (1-3,8,10,32, 35,39,51,57, 67-69)	Fewer than 50,000 cases.	No	Yes	Yes	<i>Pharmaceutical Affairs Law (1993)</i> : Regulatory fee waivers, clinical and non-clinical study grants, 15% tax credits and up to 14% tax reduction (6% tax reductions for preclinical research). Protocol assistance and fast track approval. 10 year market exclusivity. <i>"Revision of Measures to Combat Intractable Diseases"</i> : Strategies stressed treatment and improve care for those affected, tools to reimburse medical costs, and promote participation. <i>Specified Disease Treatment Program</i> : Focused on funding to encourage research and orphan drug development
Philippines (32,33,70)	1 case per 20,000 people.	No	Yes	Yes	<i>Rare Disease Act of the Philippines (2016)</i> : Focuses on several elements of rare disease management (diagnosis, clinical management, genetic counseling and drug research development), registry, research, and newborn screenings.
Singapore (1,2,32,34)	Fewer than 20,000 cases.	No	Yes	Yes	<i>Medicines Act (Chapter 176, Section 9) (1991)</i> : Focuses on managing and encouraging the use of orphan drugs for rare disease patients. Physicians and dentist should prescribe orphan drugs for these patients if there were no substitute medications available. 10 year market exclusivity.
South Korea (32,35,36, 67)	Fewer than 20,000 cases.	No	Yes	Yes	<i>Orphan Drugs Guideline (2003)</i> : Medical reimbursement and research. 6 year market exclusivity. <i>Research Center for Rare Diseases</i> : To do research as a single center or collaborate in clinical research networks. <i>Korean Biobank Project</i> : The project would manage and collect specimens from rare disease patients, and launch a network of healthcare providers working with these patients disease or would gather bio-resources from research projects.
Taiwan (1,2,25,32,35, 37,57,67)	No more than 1 case per 10,000 people.	No	Yes	Yes	<i>Rare Disease and Orphan Drug Act (2000)</i> : Grants, copay can be waived, fast track approval, protocol assistance, and medical reimbursement. 10 year market exclusivity.

to produce medicines for patients with rare diseases (10,29); and the Life Saving Drugs Program, which subsidizes expensive and life-saving drugs for patients with serious, rare medical conditions (29). A China pilot project was implemented in 2013 (30,31) and the Rare Disease Clinical Cohort Study was implemented in 2016 for rare disease patients (31). The objectives reported for this pilot are to develop and apply guidelines and clinical pathways for rare diseases, to establish patient registries and data repositories and to promote molecular testing for rare diseases (30). We identified reports stating that Japan has policies promoting orphan drug research and development (32). For instance, Japan's Pharmaceutical Affairs Law (PAL)

encourages research that examines orphan drugs (3). The Rare Disease Act of the Philippines, approved in 2016, covers topics such as rare disease management, registry, research, and newborn screening (33). In 1991, Singapore implemented the Medicines Act (Chapter 176, Section 9) which focuses on managing, and encouraging the use of, orphan drugs (34). In 2003, South Korea created the Orphan Drugs Guideline (35) and, in 2013, the Korea Biobank Project (KBP) for rare disease (36). In Taiwan, the Rare Disease and Orphan Drug Act provides support for rare disease patients by encouraging rare disease research, and increasing awareness of rare disease (25,37). Furthermore, this act also facilitates access to orphan drugs (35,37).

Table 4. Rare disease plans, legislation, programs or strategies in Latin American Countries

Country	Definition of rare disease	National Plan	Legislation	Program or Strategy	Highlights
Argentina (25,38,39)	EU Definition	No	Yes	Yes	<i>Law 26.689 (2011)</i> : Intended to help rare disease patients and their caregivers by promoting the development of patient registries and screening programs, and educational and social support activities.
Brazil (25,39,40)	No more than 65 cases per 100,000 people.	No	Yes	Yes	<i>"National Policy for Rare Diseases"(2014)</i> : Includes equal healthcare services, create care guidelines for these patients at every stage of a Unified Health System care, offers comprehensive care in the Health Care Network, improves universal and regulated access for rare disease patients, ensures access to care, and quality healthcare.
Chile (39)	EU Definition	No	Yes	N/A	The Ricarte Soto law aims at providing funding for care of rare disease patients. It assigned a grant of 200 billion pesos for 4 years.
Colombia (39,41,72)	1 case per 5,000 people.	No	Yes	N/A	<i>Law 1392 (2010)</i> : Identifies the lack of orphan drugs as a health issue impacting the healthcare system. Considers social protection policies. It contemplates creating a registry for rare disease patients and collaborating globally for research.
Mexico (25,39)	EU Definition	No	Yes	No	<i>Article 224 revision (2012)</i> : Recognizes orphan drugs and their treatments. Ministry of Health may enforce market authorization, no rules for market exclusivity.
Peru (38,39)	No Definition	No	Yes	N/A	<i>Law 29698 (2011)</i> : Includes diagnosis, surveillance, prevention, care and rehabilitation.

3.4. Latin America

As seen in Table 4, our scoping review yielded publications from six countries in the Latin America region. The literature shows that Argentina, Chile and Mexico have adopted the proportion of cases in a population to define rare diseases. Brazil and Colombia have their own definitions, and Peru does not have a definition of rare disease in the document found for this review. None of the publications retrieved indicated whether or not any of the six Latin American countries had a national plan (explicit priorities, timetable, and a budget) for rare diseases. However, the literature revealed a number of legal approaches in Central and South America. Argentina implemented legislation in 2011 to aid patients with rare diseases and their caregivers (38,39). Brazil created the "National Policy for Rare Diseases" in 2014 aimed at decreasing morbidity and mortality and increasing quality of life for patients with rare diseases (39,40). Also, this policy called for the establishment of reference treatment centers that would provide genetic testing and counseling (25,40). Recently, Chile approved a law to provide funding for the care of patients with rare diseases (39), and Colombia approved a law in 2010 that identified rare disease as a public health issue (39,41). Mexico's legislation for rare disease was a revision to the general health law that authorized Seguro Popular, a national health insurance institution, to provide health insurance coverage and access to orphan drugs for Mexican patients (39). Finally, Peru passed legislation for rare diseases in 2011. This law covers from diagnosis

to rehabilitation of patients with rare diseases (38,39).

4. Discussion

For this review, we searched the academic literature for articles about national plans, policies, legislation, strategies and programs for rare diseases from countries around the world. For the study period (2000-2017), we found 56 eligible publications on these subjects from 23 countries organized into four large geographic regions (Canada and the US, Europe, Asian-Pacific countries, and Latin American countries). Of these four regions, the publications reviewed suggest that the countries from the EU presented the most unified legislative approach to rare diseases. For example, the reports for the eight European countries indicate that all of them have adopted a common definition of rare diseases and have developed national plans, laws, and programs or strategies for these diseases. Reports reviewed for the countries within the other three regions indicate that none of these countries has developed a national plan for rare diseases with explicit objectives, a timeline and a budget; however, most countries in these regions appear to have laws and programs or strategies in place for these diseases. Further, according to the literature reviewed, even within a region, the definition of a rare disease varies widely from country to country. In general, our scoping review demonstrates that the legislative approach from all 23 countries seeks to promote the development of, and access to, orphan drugs to facilitate research on rare diseases, to stimulate the development of programs for screening, diagnosis, and registries, and to foster international

collaborations.

Previously, we mentioned studies highlighting the coherent approach of the EU to rare diseases (16,19,20), including countries from Eastern Europe (42). Other studies have focused on the comparison of specific laws among multiple countries and regions; for example, laws related to facilitating treatments with orphan drugs (1) or laws seeking to address the multiple needs of patients with rare diseases (25). Our scoping review was specifically designed to identify publications in the academic literature, for the past 18 years, about countries with existing or contemplated national plans, laws, or programs/strategies related to rare diseases. Together, the studies we found indicate that legislation is a widespread approach to addressing the care of patients with rare diseases in populations. Nevertheless, for the period of our research, we found no evidence published in English of the use of this approach in vast areas of the world, such as Africa, India, and Russia.

The enactment of legislation to address the collective needs of patients with rare diseases can vary from country to country and follow a complex path. It requires that a variety of elements are in place not only to promote the passing of a law but to follow through with its implementation. For example, the US Orphan Drug Act of 1983 and its implementation resulted from the combined efforts of patient advocacy groups, medical researchers, healthcare providers, medical associations, government agencies, legislators, and the pharmaceutical industry (43). With the help of political and economic treaties, which have facilitated the creation of a common system of laws, the countries of the EU have taken government action for rare diseases one step further by including not only treatments and drugs but also timely diagnosis, access to care, and social support for patients with rare diseases in a multinational setting (25). Our compilation also identified multi-country regions with a less cohesive approach to rare diseases than the EU approach. Among the publications that we found, one discusses Latin American as one example of such regions (44).

Our compilation highlighted wide variation in government policy approaches to rare diseases around the world, from incipient to comprehensive. This variation has also been noted in another publication (1) but here we have included the definition of rare diseases found in the literature as a key feature for comparison. We found that these definitions vary widely among countries, even among countries with well-established plans and strategies. This variation, which is much wider than the differences in definitions described in this report (45), could be an obstacle to the integration of national plans into larger international plans. Researchers on rare diseases have emphasized the need for the integration of rare disease plans and studies into international consortiums. This would replace the fragmented approach currently in place with a more coordinated effort that would include larger numbers of patients and

caregivers (46-48).

Because we only used English keywords and a limited period for the search, the key limitations of this study are that our results were restricted to documents and journal articles published in the last 18 years that were either completely written in English or had informative summaries written in English; therefore, we captured only a sample of all existing national laws or national law-based approaches to rare diseases. Other limitations include that we did not examine the actual pieces of legislation, our scoping review is based only on documents and articles that describe these pieces of legislation for the scientific community or for the general public. Finally, our search did not distinguish between proposed and enacted legislation; although, most of the publications selected for this exploratory review were about laws already in place, some of them for decades.

In conclusion, the specific creation of laws on rare diseases appears to be a common approach to providing care and support to individuals affected by these diseases, who are few and scattered over large national or international regions. The obstacles to this approach are many, but some countries and regions have made great advances in integrating into their legal system the view that rare diseases collectively deserve public health attention. Future research should bring attention to the evaluation of national or multinational enacted laws on rare diseases, in particular the ones enacted decades ago, to formally ascertain the extent to which the intention of these laws has been fulfilled.

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