

RARE DISEASES:

shaping a future with
no-one left behind





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EXECUTIVE SUMMARY

Rare diseases are a group of conditions which affect very small numbers of people. Definitions vary, although generally a disease is considered rare if it affects fewer than 1-5 individuals per 10,000 in the general population.

Most people suffering from rare diseases do not have any treatment options available for their condition. Yet many countries do not have plans, policies or legislation to help lead research on rare diseases and improve the management of these many conditions.

Awareness and understanding of rare diseases is often low, and many patients struggle to find adequate information about their condition. As a result, upon diagnosis, patients may feel isolated, overwhelmed and unsupported. The emotional, psychological and financial impact of being diagnosed and living with a rare disease is also considerable.

Traditionally, research and development of treatments for rare diseases has been neglected in favour of more common diseases. However, in the last twenty years, concerted public policy efforts have led to a marked improvement in our understanding of many rare diseases and availability of effective treatment options.

Rare diseases pose particular challenges for research and clinical development. This is due to the small numbers of patients, limited epidemiological data on the natural history of many rare diseases, and all stages of research and development being more challenging and lengthy than for more common diseases.

Generally, patients face difficulties in accessing high-quality care and support. Even if treatments exist, patients may wait several years for a correct diagnosis, and many patients are unable to receive them as often they are not reimbursed by their national health care system, or are simply not available in their country.

It is essential that rare diseases be seen as a policy priority in all healthcare systems. Patients with rare diseases should have the same right to treatment and care as patients with more common diseases. Improving care for patients affected by rare diseases should therefore be prioritised by national governments across the globe.

This brochure aims to present a clear view of the unique challenges that rare diseases present to health care systems, and to outline what policies may help improve their management for the benefit of patients around the world.

Key recommendations include:



Ensure rare diseases are a public health priority, raising awareness of rare diseases among policymakers, health care professionals and the general public



Empower patients and their wider communities, enabling better disease management and for patients to further influence the decisions that affect them



Promote continued research and development, building political commitment to drive research, innovation and policies for rare diseases and increasing collaborative research efforts to enhance scientific understanding of all rare diseases



Ensure sustainable access to diagnosis, treatment and care, improving the workforce and infrastructure to treat rare diseases and developing and strengthening legislation that enhances access to orphan drugs

INTRODUCTION - ABOUT RARE DISEASES

What are rare diseases?

Rare diseases are a diverse group of conditions, generally defined by the fact that very few people are affected by them in comparison to more common conditions like diabetes or heart disease.¹⁻³

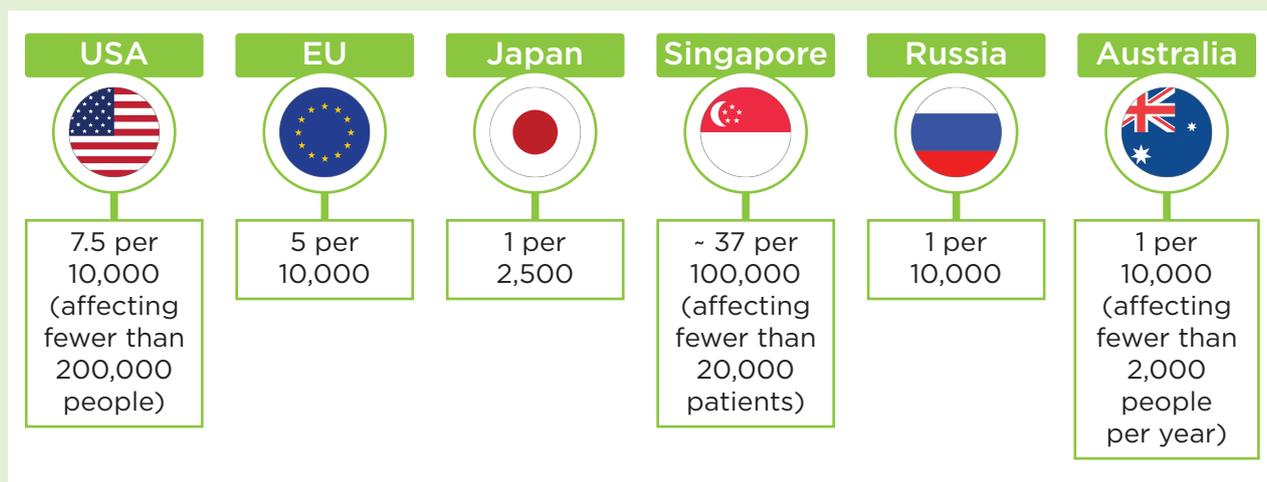
Rare diseases tend to be severe, chronic conditions and in many cases, they are progressive, debilitating, and life-threatening.¹⁻⁸ For example, 30% of rare disease patients die before the age of five.²

There is no universal definition of rare diseases,⁹ and countries differ in the threshold they use to define a disease as 'rare' (see **Box 1**).

BOX 1 – Definitions of rare diseases around the world

The threshold that defines rare diseases varies by country, as can be seen in Table 1. Many countries do not have an official definition,¹⁰ although suggested thresholds often exist.¹⁰⁻¹¹ Due to the complex nature of rare diseases, it is important that each country or region develops a definition in the context of their own population, culture, resources and health care system.¹⁰⁻¹² However, along with prevalence, there may also be other situations which apply for rare diseases. For example in Japan, rare diseases are defined mainly as diseases that chronically develop, and require a significant amount of care from the patient and their families.¹³

Table 1 - Rare disease prevalence (cases per population) across various countries¹⁴⁻²⁰



How many people are affected by rare diseases?

While each individual rare disease affects a small population, it is estimated that collectively 350-400 million people worldwide have a rare disease.^{21 22} Together, rare diseases affect approximately 6-10% of the population and 3-4% of births.^{1 8 10 23}



350-400 million
people worldwide

What causes rare diseases?

80% of rare diseases are genetic, and the rest may occur as a result of viral or bacterial infections, allergies and other environmental causes.^{1 2 5 24}



80% of
rare diseases
are genetic

How many rare diseases are there?

There are between 5,000-8,000 rare diseases, and new rare diseases are being discovered all the time.^{1 2 4 5 25-27} These diseases can affect people very differently - even people with the same condition can have very different signs and symptoms, or there may be many subtypes of the same condition.^{1 6 8} This diversity presents a significant challenge to healthcare practitioners and scientists alike in terms of being able to acquire sufficient experience of a given condition for the most appropriate and timely definition, diagnosis and management.

Rare cancers are a sub-group of rare diseases, and there are 198 estimated types of rare cancer. In the European Union, rare cancers account for 22% of all cancer diagnoses.²⁸



There are between
5,000-8,000
rare diseases

KEY CHALLENGES IN THE DIAGNOSIS AND CARE OF RARE DISEASES

“No human life should be judged by a statistic – every rare disease patient deserves treatment and support, no matter their disease or where they live.”

Prasanna Kumar B Shirol, Organisation for Rare Diseases India

Diagnosis and care - key challenges presented by rare diseases:



Delays and frequent errors in diagnosis, often with severe consequences for patient outcomes



Lack of clinical expertise, leading to variable quality of care



Few treatment options available



Limited information and support for patients



A considerable impact on the quality of life of patients and their families

Delays to diagnosis are common, often with severe consequences for patients.

Delays to diagnosis are commonly experienced by patients and may be due to poor awareness of rare diseases by health professionals and the small number of patients affected.

These delays in diagnosis can be significant for many patients and may lead to irreversible progression of the patient's condition.^{1 2 7 24} For example, in the UK and USA, the average time to obtain a correct diagnosis for rare diseases was found to be 5-7 years, and in this time there were 2-3 incorrect diagnoses for a given condition.²⁹

As a result of incorrect and delayed diagnosis, unnecessary tests and treatments are often carried out, sometimes at the patient's expense⁸ but often also coming at a significant cost to the healthcare system.⁸ Patients are often left feeling frustrated and anxious, and may lose confidence in the healthcare system as a result.¹

Expertise in rare diseases is limited due to the rarity of these conditions.

It is often difficult for rare disease patients to find healthcare professionals with adequate experience in their condition to provide the best quality care.

It can be challenging for healthcare professionals to gain adequate experience in rare diseases due to the small numbers of patients.¹ However, if treatment and management are not led by specialists, this may result in incorrect diagnosis, inappropriate treatment and poorer patient outcomes.^{27 30 31}

Even when specialists are available, patients often must travel significant distances for treatment, at great cost to their families.¹

Treatments are unavailable for many rare diseases.

It is estimated that 95% of rare diseases do not have a treatment option.⁶

The limited number of treatments available for rare diseases is possibly the greatest challenge for patient care – and may be explained by lack of research on rare diseases and barriers in making treatments available in different countries. (See **Section 3**) Lack of research on rare diseases has hindered the development of evidence-based clinical guidelines to inform best practice.¹

The different regulatory processes across the globe mean that even if a drug exists, it may not be available in every country.

Patients often do not receive support and information to help them cope with their diagnosis and condition.

Receiving a rare disease diagnosis may have a significant psychological and emotional impact on patients and their families.

Studies suggest that many patients feel they receive limited information and support after diagnosis.^{17 8} This may be a result of wider system challenges including poor support networks and limited resources for information, follow-up or psychological care.

Patients are often left feeling isolated, overwhelmed and in many cases deeply frustrated after their diagnosis. Peer-to-peer support groups may be very helpful to patients and their families. However, the small patient populations involved often mean that many rare diseases do not have support groups available.^{1 2 7}

There are, however, examples of organisations providing helpful support for rare disease patients and their families. **Case Study 1** describes an example of a support service available in Norway.

CASE STUDY I

Frambu Resource Centre for Rare Disorders, Norway

The Frambu Resource Centre is a multidisciplinary centre of excellence for rare disorders in Norway, providing care for over 2,000 people each year. Its aim is to “collate, develop and impart knowledge about rare disorders and disabilities”,³² and to provide the best possible quality of life for all rare disease patients it sees.^{32 33} It provides:

- ▶ Educational courses and camps for children and families
- ▶ Specific services for parents to help better understand and care for children with rare diseases
- ▶ Research into the patient experience and perspectives to improve services and care
- ▶ Communication and outreach work within the local community
- ▶ Home visits to patients and their families
- ▶ Advice for both patients and professionals

“There is too little support for patients and their carers in dealing with the day-to-day impact of a rare disease and how to best manage life beyond their condition. Patient groups can meet this need; however, most are underfunded and need greater support to fulfil their potential.”

Florá Raffai, Findacure

A rare disease diagnosis may have a considerable financial and quality of life impact on patients and their families.

The diagnosis of a rare disease is often associated with many additional and unforeseen costs. Patients and their caregivers are also often unable to fully participate in work or education - deeply impacting their quality of life and financial stability as a result.^{1 8 12 31 34}

For example, it has been estimated that 61% of rare disease patients and their families in Europe have experienced reductions or interruptions to their professional activities.⁸ In many countries, there are few government benefits or supportive policies in place to help patients with rare diseases and their families.^{10 12 31 35}

Patients may also incur significant expenses for their care, linked to obtaining a second opinion, travel to specialists and adaptations to their homes.^{1 2 7 8 12} Delays in access to treatment, particularly in low resource settings, may often mean that patients have to pay for drugs out-of-pocket.^{10 34 35}

ISSUES IN CLINICAL DEVELOPMENT AND ACCESS TO TREATMENT AND CARE

“Advances in the diagnosis, treatment and care of rare diseases only began in earnest when patient groups began demanding political commitment and orphan drug legislation. Mobilising patient groups is central to change.”

Dr Durhane Wong-Rieger, Rare Diseases International

The process of drug development and approval is expensive and time-consuming and poses specific challenges for rare diseases, ultimately affecting patients' access to new treatments. Development of therapies for these conditions is also challenging due to differing definitions of rare diseases between countries (see **Box 1**).

To encourage pharmaceutical companies to conduct research and develop drugs for rare diseases, the special designation of ‘orphan drugs’ has been given to medicines that treat rare diseases - with specific legislation to match.³⁶ However, not all drugs used to treat rare diseases have an orphan designation.

Orphan drug legislation has made a significant difference to the number of treatments available for rare diseases.^{1,36-39} For example, in the European Union only 8 treatments were authorised for rare diseases before the Orphan Medicinal Products Regulation was enacted, whereas since its launch, over 125 products have been authorised.⁴⁰ However, treatments are still only available for approximately 5% of rare diseases, and many challenges remain.⁶

Orphan drugs - key challenges from discovery to patient access:



Limited scientific knowledge of many rare diseases to guide discovery and early phase research



Difficulties in recruiting patients and conducting traditional clinical trials



Lack of expertise in rare diseases amongst regulatory agencies, often leading to delays in marketing authorisation



Significant differences in access to medicines and high quality care between and within countries

Discovery and early phase research

Greater scientific understanding of rare diseases is essential as it will lead to the development of new orphan drugs and treatments.^{2 11 27 30}

As mentioned above, inadequate knowledge and understanding of the causes and clinical progression of rare diseases may make it difficult to determine the best strategy for targeting a given condition.^{5 6 36} Also, research efforts are often scattered with little overarching organisation between groups,^{19 27 41} which may result in duplication of research. This may, in turn, slow down research efforts and possibly the development of new drugs for rare diseases.

Clinical trials

Clinical trials are designed to test if a new medicine is effective and safe for use in humans. Specific challenges for clinical trials in rare diseases are:

- ▶ Small patient populations make recruitment of sufficient participants difficult, making it challenging to obtain statistically significant results.^{5 6}
- ▶ Patients may be spread across large geographic regions, making trials expensive and complex to run.³⁶
- ▶ A large proportion of rare diseases affect children, often in very small numbers, and they need special considerations in clinical trials.⁶
- ▶ There are often no other available treatments for a rare disease. However, using a placebo as a comparison in a clinical trial may present ethical challenges if the new product is very effective.³⁶ This is a challenge for other diseases as well, but is a much more common occurrence for rare diseases.

Registration and marketing authorisation

In order to bring new medicines to market, registration or marketing authorisation must be obtained in each country. Regulatory processes differ considerably between countries, resulting in significant variations in when potentially life-saving medicines become available to patients.⁹

^{24 27 36 37 39 42 43}

Existing regulatory processes are often ill-suited for rare diseases. For example, regulators and their advisors often lack expertise on given rare diseases, causing significant delays in the regulatory approval process.^{36 37} In addition, countries do not have legislation to promote the registration and marketing approval for orphan drugs. Patients in these countries are therefore forced to access medicines through other means, some of which are described in *Case Study II*.



Discovery and development takes approximately 6 years for medicines for common conditions.

It can take much longer for rare diseases.



Clinical trials are very lengthy and pose many challenges for more common diseases.

However, rare diseases present their own set of issues and obstacles, making clinical trials more challenging to run.



Registration and marketing authorisation is a lengthy process for all medicines,

but for rare diseases processes may be difficult to streamline.

CASE STUDY II

Increasing access to orphan medicines in Turkey

As of yet, there is no Turkish legislation to promote the development and marketing of orphan drugs,⁴² and so equitable access to care and treatments is a significant challenge. In the absence of approved medicines, patients must gain access to treatment via other means including:^{42 44 45}

- ▶ **Named-patient imports** - medicines can be imported for personal use by the patient's physician if approved for use in other major regions. Permission for this is granted on a case-by-case basis
- ▶ **Off-label use** - drugs which are approved by the Turkish Medicines and Medical Devices Agency for a given indication are used to treat a rare disease
- ▶ **Compassionate use programme** - medicines which are currently going through phase 3 trials overseas can be used in Turkey if there are no existing Turkish trials

Access to high quality, safe and effective treatment

Even once a new medicine is approved, it is not necessarily available immediately to patients. Each country must decide whether it will fund or reimburse each drug and this can be a lengthy process.

Delays in access may depend on who is paying for new treatments - governments, private insurance or patients. In some countries, these decisions take place at the regional level, which may further delay the time it takes for new treatments to reach patients.³⁶

In addition, existing access processes are often not adapted to the specific challenges of rare diseases and orphan drugs, leaving patients responsible for paying out-of-pocket for new treatments, often with crippling financial consequences.^{36 37}

As comprehensive and structured reimbursement or regulatory processes are rare, particularly in low- and middle-income countries, many patients do not have access to treatment. And as such, in some places the only way to gain access to treatment has been through litigation and court cases, such as in Brazil and India.^{31 46}

General access to high quality care

Even when medicines are available, patients may face challenges in obtaining high-quality and timely diagnosis, care and support due to lack of available specialist services.^{1 2 8 27 30 31} (See *Section 1*)

Few rare diseases have clinical guidelines for best practice, challenging the provision of optimal care for patients.¹ Even when guidelines exist, healthcare practitioners may not be aware or fully trained on their contents.

Due to the often complex nature of their condition, it has been recommended that rare disease patients be managed by a multidisciplinary team.⁴⁷⁻⁴⁹ However, in many cases this does not happen, contributing to poorer outcomes for patients.^{1 7}

POLICY PRIORITIES FOR RARE DISEASES

In light of the challenges identified previously, there is a clear need for continued political commitment to improve the care offered to patients with rare diseases.

Key policy priorities for rare diseases are listed in the table below and described in more detail in the following section.



Ensure rare diseases are a public health priority, raising awareness of rare diseases among policymakers, health care professionals and the general public



Empower patients and their wider communities, enabling better disease management and for patients to further influence the decisions that affect them



Promote continued research and development, building political commitment to drive research, innovation and policies for rare diseases and increasing collaborative research efforts to enhance scientific understanding of all rare diseases



Ensure sustainable access to diagnosis, treatment and care, improving the workforce and infrastructure to treat rare diseases and developing and strengthening legislation that enhances access to orphan drugs

Ensure rare diseases are a public health priority

Awareness of rare diseases needs to be increased

Awareness of rare diseases is often low and greater public and political awareness of these conditions is essential to adequately support those affected by rare diseases.

Political awareness is essential to create supportive policies for rare disease patients, such as legislation on equal access to healthcare, orphan drugs, or employment and education for individuals with disabilities.¹¹²

Increased awareness in the general public may also help prevent some cases of rare diseases caused by various cultural and social practices such as consanguineous marriages (e.g. marriages between cousins).^{10 44}

Rare Disease Day exists to raise awareness of rare diseases and of their impact on the lives of patients (see *Case Study III*), but much more can be done to increase the awareness of rare diseases.

CASE STUDY III Rare Disease Day

Rare Disease Day was initiated in Europe by EURORDIS, but over the past 10 years it has grown significantly and now over 80 countries participate in awareness raising activities and events.⁵⁰ EURORDIS works closely with patient organisations around the day, which takes place on the last day of February each year and aims to raise awareness and increase understanding of rare diseases amongst the general public, researchers and policymakers across the globe.

Establishing Rare Disease Day has been essential to create the political momentum and commitment necessary to help rare disease patients to access new medicines and the best possible care. Its establishment and ongoing actions has contributed to the development of national plans, strategies and policies for rare diseases in a number of countries.⁵⁰

Patients and caregivers need to be empowered as experts in their rare disease

Due to the limited support and information in place, patients often must become experts and advocates in their own condition. Patients should therefore be further supported to engage with and shape the policies and systems which affect them.

Patients and carers have unique insights and perspectives that should be better heard throughout research and development, regulatory processes, campaigns and policy development. Efforts such as establishing more patient groups, either in person or on social media, and developing educational materials and supportive policies across all sectors will be central to better empowering patients to drive change.

“Findacure strongly believes that patient groups have a fundamental role to play in addressing needs and advocating for what matters. Any change intended to benefit patients must include them in the process.”

Florá Raffai, Findacure

“At the Tuberous Sclerosis Alliance, we believe collaboration between those we serve with tuberous sclerosis complex, healthcare providers, researchers and funding organizations is crucial in our efforts to ensure a better future and more meaningful treatment options.”

Jaye Isham, Tuberous Sclerosis Alliance

Promote continued research and development for rare diseases

Greater collaboration at all levels is needed to help drive research and improve care

Significant collaboration and cooperation between scientists, politicians and policymakers, healthcare practitioners and patients is essential to continue to drive new research and improve care.^{9 51}

International research groups are leading the way in research, such as the International Rare Diseases Research Consortium (IRDiRC), which aims to develop diagnostic processes for most rare diseases and 200 new therapies by 2020.⁵² Another example of collaboration at a national level can be seen in *Case Study IV*.

However, the vast majority of rare diseases still do not have a treatment,⁶ and further prioritisation of research and collaboration is essential to provide treatment options and improve care for all rare disease patients.

CASE STUDY IV

Chinese Rare Diseases Research Consortium

The Chinese Rare Disease Research Consortium (CRDRC) was established in 2013 by the Huazhong University of Science and Technology. Over 20 universities are involved in research efforts, collaborating and enhancing the research base for rare diseases in China through the establishment of a rare disease registry and focusing on research and development of therapies for rare diseases. The CRDRC is a member of the wider International Rare Diseases Research Consortium.^{35 53}

“IRDiRC is focused on exponential improvement in the efficiency and effectiveness of rare diseases research, diagnosis, and treatment. The increased participation of global partners in this endeavor is key to the goal of a true international rare diseases research community and improved health of rare disease patients worldwide.”

International Rare Diseases Research Consortium (IRDiRC)

Ensure sustainable access to diagnosis, treatment and care

Inequalities in access to treatment and care must be reduced

Efforts to reduce inequalities in access to care and treatment will require strong political will in light of limited resources.^{12 31 35}

Access to treatments and care are often restricted to those who can afford to pay for their care or those able to travel to receive expert advice.^{1 54} Inequalities in access such as these are regularly seen within countries as well as between countries,^{24 36 37} driven by limited availability of specialists and differing regulatory and reimbursement processes. (See **Sections 2 and 3**)

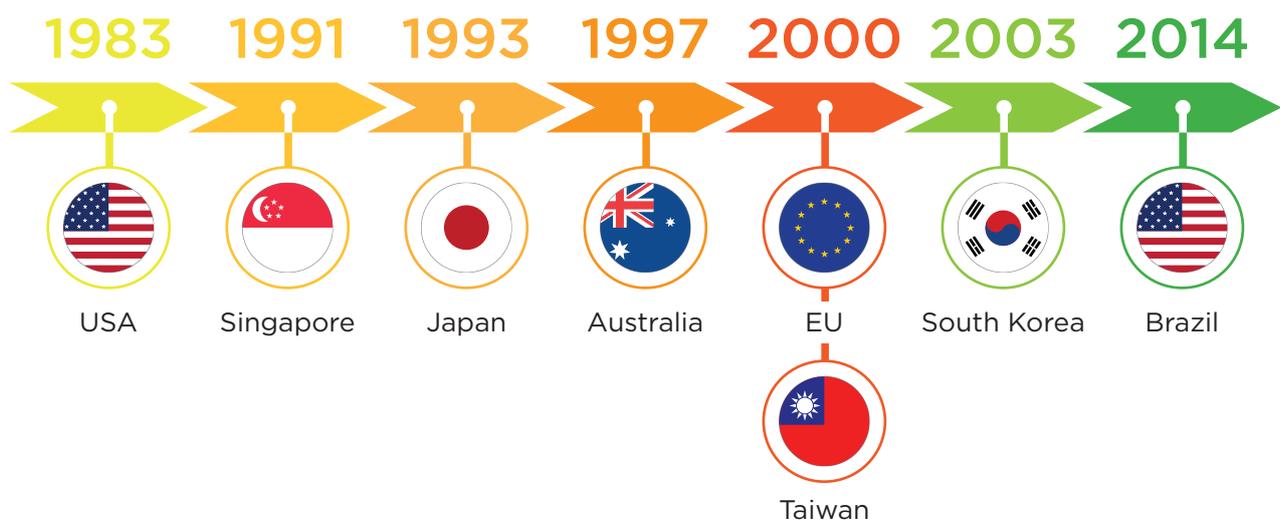
Legislation is required to continue to increase access to orphan drugs

It is important to develop orphan drug and rare disease legislation in countries without such frameworks, and to strengthen and improve existing regulatory processes - particularly as our understanding of rare diseases increases.^{34 55}

The Orphan Drug Act of 1983 in the United States of America was the first piece of legislation to recognise the lack of treatments for rare disease patients and the urgent need to prioritise these diseases in drug development.¹⁸ A number of countries have followed suit with legislation and incentives, (**Box 2**) which have led to significant improvements in treatment options for rare disease patients.

BOX 2 -

Orphan drug legislation timeline



Other countries are actively promoting regulation of rare diseases and orphan drugs. For example, many countries in south east Asia are in the process of drafting legislation.²⁷ However, many countries across the globe are still lacking legislation or even definitions for rare diseases.

Investment in the health workforce and infrastructure for rare diseases is needed

Limited expertise and infrastructure for the diagnosis and management in rare diseases is a continuous challenge for rare disease patients.

To decrease inequalities in access to treatment, it is essential to invest in the health workforce and support specialisation in rare diseases and genetics in every country.^{10 31 35} Additionally, improving physical resources for the diagnosis and management of rare diseases, such as genetic testing, newborn screening and pathology, may improve the diagnosis and prevention of rare diseases.^{10 31 35}

“Advocacy should not just stop at legislation. Patients and advocacy groups need to continuously push for greater awareness, better understanding of treatment inequalities and demand continuous improvements and investments in care from national and regional decision makers.”

Advocacy Service for Rare and Intractable Diseases' stakeholders - ASrid Japan

THE WAY FORWARD

“Collaboration between national and international patient organisations, research groups and international players, like the United Nation and the World Health Organization, can help support every country, regardless of size, wealth or health service development, to include rare diseases in their agenda.”

Dr Durhane Wong-Rieger, Rare Diseases International

In recent years, there have been significant advances in the understanding and treatment of rare diseases, and patient advocacy has been central to these developments. Despite this progress, much work still needs to be done to reduce the unmet needs of patients and their families.

Many policymakers may not be aware of the various challenges faced by patients to obtain a diagnosis or adequate treatment. Awareness raising efforts are essential to ensuring that rare diseases are seen as a key public health priority.

Access to treatment remains a key issue for rare disease patients across the globe, and stakeholders must work together to establish rare diseases as a global priority on the health agenda and increase equitable access to treatment and care.

Existing knowledge and understanding of rare diseases must be shared. Collaboration between all stakeholders is critical to make the best possible use of existing understanding and ensure that efforts are not duplicated.

The unique expertise and insights provided by patients should be integrated into research and policies, allowing patients to help shape the decisions and policies to meet their specific needs.

Enabling legislation to facilitate the development and access to orphan drugs must be continued. Regulatory processes should continue to be improved and efforts are needed to reduce inequalities in access to treatment and all aspects of care.

Rare diseases are a key health challenge that should not be ignored. A supportive global, regional and national policy environment is essential to ensure that patients receive the high-quality specialised diagnosis, care and support that is essential to manage their condition - and to offer the 95% of patients who still have no treatment options available to them a chance at improved outcomes and better quality of life.

ABOUT IFPMA



IFPMA

IFPMA represents research-based pharmaceutical companies and associations across the globe. The industry's 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

The IFPMA Rare Diseases Working Group was established to recognise the importance of addressing the unmet needs in rare diseases around the world. It aims to support the rare disease community through focused activities in four critical areas: awareness, incentives, partnerships and access.

The vision of its members is to promote equitable and timely patient access to the tools and solutions that are essential for the management of rare diseases. Based on shared experiences, Members propose guiding principles to inform and help improve the policy environment to enable better care for all rare disease patients.



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