ECONOMIST IMPACT

Universal health, rare diseases and the promise of the UN Resolution

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Contents

About this report

Universal health, rare diseases and the promise of the UN resolution is an Economist Impact report, supported by Sanofi. It examines current rare-disease policies and management in Germany, Spain and the UK. It describes the performance in these countries from a health-system perspective and, more importantly, from the perspective of those living with rare diseases, their families and caregivers. It contains insights from desk research, a literature review, and in-depth interviews with a range of global and national-level experts, including those involved in the development of a landmark UN resolution on rare diseases. It concludes with a call for collaborative action from patient advocates, bio-pharmaceutical companies, researchers, healthcare professionals and policymakers to accelerate change and optimise the health and wellbeing of people with rare diseases. We could not have developed the research without the input and support of key experts (in alphabetical order):

- **Lieven Bauwens**, Director at Child-Help International and Former Board Member of EURORDIS (until 2021), Belgium
- **Yann Le Cam**, Chief Executive Officer of EURORDIS- Rare Disease Europe, France
- **Tanya Collin-Histed**, CEO of International Gaucher Alliance, UK
- **Dolores Cviticanin**, Public Affairs Manager at Rare Disease International, Belgium
- **Daniel De Vicente**, President of ASMD Spain, Spain
- **Dr Christine Lampe**, Director of Centre for Rare Diseases, University Hospital of Giessen, Germany
- **Nick Meade**, Head of Policy at Genetic Alliance UK, UK
- **Oriol Sola-Morales**, Chair of Health Innovation Technology Transfer (HiTT) Foundation, Spain
- **Sheela Upadhyaya**, Consultant, Former Rare Diseases Strategic Advisor at NICE, UK

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Executive summary

On an individual basis, rare diseases (RDs) can affect relatively small numbers of people. Collectively, however, they wage a significant burden—there are over 7,000 RDs and together they affect 300m people globally. The impact of RDs extends beyond their prevalence, stunting economic development the world over; although evidence on the economic burden in Europe is scarce, to provide perspective, in the US the annual costs of 15.5m people with 379 RDs equates to over US$1trn, with inpatient care and prescription medications driving 50% of total direct costs (US$449bn). Despite this, RDs continue to be relatively neglected. For bio-pharmaceutical companies, the development of treatments for relatively small populations is often not economically viable, at least not at the prices that health services are accustomed to pay for new treatments. Meanwhile, policymakers struggle to allocate resources for specific RDs, meaning that patients face a range of challenges from securing accurate diagnosis to accessing treatment and to receiving additional support, such as psychosocial care. Put simply, even in the high-income countries of Europe, people affected by RDs face an array of health, social and economic barriers that many other patients do not.

This report seeks to both assess the RD landscape in Western Europe (focusing on RD burden, health-system infrastructure, time to diagnosis, treatment access, RD awareness and care coordination in three European countries: Germany, Spain, and the UK), to highlight progress, while evaluating existing barriers and working towards solutions and action points. Although our assessment of the specific issues in the select three countries backs up much of the evidence that reveals the broad issues highlighted above, it also reveals country-specific issues and variation in areas such as diagnosis, treatment access, social support, and treatment development and approval. All three countries discussed in this paper have made progress, yet all are affected by serious issues that must

be resolved—and all must embrace a collaborative approach that links stakeholders (notably government, policymakers, bio-pharmaceutical companies, scientific and medical experts, and patients) and crosses borders.

The UN Resolution on Rare Diseases adopted in 2021 provides a base from which health systems can not only combat the challenges and inequities faced by RD patients and their caregivers and families—it also provides an opportunity for policymakers to expand the provision of universal healthcare within their countries and health services.

We recommend the following actions in relation to the UN Resolution on Persons Living with a Rare Disease:

- **Prioritise diagnosis, giving children with RDs a better start to life**
- **Better integrate RD management into existing healthcare structures**
- **Enhance the patient voice in decision-making, including for individual patients and patient-advocacy groups**
- **Improve the codification of rare diseases both nationally and internationally**
- **Expand and enhance international collaboration and collaborative research networks**
- **Ensure equitable access to available treatments**
- **Unravel the cost of inaction**

Although the three countries covered in this report have made progress pertaining to these recommendations, there is plenty to be done. They must ensure that political commitments set out by the UN Resolution yield ground-level progress. Meanwhile, it is time for patient advocates, bio-pharmaceutical companies, researchers, healthcare professionals and policymakers to work better together—only collaboration will encourage broad acceptance and implementation to ensure that those impacted by even the rarest RDs are not left behind.

Background

Rare diseases: Individually rare, collectively common

A rare disease (RD) is a condition with distinct signs, symptoms and findings that affect fewer than or equal to 1 in 2,000 persons living in a WHO defined region of the world.[1] Despite their individual rareness, RDs, which include, but are not limited to, rare forms of genetic disease, cancer, infectious disease, poisonings, immune-related disease, idiopathic diseases and undetermined conditions, are common and substantially impactful. With over 7,000 classified RDs, the collective epidemiological burden is large, accounting for 300m persons living with a rare disease (PLWRD) globally and 30m in the European Union (EU).[2,3] Despite this vast number, RDs continue to receive limited attention as a health priority. For instance, cardiovascular diseases affect 49m people living in the EU; and HIV affects over 2m people in Europe, equating to less than 10% of the RD burden, yet they remain higher health priorities among policymakers.[4,5] Until last year, the International Classification of Diseases (ICD), a global disease codification system managed by the WHO that facilitates the monitoring of diseases and supports evidence-based decision-making, only accounted for five RDs.[6] Since then, recognition of RDs has improved: the latest iteration, ICD-11, includes 5,500 RDs, however the tool far from captures all known RDs which currently equate to over 7,000.[7]

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Despite remarkable advancements in RD drug discovery, treatments are often centred around managing symptoms.[8] RD symptoms are complex and chronic, ranging from a physical loss of function to cognitive and communication impairments, therefore PLWRD require greater healthcare resources.[6,9] The cumulative effects faced by PLWRD and their caregivers impact quality of life, increase economic burden and cause a significant mental health burden.[10,11] A survey conducted by EURORDIS, a non-governmental organisation (NGO), found that 58% of caregivers were absent from work over 15 days each year and 70% had to halt or reduce employment.[12] The caregiving burden heavily falls on women—mothers make up 64% of primary caregivers for PLWRD.[13]

The societal disadvantages faced by PLWRD and their caregivers circle back into society, reducing productivity and labour force participation.[14]

The caregiving burden heavily falls on women—mothers make up 64% of primary caregivers for PLWRD.

Although difficult to estimate with great certainty, the economic burden of RDs is estimated, on a per patient per year basis, to be 10 times higher than that of common conditions such as diabetes, cardiovascular disease, back pain, Alzheimer's and arthritis.[15,16] A US study estimated that the yearly cost for 8.4m people impacted by 373 RDs amounted to US$2.2trn.[16] This figure alone does not capture the true extent of the economic burden of RDs as it omits the inefficiencies, for instance delayed diagnosis and unnecessary examinations/treatments, within health systems.

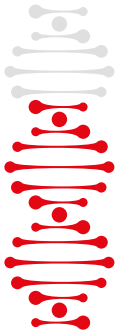
Although the unmet needs of PLWRDs are now better recognised, this awareness must now yield action, motivated by the cumulative health, societal and economic consequences of RDs.

The unique challenges faced by PLWRD

PLWRD continue to face unique challenges which unjustly result in poorer health outcomes and quality of life for both them and their caregivers. People face years waiting for a diagnosis, a deficit in RD awareness of among healthcare professionals, poor access to specialist care and treatment, and fragmented healthcare systems.[17]

A central challenge for the improvement of overall management of RDs remains timely and accurate diagnosis, which is pivotal to ensuring that PLWRD have access to appropriate care and treatment. However, in 2009, a survey of 12,000 PLWRD across 17 European countries revealed that around 25% of PLWRD wait 5-30 years between early symptoms and diagnosis.[18]

The diagnostic odyssey can face a challenging start with primary care physicians, who report lower RD awareness than paediatricians and other specialists.[19] Lack of RD knowledge amongst healthcare professionals causes delayed diagnosis and even misdiagnosis, and ultimately prolongs the journey towards effective treatment.[19] Furthermore, primary care physicians lack awareness of key RD information resources including Orphanet, the international RD database.[20] The lack of RD awareness amongst healthcare professionals, coupled with the time constraints they face during medical consultations, can lead to missed



70%

of RDs are genetic

therefore symptoms can manifest as early as childhood, meaning that affected individuals are early users of the healthcare system[27]

opportunities for PLWRD. Overall, there is a need to strengthen RD awareness and medical training for all healthcare professionals.

Newborn screening (NBS) is an important tool in the detection of RDs. It enables RD detection in infants, allowing for early intervention, ultimately helping to reduce the chance of severe disability and mortality.[21,22] However, the use of NBS in the detection of RDs is insufficient and varies greatly within and between European, with countries like Italy screening for as many as 45 diseases, while Romania and Cyprus only screen for 2 diseases nationally.[23] The disparities in NBS across nations are partly due to limited political alignment and budget allocation.[24] In some instances, RD diagnosis can occur as early as the prenatal stage; however, sometimes the prospect of healthy life outcomes is so poor that clinicians may advise on termination of pregnancy, which comes with ethical considerations.[25] For instance, the prenatal diagnosis of neural tube defects has seen an upward trend in termination of pregnancies in England and Wales, despite efforts to promote the uptake of folic acid supplements.[26] Overall, prenatal diagnosis and NBS have led to improvements in the detection and diagnosis of RDs.

The unique healthcare challenges faced by PLWRD do not stop at diagnosis; instead, treatment hurdles persist. While countries within the EU benefit from the standardisation of orphan designation and marketing authorisation by the European Medicines Agency (EMA), access to orphan drugs and/or technology (those used to treat, prevent or diagnose an RD) usually fall upon individual member states, who each have different health technology assessment (HTA) processes and evidence thresholds, resulting in access-related inequities within and between European countries.

Navigating healthcare delivery systems remains a prominent challenge for PLWRD. Firstly, 70% of RDs are genetic, therefore symptoms can manifest as early as childhood, meaning that affected individuals are early users of the healthcare system.[27] Secondly, the period from childhood to adulthood is often a critical time, as not only do PLWRD experience the changes accompanied with the biological transition, but they also often face a disruption in healthcare delivery as they move from paediatric to adult services.[28] Uncoordinated care leads to poor and unjust outcomes, such as fatigue, loss of earnings and travel costs, disruption to school and work, and a higher emotional burden.[29] The extent of such challenges also varies between patients—for example, the impact is magnified for ethnic minority groups who are more likely to experience difficulties in accessing healthcare and research, greater financial trouble, and poorer health outcomes.[30]

The Covid-19 pandemic also exacerbated the existing challenges faced by PLWRD and their caregivers, due to factors including patient vulnerability, care access and cancellations, and disruption to NBS.[31,32,33,34] That said, the digital shift driven by the pandemic enabled PLWRD to receive virtual medical consultations, access medicines via e-prescriptions and receive medical treatments such as infusion therapy at home.[33,35]

The promise of the UN resolution: a global ambition

"Leaving no one behind" is the fundamental, transformative promise of the UN Sustainable Development Goals (SDGs) agenda, and that includes PLWRD and their families. In December 2021 the UN General Assembly adopted the first-ever resolution recognising the needs of 300m PLWRD globally.[36] It calls for the end of discrimination of PLWRD, as well as addressing

disparities in access to health and education, poverty, and gender.[37,38] Since the adoption of the UN resolution, many more countries have begun developing new and updating existing national policies and plans to address the challenges faced by the RD community.

In this report, Economist Impact describes the current system performance of three select European countries—Germany, Spain and the UK—in addressing the four required priorities to improve the management of RD including: timely diagnosis; access to specialist care, treatment and drugs; increased awareness of RDs; and better coordination of care. We draw particular attention to best-practice case studies that serve as an example of success. We also explore how the UN resolution, with the SDGs as a backdrop, can be a catalyst for change, setting out clear recommendations to mitigate the impact of RDs on individuals, families and societies.

Rare disease management in Europe

The myriad healthcare challenges faced by PLWRD and their families result in disproportionate health inequities. In this section we describe the system performance of RD management in Germany, Spain and the UK, including country-specific challenges, strengths and areas for development.

Germany

RD burden

There are more than 4m PLWRD in Germany, accounting for just over 10% of the European RD burden.[39] A cost-of-illness study looking at the cost of non-cancerous RDs found that annual treatment costs increased in step with the rarity of the disease, with annual drug costs ranging from €27,811 to €1.6m per patient.[40] While these figures appear to be significantly costly, expenditure on orphan medicinal products constituted to less than 8% of total pharmaceutical expenditure and accounted for just 1.08% of total healthcare expenditure in Germany in 2017 (latest available data).[41,42] As in other countries, the burden not only lies with the cost of drugs but also in indirect costs incurred along the care journey.

Healthcare system and RD infrastructure

Germany has a social insurance-based healthcare system, where health insurance is mandatory and coverage near-universal.[43] Germany spent €390.6bn on health in 2018, which corresponds to 11.7% of GDP. Per-capita health expenditure is the third highest in Europe and cost-sharing remains low, with only 13.6% of health spending coming from out-of-pocket payments.[43]

Health technology assessment (HTA) in Germany is centralised at national level, with leading HTA agencies including IQWiG and G-BA tasked with evaluating all new drugs entering the market in Germany.[44] IQWiG and G-BA have strict evidentiary standards based on head-to-head RCTs that also apply to orphan drugs; only in isolated cases non-interventional studies including real-world data trials are considered. Companies can also be obliged to carry out registry based non-interventional studies of orphan drugs.

Germany is part of the European Reference Networks (ERNs), which were launched in March 2017 to facilitate multidisciplinary discussion between healthcare providers and researchers on RDs and conditions that require highly specialised treatment.[45] There are currently 24 ERNs, enabling information and knowledge exchange across a range of thematic issues such as bone and metabolic disorders.[46]

Time to diagnosis

According to the International Rare Disease Research Consortium, known RDs should be diagnosed within a year.[47] However, in Germany, PLWRD experience diagnostic

delays of up to six years.[48] A recent survey of 166 PLWRD in Germany, found that most participants had endured seeing up to 38 medical specialists before receiving a correct diagnosis.[48] Participants also felt stigmatised by medical professionals—for example, doctors referred to symptoms as psychological issues when they were unable to make a diagnosis. Women seeking RD diagnosis often felt that doctors "blamed" their hormones for their symptoms, while neglecting other possible diagnoses.[48] Marginalisation and stigmatisation of PLWRD results in missed opportunities for diagnosis, subsequently preventing access to treatment and causing a negative impact on the quality of life.[49]

Germany provides NBS for a total of 19 congenital diseases, far less than other European countries (Italy currently screens for 48 RDs).[50] However, a National Strategy for Genomic Medicine launched in 2019 includes building a national genomic data centre that aims to streamline whole-genome sequencing and eventually diagnosis of RDs in newborns.[51,52] This means RDs may be more likely to be detected early and treated in a timely manner.

The National Action Plan for People with Rare Diseases recognises the priority of a timely diagnosis and aims to both accelerate diagnosis for RDs and develop strategies to address unclear or incorrect diagnoses.[39] Policymakers will need to consider specific interventions to address early barriers to diagnosis in terms of the RD knowledge and awareness deficit.

Treatment access

Following diagnosis, PLWRD face several obstacles to accessing specialist care. These include finding the right specialist and accessing appropriate treatments.[53] In Germany, there is an absence of clinical guidelines for many RDs, which can increase misdiagnosis and limit treatment access.[39,54]

Moreover, treatment is available only for around 5% of the 7,000 RDs classified by the National Institutes of Health (NIH), partly due to RDs being under-researched.[2,3,55] Germany has a less centralised system than the UK and Spain—31 specialised RD centres across the country have the autonomy to spearhead local initiatives to improve RD diagnosis and management.[56] These centres are organised across three tiers: Tier A centres, normally based within a university hospital, focus on individuals that have not received a clear diagnosis and are tasked with organising further care; Tier B centres specialise in certain diseases; and Tier C specialise in specific RDs and provide care closer to home. There is scarce monitoring and evaluation to understand how well this system works.

The introduction of the EU Regulatory Framework governing orphan drugs has been pivotal in driving momentum towards RD drug discovery and development.[57] When assessing orphan drugs entering the market, Germany grants automatic full reimbursement without requiring a full HTA for the new treatment or drug, with additional benefits of the orphan drug being assumed.[44] Price negotiation takes place during the year after the drug enters the market. This means that new treatments enter the market very quickly, providing patients with

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Christina Lampe, Director of the Centre for Rare Diseases at the University Hospital of Giessen

faster access in as little as 3 months from market authorisation.[58] Recent legislative changes are pointing towards a tighter landscape in the future, meaning that a full HTA dossier and a new round of negotiations will apply if annual turnover revenue exceeds €30m, instead of €50m previously.[59]

Given the lack of approved therapies, treatment is not limited to orphan drugs, but should also encompass alternative therapies such as speech therapy and physiotherapy.[60-62] "In order to achieve good care, you need the combination of treatment [such as drugs] plus symptomatic treatment [such as rehabilitation]," says Christina Lampe, Director of the Centre for Rare Diseases at the University Hospital of Giessen. However, a cumbersome referral process means that PLWRD face longer waiting times to receive such treatments, potentially leading to a deterioration in symptoms. "In Germany I don't have a problem prescribing rehab or physiotherapy, but I don't have a specific [treatment] code for RDs, so I spend a lot of time explaining the reason for referral through letters and discussions with health insurance providers," says Dr Lampe. "This differs from Italy, where they have a database that includes RD codes. With that code, I wouldn't have to discuss everything from scratch."

BEST-PRACTICE CASE STUDY: ACCESS TO ORPHAN DRUGS

Germany is a European and global leader when it comes to reimbursing orphan drugs. Unlike other countries that must go through lengthy reimbursement processes for new orphan drugs, Germany provides automatic reimbursement. This means that Germany has the shortest delay between authorisation and reimbursement. PLWRD living in Germany have the greatest access to new drug treatments, which is particularly promising, as less than 5% of RDs have approved treatments.

RD awareness

RD awareness remains a key challenge within the German healthcare system. A recent survey conducted found that only 12% of German primary care physicians felt confident in managing patients with RDs and 62% felt that the internet was the most commonly used source of information on RDs.[56] "Whilst it may be unrealistic to know all 7,000 RDs, we must improve public and physician awareness of at least the treatable ones, and there is still a big gap in this area," says Dr Lampe. She goes on to explain that low levels of awareness have also been fuelled by a generally low level of philanthropic spirit in the country, making it difficult for patient advocacy groups to raise the profile of individual RDs.

To address this lack of awareness, the National Action League for People with Rare Diseases (NAMSE) was founded in 2010 by the Ministry of Health, the Ministry of Education and Research, and the Alliance for Chronic Rare diseases. A three-year consultation with various stakeholders subsequently yielded a National Action Plan for PLWRD, consisting of 52 action points.[39] The action point "information management" aims to increase RD awareness among both the public and experts, and improve the level of information available to (and accessed by) PLWRD and their networks, as well as to improve the training and education of health and care workers.[39] Patient advocate organisations such as the Alliance for Chronic Rare Diseases have been heavily involved in raising the profile of RDs and supporting the needs of PLWRD.[63]

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Care coordination

Lack of coordinated care is a key challenge for RD management in Germany. A recent survey of primary care physicians revealed that 53% had no knowledge of any RD centre in the country, which prevents many PLWRD from receiving timely and coordinated care.[56] For many adolescents with RDs in Germany, the transition period from paediatric to adult healthcare services creates additional challenges in care coordination. Despite the country moving towards a structured transition pathway, one study found that 12 of 286 adolescent PLWRD placed on structure-transition pathways led by designated care coordinators were unable to transfer from paediatric care, as no adult specialists were identified for their needs.[64]

ERNs have been a key resource in knowledge sharing and coordination. "When I see only one or two patients [with an ultra-rare disease] and I have no idea what to do with the patient, I can ask another expert, so we can collect quite a lot of information in a very simple way," says Dr Lampe, adding that the ERNs help to set standards of care and safety. However, Dr Lampe also emphasises that ERNs are underfunded and rely on the voluntary participation of (usually time-poor) specialists. There are further issues with integration into the German healthcare system. First, conflict can arise between national responsibility and cross-border availability of healthcare services. Second, ERNs are harder to establish in EU member states where implementation of national RD action plans for people is lagging behind.[65]

In 2017 The TRANSLATE-NAMSE project implemented measures proposed in the National Action Plan for Rare Diseases through integrating national experts on case management and enabling providers to access data from the nine RD centres involved in the project. Evidence suggests that primary care physicians have subsequently been satisfied with the level of communication between the centres and themselves.[56] As such, TRANSLATE-NAMSE has had a positive impact on care; its structures have since been recommended for introduction across the healthcare system to further enhance care for PLWRD.

Spain

RD burden

As of 2021, Spain accounts for around 3m PLWRD, representing about 10% of the European RD.[53] Whilst surveillance data provides a comprehensive perspective on the epidemiological burden, the economic burden is less well studied for RDs collectively. At a specific disease-level, a study published in 2016 found the annual estimated cost of disease for a patient with Prader-Willi syndrome, a rare genetic condition that causes a range of physical symptoms and learning disabilities, ranged from €3,937 to €67,484, with direct non-healthcare costs making up the majority.[66,67] A study published in 2017 exploring the quality of life and socioeconomic impacts on people with spinal muscular atrophy (SMA), a genetic disease and neuromuscular disorder, found that non-direct healthcare costs amounted to about a third of the total.[67]

Healthcare system and RD infrastructure

Spain's National Healthcare System was founded on the premise of providing universal health coverage (UHC) and free healthcare access; it is predominantly financed through taxes with budget allocations to different regions of the country. Spain also has a decentralised HTA system. For example, manufacturers are asked to submit cost-effectiveness evidence at both the national and regional levels.[68] The Spanish Agency for Evaluation of Medicines and Healthcare

"I started developing symptoms when I was six months old but was only diagnosed at age 36."

Daniel De Vicente, president of ASMD Spain

Products (AEMPS) conducts clinical HTA of new drugs alongside that of 17 autonomous regions.[69] While the Ministry of Health negotiates the price of drugs, the final decision on pricing and reimbursement (P&R) lies with the Interministerial Committee for Pricing where regions are also involved in the decisions, which primarily uses criteria including therapeutic usefulness, budget impact and cost-effectiveness.

Time to diagnosis

Spain faces significant challenges when it comes to timely RD diagnosis. As in Germany, the average delay between symptom onset and correct diagnosis is six years.[47] Yet the diagnostic odyssey can vary significantly from person-to-person. "I started developing symptoms when I was six months old but was only diagnosed at age 36," says Daniel De Vicente, president of ASMD Spain, a patient advocacy group.

BEST-PRACTICE CASE STUDY: RD DIAGNOSIS

In response to regional differences and delayed RD diagnosis of rare diseases, Spain has taken significant, pragmatic steps. The development of the Spanish Undiagnosed Rare Disease Programme (SpainUDP) has introduced a more centralised, multidisciplinary approach to RD diagnosis. It primarily supports the diagnosis of unknown RDs through whole exome sequencing methods and in doing so promotes the visibility of people with these conditions. Once patients enter SpainUDP, they are also supported to access appropriate healthcare services. To date, the programme has approved 335 applications, with 83 receiving diagnosis; the remainder are currently under review. SpainUDP is part of an international RD research collaborative, incorporating European projects RD-Connect and Solve RD, the Undiagnosed Diseases Network International, and the MatchMaker Exchange platform.

Part of Spain's diagnostic challenges lie in the paucity of NBS. Currently, only seven RDs are subject to nationwide screening.[70] Beyond these, different clinics and programmes can expand their RD screening capabilities, resulting in regional variations; between seven and 39 RDs are currently screened across Spain.[70-72] There are 21 screening centres in Spain - all of which are public. However, some Spanish regions have more laboratories than others, resulting in some centres screening up to 100,000 samples a year while others sample less than 10,000.[73] These disparities are particularly salient for the RD community, as more than 70% of all RDs have paediatric onset.[74] Nonetheless, Spain has taken strides to address diagnostic challenges by expanding its research infrastructure. For example, it participates in RD Connect, which allows for the analysis of DNA sequencing data while linking it to patient reported symptoms; driving RD knowledge and awareness.[75]

More generally, Spain has a noticeably unequal distribution of healthcare infrastructure. Urban areas tend to have a higher density of services, which can exacerbate urban-rural structural disparities and widen RD-linked inequities.[76]

Treatment access

Spain has seen a general increase in RD infrastructure, which includes 21 screening clinics and 52 centres with RD specialisations.[47] The most comprehensive treatments are concentrated in the more developed areas of Spain, such as Madrid, Catalonia and Andalusia.[77] This has negative consequences on PLWRD—one survey revealed that most RD patients had to travel outside of their region to access care, and 17% lacked treatment because they could not travel.[78]

Of EU-authorised orphan drugs between 2018-2021 (total 61 orphan products), 51% reached Spain (31 orphan products), but only 52% of the products in Spain have full public availability without any restrictions to the patient population, while 48% have limited

availability.[79,80] The latest figures from the health ministry indicate that the current time to reimbursement for orphan drugs increased by 10 months between 2021 and 2022, reaching 34 months. The regional disparities inherent in the decentralised reimbursement process often result in unequal distribution of drugs across different regions, giving rise to further access-related health inequities for PLWRD.[81] Limited treatment access can worsen symptoms and further increase the need for care, thereby increasing the socioeconomic burden.[82]

Access to the appropriate treatments remains a key challenge for physicians. In one survey, 45% of physicians felt that the lack of available drug treatments is a key challenge to RD management, and 22% reported that difficulties accessing new, as-yet unlicensed drugs (or those only available overseas) is a key challenge.[83] However, according to the 2023 Annual State Regulation Plan, the government is looking to standardise HTA processes across agencies, with scientific assessment and consultation set to include patient engagement as part of an independent and transparent process.[84] This should be a positive step towards improving equitable access to orphan drugs.

Access-related challenges faced by PLWRD extend beyond treatment to include poor access to mental health, physical and occupational therapy, adaptation of housing, personal support, education, labour-market integration.[82] These challenges have wide-ranging repercussions for PLWRD, increasing financial strains for families, worsening health outcomes and widening the gap in equitable integration into society.[54] However, policymakers in Spain are taking positive steps. In February 2022 the former health minister, Carolina Darias, announced that Spain is updating its national RD strategy, including developing a clinical management IT platform and incorporating digital technologies that will facilitate patient access to specialist care and information within the ERNs, eroding location-based limitations.[54]

An additional barrier to access lies in the absence of formal recognition of clinical genetics as a healthcare speciality.[85] Clinical genetics provides diagnostic services and genetic counselling that is essential in providing support for PLWRD. Not formally recognising the field creates additional hurdles in the form of lack of knowledge and psychosocial support, and uncertainty for people already navigating the difficulties of living with their disease.

RD awareness

Patient advocacies such as the Spanish Federation of Rare Diseases (FEDER) are taking the lead in raising public RD awareness through advocacy, social and educational campaigns.[86] Yet poor RD awareness remains a key challenge among Spain's health workforce. One survey found that the main difficulties in primary care and hospitals when caring for RD patients stem from the lack of diagnostic guidelines, delay in diagnosis and uncertainty about where to refer patients for specialist care.[83] Part of the problem relates to primary care physicians' limited awareness—due to limited academic and professional training—of specialised services and infrastructure such as socio-health and referral centres.[83] Spain is not alone in facing this challenge. A recent study in Belgium revealed that 83% of GPs and 97% of paediatricians reported requiring additional information on RD.[19]

Lack of awareness among healthcare professionals does not just impact PLWRD to the point of diagnosis and treatment. "The problems we face are not only inequity and delayed diagnosis," says Mr de Vicente. "Rare disease patients experience social exclusion and discrimination, [and] their families can be very vulnerable, not only economically but also psychologically and socially." In one survey 43% of PLWRD reported facing stigmatisation and discrimination, primarily linked to interpersonal relations and healthcare and educational facilities.[78]

General public knowledge of RDs has gradually increased over time, in part thanks to high-profile stories in the media. Interestingly, the public tends to be in favour of proportional investment for RDs, seemingly recognising the increased complex needs that PLWRD face. This is a conviction that is not always shared by policy makers. "For payers, [one of] the main concern is how expensive orphan medicinal products can be, and how to keep within budgets if approved" says Oriol Sola-Morales, Chair of Health Innovation Technology Transfer (HiTT) Foundation.

Care coordination

According to the health service's Rare Disease Strategy (2009), comprehensive and multidisciplinary care as well as integrated health and social care are some of the key elements required to improve the management of RD patients.[87] The strategy recognises that PLWRD require a range of expertise spanning primary care, paediatrics and rehabilitation; therefore, a single coordination framework should be adopted. Furthermore, it recognises that PLWRD often face physical or psychological disability, necessitating greater educational, social and occupational needs throughout the life course and, ultimately, integration of health and social care services.[88] Although Spain has set out initiatives to improve the coordination of care for PLWRD, there is little evidence on the effectiveness of such initiatives, warranting greater monitoring and evaluation.

Spain's RD infrastructure has seen continual improvement, with 60 Referral Centres, Services and Units established by the Inter-regional Council of the National Health System.[89] These centres provide specialised care, support and information provided by specialist staff. The role of the CISNS, apart from acting as a coordinator between regional governments and the national administration, is to ensure equitable access to these centres throughout the country.[90] Spain is also well established within the ERNs. The health system is involved in 17 of the 24 existing ERNs, representing significant national commitment to international collaboration in RD management.[90]

Despite these strengths, RD patients and their families continue to suffer as they navigate through seemingly endless hospital appointments, re-telling their stories to different specialists and even receiving different diagnoses from different professionals. Elsewhere, intersectoral coordination between schools and healthcare services is essential in streamlining care pathways for children living with RDs, yet coordination between education professionals and health professionals is poor. This negatively impacts both the care of children and their families, who are forced to take on intermediary roles in communication.[91]

From a national perspective, policies have been in place to underscore the importance of improved coordination between health

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and social care. The National Health System Cohesion and Quality Law, passed in 2003, highlights the need for streamlined clinical pathways between acute and community services.[92] The challenge lies in percolating these policies into regional implementation. In 2022 the government started the review of the Law on Equity, Universality and Cohesion of the NHS, which aims to implement a more centralised national health data space to fuel innovation and improve care coordination across the country, whilst also mandating the process of formal patient engagement within the key NHS decision-making bodies.[93]

United Kingdom

RD burden

There are currently around 3.5m PLWRD in the UK.[94] To date, it has been difficult to ascertain the true economic burden of RDs in the UK. However, a systematic review of cost-of-illness evidence found that RDs are associated with significant direct and indirect economic burdens.[95] Additionally, there are important hidden costs (both financial and psychological). A qualitative study led by Genetic Alliance UK, a charity, found that PLWRD consistently mentioned "time" as a cost, particularly in the absence of efficiently coordinated services.[96]

Healthcare system and RD infrastructure

The UK's National Health Service (NHS), funded by taxpayers, theoretically provides UHC in England, Wales, Scotland and Northern Ireland. The 1990s saw a devolution of healthcare services to Scotland, Wales and Northern Ireland, resulting in a divergence of policies. In terms of RD infrastructure, the government invested in an ambitious programme in 2012 to create a structured and efficient system to manage RD.[97] This system involves 76 Highly Specialised Services within the NHS that focus on patient care and empowerment and treat no more than 500 patients each year.[98]

The government published the UK Rare Disease Framework in January 2021, setting out a nationwide commitment to meeting the needs of PLWRD and their families. The framework outlined four main priorities: quicker final diagnosis, increased awareness among healthcare professionals, improved care coordination, and improved access to specialised care. Although the framework is a nationwide policy, each of the devolved nations have developed country-specific action plans to ensure that interventions are tailored to PLWRD and their families within each community.[99-101]

Despite being part of the UK, England, Wales and Scotland have their own HTA agencies, the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and the All-Wales Medicines Strategy Group. All three primarily base their appraisals on clinical and cost-effectiveness evidence. In England, orphan drugs are appraised by NICE and usually follow the highly specialised technology process for new drugs to treat ultra-orphan conditions or, more

BEST-PRACTICE CASE STUDY: GENOME UK AND THE 100,000 GENOMES PROJECT

The UK has positioned itself as a global leader in the diagnosis of RDs, partly due to its capabilities to conduct WGS, which gave rise to the 100,000 Genomes Project. The 100,000 Genomes Project was a five-year pilot project led by Genomics England that saw the sequencing of 85,000 genomes belonging to patients affected by RD or cancer. The project aimed to enhance research, uncover answers for PLRWD and make genomics a routine part of healthcare. Following its completion, it successfully led to 25% of participants receiving a new genetic diagnosis, of which 14% found variations in regions of the genome that would be missed by other methods. As part of the NHS Long Term Plan, the UK is rolling out WGS as part of routine care at the NHS England Genomics Medicine Centre, which will see the sequencing of 500,000 genomes, routine genetic testing for all cancer patients, early detection and treatment of high-risk conditions, and using genomic data in the development of new treatments, diagnostic approaches and patient decision-making.

commonly, the single technology appraisal for new drugs to treat orphan conditions. The SMC provides an "ultra-orphan pathway" for patients affected by ultra-rare diseases (defined as affecting less than or equivalent to 1 in 50,000 people).[102] If new products meet this "ultra-orphan" requirement, it will be made available on the NHS for at least three years, providing time to gather data on its effectiveness.

Time to diagnosis

The current average time between symptom onset and accurate diagnosis is five years, with at least half of the individuals receiving one misdiagnosis in this time.[103] The UK has taken positive steps in closing this diagnostic gap in the past ten years, primarily through the introduction of Genome UK, the largest genomic sequencing programme in the country. This programme has enabled an expansion of NBS, yielding improved targeted screening and early detection.[104] Nine conditions are systematically screened for, significantly lower than Germany (19 RDs) and Italy, which leads in this respect, screening for 48 RDs.[50] The UK has set out a clear set of actions to improve the time taken to diagnose a RD in England, in line with its priorities in the UK Rare Disease Framework (Figure 1).

Some programmes have already spearheaded the quest for faster diagnoses. A world-first study using data on the 100,000 Genomes Project

Figure 1: UK government action points to improve time to diagnosis in England[105]

Action 1: Improving RD screening processes and decisions around NBS. This would improve timely diagnosis, treatment and overall management of paediatric rare diseases.

Action 2: Whole genome sequencing (WGS) to screen for genetic conditions in healthy newborns. WGS could significantly increase the diagnosis of genetic conditions not currently covered by the NHS Newborn Blood Spot Screening Programme. Genomics England and NHSE/I are leading a programme to explore the benefits, risks and broader implications of newborn WGS

Action 3: Continuously develop the National Genomic Test Directory for the approximately 80% of rare diseases with a genetic origin. Genomic technologies can enable quicker diagnoses and match patients to the most effective medications and interventions. The NHS Genomic Medicine Service continues to support the implementation of the UK Rare Diseases Framework through a national network of seven Genomics Laboratory Hubs.

Action 4: Further develop the Genomics England clinical-research interface over the next year. Genomics England commits to further developing its clinical research interface so that when genomic researchers find information of relevance to an individual's health, it can be passed back to the NHS. This will support researchers and clinicians in collaborating to resolve complex or novel findings from genome data.

Action 5: Pilot new approaches for patients with undiagnosed rare conditions.

has demonstrated for the first time that WGS can uncover new diagnoses for people across a range of rare diseases and improve the overall diagnostic journey for patients.[106] The study looked at over 4,000 people from 2,000 families who were early participants in the 100,000 Genomes Project. It found that using WGS led to a new diagnosis for 25% of participants.[107]

Treatment access

Access to specialist care, treatments and drugs is challenging for PLWRD in the UK. Since Brexit, the UK has left the 24 ERNs, meaning that PLWRD in the UK no longer have access to this wealth of resources. "Prior to Brexit, we relied on European frameworks and ERNs for clinical expertise exchange," says Nick Meade, head of policy at Genetic Alliance UK. Since leaving the EU, says Mr Meade, his organisation "[continues] to be fully oriented towards our European partners, and we are looking to connect with organisations like Rare Disease International to work together and support people living with RDs". UK policymakers will need to build on the efforts of patient advocacy groups by aiming to reintegrate into collaborative healthcare networks, such as the ERNs, at the global level, to enhance resource sharing pertaining to the awareness, diagnosis and management of RDs.

Access to orphan drugs remains a key challenge across the UK as HTA criteria, decision-making processes, waiting times and outcomes differ across the constituent countries, resulting in regional inequities.[108] Between 2000-2016, 143 orphan products were authorised in the EU, yet just 47% were funded by the NHS in England, while Scotland funded 39% and Wales funded 33%.[109] Furthermore, in England the average time to availability (the days between marketing authorisation and the date of availability to patients) is 351 days, and in Scotland it is 428 days.[110] Between 2018-2021, there were no signs of improvement as time to availability was longer for both England (362 days) and Scotland (457 days).[58]

In the case of ultra-rare diseases, the SMC's "ultra-orphan pathway" allows faster access to ultra-orphan medicines for patients with ultra-rare conditions through a set criterion that uses a prevalence-based definition of ultra-rare conditions and offers a three-year period to gather evidence whilst concurrently providing access to patients and the opportunity to consult patients and clinicians on the approval of drugs.[111] England provides NICE's HST pathway, which also offers similar flexibility to accessing ultra-orphan products but with differing criteria.[112] Furthermore, NICE acknowledges the importance of the significant burden placed on the caregivers of PLWRD, thereby the HTA body includes the caregivers health-related quality of life measures within its economic evaluations for RDs.[113]

"Policymakers need to include RD [service] provision within the wider existing healthcare system, instead of providing separate provisions [for PLWRD]."

Sheela Upadhyaya, consultant and former Rare Diseases Strategic Advisor at NICE

Last year, NICE launched the Innovative Medicines Fund (IMF), which aims to overcome some of the delays resulting from the generation of clinical and cost-effectiveness evidence requirements for orphan drugs, meaning that patients in England are no longer required to wait for evidence submission to be completed and can instead benefit from faster access to promising treatments, whilst concurrently drug marketers collaborate with the NHS to gather real-world evidence to support further HTA evidence requirements.[114] While the IMF aims to provide faster access to orphan drugs and is generally well-received by key stakeholders such as patients and bio-pharmaceutical companies, its impact is yet to be fully evaluated. The Association of the British Pharmaceuticals Industry (ABPI) has expressed some early concerns about the IMF process which relates to the existing challenge of data collection for innovative treatments. In the current IMF, if sufficient data cannot be collected within 5 years to gain a positive NICE recommendation, then the responsibility to fund the medicine for a lifetime for patients accessing medicines in the fund inevitably lies with the manufacturer. This may pose as an unfeasible risk, particularly for SMEs (Small and Medium-Sized Enterprises), and potentially disincentivise the development of innovative treatments for PLWRD.[115]

PLWRD often experience multiple comorbidities, adding complexity when it comes to treatment; many needs often go unmet.[116] It is essential that such patients have access to a range of multidisciplinary healthcare services that can provide holistic treatment. Although the NHS provides UHC across the UK, some areas have poorer coverage and access.[117] In addition, service provision data is limited at the regional level, therefore it is difficult to ascertain the extent of inequities related to service access for PLWRD. Inequitable service provision remains a recognised problem for all patients living with disabilities, but it is more pronounced for PLWRD, who are susceptible to a multitude of complex needs.

It is pivotal to narrow the gap in inequities, striving for not only equitable healthcare access but also by addressing the social determinants of health. "Policymakers need to include RD [service] provision within the wider existing healthcare system, instead of providing separate provisions [for PLWRD]," says Sheela Upadhyaya, consultant and former Rare Diseases Strategic Advisor at NICE. Achieving this will not only require a top-down policy approach, but a bottom-up increase in awareness among healthcare professionals.

RD awareness

The number and complexity of RDs can be a major challenge when raising awareness among health workers. A recent UK study found that around 88% of patients perceived that healthcare professionals had limited knowledge of their condition and felt that they weren't taken seriously, which consequently impacted their mental health.[118] Health Education England, a public body responsible for health workforce education and training, has made concerted efforts to address this, recently launching a new online education hub aimed at health professionals to improve awareness, diagnosis and management of RD.[119] Additionally, non-profit organisations such as Rare Disease UK and Genetic Alliance UK are among many stakeholders that work to generate educational materials to increase awareness of RDs.[120,121]

The UK has seen improvements and growth in the awareness of challenges faced by the RD community through advocacy and policy. Patient organisations have been paving the way in raising the profile of RDs.[122] Although patient organisations such as Genetic Alliance UK do not collect extensive disease-related data, they do play a pivotal role in promoting awareness of RD research, as well as supporting inclusion of PLWRD in clinical trials and policy discussions.[123] The introduction of the UK's Rare Disease Framework in 2021 highlights the important role of patient advocacy groups in raising awareness of RDs. "The RD community is the stakeholder group that has been most involved in policy development" says Mr Meade. "The reason for this is because that engagement is useful for the civil service and because it yields the best outcomes".

Patient advocates also play a key role in empowering the RD community to be part of the wider policy dialogue. "When Sajid Javid was Secretary of State for Health, he had a round table with people living with rare conditions," says Mr Meade. "He had a few priorities, [of which] one was a disparity in health outcomes for people from minority communities. And so, we were able to collaborate with the Department of Health and Social Care to get a really representative sample of the community [including ethnic minorities] living with rare conditions in the UK into the room to talk to Sajid Javid and work with him." This process is critical to ensuring that PLWRD, who often face stigma, particularly those from ethnic minority groups, feel included in upstream and downstream decisions about their health.[124]

Care coordination

A seamless transition of care from childhood to adulthood is often not the case in the UK. Patients and their families can find themselves left to manage periods of uncoordinated care when transitioning from paediatric to adult services without the support of a designated care coordinator. One report found a lack of coordination between adult and paediatric services as well as between medical and social services.[125] Care should be long-term, coordinated through transition periods, across multiple sectors such as schools, and must consider the needs of PLWRD and their caregivers/families.[126] There are some examples of early progress pertaining to this, including the development of purpose roles such as Children and Young People Lead Nurses in hospitals to streamline clinical pathways.[127]

Furthermore, healthcare providers are required by NHS England to give an alert card to every RD patient, carrying important information about that patient's condition, considerations that need to be made when providing care to the patient and the contact details of their specialist. Yet many people living with rare diseases still do not have alert cards and often experience poor quality of care as an indirect result of poor communication and lack of data sharing.[128]

"Effective integration of rare disease needs into existing healthcare infrastructures, as we cannot build separate provisions, and we cannot accept provisions that do not cater for those needs."

Sheela Upadhyaya, consultant and former Rare Diseases Strategic Advisor at NICE

The importance of better coordinated care is recognised in the UK's Rare Disease Framework, which aims to build on the technological advancements, linked to telemedicine and electronic health records, that were implemented during the covid-19 pandemic. However, since the framework was introduced in February 2021, its progress is yet to be evaluated. The fragmentation of healthcare systems and services remains a key challenge that is multiplied for PLWRD, as they are often afflicted by several comorbidities and complex needs. Such challenges are supported by research that reveals that greater care coordination is required in instances of greater system fragmentation, clinical complexity and limited capacity.[129]

Coordination of care should also be tailored according to the unique needs of PLWRD. As such, PLWRD and their caregivers have an important role to play when it comes to coordinating care, recognised as a key commitment in the Rare Diseases Action Plan for England 2023.[130] Relating to her experience as former Rare Disease Strategist at NICE, Ms Upadhyaya says that care coordination in England must shift towards "effective integration of rare disease needs into existing healthcare infrastructures, as we cannot build separate provisions, and we cannot accept provisions that do not cater for those needs". Streamlining specialised clinical pathways as well as improving coordination between acute and social care should remain a priority for policymakers in the UK.

Leveraging the UN Resolution on Rare Diseases

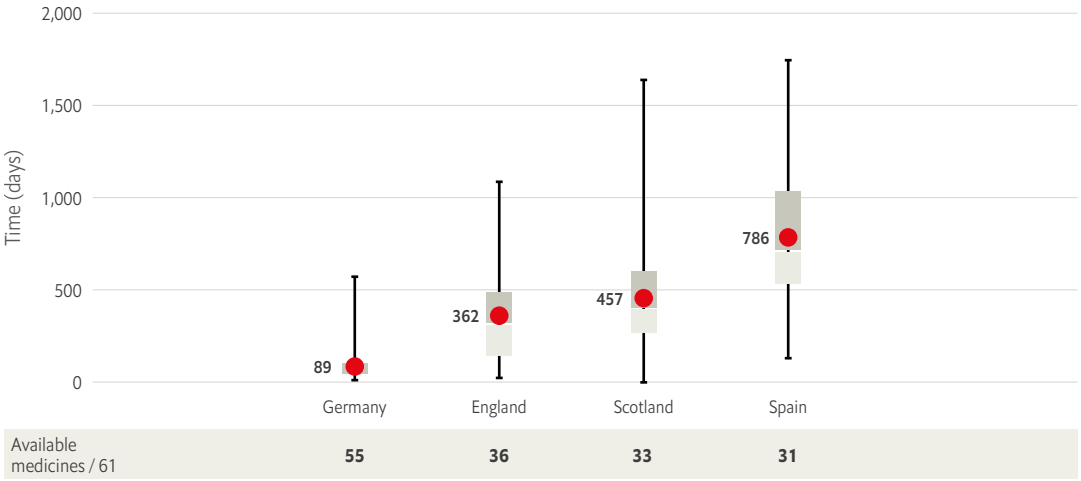
The landmark UN Resolution on Rare Diseases, adopted on 16 December 2021, calls to end the discrimination faced by PLWRD. It emphasises leaving no one behind and highlights synergies with the SDGs, including access to education, reducing poverty, supporting integration into society, and reducing inequities.

The Resolution signifies a significant step towards the recognition of PLWRD and their unique challenges and sets the precedent for policymakers across the world to make real change for the RD community. To do so, the Resolution can be leveraged in two overarching ways. The first is through its push for closer collaboration between the RD community and UN agencies—the WHO in particular has shown increasing interest in supporting global action to improve RD awareness, diagnosis and management.[130] The second is its role as a platform to encourage dialogue between patient advocacy groups and policymakers on how to achieve its commitments within specific national and international contexts.

Reaching for UHC

A primary goal of the UN resolution and the WHO alike is to advocate for UHC globally. Many countries in Europe, including Spain, the UK, Italy, Norway and Portugal, have seen real strides towards UHC, providing healthcare to all citizens regardless of their income.[131] But further local action is needed on RDs as PLWRD often face inequitable access to diagnosis and treatment within and between European nations, and for the latter, the current variations in HTA remain a key obstacle to ensuring equitable and timely access to available treatments (as reflected by EFPIA's WAIT indicator in Figure 2). The extent of these inequities has the potential to magnify beyond the three countries detailed in this report. For instance, in October 2020 the UK joined the ACCESS Consortium – a group of pharmaceutical regulatory authorities in Australia, Canada, Singapore, Switzerland

Figure 2: Orphan drugs time to availability (the days between marketing authorisation and the date of availability to patients)[58]



assessing the benefit-risk of innovative pharmaceuticals, and in 2022 HTA agencies in Australia, Canada and the UK had begun work-sharing on the value assessment of innovative pharmaceuticals.[132] Such multi-national strategic alliances have the potential to align HTA processes across these three countries allowing for an integrated regulatory and access strategy, evidence generation and reduced wait times for reimbursement. However, its uncertain what influence NICE in England would have over the HTA practices in other countries within the ACCESS Consortium.

There is still progress to be made to ensure that UHC is attainable for the entire global population including PLWRD. Although healthcare coverage is generally good across the EU, many countries continue to exclude certain vulnerable groups. For instance, in Germany, EU citizens who are unable to cover their living expenses are excluded from receiving statutory health coverage, with no alternative available.[133] Germany and neighbouring countries, including Belgium, Estonia and Sweden, also have separate funding mechanisms for asylum seekers, refugees and undocumented migrants, which often act as a deterrent to accessing healthcare, as migrants feel they will be reported to immigration authorities.[133]

From a promise, to scaling national implementation

The challenge now lies in translating the political commitments of the UN Resolution into ground-level implementation within national healthcare systems and the wider rare disease space. "The UN resolution can be used as a roadmap to life, it's about education, it's about access to healthcare, access to the built environment and representation within the policy environment," says Mr Bauwens. This highlights the importance of

"The UN resolution can be used as a roadmap to life, it's about education, it's about access to healthcare, access to the built environment and representation within the policy environment."

Lieven Bauwens, Director at Child-Help International and Former Board Member of EURORDIS

not only strengthening health systems but also addressing the wider social determinants of health.[134]

Given the wide scope of the UN Resolution, governments and policymakers will need guidance with implementing reforms. Some of the challenges that the Resolution highlights can be partly addressed by multistakeholder collaboration including other UN agencies, says Dolores Cviticanin, public affairs manager at Rare Disease International: "The Resolution actually falls within the scope of implementation of agencies such as UNICEF, UNDP and UN Women". These agencies can monitor and evaluate progress of elements of the Resolution within their operations at the national level, benchmarking countries' progress against best-practices.

In addition, several processes that can be put into place by policymakers at the national level would yield improvements in RD management. These include comprehensive codification of RDs by implementing the ICD-11 to detect and manage conditions that are currently "invisible", sharing best practice on NBS, and integrating centres of expertise into the ERNs. All of these action points require national willingness and international collaboration. Currently, only a fraction of RDs are codified in healthcare systems.[135] Policymakers at the national level should perform an analysis of the number of RDs currently coded, which would shed light on the diseases that are not being traced, allowing healthcare systems to improve their clinical pathways and their impact on specialised healthcare services. In turn, this will mean improved recognition for PLWRD, enrolling many into services to access the support that they need.

The ERNs represent a clear strength in the management of RDs in Europe and Brexit has negated the progress made by the UK RD community who had led six of the ERNs.[136] These pan-European networks are invaluable in resource sharing, connecting patients with healthcare specialists and other persons living with the same condition, and provide an essential platform for international collaboration. However, five years since having been established, they still have not been systematically reviewed. However, in December 2022 the European Commission set up an evaluation committee to monitor the performance of ERNs across a set of 18 indicators.[137] Monitoring and evaluation of ERNs and clinical pathways will allow decision-makers to determine their effectiveness—and how to maximise their reach and operability.

Going forward from the UN Resolution, non-governmental organisations like Rare Disease International and EURORDIS are working towards getting a WHO Universal Health Coverage for Rare Diseases resolution in 2024. This would distil the wide-ranging advocacy put forth by the UN Resolution into technical pillars that can be implemented by national policymakers with the support of WHO regional offices. "A WHO Resolution would formalise the commitment by the [WHO] Director-General and its Member States to implement UHC for RD," says Ms Cviticanin. Evaluating interventions is fundamental to ensuring the right approaches are taken to meet the needs of the RD community and that stakeholders remain accountable beyond good intent. "The UN Resolution can really change things, but it is [currently] only paper and political intention," says Yann Le Cam, Chief Executive Officer of EURORDIS- Rare Disease Europe. "We need to make Member States accountable to their commitments, and this can be achieved by periodically revitalising the Resolution within the UN."

Generating evidence

Historically, evidence generation has been a challenge for RDs, given the relatively low number of patients afflicted by individual diseases. New treatments or orphan drugs looking to enter the market must go through HTA to demonstrate their benefit in comparison to existing treatment options. Currently, the gold standard for evidence generation are

randomised control trials (RCTs). Given the smaller number (and often cross-border distribution) of individuals with specific forms of RDs, conducting RCTs presents challenges for researchers and drug manufacturers. The impact cascades down to PLWRD, who have limited or no treatment options.[138] An alternative approach is to incorporate various types of evidence and take a multi-methodological approach but this will require international consensus.[139] Tanya Collin-Histed, CEO of the International Gaucher Alliance, explains how the majority of HTA and regulatory bodies focus on the clinical aspects of treatments such as biomarkers and blood tests, which, on their own, do not accurately reflect what these treatments mean to a patient in their everyday life. There is scope, therefore, to integrate patient history data and lived experience, into the process of evidence generation and assessment. In response to this and the new EU HTA regulations that will be applied in 2025, incorporating the involvement of patients in scientific consultations and assessments, patient organisations such as EURORDIS are playing a pivotal role in empowering PLWRD and their families to participate in HTA decisions through the European Capacity Building for Patients project.[140] The inclusion of PLWRD into HTA decisions provides a more holistic and inclusive approach, hence empowering PLWRD to become experts in their condition and allowing them to inform meaningful outcomes for treatments.

Another challenge to evidence creation is the fragmentation of data collection. “You have patient groups, governments and pharmaceutical companies doing data collection, but we need to bring all of these databases together in a centralised manner,” says Ms Collin-Histed. The EU has seen some progress in this respect. The EMA has begun implementing the Data Analysis and Real-World Interrogation Network (DARWIN) EU, designed to create a network of verified, secure data that can be used to support scientific evaluations and regulatory decision-making.[141] Another recent initiative, Together4RD, aims to support ERNs to harness real-world RD data by collaborating with multiple stakeholders across Europe.[142]

Mobilising existing resources

The UN Resolution can be leveraged to promote best practice in the management of RDs, particularly in countries where frameworks and infrastructure are not as advanced. Much of the strength of the EU lies in the presence and development of ERNs that allow for sharing of expertise. EURORDIS is campaigning to strengthen and expand these types of networks beyond the EU and into geographical Europe, but this has not yet been achieved. With the notable exception of Serbia, the Balkan region performs worse when compared to its EU counterparts when it comes to RD policy planning, implementation and overall management. The primary challenge relates

to accessing timely, specialised care through clinical referral pathways.[143]

It may be unrealistic to entirely build new infrastructure around the needs of the RD community; instead, the key will be to integrate the unmet needs of PLWRD into existing healthcare systems. "We are seeing many institutions working on policies in silo," says Mr Le Cam. "We need to promote an approach of integration between medical and social care and into other sectors of government." Intersectoral integration will allow for a more holistic, coordinated care experience for PLWRD and caregivers, and can facilitate wider functions of an individual's life which overarchingly impact their health, including education, social rights and financial compensation. Furthermore, PLWRD face cumulative vulnerabilities starting from childhood. There are three main threats, says Mr Le Cam: "The multiple comorbidities that affect mental health, the increased physiological impact across all stages of life, and the increased exposure to inequalities and discrimination." Living with RD significantly affects mental health; a recent study found that 33% of PLWRD and 57% of their caregivers went on to experience depression.[144] Policymakers can address this by integrating psychosocial support throughout the various stages of life, thereby improving wellbeing and quality of life. These interventions are likely to be financially advantageous for policymakers, as they would save money in the long term by preventing the downstream health impacts of unmanaged psychological symptoms.

"There are three main threats. The multiple comorbidities that affect mental health, the increased physiological impact across all stages of life, and the increased exposure to inequalities and discrimination."

Yann Le Cam, Chief Executive Officer of EURORDIS- Rare Disease Europe, France

Looking ahead to an equitable future

In the wake of a UN Resolution on Rare Diseases and with a potential WHO resolution on the horizon, it is no longer possible to ignore the significant epidemiological, economic and societal burden of RDs. Current conditions continue to present inequitable landscapes for PLWRD, spanning access to healthcare and education, care pathways, and integration into wider society. Policymakers and the wider RD community in Europe have been making positive strides in ameliorating this situation through developing national frameworks, expanding ERNs and improving RD awareness. Although the situation is far from perfect, these improvements have changed the RD landscape in Europe.

To capitalise on the momentum provided by the UN Resolution, these advances will need to be better integrated within existing systems and infrastructures. This report has identified some key policy areas where early improvements can be built on to ensure that no one is left behind:

- **Diagnosis first, giving children with RDs a better start to life.** Over 70% of RDs manifest in childhood. Early diagnosis is essential for early intervention, thereby optimising life prospects such as educational attainment for children with RD.[145] Currently, the UK, Spain and Germany currently only screen for 9, 7 and 19 RDs respectively, low in comparison with other EU countries—Italy screens for 48 RDs.[50] Policymakers must advocate for a harmonised criteria and adequate policies to expand NBS coverage across RDs and geographical regions.
- **Seamless, effective integration of RD management into existing healthcare structures.** Building separate provisions and pathways for RDs may not be financially and economically viable. Instead, policymakers should focus on using existing infrastructure as a springboard to integrate the needs of PLWRD. Health systems must ensure that that coordination is multifaceted while considering the different stages of an individual's life, such as childhood to adulthood; or through multisectoral collaboration including schools to ensure a smoother transition pathway and better integration of health and social care.
- **Bigger patient voice in decision-making.** PLWRD and their families are experts in their conditions with lived experience of their unmet needs. Their voices should be more prominent in the policy dialogue. The EU regulation on HTA coming to effect in 2025 provides a good opportunity for HTA agencies to revise their processes to ensure that patient engagement is a core part of scientific consultation and assessment. Patients must be supported to fulfil this extended decision-making role. Patient organisations have a pivotal role in ensuring that all PLWRD are reached, including those from minority groups who may have additional needs.

- **Expand the codification of rare diseases both nationally and internationally.** Creating central registries to classify RDs can enhance data generation as well as raise awareness. This will help to streamline clinical pathways. Comprehensive registries can also help to identify suitable patients for clinical trials and other research or policy initiatives. The World Economic Forum recently published an article on global data access and the creation of meta-databases made up of constituent databases that are transparently interconnected to support data sharing.[146] This type of well-annotated dataset would be valuable but would require investment and contribution from different countries to enable global and national data solutions to RD.
- **Strengthen and expand international collaboration and collaborative research networks.** The ERNs are a significant tool for information-sharing and connecting patients to clinical RD specialists across EU nations' borders. Stakeholders should strive to expand these existing structures of expertise into robust clinical research networks, thereby addressing the challenge of evidence generation for RDs that are under-researched due to low trial recruitment levels. This will alleviate the gridlocked HTA process that currently exists in many European nations and incentivise drug manufacturers to develop treatments covering a broader range of RDs. These networks will need investment to ensure that they run effectively as the current model is primarily running on the good-will of clinicians who volunteer their time to participate.
- **Ensure equitable access to care. PLWRD face greater barriers than the general population and therefore need more support.** Yet, historically their needs have not been met entirely, as continues to be the case today. More focus should be placed on the impact of the severity of disease, rather than the prevalence. UHC has not been achieved in the three countries mentioned in this report, despite them having "universal" health systems such as the UK's NHS. Regional inequities pertain to treatment access within and between countries, partly due to variations in HTA processes, decision-making and wait times. These disparities do not only impact the countries mentioned in this report but may also extend to those with strategic HTA alliances such as the ACCESS Consortium. HTA processes must be more flexible and transparent to ensure fair access to promising treatments, regardless of geography.
- **Unravelling the cost of inaction.** Although evidence generation is not optimal for RDs, it is the best that it has been over the past few decades, demonstrating continued progress. With tight budgets and increasing population health needs, getting the right balance is crucial. To make the case for greater investment in RD management and pursuing true UHC, further research must ascertain inefficiencies in the current systems to provide an added layer of evidence to policy decision-making. Inefficiencies can include requiring multiple consultations to get a diagnosis and the impact of secondary health complications because of untimely treatment. There is also a lack of studies quantifying the cumulative economic impact of RDs in Europe—published studies tend to focus on individual diseases. To shift the narrative towards a collective approach, these diseases also need to be quantified collectively to understand the true economic and societal burden at the European level.

Although the three countries covered in this report have made progress pertaining to these recommendations, there is plenty to be done to meet the unmet needs of PLWRD and their caregivers. All three must work to ensure that political commitments set out by the UN Resolution yield ground-level interventions. Meanwhile, global organisations must be proactive in monitoring progress towards an equitable future for PLWRD and their caregivers and families.

Conclusion

This report assesses the system management of three European countries, exploring their strengths and areas for improvement in RD management. It examines the system performance of the RD ecosystem, bringing particular attention to why nations should prioritise optimising the management of RDs: this is not just a health and development issue, but also a societal problem that threatens the survival of many millions of PLWRD. The recent UN Resolution offers hope and pragmatic guidance; however, PLWRD in even high-income countries such as Germany, Spain and the UK face significant inequities in accessing the care they need. The rarity of RDs in prevalence terms has meant that they are not always a key policymaking priority, despite their widespread impact, complexity and severity. Policymakers must adopt a new lens to ensure that the needs of PLWRD are fairly met. It is time for the entire RD community, including patients and patient advocates, bio-pharmaceutical companies, academics, researchers, healthcare professionals, politicians and policymakers to work better together—only collaboration will ensure that those impacted by even the rarest RDs are not left behind.

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Appendix

Methodology

This study has used primary and secondary research. The first step of the research program included a comparative literature review on rare diseases and UN resolutions. This was a rapid scoping literature review covering formal databases and grey literature. It was not systematic in nature, neither did it cover a specific research question. Rather, it aimed to give a high-level overview of rare disease management and care at a European level with an emphasis on the UK, Germany and Spain.

Databases sources:

- Embase
- Medline

Grey literature sources:

- Google
- Google scholar
- National government websites

The formal search on the databases yielded an initial 584 results. These were then transferred to the reference management program EndNote and screened by title and abstract to only include the articles that would be most relevant to the current research project. Secondly, we conducted semi-structured interviews for nine experts in the field of RDs, geographically ranging from Germany, Spain and the UK, as well as those with a global perspective and key involvement in the development of the UN resolution on RDs.

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