

RARE AND ULTRA-RARE DISEASES

PRIORITISATION AND SUSTAINABILITY:
A REPORT FROM THE FRONT-LINE

Job number: VV-MED-00592
Date of Preparation: FEBRUARY 2021



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THANK YOU

We thank all contributors for their time and valuable insights. Collaborating with experts across all aspects of rare disease diagnosis, treatment and care, we can change rare disease patients' lives.

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FOREWORD

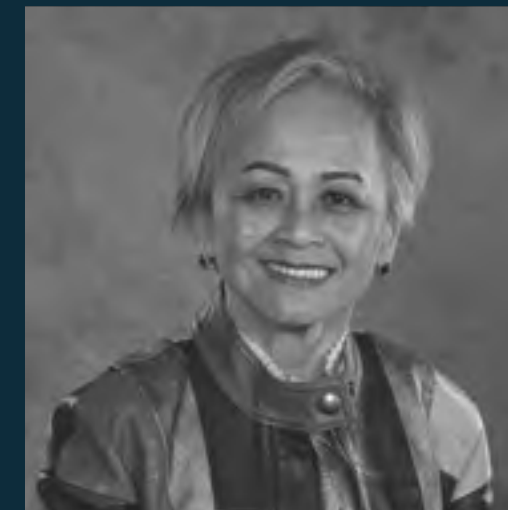
BUILDING A SUSTAINABLE FUTURE FOR RARE DISEASE PATIENTS AND THEIR FAMILIES

Globally there are an estimated 300 million people living with rare or ultra-rare diseases of which there are more than 7,000 different types.¹ It is estimated that there are 30 million people in Europe, more than 60 million in Latin America and more than 25 million in North America living with a rare disease.^{2,3,4}

Approximately 80% of rare and ultra-rare diseases are inherited and sadly, it is estimated that a third of rare disease patients will die before their fifth birthday.⁵ These orphan diseases are a global health problem that affect people of all nationalities, races, ethnicities, genders, ages and socio-economic groups. While the diseases are as diverse as the people they affect, symptoms and signs can vary widely, not just from

disease to disease but also from patient to patient.

Because each rare and ultra-rare disease affects small numbers of people compared to more prevalent diseases that have much greater public and societal awareness, medical expertise is harder to find, knowledge and research are not as advanced and healthcare systems are often not geared up to care for people living with rare diseases, let alone ultra-rare diseases which affect 1 in 50,000 people or fewer⁶. Although the overall number of people affected collectively is large, rare disease patients are often neglected by research and health systems. This is even more of a challenge for patients with ultra-rare diseases, the burden for patients at the rarest end of the spectrum being even greater. Getting a definitive diagnosis



DURHANE WONG-RIEGER

CEO, Canadian Organization for Rare Disorders (CORD), Council Member, Rare Disease International (RDI)



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FOREWORD

BUILDING A SUSTAINABLE FUTURE FOR RARE DISEASE PATIENTS AND THEIR FAMILIES

of rare and ultra-rare disease patients can take many years, leading to delays in starting effective treatment, should such treatments exist at all, and a multitude of other challenges for health systems and patients alike. It is estimated that only 5% of rare diseases have a treatment.⁷

The quality of life of someone living with a rare disease is often heavily impacted. Often life threatening, these diseases can often be progressive, degenerative and life limiting and in most cases, there are no effective treatments.

Those living with rare and ultra-rare diseases, their families, friends and caregivers suffer from a lack of prioritisation in most societies. A 2020 public survey showed that 91% of people think that rare diseases affecting small numbers of patients should have

resources allocated to treat and manage them, but the reality is very different.⁸ The same survey showed that 75% of people feel that governments and health authorities should treat each patient equally regardless of whether they have a common or rare disease, but rare and ultra-rare disease sufferers and their advocates have to battle at every step to get proper diagnosis and effective treatment.⁸

This report brings together first-hand experiences of those working on the front-line of rare and ultra-rare diseases. Whether they be specialist professionals, advocates, health economists or people working to raise awareness and understanding, they are united in bringing greater support and access to care for people living with rare and ultra-rare diseases.

Whilst research programmes and effective medications do exist for some of these conditions, less than 10% of all rare diseases are being researched in clinical trials.⁹ Therefore, we must continue to increase awareness and understanding about rare and ultra-rare diseases and call on decision-makers to focus more attention and resources so that those living with these often debilitating conditions have a sustainable future. There needs to be a recognition of how rare diseases differ from non-rare diseases and furthermore an understanding that rare and ultra-rare diseases also differ in terms of awareness, diagnosis and access to treatment.

By broadening the conversation about rare diseases and raising their profile, particularly ultra-rare diseases, we

hope to ensure that friends and family, healthcare professionals, employers, government officials, health insurers and pharmaceutical companies become more aware and informed of the many and varied challenges that people with rare and ultra-rare diseases face. In particular, we ask the medical community, government regulators and the pharma industry to act on their new-found knowledge to bring more effective diagnosis, access to treatment and support for patients who are in desperate need.



AMRYT RARE HOPE SURVEY

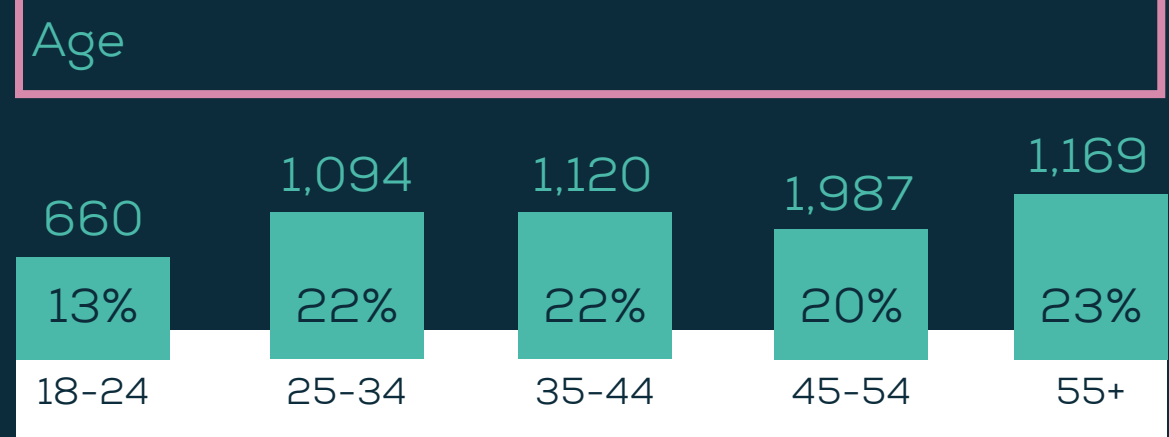
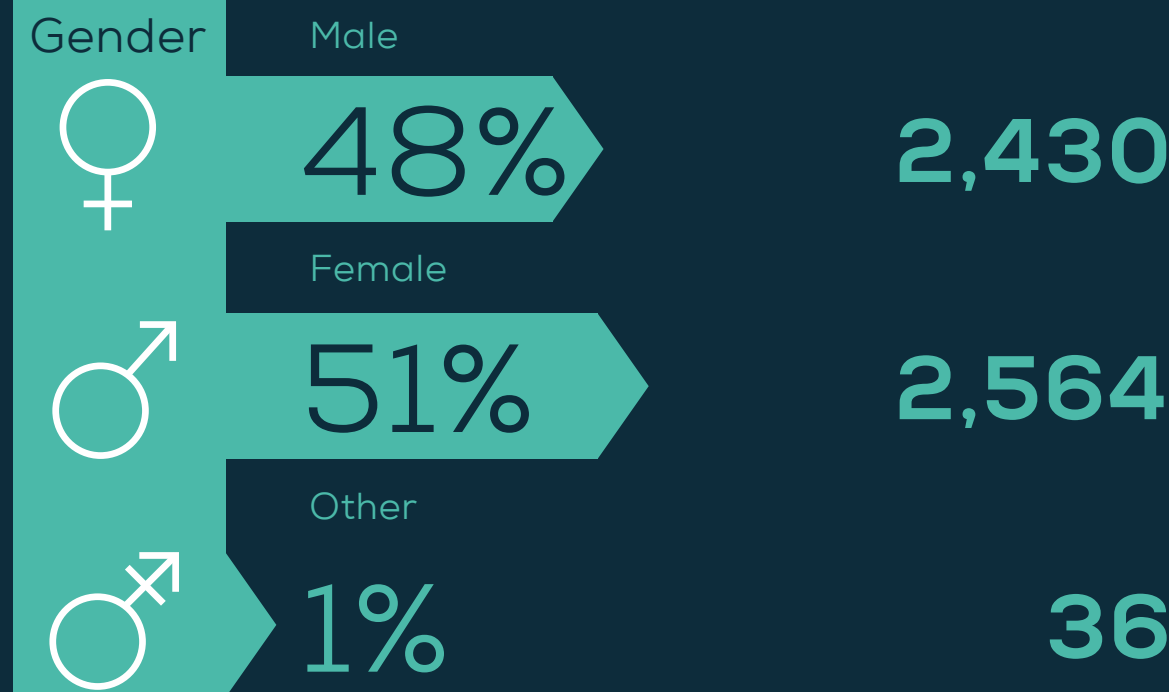
PUBLIC PERCEPTIONS AND PRIORITIES

Overview of respondents' demographics

5030 adults



UK: 2,020 Ireland: 1,001 US: 2,009

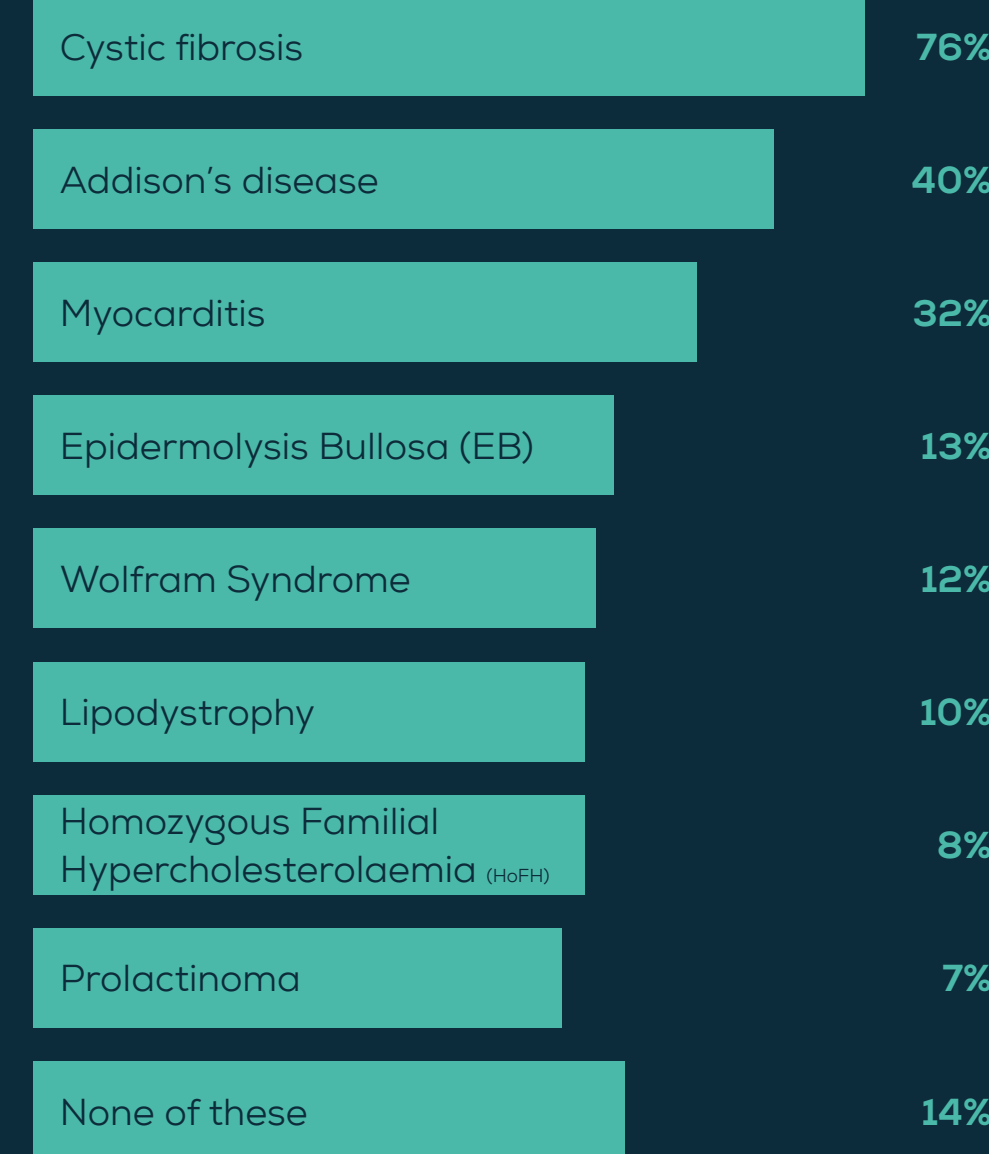


More than 3/4 (77%) of people do not know what an orphan disease is

3/4

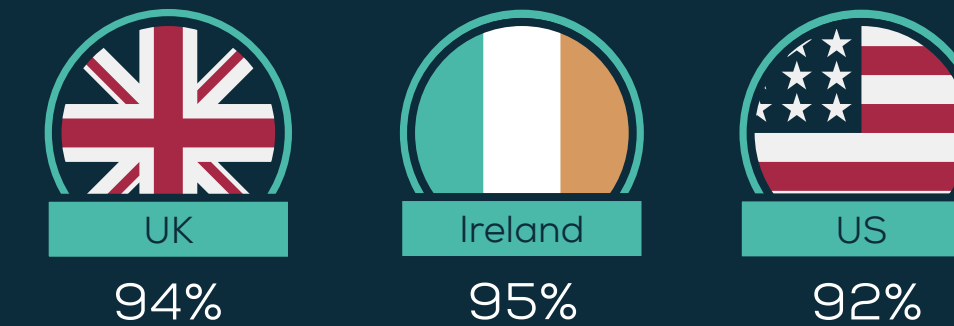


How many people have heard of rare diseases?

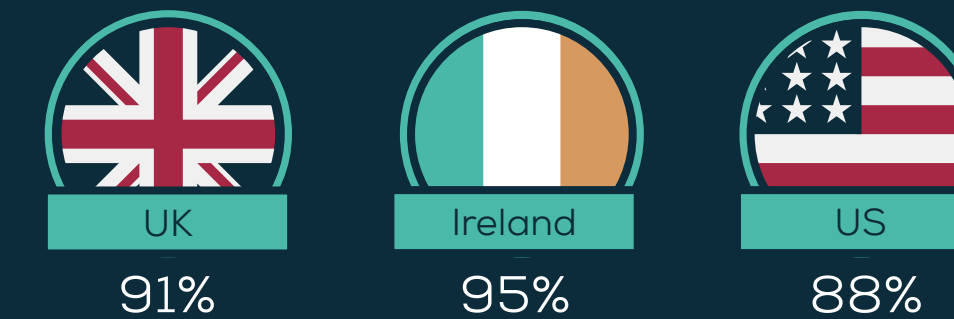


93% of people think if they were diagnosed with an illness, it is likely there will be a treatment available for it

93%

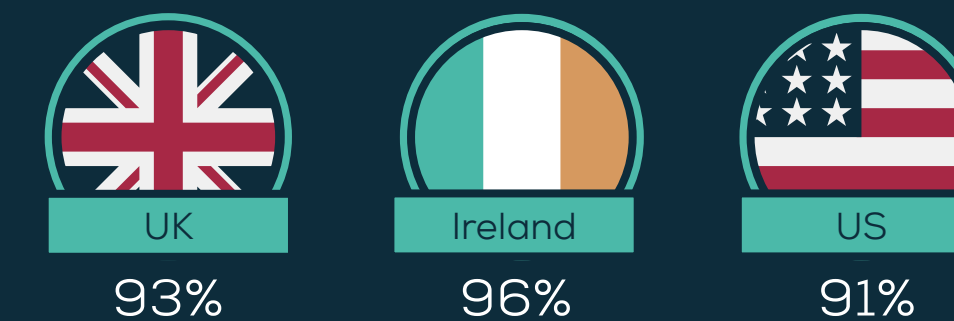


91% of people think that rare diseases affecting small numbers of patients should have resources allocated to treat and manage them



93% of people think that everyone should have the same rights to treatment, regardless of the type of disease they have?

93%



Three quarters (75%) of people agreed that governments and health authorities should treat each patient the same regardless of whether they have a common or rare disease



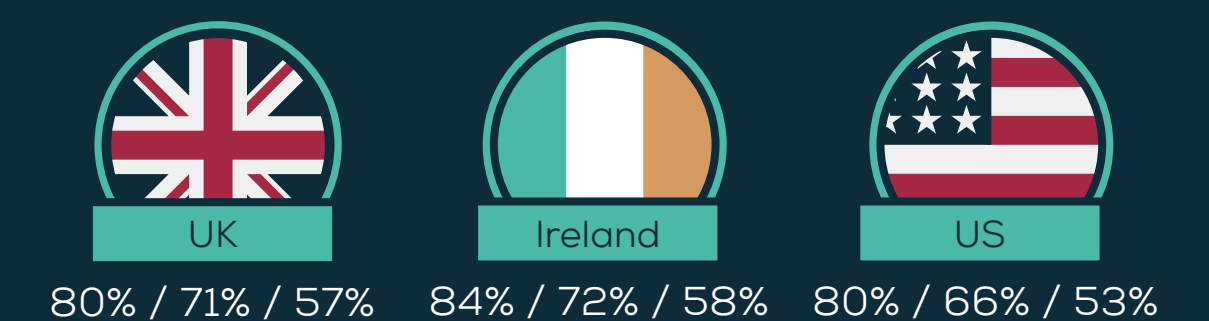
71%

71% of people did not think resources for other diseases should be deprioritised during the COVID-19 pandemic



four out of five

More than 4 out of 5 (81%) people think that effective and potentially life saving treatments should be made available for all patients of rare diseases regardless of cost compared with 69% for common diseases. 56% think they should be made available for both rare and common diseases regardless of cost.

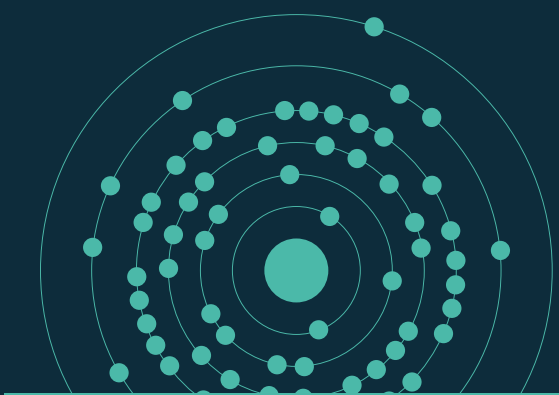


Key Facts

What is the difference between *rare* and *ultra-rare* diseases or conditions?

ONE
IN
2,000

European Union definition of a rare disease: affects fewer than **5 people per 10,000** of the population – or **1 in 2,000**.⁽¹⁾



ONE IN A million

An *ultra-rare disease* is one that affects **1 in 50,000**.⁽²⁾ Most ultra-rare diseases affect **1 in a million** people or fewer.⁽³⁾

200,000

The *Orphan Drug Act* defines a rare disease as a disease or condition that affects less than **200,000** people in the United States.⁽⁴⁾



Rare diseases are also known as "*orphan diseases*"⁽⁵⁾. There is no legal definition of an "*ultra-rare*" disease⁽²⁾

How many people are affected?

6,000

Around **6,000** children are born in the **UK** each year with genetic conditions so rare that they cannot be named and are unlikely to be diagnosed.⁽⁶⁾

THIRTY million

Over **7,000** rare diseases affect more than **30 million people** in the United States.⁽⁴⁾

300m

Approximately **5,000-8,000** distinct rare diseases affect **6-8%** of the EU population.⁽⁷⁾ Rare diseases affect **3.5% - 5.9%** of the worldwide population an estimated **300 million** worldwide.⁽⁸⁾

Who can be affected?

3/4 of all rare diseases affect children⁽⁹⁾

Globally, **3** out of **10** children with a rare disease won't see their **5th** birthday⁽¹⁰⁾

What causes rare and *ultra-rare* diseases?

72% of rare diseases are genetic.⁽⁸⁾ Others are the result of infections (bacterial or viral), allergies and environmental causes.⁽¹¹⁾



70% of those genetic rare diseases start in childhood.⁽¹²⁾

Rare and *ultra-rare* diseases are chronic and life-threatening⁽¹³⁾

Living with an Ultra-Rare Disease

Mental health and wellbeing

Rare disease patients and carers report a huge emotional impact from living with their rare disease.⁽¹⁴⁾

Impacts on mental health and wellbeing arise from

A Difficulties faced in trying to reach a diagnosis, Low awareness among healthcare professionals when presenting with symptoms.

B Lack of treatment options

C Poor care coordination

D Carers of children with very complex conditions which frequently remain undiagnosed for life also face mental health challenges.⁽¹⁴⁾

E Patients and families face significant ('hidden') costs⁽¹⁵⁾

Living with an ultra-rare condition



88% of individuals feel emotionally exhausted by living with a rare condition.⁽¹⁶⁾

Importance of support groups

Why support groups matter. **7** perceived benefits of rare disease support groups.⁽¹⁷⁾



1. meeting and befriending; **2.** learning about the disease; **3.** emotional support; **4.** a place to speak openly; **5.** coping skills; **6.** feeling empowered and hopeful; **7.** advocating to improve healthcare for others



Patients are frequently left to research their condition unless they connect with a patient organisation. Increased awareness and understanding can help.⁽¹⁸⁾

one in two



1 in 2 rare diseases don't have a foundation or support group⁽¹⁰⁾

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18. Rare Disease UK. 2016. The Rare Reality. An Insight into the Patient and Family Experience of Rare Disease. the-rare-reality-an-insight-into-the-patient-and-family-experience-of-rare-disease.pdf (Last Accessed 21 January 2021)

A photograph of a woman with long dark hair holding a young child who is crying. The woman is looking down at the child with a concerned expression. The child is holding a small white bottle. The entire image is overlaid with a semi-transparent teal filter. Centered over the image is the text "CHALLENGES IN RARE DISEASES" in a bold, white, sans-serif font.

CHALLENGES IN RARE DISEASES

CHALLENGES IN RARE DISEASES

Rare diseases are a family of more than 7,000 medical conditions, each of which shares the common feature of affecting a small to ultra-small population of patients – typically less than 1 in 2,000 people. Many of them are of genetic origin, approximately 80% and manifest from birth or early childhood onwards. They are frequently chronic, degenerative and disabling, and often shorten the life expectancy of affected individuals.¹⁰

An ultra-rare disease is one that affects 1 in 50,000.¹¹ Rare diseases currently affect 3.5% – 5.9% of the worldwide population, an estimated 300 million worldwide.¹² Rare and ultra-rare diseases are often life-threatening.¹³

This section of the report discusses

the challenges faced in rare and ultra-rare diseases, highlighting the difficulties faced by patients, healthcare professionals, patient advocacy groups and industry when it comes to managing and treating rare diseases. These challenges include awareness, diagnosis, access and research, all of which play a key role in shaping the overall environment for rare disease patients.



Rare diseases were recognised as an issue deserving the attention of society less than 35 years ago. All over the world, seemingly simultaneously, representatives of patient organisations came together with medical professionals to look at the challenges associated with rarity. They also began to look at ways to mobilise society to address the serious problems posed by these diseases to patients and their families.¹⁴

Over time, the rare diseases community has structured itself more effectively, at national level, regional level and now increasingly at global level. Rare Disease Day was initiated in 2008, and some patient advocacy groups have come together in international consortia. In 2016, the United Nations founded the

NGO Committee for Rare Diseases.¹⁴ These advances represent the great strides being made in the rare disease community to improve lives of patients and put rare and ultra-rare diseases more prominently on the agenda of stakeholders.

But awareness of rare diseases, and particularly ultra-rare diseases, is still too low, even among medical practitioners.

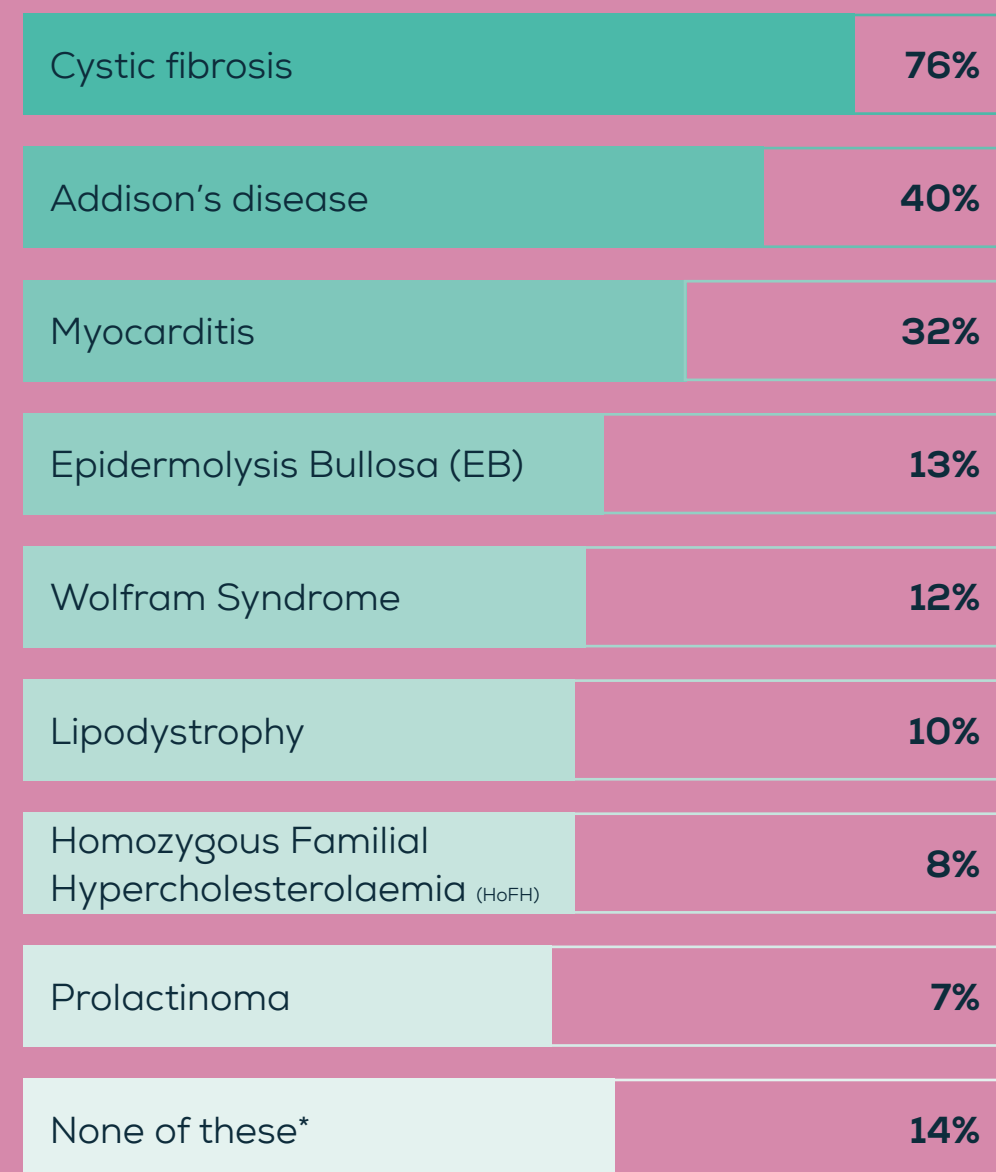


SOME RARE DISEASES ARE BARELY KNOWN

The Amryt Rare Hope Survey of over 5,000 adults from the UK, Ireland and the USA conducted in October 2020 showed lack of public awareness about orphan (rare and ultra-rare) diseases in stark terms.⁸

- Less than a quarter (23%) said they knew what an orphan disease is

A summary of the full survey is available on page 6.



*percentage of people who have heard of different rare diseases

LOW AWARENESS

CHALLENGE 1

Rare diseases have a wide diversity of symptoms and signs that vary not only from disease to disease but also from patient to patient suffering from the same disease. Relatively common symptoms can hide underlying rare diseases leading to misdiagnosis and delaying treatment.¹²

The rarity of these diseases contributes to low awareness, even amongst healthcare professionals. It's probably no wonder the general public has little if any knowledge about rare and ultra-rare diseases.

The difficulties people face in trying to obtain a diagnosis and not being adequately investigated by healthcare professionals are exacerbated by low awareness.¹⁵



JULES PAYNE

Heart UK

One key challenge is awareness, because people often get

misdiagnosed in the first place and that is a worry. There is not enough knowledge, both in the healthcare arena but also with patients – how are they going to know that they're being misdiagnosed? Specialists will have some information about rare and ultra-rare diseases, but it's about sharing that knowledge and breaking it down in simple ways for other healthcare professionals from secondary care into primary care. One can feed into the other.



LOW AWARENESS

CHALLENGE 1



TONY BYRNE

DEBRA UK

Raising awareness for a genetic skin condition like EB (epidermolysis

bullosa) is essential for early diagnosis, treatment and support. It is vital to ensure all families living with EB receive the appropriate specialist healthcare and have access to information, advice and support. We need to ensure more widespread EB knowledge and expertise is available throughout the UK and we work with DEBRA International to extend best practice worldwide. We are also committed to ensuring awareness of the need for cure and treatments and the funding we provide to enable EB research to thrive. Using opportunities such as the annual EB Awareness Week, social media campaigns educate and engage new audiences with support

and advocacy from our EB community. Raising the profile of EB and increasing public understanding is essential to encourage donations, sales and volunteering for our charity retail and fundraising income to support investment into research for cure and care. Achieving awareness and understanding is an essential starting point in our journey to #FightEB



JULIA JENKINS

Everylife Foundation for Rare Diseases

Advocacy raises awareness. There is

continued momentum for legislative advocacy in our community, we had more than 900 people join for Rare Disease Week on Capitol Hill, including patients, caregivers and federal and congressional staff. We also have an incredibly active

Congressional Caucus, with Members of Congress wanting to introduce legislation.



VICKY MCGRATH

Rare Diseases Ireland

We had a momentous day recently with the formation of the new

Irish government where the programme for government actually recognised the rare diseases community as a vulnerable group. It's a big win in terms of recognition. We had to work hard to achieve this, but it's there. We are very happy about this and I believe that the recognition will help greatly in the years ahead.

Progress has been made in the past 10 years toward raising awareness about rare and ultra-rare diseases and there are organisations working tirelessly to raise it further. But awareness of these often debilitating diseases is still too low. That makes obtaining diagnosis and treatment more difficult. The more awareness there is of these devastating conditions, the more they will be supported and considered.

We hope this report will add to the momentum, and we call on readers to share it with doctors, nurses, teachers, employers and decision makers.





THE DIAGNOSTIC ODYSSEY

THE DIAGNOSTIC ODYSSEY

CHALLENGE 2

The 'diagnostic odyssey' refers to the time taken between a patient first developing symptoms and receiving a correct medical diagnosis.

Awareness of rare diseases, as discussed in the previous section, is low for rare and ultra-rare diseases which has a direct impact on diagnosis. In rare and ultra-rare diseases, early diagnosis can be key to saving lives, as well as finding the right treatment but these diseases this can take years. Even when they do receive an accurate diagnosis, patients and families are often given very little information about their condition. They are frequently left to research the specific rare or ultra-rare disease on their own unless

they can connect with a patient organisation.

A diagnosis of a rare or ultra-rare disease greatly affects many aspects of an individual's life including their social, educational and employment opportunities in addition to their health. It is essential that diagnosis is quick and accurate, and that appropriate education is offered to the patient and family.

The EURORDIS diagram on page 15 illustrates the complexity of the diagnostic odyssey.

“The Diagnostic Odyssey is the biggest gatekeeper, the biggest obstacle to overcome”

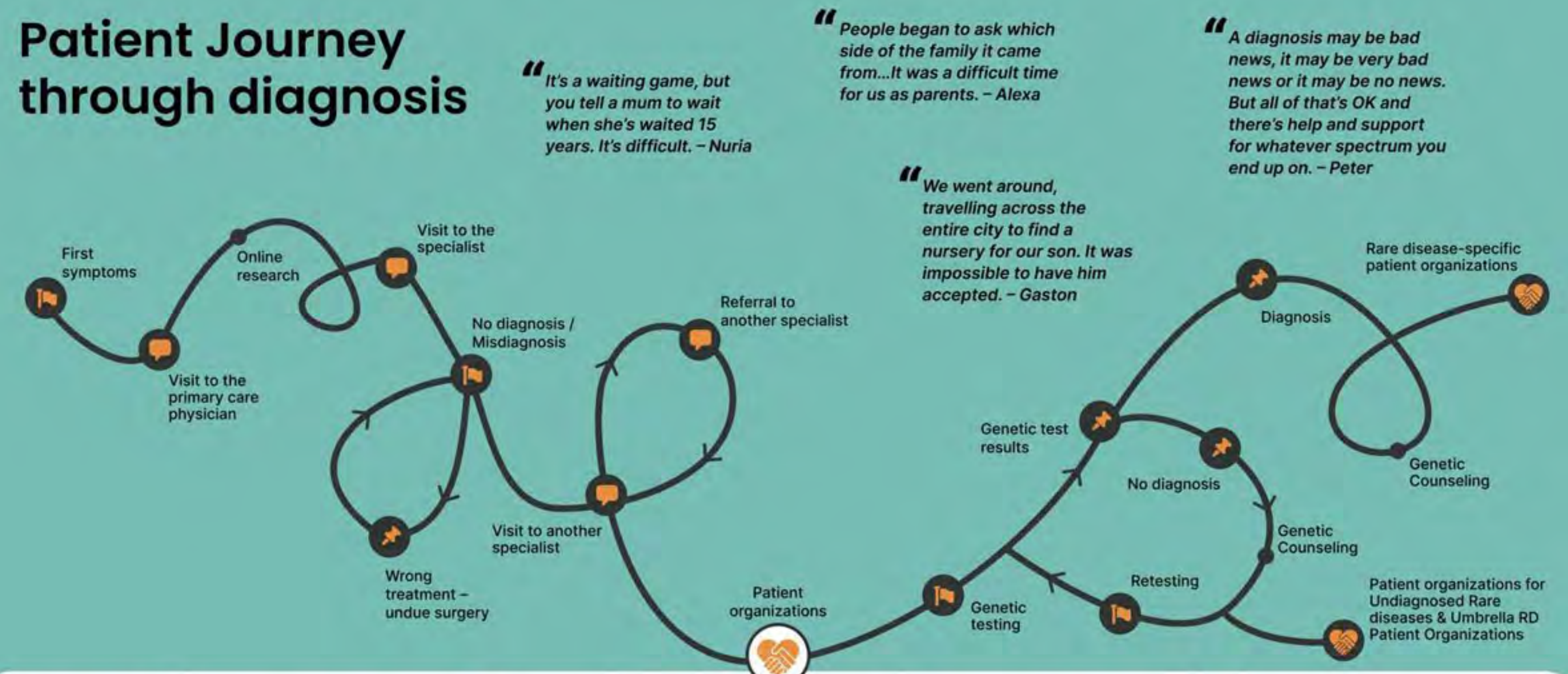
CHRISTIAN RUBIO, GLOBAL GENES



THE DIAGNOSTIC ODYSSEY

CHALLENGE 2

Patient Journey through diagnosis



3 Patient advocates report that on average rare disease patients receive **three** misdiagnoses¹⁶

Some patients see an average of five physicians before diagnosis¹⁶

On average, it takes over **4 years** to receive an accurate diagnosis of a rare disease, and it can take up to **20 years¹⁶**

FOUR YEARS



Ref: EURORDIS. Patient journey through diagnosis. <https://www.eurordis.org/sites/default/files/solverd-infographic.JPG> Last accessed December 2020



JULES PAYNE

Heart UK

Familial

Hypercholesterolaemia (FH) is an inherited

condition that leads to levels of cholesterol that are higher than that of the general population, sometimes double or even three or four times. FH is linked to an increased risk of early cardiovascular disease, in particular coronary heart disease.

Homozygous FH happens when a child inherits two copies of an altered gene that causes FH, one from each parent. A good example of misdiagnosis with homozygous FH: We know a child that had xanthomas (lesions containing fat and cholesterol) on their hands, and they were sent to a dermatologist who had the growths surgically removed.

That was an unnecessary procedure, because no sooner were they removed, they came back. That's a good example of what's not picked up in primary care and not picked up by one specialist in the system, thankfully this child was referred eventually to the correct specialist and was treated appropriately.

Getting the right diagnosis is absolutely key to getting to the right specialist.

THE DIAGNOSTIC ODYSSEY

CHALLENGE 2



MAGDALENA

DACCORD FH Europe

Speaking on behalf of homozygous familial hypercholesterolaemia

patients and wider stakeholder groups such as their families and carers - no matter who you talk to, the biggest concern is always the same: early detection of a disease. Early correct diagnosis is extremely difficult. Very often in their whole lifetime a doctor may not have seen the patient or the condition they have heard about in books.



DURHANE WONG-

RIEGER CORD, Rare Disease International

The technology for ultra-rare diseases is coming

into its own - it is becoming possible to find and accurately diagnose some

ultra-rare diseases that before would take years to diagnose. And suddenly, with the kind of databases you can now put together you can identify multiple families and build a community - that would have been very challenging in the past. Using this technology to design treatments - that will be the next big breakthrough.

As Christian Rubio of Global Genes says, diagnosis is possibly the biggest obstacle to progress, but probably the least political of all the rare and ultra-rare disease challenges. In theory, this should make improvements easier to tackle. However, this requires recognition of the vital importance of this first step to admit and address bottlenecks and flaws in the process. Prompt and accurate diagnosis can help to ensure patients receive the care they need as quickly as possible.

A teal-tinted photograph of a hand holding a white pill bottle and a pill. The text "ACCESS TO TREATMENT" is overlaid in the center in a bold, black, sans-serif font. The background is a solid teal color.

ACCESS TO TREATMENT

ACCESS TO TREATMENT

CHALLENGE 3

Once patients receive a diagnosis of their rare or ultra-rare disease, the next question is inevitably 'how can we treat it?' Unfortunately at the current time, this is a question for which there is no straightforward answer.

The Amryt Rare Hope Survey showed that 93% of people think if they were diagnosed with an illness, it is likely there will be a treatment available for it. The reality is that the majority of rare diseases currently have no effective treatment.¹³ In fact, there are licensed medicinal products available for only a small minority of rare diseases. In addition, even when there are potentially life-changing treatments available, patient

advocacy groups maintain that it can be incredibly difficult for patients to access these.¹⁷

Access to medicines is a live issue for people living with rare diseases; the majority have delayed, or no access to the medicine they need, or it simply does not exist.¹⁸

As the Rare Disease International (RDI) notes in its position paper, *Rare Diseases: Leaving No One Behind* in Universal Health Coverage, "The failure to live up to the social obligation to the most vulnerable populations is no longer acceptable, and the lack of policy action to address the dramatic consequences of disability is no longer justifiable."¹⁴

The Amryt Rare Hope Survey showed strong support for treatment of all diseases no matter what the cost

91%

91% said rare diseases affecting small numbers of patients should have resources allocated for treatment/management⁸

93% said everyone should have rights to treatment regardless of the type of disease they have⁸

93%

75%

75% said governments and health authorities should treat each patient the same regardless of whether they have a common or rare disease⁸



ACCESS TO TREATMENT

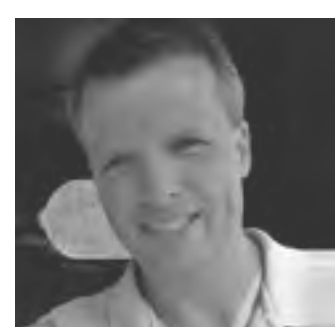
CHALLENGE 3



**PROF MANUEL
POSADA DE LA PAZ**
ISCI, ICORD

Some groups reject the fragmentation between

rare and ultra-rare but it is clear that those lower prevalence diseases present many more difficulties to find solutions than traditional rare diseases (such as Cystic Fibrosis). The main problem is the diagnosis, the search for treatments and the follow-up of a large number of patients in order to describe the real natural history of these diseases.



**DR MARTIN PRØVEN
BOGSRUD** UCCG, Oslo
University Hospital

When the doctors argue for some kind of

treatment, then I think it's more often the cost determining the decision,

rather than the evidence. Even though sometimes the evidence might be used in official documentation, it's usually the cost that is the deciding factor.



**DURHANE WONG-
RIEGER** CORD, Rare
Disease International

What if I gave you the world? What if we had a

global access programme (like vaccines) where you can treat every patient who might have this condition? How much would you charge then? That's where we need to be with a global programme – we need to invest in diagnostics and clinical care at the same time. Don't just develop a therapy – commit to developing the diagnostics and the clinic that would be necessary to bring the therapy to patients no matter where they live.



**NACA PÉREZ DE
TUDELA AELIP**

Having a specific treatment for any of the rare diseases currently

is known as a window of hope. Eighty percent of enquiries that we receive from patients that have been diagnosed are about if there are specific treatments for the disease, if they are candidates for receiving them, and if they are covered by the national health system. A treatment may allow people affected to improve their quality of life substantially.



ACCESS TO TREATMENT

CHALLENGE 3

EUROPEAN REFERENCE NETWORKS (ERNS)

Health systems in the European Union aim to provide high-quality, cost-effective care. This is particularly difficult however, in cases of rare or low-prevalence complex diseases which affect the daily lives of around 30 million EU citizens.

European Reference Networks (ERNs) are virtual networks involving healthcare providers across Europe. They aim to facilitate discussion on complex or rare diseases and conditions that require highly specialised treatment, concentrated knowledge and resources. To review a patient's diagnosis and treatment, ERN coordinators convene 'virtual' advisory panels of medical

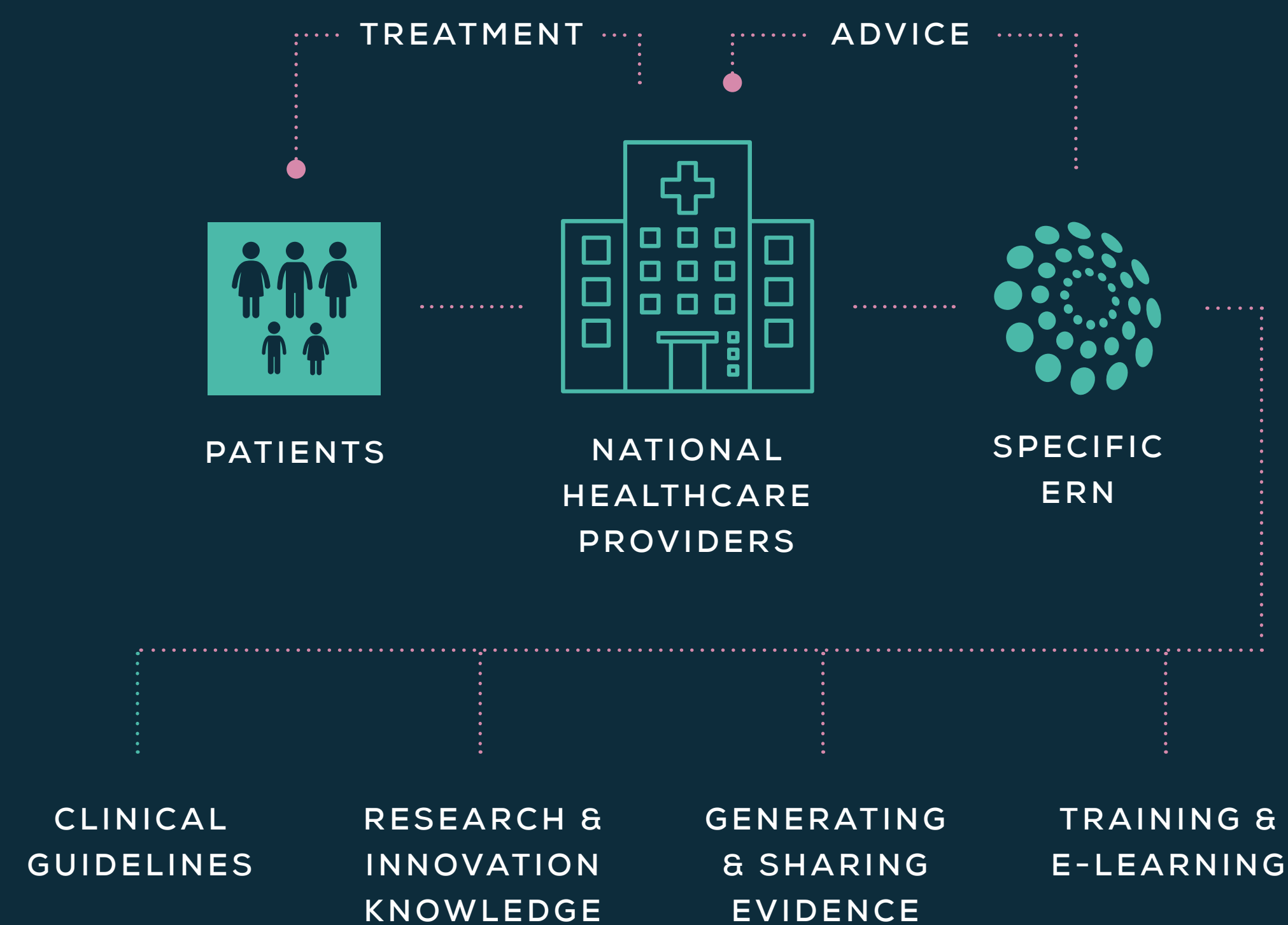
specialists across different disciplines, using a dedicated IT platform and telemedicine tools called CPMS (Clinical Patient Management System).

The process and criteria for establishing an ERN and for selecting its members are set in EU legislation.¹⁹

TREATMENT OF PATIENTS WITH RARE OR COMPLEX DISEASES

ERNs are not directly accessible to individual patients. However, with a patient's consent and in accordance with the rules of their national health system, a patient's information can be referred to the relevant ERN member in their country by their healthcare provider.

SIDEBAR



CASE STUDY



JAYNE SPINK

**Genetic Alliance UK,
EURORDIS**

Last year Genetic Alliance UK published a report,

Action for Access, which looks at the fundamental and systemic barriers to accessing proven treatments in the NHS across the UK. The report highlights the fundamental problem of uncertainty and examines the issues in relation to affordability. The way that medicines are evaluated would benefit from a greater degree of flexibility. Take for example a medicine licensed for an ultra-rare condition that may affect a very small number of individuals in each nation of the UK; it's quite possible that there might be different decisions as to the affordability and cost-effectiveness of that drug, depending on which nation. In England, the only bespoke mechanism for

evaluating rare disease medicines is the HST (Highly Specialised Technology appraisal), but this is limited by the ways in which entry criteria are applied used and by capacity.

We have experienced a long period during which there have been incremental changes to health technology assessment, but (prior to the current methods reviews) there hasn't been a comprehensive strategic overview where the end game is getting rare disease medicines to that patient.

ACCESS TO TREATMENT

CHALLENGE 3



**ANNALISA
SCOPINARO
UNIAMO**

We need to discuss the number of patients that

at the moment are required to run clinical studies. Often ultra-rare patients cannot reach the minimum numbers required for the enrolment. We have to think about how to preserve safety and at the same time how to test new therapies. This is described in a Eurordis paper on access to treatments [<https://www.eurordis.org/accesspaper>] where different models are presented to overcome challenges represented by small patient numbers.

On 23 September 2019, the UN adopted a political declaration on universal healthcare coverage that mentioned rare diseases.

In response, Rare Disease International's Durhane Wong-Rieger said, "The inclusion of people living with a rare disease within the declaration is the result of years of coordinated advocacy work from a number of organisations and led by Rare Diseases International, EURORDIS and the NGO Committee for Rare Diseases. The rare disease community remains committed to driving support for universal health coverage, to collaborating with relevant actors, to holding governments to account and to



ACCESS TO TREATMENT

CHALLENGE 3

ensuring that traditionally left-behind communities like ours are actively engaged to plan, budget and implement the policies that will ensure services are more acceptable, appropriate and sustainable”.

This was a major first step in boosting recognition that rare disease patients deserve to be included in the debate about universal health coverage. It also proved the value of international patient advocacy groups working together to improve access for rare and ultra-rare disease patients.

There is strong support for the vision that everyone has equal rights to treatment regardless of what

condition they have and whether it is rare or common and making this a reality should be a priority in order than rare and ultra-rare disease patients have hope for the future.



A dark blue-tinted photograph of a scientist in a lab coat looking through a microscope. The scene is dimly lit, with the primary light source coming from the microscope's illumination. In the background, there are shelves filled with various laboratory glassware, including test tubes and beakers. The overall atmosphere is one of focused scientific inquiry.

RESEARCH

“Research is important in all clinical areas. However, in rare and ultra-rare diseases, it is the only option, the only tool that exists to treat them.”

JUAN CARRIÓN, FEDER, ALIBER

RESEARCH AND DEVELOPMENT IN RARE AND ULTRA-RARE DISEASES

CHALLENGE 4

The previous section on access to treatment discussed the lack of available treatment options for rare and ultra-rare diseases patients. The majority of rare diseases currently have no effective treatment and many may question why this is the case.¹³ There are a number of factors involved but one significant issue is that the research and development process for new drugs to treat very rare diseases requires considerable investment and the allocation of highly sophisticated resources. By definition rare disease patient populations are small, and for ultra-rare diseases vanishingly small. This presents major challenges as medicines for rare and ultra-rare diseases may not have sufficient

evidence to satisfy the demands of health technology assessors who will ultimately approve or reject a new treatment. There can also be wide variation from country to country in terms of requirements, which makes the system complex and costly to navigate for manufacturers.

Currently, incentives for drug manufacturers are limited and lack of evidence supporting regulatory and reimbursement applications limits the number of new orphan drugs that reach the patients who need them which in turn reduces the willingness to invest at risk in research for these conditions



RESEARCH AND DEVELOPMENT IN RARE AND ULTRA-RARE DISEASES

CHALLENGE 4



JULIA JENKINS,

Everylife Foundation for Rare Diseases

The US Orphan Drug Act created important

incentives to invest in developing therapies, however we need new and expanded incentives. Tax credits help large biotech, but not the small ones, and smaller biotechs are leading in ultra-rare disease innovation and are more at risk when faced with regulatory roadblocks. We also need to reduce regulatory hurdles. There have been a lot of positive actions helping build awareness and build the community and there are many new treatments in development, but the challenges for research and development remain.

RESEARCH CASE STUDY

Investing in a future free of EB is a report initiated by DEBRA International to summarise the investment into EB research to date and gives an overview of the spend and nature of the investment. It was developed with forward from **PROF JEMIMA MELLERIO**, St John's Institute of Dermatology, Guy's & St Thomas NHS Foundation Trust, London and comment from **PROF ADRIAN HEAGARTY**, Acting Chair, DEBRA International MSAP. The document was researched and designed by DEBRA UK.

DEBRA Ireland has a long history of driving and supporting research with the potential to improve the lives of people living with epidermolysis bullosa (EB). While there is currently no cure for EB, we are working hard to change that. We

believe that children born now will benefit from treatments that will lessen the impact of the condition. This dream will only become a reality with investment in the best scientific minds.

Research and development of new treatments for EB is the key to a breakthrough. In recent years we are beginning to see the rewards from years of hard work by dedicated scientists. They are the hidden heroes that will help us to assign EB to the medical history books. Therapies are making their way to clinical trials. Across the world there are now over 20 clinical trials assessing improvements that cell and protein therapy, gene editing, skin transplants, and other developments may make to improve wound healing, reduce blistering and itch, as well as halting extreme levels of pain. It's a very exciting time.



RESEARCH AND DEVELOPMENT IN RARE AND ULTRA-RARE DISEASES

CHALLENGE 4

RESEARCH CASE STUDY

EB research worldwide is partly funded by DEBRA International through national DEBRAs. DEBRA Ireland is committed to driving and funding research to make the future for our families brighter and create an EB free world. With investment and support this will be our new reality.

Research pursuits in EB are truly international with laboratories and clinical reference centres throughout the world working together to alleviate the suffering of people living with EB. Many of the projects that DEBRA funds bring together expertise from different centres and numerous countries, combining technical know-how, resources such as animal models of EB and patient groups for clinical trials. DEBRA-led international meetings provide a forum for scientists, clinicians, and people living with EB to come together, share

knowledge, and enhance collaborative efforts in the EB arena. In supporting the development of best clinical practice guidelines for important areas of EB management and diagnostics, DEBRA combines the best evidence-based information with internationally guided expert consensus and patient experience to raise standards across the world, in whatever healthcare setting prevails. An international registry for EB patients is another DEBRA-funded initiative offering opportunities for improved knowledge, a better understanding of epidemiology, and targeting for inclusion in future clinical trials.

When DEBRA began funding research in the 1980s, the biotech and pharmaceuticals (biopharma) industry was only just starting to invest in combating diseases and understanding

the human body.

Today, biopharma is investing many millions of Euros in EB research. This surge of interest covers a broad mix of approaches to treatment and could mean a major breakthrough in the treatment and/or management of EB sometime in the next few years.

DEBRA International has been responsible – through its researchers – for establishing much of what is now known about EB, providing a solid basis for the development of treatments. With more interest in EB research, DEBRA has been joined in its strategic focus by other charitable organisations (e.g. Cure EB, EB Research Partnership, EB Medical Research Foundation and others), whilst still providing direct care and support to our members.



RESEARCH AND DEVELOPMENT IN RARE AND ULTRA-RARE DISEASES

CHALLENGE 4



CHRISTIAN RUBIO

Global Genes

I think investment in artificial intelligence (AI) as a decision-

making tool and a diagnostic tool will be really helpful, because we'll be able to get earlier indicators if something is wrong. I do believe that there's a growing network of people like us who will be pushing the acceptance of whole gene sequencing as a reimbursable standard of care state by state across the country in the coming months and years. That can really change the patient counts for some of these diseases and really develop better understanding of where people are between one ultra-rare disorder and another, if there are genetic underpinnings. So, there's hope for finding more patients. I think there's hope for increased access and I think

there's hope for communities to get more involved and become even stronger partners with researchers including industry sponsored research to build out those registries and patient datasets.

In rare and ultra-rare diseases, research is the only option when it comes to hope of a treatment and whilst there are currently some challenges and barriers to research as outlined there is also widespread agreement on some actions that could spur more rare and ultra-rare disease research including:

1. Develop disease registries
2. Reduce regulatory hurdles
3. Offer more incentives to drug developers
4. Create more international research partnerships
5. Invest more in AI and genomics

By identifying what can and needs to be done to boost research in rare and ultra-rare diseases, and by working with the relevant stakeholders to make the research environment more favourable and appealing, we believe we can ultimately ensure that rare and ultra-rare disease patients have the options they deserve.



IMPACT OF COVID-19 ON RARE DISEASE PATIENTS

COVID-19 has had a hugely detrimental effect on healthcare services globally, including in rare and ultra-rare diseases as the below statistics illustrate. Research, access to treatment, healthcare services and support services have all been disrupted. With this in mind, it is as important as ever that we ensure the progress being made in rare and ultra-rare diseases is not lost and that we continue to support rare and ultra-rare disease patients when things may be even more challenging for them.

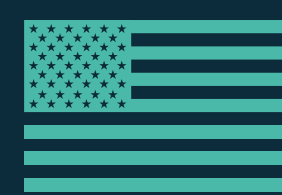
Impact on health



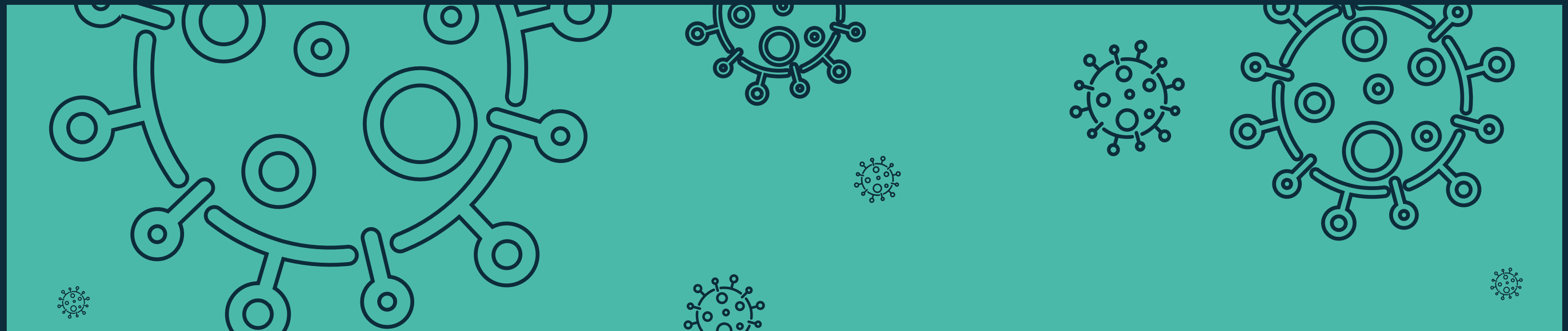
In the UK, routine rare condition healthcare has been interrupted – **66%** say interruption has been detrimental to their wellbeing. ⁽¹⁾

66%

In the US, over 25 million patients and families who are impacted by rare diseases are now managing consequential challenges brought on by COVID-19. ⁽²⁾

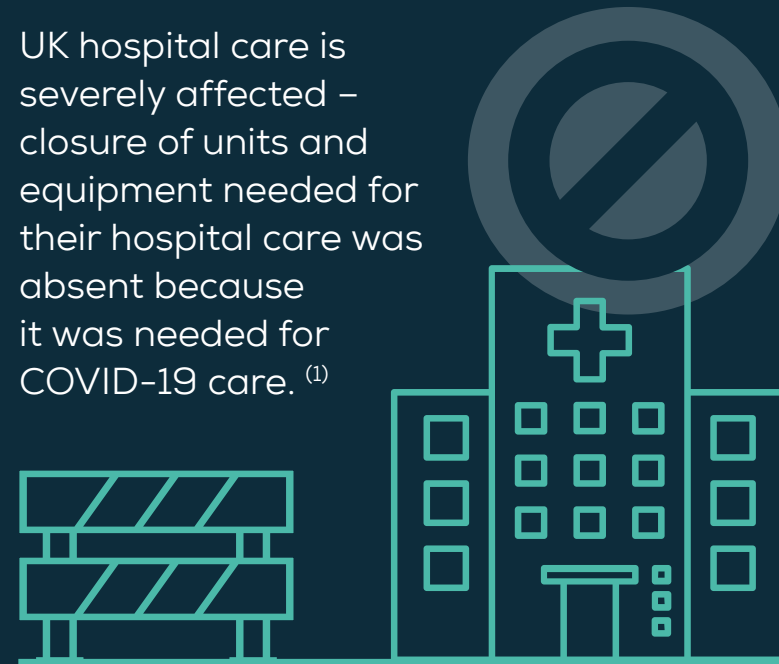


TWENTYFIVE million



Access to treatment

UK hospital care is severely affected – closure of units and equipment needed for their hospital care was absent because it was needed for COVID-19 care. ⁽¹⁾



Access to medicines disrupted – 1 in 5 people affected by a rare condition have experienced disruption to access to their usual medication. ⁽¹⁾



one in five

Impact on wellbeing

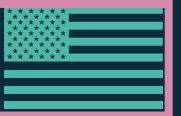
Support from neighbours, family, psychological services, home care, respite care and day care have been reduced or taken away. More than **40%** of respondents thought COVID-19 posed a very high level of threat to themselves or the person with a rare condition they cared for. ⁽¹⁾



- Sudden switch to remote consultations ⁽¹⁾
- Access to PPE has been difficult ⁽¹⁾
- Many children have lost all or a portion of their education support. ⁽¹⁾
- Tests have not been available. ⁽¹⁾

In the Amryt Rare Hope Survey, **71%** said that resources for diseases other than COVID should not be deprioritised during the pandemic.

US study showed:



95%

95% of respondents have been impacted at a cost to their immediate and long-term health and wellbeing

98%

98% are worried about COVID-19; of those, 67% are very or extremely worried

67%

74% have had a medical appointment cancelled; of those, 65% were offered an alternative appointment via telephone or video



69%

69% of respondents are concerned about medication and medical supply shortages ⁽²⁾

1. The Rare Reality of Covid, Genetic Alliance UK 2020 <https://geneticalliance.org.uk/wp-content/uploads/2020/10/Covid-19-Rare-Reality.pdf>
 2. COVID-19 Community Survey Report 2020 NORD <https://rarediseases.org/new-community-survey-from-nord-reveals-significant-impact-of-covid-19-on-americans-living-with-rare-diseases/>
 3. Data on file. Amryt Rare Hope Survey, Research conducted by Yolo Communications, October 2020

IMPACT OF COVID 19

CASE STUDY



CHRISTIAN RUBIO

Global Genes

The pandemic has had a real impact on the state of research.

As the pandemic took hold in March, we convened our community through our Alliances, which is how we do a lot of our work. On the Foundation Alliance side, which is a group of more than 600 (almost 650) rare disease foundations – advocacy foundations. On the Corporate Alliance side, over 110 industry companies, many of which are in biotech and in cell and gene therapy.

Through the two, we actually made a lot of inroads with a lot of research institutions, to understand what was going on, what was the impact being felt. We were able to break down the impact

of the pandemic of COVID-19 into two main buckets: 1) threats to continuity of care, and 2) threats to continuity of research.

There were probably around 1000 gene therapy trials in some state of activity that were either being paused from launching or were at major risk of disruption. With gene therapy trials in particular the big risk is the loss of cell lines that are so precious – especially in the ultra-rare community. If we didn't work quickly to move equipment and storage facilities around and make sure that storage was organised for everything that was needed, there was a risk that during lockdown anywhere where we were using animal models, the animals would not be able to be fed or accessed.

“The big state of play now is going to be the restart, and how quickly we can start back up. There’s a tremendous additional cost implication.”

CHRISTIAN RUBIO, GLOBAL GENES



A woman with long dark hair, wearing a white cable-knit sweater, is sitting and looking down at a tablet computer she is holding in her hands. Her right hand is resting on her chin, suggesting a thoughtful or concerned expression. The background is a blurred hospital ward with several beds and white curtains. The entire image has a teal/cyan color overlay.

PATIENT PERSPECTIVES

“Rare disease patients are a particularly vulnerable group of citizens who experience scarcity of medical knowledge, difficulties in accessing adequate care, as well as isolation from society due to the rarity of their condition and the scattered expertise.”

RUDIGER KRECH, WHO¹⁴

THE BURDEN OF RARE & ULTRA-RARE DISEASES ON FAMILIES AND EVERYDAY LIFE

We have discussed so far some of the very tangible challenges and impacts related to rare and ultra-rare diseases. However, there are also a number of more hidden factors that living with a rare or ultra-rare disease has on patients and their families which are acknowledged to be harder to quantify. Rare diseases affect many aspects of an individual's life including their social, educational and employment opportunities.¹⁶

From a patient perspective, there is the feeling of intense personal impact, the real physical, emotional and mental impact of having a condition and having a condition that may not yet have treatments.

Families may struggle to provide the right kind of support to patients and face significant hidden costs associated with the way that their care is managed that are not accounted for by health and social care systems.

All of these aspects have a devastating impact on quality of life for patients and their carers. They are therefore factors that must be recognised and taken into account in all elements of rare and ultra-rare disease patient care, so that every aspect, from design of trials, to administration of treatment, is practical for patients given their unique and difficult circumstances.

88%

of individuals
feel emotionally
exhausted by living
with a rare condition¹⁵



THE BURDEN OF RARE & ULTRA-RARE DISEASE ON FAMILIES AND EVERYDAY LIFE



JIMMY FEARON
DEBRA Ireland

The psychosocial impact of EB impact is enormous. A part of

my job is meeting people living with EB and families with a child with EB. They talk about the stress they feel, and the stigma their child feels. EB is visible and the general public tend to look and stare due to the open sores and bandages. Very difficult. There is also pressure on marriages as caring for a child is a 24/7 job leaving it hard work to develop a career. Marriages are tested to the limit as are general family dynamics and it can often lead to separation.



MAGDALENA DACCORD FH Europe

I appreciate that in order to develop treatment, it takes many years

and many patients. It's important that regulators talk to pharma and pharma talks to regulators, but it's also key that patients are involved right from the beginning from the design stage. It's important to acknowledge that everyone has got a critical role in this process.



PROF DR MERAL KAYIKÇIOĞLU
Ege University

It's not easy to be a physician with rare disease patients. You have to educate the whole family, and get them to accept treatment, if they are lucky enough to have access to that. For HoFH, you can

have adult patients as well as children – it is a disease of families.



NACA PÉREZ DE TUDELA AELIP

Disease has an impact on other areas of life, such as employment and the

social and economic setting. On many occasions, both the families and the people affected are obliged to give up their jobs due to their disease. Moreover, families and affected people state that they have found it difficult to do everyday tasks, and go through moments of disorientation, uncertainty, despair and loneliness caused by the unknown origin of the disease. There is a lack of economic assistance, and often a lack of information about care and technical assistance that could make their life easier.

Psychological support can be one of the most effective services in helping people and families with such diseases to cope, since they are obliged to contend with the negative social effects of the disease in their day-to-day life.



JAYNE SPINK
Genetic Alliance UK,
EURORDIS

A family or an individual who is faced with an

ultra-rare diagnosis, faces a huge emotional burden on top of the physical and emotional impacts which is linked to not knowing what the prognosis is, not knowing what their treatment options might be, and not knowing what the future is going to hold. You have the anxiety of an uncertain future. And on top of that, if you're a parent, you could find yourself facing a lot of new



THE BURDEN OF RARE & ULTRA-RARE DISEASE ON FAMILIES AND EVERYDAY LIFE

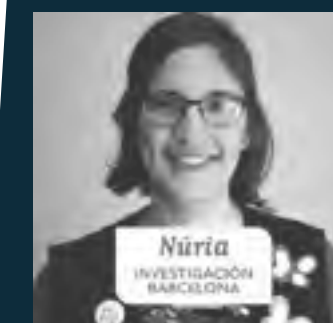
practical and financial challenges that come with caring for a loved one who has potentially complex needs.



**ANNALISA
SCOPINARO**
UNIAMO

Patients need health professionals who really know their disease. We need connection among clinicians at European level (and we are coming to this with the ERN, the European Reference Network). We need a multidisciplinary approach in care, and to have therapy accessible as close as possible to home. We need rehabilitation, social support, and all the technological aids that are increasingly available to help with the special needs of rare and ultra-rare disease patients.

CASE STUDY - HOLISTIC CARE



NURIA TARRATS
DEBRA Spain

We are the Spanish national charity for people affected by epidermolysis bullosa or EB, and we are an officially registered charity which has been awarded recognition by the Government of Spain. The team is comprised of 38 people all motivated by working for the same important cause, including the admin team, fundraisers, psychologists, social workers, nurses and 12 charity shop partnerships.

DEBRA Spain was created to support, inform and accompany both families and healthcare professionals. Our aim is to secure mutual support between families. Thanks to our team of psychologists, nurses and social workers, we help resolve problems and answer questions

on a daily basis. EB sufferers often feel rejection from society, a stigma. This cruel disease can affect the whole family.

School teachers are eager to understand, but others are often not. Employers may not believe that parents need time off from work to take children to appointments.

We are raising awareness with the hope that in the near future, people will not move away from someone with EB for fear of catching the disease.

We help to improve knowledge and understanding for professionals working in healthcare, social care and the education system.



“I AM NOT JUST A PERSON WITH A DISEASE”

Corporate ‘patient-centricity’ – or ‘patient focus’ – are popular buzzwords backed by actions to develop a more thoughtful and holistic approach to pharmaceutical development.

This chart, developed by Patient View (<https://www.patient-view.com/>), explains the concept of patient-centricity based on extensive feedback from patient organisations. Patient groups described nine attributes that are integral to corporate patient-centricity.

Patients are not just people with illnesses. They may be mothers, fathers, children, aunts and uncles. They have friendships and may have careers. They may even be medical professionals. As the patient-centricity diagram illustrates, when patients are the focus, they are involved in R&D, patient advocacy and other

aspects of pharmaceutical development.



DR MERAL KAYIKÇIOĞLU

Ege University

It’s very important for patients to be involved and organised during planning of clinical trials, other medical discussions and interventions. Some medical journals, like the BMJ, have patient editors.



JULES PAYNE

Heart UK

‘When NICE said no to a particular group of drugs, PCSK9i, we launched a campaign, because this decision was denying patients access to that group of drugs. We called it “Say yes to PCSK9 campaign.” We got healthcare professionals and the public



“I AM NOT JUST A PERSON WITH A DISEASE”

– the FH patients and their families – involved and together we overturned the decision’. That’s people power, really – healthcare professionals and patients coming together and the families coming together to make a change. In this space which is so ‘rare’, that is quite difficult, but I’m a great believer that small can still be powerful and mighty.

Nobody knows the impact of a rare disease better than patients themselves. Patients can bring great value to the medical world through involvement in every aspect of their treatment and can be enthusiastic and powerful advocates in the policy making arena. Aside from this however, patients with rare and ultra-rare diseases need to be viewed as people with the same social and psychological needs as everybody else. Ensuring these non-clinical needs are taken into account when considering the care and management of rare and ultra-rare disease patients is imperative to providing holistic care to improve lives for patients beyond their clinical symptoms.





SUSTAINABILITY AND HEALTHCARE ECONOMICS

DEVELOPMENT & SUSTAINABILITY: HEALTH ECONOMICS

One of the key factors in treatment development for rare and ultra-rare diseases which we have touched on in the other sections is access. Health economics plays a key role in this and in this section, we look more closely at the role of health economics in rare and ultra-rare diseases and related challenges.

The results of the Amryt Rare Hope Survey presented throughout this report show compelling support for the vision that rare diseases should be prioritised and that patients should be entitled to treatment despite the fact that their condition is rare or even ultra-rare.⁸ However currently, the reality for patients with rare and ultra-rare diseases

is very different for a number of reasons. The top three issues related to access to innovative therapies for people with rare diseases are:

1. The economic model is currently unsustainable
2. New products being approved for commercialisation by regulatory authorities often never make it to the patients who need them most because they are deemed too expensive
3. The cost of developing new therapies remains high and there are too few incentives

More than 300 million people around the world live with at least one rare disease. In most cases, the nearly 7000 diseases which are classified as rare do not constitute a large enough market to incentivise much needed medical innovation. Where treatments do exist, they are often expensive, and place economic strain on individual patients and their families, as well as on health systems. Numerous studies from around the world, including studies by UNDP, show that ill health and the costs associated with it are major factors which push people into poverty.

HELEN CLARK, UNITED NATIONS DEVELOPMENT PROGRAM (UNDP), STATEMENT AT THE 11TH ANNUAL INTERNATIONAL CONFERENCE ON RARE DISEASES AND ORPHAN DRUGS, 20 OCTOBER 2016



DEVELOPMENT & SUSTAINABILITY: HEALTH ECONOMICS



CHRISTIAN RUBIO

Global Genes

When there's a therapy, there's still the battle when it comes to pricing and making sure that those therapies are accessible. I think there's a real anxiety at the level of state Medicare and Medicaid managers or administrators who are seeing serious declines in state tax income because of the economic challenges this year to be able to afford some of these therapies. They do not have great surety that there won't be a deluge of these kinds of therapies coming for rare and ultra-rare disease, as they're entered under a therapeutic development. I think there are groups working on this that are starting to develop some really innovative models.

One of the issues patient advocacy organisations need to address is the creation of meaningful data sets from a burden side; from a quality of life perspective; and of course, working with sponsors and researchers, on the clinical data. The FDA has already shown a lot more interest in quality of life data and disease burden data that can help an approval get through, but those communities really need to be on top of collecting that data and how they're collecting it.



**DR MERAL
KAYIKÇIOĞLU**

Ege University

My main concern is lack of affordability. Clinical diagnosis can be the easiest part. One big problem is doctors don't like telling

patients they can't get treatment because of cost. Ultra-rare can be ultra-expensive on a per patient basis but have limited overall impact on the budget.



ELENA NICOD

Dolon Ltd

Our take on how the assessment processes for orphan drugs should evolve is that, first of all, the process should allow for appraisal committees to have a good understanding of the circumstances of the disease, the treatment pathways, and what the burden of the disease is. This includes understanding what matters most to patients – what benefits matter. For example, being able to take treatment in a pill, rather than having to travel to a hospital. Value needs to be understood

within this broader context, not only on clinical benefits. These processes should also ensure that the value of treatments is captured appropriately and consistently throughout the whole process. Appraisal Committees should involve other stakeholders such as clinicians and patients that can help resolve some of the uncertainties. Finally, a structured and flexible appraisal framework, with clarity on how decision-making works, is needed to ensure fair decision-making.

These are reflections based on work conducted within the EU-funded project IMPACT-HTA on appraisal for rare disease treatments, co-lead by Dr Karen Facey and Elena Nicod.



DEVELOPMENT & SUSTAINABILITY: HEALTH ECONOMICS



ADAM HUTCHINGS

Dolon Ltd

The 2000 EU Regulation on orphan medicinal products (OMP) was

introduced to mitigate the significant scientific and economic challenges inherent to the development of therapies for low-prevalence conditions with high unmet medical need and of medicines unlikely to attract investment. It established a set of incentives aimed at stimulating investment in rare diseases, by supporting development processes (through research grants and protocol assistance) and heightening potential economic returns (through orphan marketing exclusivity).

Dolon released a study in 2020 to contribute evidence on the current economic case for investment in OMP

and the impact on Regulation. We found that over half (74) of the 142 OMPs developed between 2000–2017 would not have been economically viable in the absence of the Regulation. The study showcases the extent to which the Regulation has stimulated innovation in orphan medicines. But despite the value brought to patients and health systems from this innovation, concerns about prices, patient access and sustainability of expenditure have led to increased scrutiny of rare disease treatments and a lower willingness to pay in recent years.

Dolon have published a report on building a sustainable business model which provides an in depth analysis of the orphan drug business model. This report can be accessed here: <https://dolon.com/rare-knowledge/publications>



JULIA JENKINS

Everylife Foundation for Rare Diseases

There is much discussion on the high costs of

drugs for rare diseases, however no one ever asks what is the cost of not treating rare diseases. Through our work in newborn screening, we found that end of life care for a child with adrenoleukodystrophy (ALD) costs \$3.4 million. It's easy to see that if a cure were to be developed, there be significant savings to the healthcare system, AND you also have a healthy child. With 93% of the 7000 rare diseases not having an FDA approved treatment, what is the true economic impact of rare disease? What is the cost of seeking a diagnosis, the costs hospitalisations, of traveling out of states to an expert, loss of work for caregivers, costs for home and car

modifications, paid caregivers, and the cost of special education? In 2019 the Foundation set out to answer these questions by launching a U.S. Economic Burden of Rare Disease Study. Data from our study (that includes private insurance data, Medicare and Medicaid and a study of the indirect medical costs collected from a patient survey) will be shared at our Rare Across America events surrounding Rare Disease Day. Additionally, the Foundation led efforts in the 2020 Appropriations bill tasking the Government Accountability Office (GAO) to study the costs of rare and undiagnosed diseases. Both the GAO and Foundation's studies will be published in the spring of 2021.



DEVELOPMENT & SUSTAINABILITY: HEALTH ECONOMICS

When it comes to reimbursement of treatments, currently, rare and ultra-rare diseases are largely assessed in the same way as other conditions, which, given their small populations, is not necessarily appropriate for these treatments. Whilst the regulatory environment is favourable for research and development, this doesn't follow through to the reimbursement stage, meaning potentially life-changing treatments often do not reach the patients who need them. There is both strong support and a will from key stakeholders to change this model to ensure that the whole process becomes more streamlined to ensure the innovations in research translate into improved lives for patients.





THE ROLE OF INDUSTRY

INTERVIEW WITH AMRYT PHARMA CEO DR JOE WILEY



Throughout this report, we have included perspectives from patient advocacy, healthcare professionals and healthcare economists. Here we discuss with Dr Joe Wiley, CEO of Amryt Pharma, the state of play in rare and ultra-rare diseases from his perspective both as a doctor and as an industry leader focusing on rare and ultra-rare diseases.

What is the state of play in ultra-rare diseases and what are the things that need to be agreed to have a sustainable future?

People need to understand that orphan and ultra-orphan are different and there is a general lack of understanding of that. I can think of very few instances

in which there are bodies that from a reimbursement perspective look at orphan diseases differently from ultra-orphan.

To put numbers on it, in the EU, orphan is less than 1 in 2,000, and ultra-orphan is less than 1 in 50,000. That is a huge difference that is significantly underappreciated.

That creates challenges across a whole host of metrics.

Trying to develop a drug for a disease that is that rare is enormously challenging. We have seen that with our EASE study in epidermolysis bullosa which we just completed. In order for us to do a Phase 3 study in EASE, it took us over three years, with 58 sites in 28 countries in order to recruit 223 patients.



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It was very time consuming and costly.

The regulatory agencies need to understand how difficult it is to recruit patients with these ultra-rare diseases. As we start looking for more products for ultra-rare diseases, the agencies will need to rethink how they look at this.

There has been some flexibility shown from the regulatory perspective. They seem to recognise that if you have fewer and fewer patients it becomes more challenging to have a traditional Phase 3 double-blind placebo-controlled study as the mechanism of approval.

Also, agencies in both Europe and the US have put in place appropriate incentives for companies to try to navigate these difficult waters and to do studies in these very rare diseases.

The problem then comes in post approval and launch, when we seek reimbursement. We face the barrier globally where reimbursement agencies would prefer the certainty of two robust Phase 3 studies with full data sets. Otherwise, they are not readily going to accept that there is a clinical benefit and they struggle to deal with the uncertainty. That is deeply unfair to patients with ultra-orphan diseases because it is impossible to bring that level of data.

So old metrics like saying that we want to see two double-blind placebo-controlled studies are unrealistic. And also, we see that some countries want to see data in their own populations. Again, that may be unrealistic.

I believe that Amryt needs to take leadership here in terms of increasing

the awareness of what an ultra-orphan disease actually is and what that means and just how rare these conditions are.

The cheap headline is the high price per individual who gets treated, but that actually fails to recognise the reality of the small number of patients who are actually getting treated with these drugs.

And thinking about national reimbursement, particularly in Europe, increasingly we're seeing a notional tax being applied to what reimbursement parties are willing to pay for orphan diseases. Quite frankly, for companies developing drugs in the broader orphan disease area, these caps can be applied and can work from an economic perspective. But if you apply that same metric to an ultra-orphan, that's deeply unfair because of the tiny, tiny number

of patients. Trying to make an economic case for launching products becomes increasingly difficult.

Governments around the world need to be aware of these facts if they are saying we want patients to have access to these drugs if they have these really rare conditions. There needs to be a recognition of what does that mean, and how does orphan differ from non-orphan disease and how does a drug for a rare disease differ from one for an ultra-rare disease.

[How can we continue to stimulate research and continued stakeholder support in ultra-rare diseases where patient numbers are very small, so that there is hope for patients with these diseases now and in the future? In particular, for ultra-rare diseases for](#)



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which there are currently no treatments?

That's a great question. We focus on this area. There is still a huge unmet need for the vast number of diseases for which there is still no treatment. For example, epidermolysis bullosa, EB. There is no approved treatment for EB. With the positive data in our Phase 3, we have the potential for the first ever approval in EB. Developing products for patients who have nothing else is hugely motivating for me and my team.

In terms of research, as I've already alluded to, there needs to be more flexibility in terms of how we get drugs approved in these vanishingly rare conditions.

The incentives that are already in place are extremely helpful. For example, the

Priority Review Voucher in the US. That is extremely helpful for companies that are in this space because it attracts investors to this area and allows us to raise capital to go and do the studies required.

I believe it has worked fundamentally and I would like that it continues. I would like to encourage Europe to do something similar. There is a reluctance in Europe to incentivise in that way. I believe that thinking should change.

We need investors who will make returns so that they will invest again in the next ultra-orphan drug development that we are trying to bring to patients.

When I talk about 'vanishingly rare' diseases, it means, for example, in HoFH, approximately 3 per million people globally. In generalised lipodystrophy it

means typically less than 1 per million. That's up to 65 patients in the UK, and 350 in the US. And we would be treating a smaller proportion of those.

That is why I refer back to the cheap headline about pricing. The economic impact of treating that small number of patients is negligible compared to treating much more common diseases and yet the focus is on the per capita cost rather than the cost to the entire system. I believe we need to change that attitude.

What evidence do we need to encourage spending on ultra-rare diseases?

The agencies are working with industry to try to get these drugs approved but then there is the barrier to access. Our biggest issue is getting access for patients to treatments. Again, systems have been

playing catch up for some time. Quite a number of countries have a different system for orphan diseases, and that is to be lauded.

There are still countries using rigid models to think about how value is delivered for patients which are not truly fit for purpose, given the paucity of data that we are dealing with. Having a super high bar in the terms of demonstrating cost per QALY, for example.

It's very difficult if you have tiny numbers of patients to make arguments around that. And there are very few examples of countries which recognise the difference between orphan and ultra-orphan.

A lot of countries are playing catch up on delivery of access for patients with orphan diseases. Amryt needs to be an



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advocate to chase governments around the world and reimbursement bodies to realise that there is a difference between orphan and ultra-orphan.

Also, I see Europe applying a mechanism to control per capita costs. That hits ultra-orphan disease patients much harder than it hits orphan patients.

Do different national and regional healthcare systems present challenges in ultra-rare disease treatment environments?

Yes, every country has its own mechanism, so certain countries are easier to navigate than others. Germany is a good example of a system that really works for drugs with orphan designation, that allows for these orphan and ultra-orphan products to be launched pretty

much immediately after approval.

Other countries take an awful lot longer. The UK can take 18 months or longer to get reimbursement post approval. So, countries need to get better at this. Is it fair that the German patients with EB, a devastating condition for which there is no approved treatment, where the skin is being blistered and wounded all the time by minor trauma, can get access to treatment while patients in other countries cannot?

I think getting the reimbursement process streamlined and sped up would only benefit patients.





CONTRIBUTOR RECOMMENDATIONS

WHAT CAN WE DO TO ENSURE RARE DISEASE MANAGEMENT HAS A SUSTAINABLE FUTURE?

Our overarching question when compiling this report was 'what can we do to ensure rare disease management has a sustainable future?' It's clear that much more needs to be done to ensure that rare and ultra-rare disease patients receive the attention they deserve and need to improve their lives and provide them with hope. It is also very promising that there is such strong support for this change not only amongst the rare disease community but more broadly the general public and below are some suggestions from our contributors on how this can be achieved.



MANUEL POSADA DE LA PAZ ISCIH, ICORD

I recommend creating worldwide registries for rare/ultra-rare disease cases. The problem is that many of these diseases result in new knowledge and copyright/publication restrictions do not allow data sharing among researchers. With ultra-rare diseases it is not simple to find cases. We should develop easier ways to find cases and share their data. This would contribute to better research and therefore, to find new treatments.



CHRISTIAN RUBIO
Global Genes

The reality is that rare and ultra-rare disease research is often a door opener towards insights of larger population, more prevalent disease. We

need to protect what some might think is an undue or over indexation of resources towards rare and ultra-rare. And let's not forget rare diseases as a whole, represent one in 10 Americans, and that is those directly affected. If we count their family members - in the economic impact of caring for people with rare diseases - you're talking about three in 10 people, at least in the American economy, being impacted by the rare disease population. Globally, we're talking about 350 to 400 million patients. So, you're looking at the world's largest patient population.



MAGDALENA DACCORD FH Europe

Another recommendation is for governments and ministries of health to encourage and foster collaboration with

patient groups and patient advocacy groups. The Czech Republic is one of those countries where I'm impressed how things are structured. And in Poland there's an ombudsman, and in UK one of our patient groups has a big say in actually impacting and influencing through advocacy. It will differ in different countries. But it's about commitment from the policymakers to treat, respectfully, and partner with patient communities.



VICKY MCGRATH
Rare Diseases Ireland

There is a very important place for industry, investors and people who are willing to take risks and invest in the development of new treatments and therapies. Likewise, there is a better way for government to spend their money in



WHAT CAN WE DO TO ENSURE RARE DISEASE MANAGEMENT HAS A SUSTAINABLE FUTURE?

a more thoughtful and equitable manner that would benefit society as a whole not just those that represent the majority. If we thought more about informing and educating the majority about the challenges facing the minority they would go to bat for those living with rare diseases – they'd say these people need it a little bit more than I do. Let's raise all boats together not just mine.



DURHANE WONG-RIEGER CORD, Rare Disease International

Regarding developing treatments and getting them to patients: the whole system is not set up to support ultra-rare diseases. We need to sit down and design it from the ground up – from discovery, clinical trials, regulatory approval, support and access. It's like the undiagnosed

disease network the NIH has set up. It's a wonderful network and I applaud what they've done but they've stopped at the diagnosis. Okay, we've got a diagnosis, now what? There is no 'now what'. We should address that.



JULIA JENKINS
Everylife Foundation for Rare Diseases

Only for rare diseases does the entire burden of treatment development fall on the shoulders of the patient. A rare disease patient must start their own non-profit, find the researchers, raise money to fund the research, create registries and find patients, and then convince a drug company to begin development. Behind every approved treatment for a rare disease, you will find patients and families who did the work in the

beginning to de-risk the process for industry. We must alleviate those burdens on families. The incentives for drug development must be changed. Innovations in cell phones and computers are driven by the latest science and consumer needs, however treatments are developed based on what is reimbursed or what has patent life or exclusivity. Even though a pill might be a preferred treatment method for patients, an injectable will be developed because it has a higher reimbursement rate. Treatments are sitting on the shelves of research labs across the world that will never be developed because there is no way to recoup the investment. We need policies that ensure that the needs of the patients and the best science are the main drivers of therapy development.



NACA PÉREZ DE TUDELA AELIP

Patients and families affected by a rare disease have to cope with numerous challenges in different aspects of their lives. It takes years to receive a diagnosis, and they may receive unsuitable treatments or not receive any treatment through public health provision. These patients and their families literally embark upon a pilgrimage in search of reference physicians, clinical trials or other alternatives that will help improve their quality of life.

These challenges must be addressed in an integrated, worldwide healthcare plan that addresses all the challenges I've listed, thus making it possible to improve the quality of life for patients and



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families affected by rare disease.



**JUAN CARRIÓN
FEDER, ALIBER**

On behalf of the associative network I represent, we see the

need the need to reassess cost-benefit in providing a response to rare and ultra-rare disease. We believe research into these conditions will generate savings for the healthcare system and will also offer an indirect benefit for research into the more common diseases.



JAYNE SPINK
Genetic Alliance UK,
EURORDIS

We need to get better in terms of understanding the impacts of rare diseases: who is affected, the natural history. We need

to do this by collecting data from a range of sources in a systematic way, a comprehensive way. Unless we start doing this, we're not going to know what services are needed and what services are affected, or how we can build effective services and care pathways for the ultra-rare community. We will never know those things unless we comprehensively collect and make full and proper use of rare disease patient data.



**ANNALISA
SCOPINARO**
UNIAMO

For years, we have stressed that we should consider people with rare diseases as full persons: we cannot forget any aspect of their life. At the moment of diagnosis, we need psychological support, for the

patient and for the family, to help them in the first moments of the diagnosis (always a very stressful period) where they experience depression and isolation. It is much worse when the diagnosis is not correctly given or it is delayed in time. There is also a considerable economic burden on families as they visit different specialists in different cities far from their home place. Then they try to get the best of rehabilitation services. Very often they have to pay for them. They need support at school and in workplaces and they need to find suitable places when we go on holidays. They need home-therapy when possible and tele-assistance because it is very difficult to afford long journeys to meet specialists.



JULES PAYNE
Heart UK

We need investment around systematic testing for rare diseases. By this I mean testing in a routine way to identify rare and ultra-rare diseases in early childhood, and then we can manage the conditions going forward. I think we also need a national/international registry.



**DR MARTIN PRØVEN
BOGSRUD** UCCG, Oslo
University Hospital

In Norway we have widespread genetic testing so we can obtain genetically verified FH early. This is particularly important for HoFH patients, because if they are not identified young, they die much sooner than they would if they had treatment. I recommend more genetic



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testing for rare and ultra-rare diseases.



**ADAM HUTCHINGS
AND ELENA NICOD**

Dolon Ltd

The biggest improvement globally would be to

remove International Reference Pricing. It is the biggest impediment to global access.

investment in research and, building on the success of the first EB2020 Congress last year, our commitment to global collaboration.



**TONY BYRNE
DEBRA UK**

There is currently no cure for EB and, while there are some treatments, the

effects of severe wounds, pain and itch are often debilitating. We need to find disease-modifying treatments to improve quality of life and make them available to all who need them. If we are to succeed in curing EB, we will need to increase our





CONCLUSION

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This report is authored by experts across rare and ultra-rare diseases with contributions from healthcare professionals, representatives of patient advocacy groups, health economists and the pharmaceutical industry. These perspectives from those working on the front-line wholeheartedly agree that so much more can and needs to be done to focus stakeholder attention on rare and ultra-rare diseases and ensure patients living with these distressing conditions receive the consideration, attention and resources they deserve.

Everyone involved in this report is working to provide hope for those with the greatest need.

As outlined in this report, rare and ultra-rare diseases present specific and unique challenges to healthcare systems and

this has led to a very difficult environment for rare and ultra-rare disease patients, for whom there are limited management options and solutions. Where there are effective treatments available, patients often have little or no access to them. Rare and ultra-rare diseases are largely neglected by society despite, collectively, representing the largest patient population of all.

Rare and ultra-rare diseases can only become a greater priority if people know about them and understand the damaging impact that they have on patients' lives. We recognise that more high-profile diseases such as cancer and heart disease require attention, but so do diseases that affect smaller patient numbers.

We need to find ways to raise awareness of rare diseases to ensure

they are actively on the agenda of all stakeholders.

In rare and especially ultra-rare diseases patient numbers are very small. They don't fit the standard model for conducting clinical trials, and barriers to knowledge sharing and inflexible appraisal mechanisms exacerbate this.

There is a need for global networks and an infrastructure that supports rare diseases and accounts for these small patient numbers.

Regulatory and reimbursement systems are out of sync when it comes to rare and ultra-rare diseases. Although there is arguably a favourable environment for research and development, reimbursement models do not allow this to be translated into access for patients. **Reimbursement models for rare and**

ultra-rare diseases need to be reviewed and updated to streamline the process to ensure investments in research actually deliver positive outcomes for patients.

There is no one type of organisation or industry that can single handedly change the rare and ultra-rare disease environment for patients. A multidisciplinary approach is needed to ensure there is a continuum from research to patients. **Patients must be involved at every stage**, to ensure any progress made is not only efficacious clinically but actually effective in the real world. We must address not only the clinical symptoms but all areas of patients' lives that are affected by their condition. **The burden of illness and impact on quality of life related to rare and ultra-rare diseases are currently underappreciated; they need to be**



CONCLUSION

upweighted and considered alongside clinical data to truly alleviate the burden on patients.

As the Amryt Rare Hope Survey showed, 93% of people think if they were diagnosed with an illness, it would be likely there would be a treatment available for it. We are calling for all those in a position to help change the current landscape for patients with rare and ultra-rare diseases to act now to help make this a reality.

We are committed to working together, and constructively with all relevant stakeholder to make rare and ultra-rare diseases a priority and give patients with these diseases a brighter and sustainable future.





The Rare and Ultra-Rare Diseases
Prioritisation and Sustainability: A Report
From The Front-Line is supported and
funded by Amryt Pharma.



A young child is seated in a wheelchair, wearing large white headphones. The child is looking upwards and to the right. The entire image is overlaid with a semi-transparent teal filter. The word "GLOSSARY" is written in large, white, bold, sans-serif capital letters across the center of the image.

GLOSSARY

GLOSSARY

Rare disease: The European Medicines Association (EMA) defines a disease as rare if it affects fewer than 5 in 10,000 people (about 30 million people) across the European Union (EU).²⁰ In the US, the Food & Drug Administration (FDA) defines a rare disease as a condition that affects fewer than 200,000 people nationwide.²¹

Ultra-rare disease: In the European Union, an ultra-rare disease is classified as affecting one person in fifty thousand or fewer. Most ultra-rare diseases affect as few as one in a million people or less.⁶

Orphan disease: Rare disease is sometimes referred to as an orphan disease, but 'rare disease' is used much more often than 'orphan disease'. Ultra-orphan disease is used colloquially.¹⁵

Orphan drug: According to the US Food & Drug Administration (FDA), drugs and biologics intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200,000 persons

in the US, are orphan drugs.²³ The European Medicines Agency (EMA) uses the term 'orphan medicines' for drugs for rare (and ultra-rare) diseases.²⁴

Orphan medicinal products (OMP) are for diagnosing, preventing or treating life-threatening or very serious conditions that are rare and affect not more than 5 in 10,000 persons in the European Union (EU). The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market.²⁵

Clinical trial: The National Institutes of Health in the US define a clinical trial as a 'research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes.'²⁶

Clinical research trials may be conducted by government health agencies, researchers

affiliated with a hospital or university medical programme, independent researchers, or private industry. For some patients, clinical research trials represent an avenue for receiving promising new therapies that would not otherwise be available.²⁷

Phase 3 Clinical Trial: Phase 3 trials compare a new drug to the standard-of-care drug. These trials assess the side effects of each drug and which drug works better. Phase 3 trials enrol 100 or more patients. There can be more than two treatment groups in phase 3 trials. The control group receives the standard-of-care treatment. The other groups receive a new treatment. Phase 3 is the last phase of testing to be completed before the drug's details and clinical trial results are submitted to the regulatory authorities for approval for use.²⁸

Pricing and reimbursement (P&R): Pricing and reimbursement broadly refers to establishing a price for a new drug which considers a number of factors including how well the medicine treats patients, how many patients

might benefit from it, the value that health systems might place on a medicine in the disease area in question and the price of competing products.²⁹ Reimbursement refers to when a payor/regulatory body reimburses the manufacturer fully or partially for their product.

Bio/pharmaceutical research & development (R&D): The initial search for a molecule to treat the disease, through to having a product ready to market.³⁰

Burden of disease: this term generally describes the total, cumulative consequences of a defined disease or a range of harmful diseases with respect to disabilities in a community. These consequences include health, social aspects, and costs to society. The gap between an ideal situation, where everyone lives free of disease and disability, and the cumulated current health status, is defined as the burden of disease.³¹





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