ECONOMIST IMPACT

Connecting the Dots

Embedding Progress on Rare Disease into Healthcare

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Contents

About this report

Connecting the dots: Embedding progress on rare disease into healthcare is an Economist Impact report, sponsored by Takeda, that takes a holistic look at the challenges patients with rare disease face in accessing treatments. The report considers where healthcare and health systems have made progress in helping people living with rare disease, as well as identifying ongoing areas needing improvement.

The report focuses on seven markets in Europe and the Asia-Pacific region: Australia, France, Germany, Japan, South Korea, the UK (specifically England) and Taiwan. It includes an analysis of the speed of reimbursement decisions for eight treatments for rare diseases across the focus markets.

The report contains insights from desk research, a literature review, an expert panel, and in-depth interviews with a range of healthcare professionals, academics, patient advocates, health economists and other stakeholders. Our thanks are due to the following for their time and insight (listed alphabetically):

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- Durhane Wong-Reiger—Chair of Rare Disease International, President of Asia Pacific Rare Disease International, President and CEO of the Canadian Organization for Rare Disorders
- Serena Wu—Founder of the Taiwan Foundation for Rare Disorders, Taiwan

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Executive summary

Recent years has seen progress in the diagnosis and care of rare diseases, but health systems need to join up such "dots" of success and integrate them into mainstream care. The good news is that doing so does not involve the wholesale re-invention of existing institutions, structures and processes, so much as adjusting them. The bad news is that in the meantime the more than 7,241 identified rare diseases represent a huge collective health burden. Between 3.5% and 5.9% of the world's population live with a rare condition and, depending on what is measured, the average health system cost arising from a patient with a rare illness is anywhere between double and 20 times that of individuals treated for other causes.

This report takes stock of current progress in the diagnosis and care of rare diseases, and considers what health systems need to do to further improve outcomes. We focus on evidence from seven countries: Australia, France, Germany, Japan, South Korea, Taiwan, and the UK (specifically England). A key issue is access, and we have conducted an original analysis of the time between regulatory approval and reimbursement decisions of rare disease treatments. We have also drawn on input from a global group of 11 expert advisors and interviewees, with at least one from each study country.

We find that there are two areas where substantial progress has been seen—that is, two "dots".

The "dots" of success

Dot #1: The success of a regulatory environment that encourages R&D

In previous decades, only a handful of rare diseases had any treatment options, largely because the market for a successful product was too small to recompense the outlay. However, since late last century, all of our study countries have adopted some version of orphan drug regulation containing a combination of measures to reduce the cost of R&D for rare disease treatments or to increase potential financial returns.

More recently, regulators have created legal mechanisms to permit time-limited, conditional approval for products with promising but limited efficacy and safety evidence and the potential to address substantial unmet need. For such treatments, real-world evidence is gathered in order to make a final decision on approval at a later time.

The success of these measures vary, but they have accelerated access to treatments. The most impressive results in our study countries took

place in the EU: before the adoption of its first set of regulations in this field in 1999, only eight approved orphan products existed. By 2022, that number has risen to 207.

Dot #2: The success of shortening the diagnostic odyssey

A correct rare disease diagnosis typically involves seeing between five and seven doctors during a four-to-five-year process. Sometimes, it can take decades. To speed this process up, several countries have established dedicated rare disease diagnosis programmes.

The largest such programme in our study countries is Japan's Initiative on Rare and Undiagnosed Disease. Its multi-disciplinary diagnostic teams examine patients and, if appropriate, can order a battery of tests, including whole genome sequencing. Similar programmes exists in Australia and South Korea. Meanwhile, France and Germany have specific clinics for undiagnosed patients, and the UK is establishing "Syndrome Without a Name" facilities, which will take a multi-disciplinary look at those with as-yet-unidentified rare diseases.

Such efforts can have impressive results. Between March 2019 and March 2020, Japan's initiative gave a definitive diagnosis to over half of patients assessed. Australia's and South Korea's efforts also show good outcomes. One expert interviewee reports that, for rare disease clinicians, diagnosis has now become "not such a big issue."

Where the "lines" of better integration are needed

Line #1: The need to integrate rare disease care into the mainstream

In addition to progress on diagnosis, most of our study countries have a range of specialist centres, services or networks for rare diseases. However, these do not however, necessarily cover all rare illnesses, and in practice they are too little known by primary care providers.

To attack this problem, awareness raising within the wider health workforce about these resources is essential. Studies from various countries report a lack of confidence among doctors in treating rare disease patients. Another pressing current need is for more clinical practice guidelines. Few are available compared to the number of conditions, and too often existing ones are dated: only eight consensus and evidence-based guidelines for any rare blood disease have appeared in the past five years.

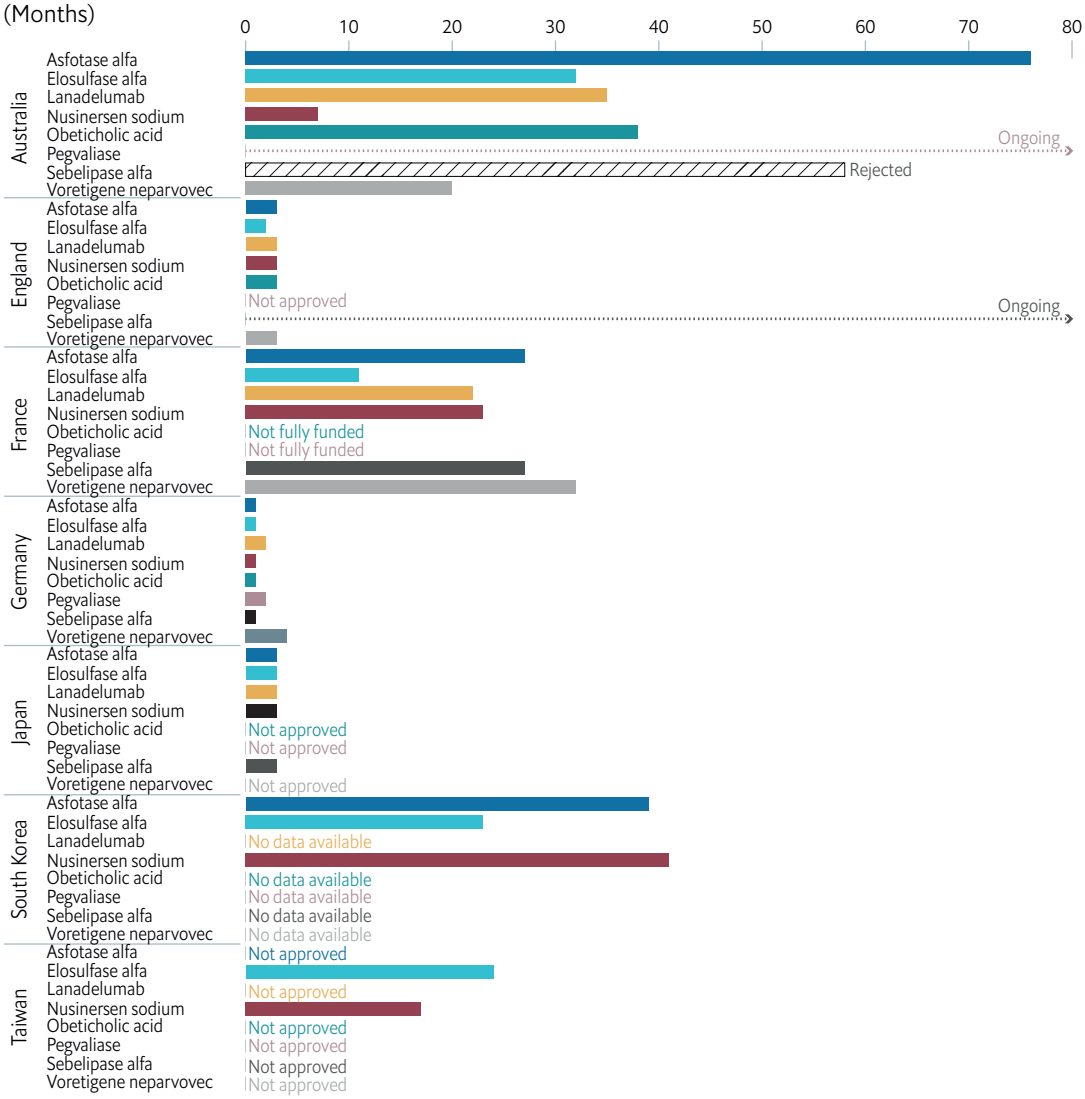
Line #2: The need to reshape HTA appraisal processes to the realities of orphan drugs

Many orphan drugs present significant challenges for health technology assessment (HTA) bodies. There are difficulties in generating evidence on a small patient population, a lack of knowledge about the disease and poor understanding of the health burden. Combine with these the frequently high cost of new products, and HTAs face a complicated task in assessing value.

HTA bodies in our study countries have been experimenting with options to deal with orphan drugs. These include using different clinical and economic evidence rules, incorporating greater data flexibility, considering alternative reimbursement rules, using conditional approval, and a higher willingness to pay figure.

Our analysis of the time from drug approval to a positive reimbursement decision for seven orphan drugs and one gene therapy treatment reveals substantial differences between countries (Figure E1; see the methods note in the appendix for how this was done). We describe "country HTA snapshots" in the next section.

Figure E1: Approval to reimbursement time for seven orphan drugs and one gene therapy treatment



Source: Economist Impact.

Note. Data on regulatory approval date, HTA submission date and reimbursement date were obtained from the MAESTrO database, developed by Wonder Drug Consulting Pty Ltd, along with grey literature searches. The data extraction was conducted between March and May 2022. Assumption for Japanese data made according to Pharmaceutical Regulations in Japan that requires the Reimbursement Pricing Process to be completed in 90 days the longest.[87]

Drugs that are labelled "Not approved" signify that there has been no regulatory approval date. "Rejected" drugs signify that a drug has been approved by a regulatory body but has not been denied reimbursement. "Ongoing" drugs signify that regulatory approval has been granted but the assessment for reimbursement is still ongoing. "Not fully funded" drugs are drugs that are not 100% reimbursed by the government. "No data available" signifies that data was not found during Economist Impact's research.

Line #3: The need for more and better registries

Data are essential to improved treatment of rare disease, as well as to better policy and programmes. The number of registries that cover one or more rare diseases—over 800 in Europe, 88 in Japan—pales next to that of known rare diseases. Moreover, many registries are small

with no common set of standards for gathering and structuring data. The result is substantial fragmentation. (A bright spot in this landscape has been the recent opening of France's Banque Nationale de Donneés Maladies Rares. After a decade of work, it now holds information on nearly a million patients with any of roughly 5,600 rare conditions).

Meanwhile, efforts to improve rare disease care have been stymied by a lack of health system information on resource use for patients with these conditions. Indeed, the 10th edition of the International Classification of Disease Codes did not even include most rare diseases. This is an omission rectified in the 11th edition, which countries should adopt as soon as possible.

The most important connection: Working with patients

Health systems are coming to understand that partnering with patients is indispensable to improved healthcare delivery and policy development. Here are two areas where a greater patient role is especially important in the field of rare disease:

Enhancing the patient role in HTA appraisal and reimbursement decisions

How patients assess the range of impacts from a given treatment should have a crucial role in determining its value. However, most HTA processes were built around payers, industry and healthcare officials. Bringing the patient voice into decisions on value is therefore essential. The HTA systems in our study countries have different weaknesses and strengths in this area.

In Asia, meaningful participation is lacking. Japan's HTA process has no formal patient role. In South Korea and Taiwan, patient input is so limited as to have no discernible impact. In other states, especially Australia, Germany and France, patients are consulted in a range of different a ways at various parts of the HTA process. However, a lack of transparency frustrates patients and their advocates. This takes at least three different forms: first, it is often unclear how to participate in the process; second, structures are not necessarily fit for purpose; third, HTA bodies provide too little clarity on the impact of patient input.

Even where patients have a role throughout the process, as with England's National Institute for Health and Care Excellence (NICE), rare disease groups are often too small to be able to develop expertise in the HTA process. Accordingly, they require support.

Patients and registries

An obvious initial decision for any disease registry is what information to collect. This has a fundamental impact on the uses of the resultant data, and to be of value to patients, registries must collect information on the fields of most interest to them. Patients thus need a role in registry management, for these repositories yield the most benefit.

Over many years, groups of rare disease patients have created a wide range of registries with data which is of particular relevance to them—not just clinical information but details of the economic and social impact of their conditions. Ultimately, however, not all rare disease groups will have the assets or skills to operate such facilities.

An Australian rare disease umbrella group, Rare Voices, is undertaking an approach that promises to raise the profile of patients within registry governance. In 2018 it founded the National Alliance of Rare Disease Registries. By convening the conversation on standards among these organisations, it has also insured that patient concerns would be a key part of the discussion.

Bringing it all together

The report identifies several areas where, although some improvements have occurred, more needs to be done. We discuss these in the report's conclusion. They include:

- Integration of rare disease awareness and care into the health system mainstream
- The comfort of HTA programmes with the challenges of assessing the value of rare disease treatment
- Improvements to patient registries and health system information to mine for real world evidence
- Empowerment of the patient voice

Progress in these ways would help people living with rare diseases to receive better care, as well as reduce the high health system costs for this group of patients. But connecting the dots for those living with rare disease is not simply a matter of providing better care to the significant minority of the population with such conditions, as important as that is; the results of these efforts will mean better healthcare for all.

Country HTA snapshots

Germany

Insurers in Germany must pay the asking price for any new drug from the moment of approval—in the case of orphan drugs, approval comes from the European Medicines Agency (EMA) rather than German domestic officials. Accordingly, coverage is rapid for all eight drugs studied (see Figure E1). However, the companies selling the drugs must provide real-world data on effectiveness and cost. After a year, the drug is reassessed in the light of such evidence, which may lead to confirmation of the price (automatically if the aggregate cost to the health system below €50m—US$49.8m), renegotiation of the price, a further period of evidence gathering or discontinuation of coverage.

England

The English National Health Service (NHS) covers nearly as many of the eight drugs as Germany—six—and almost as quickly. Here speed comes from the willingness of NICE, the HTA body, to consider the case for reimbursement before a drug receives regulatory approval. In addition, while unlike Germany, NICE has a formal willingness-to-pay level (an upper limit on price, essentially), this is five to ten times higher per quality adjusted life year (QALY)—depending on circumstances—for orphan drugs than for non-orphan ones. Following a reform made in 2022, NICE gives those making assessments for rare disease treatments greater flexibility to consider a wider range of evidence when determining the value of a new product.

France

France takes longer to formally approve reimbursement than our other European country studies. After the EMA approves an orphan drug, France's Haute Autorité de santé (HAS) conducts a cost-benefit analysis. Assessments of orphan drugs can take account of a wider range of evidence of value than those of other products. If the total annual cost of the drug to the health system is below €30m, the producer's price is accepted. If not, the HAS results feed into price negotiations between another body, the Comité économique des produits de santé (CEPS), and the drug producer. These tend to be very lengthy. To improve access speed in the interim, France has early access programmes that pay for the treatment from the time of—sometimes before—EMA approval. However, if the producer and CEPS cannot come to terms, coverage of the drug ceases.

Australia

The Australian health system covers six of the eight drugs in our study. However, access takes far longer and, unlike France, the country does not have an early access programme. The Pharmaceutical Benefits Advisory Committee (PBAC) conducts an HTA for new products, but does not have special evidence rules for orphan drugs. PBAC data then inform the decision by the Pharmaceutical Benefits Scheme (PBS) on inclusion in its formulary. Although no formal willingness-to-pay amount exists, orphan drugs are frequently turned down

one or more times before an application is made at a price that the PBS will accept. Where the PBS does decline coverage, drug makers can apply to the Life Saving Drugs Programme (LDSP), which will fund—regardless of cost-effectiveness—medications that offer increased life expectancy for a serious condition that lacks alternative treatments, and where producers will collect real-world data on outcomes. Although, most drugs eventually get covered in some way, the time between regulatory approval and patient access can be lengthy—over six years in the case of Asfotase alfa, a treatment for perinatal/infantile and juvenile onset hypophosphatasia.

Japan

The Japanese health system also covers six of the eight drugs in our study, although only two were assessed under new HTA rules in place since 2019. Under these rules, the system must reimburse all drugs at the producer's requested price within 60-90 days of approval. Unlike other treatments, drugs with purely rare disease indications do not need to go through any further HTA process. Drugs that can treat both an orphan and non-orphan condition must go through a year of real-world data collection. Following this, the Ministry of Health, Labour and Welfare mandates a price based on complex formula involving improvement over any existing therapy, a premium to reward innovation and reductions that kick in when the price exceeds a certain level of cost per QALY. These cost per QALY levels are one and a half times higher for mixed-use drugs than they are for non-orphan drugs.

South Korea

The South Korean health system currently covers only two of the drugs studied here. Under rules adopted in 2015, if orphan drugs can demonstrate substantial clinical effectiveness, the national insurance system will pay a price based on those paid in other major markets. For most products, proof is too limited to fall into this category. However, should a drug be reimbursed in three of seven major pharmaceutical markets, the health system is willing to try to negotiate a price. This system has had limited success, with the health system paying for just 56% of approved orphan drugs. The impediments to greater coverage are various: manufacturer reluctance to apply for reimbursement in such conditions, official concern about increased spending on rare disease, a typical one-to-three-year period to assess an application and a 30% rejection rate.

Taiwan

The Taiwanese health system also funds only two of the examined drugs. The country's HTA system for both orphan and non-orphan drugs in that it includes an assessment of cost per QALY for both. Although the willingness to pay figure is higher for orphan drugs, the authorities do not make it public. Moreover, while a ring-fenced budget exists to pay for rare disease treatments, this only applies to medication for 236 recognised rare diseases. Even where a drug is reimbursed, strict conditions can reduce access. For example, Nusinersen sodium, a treatment for spinal muscular atrophy, is covered for just 10% of patients who could benefit. Concerns about high cost are likely to slow any change.

Background

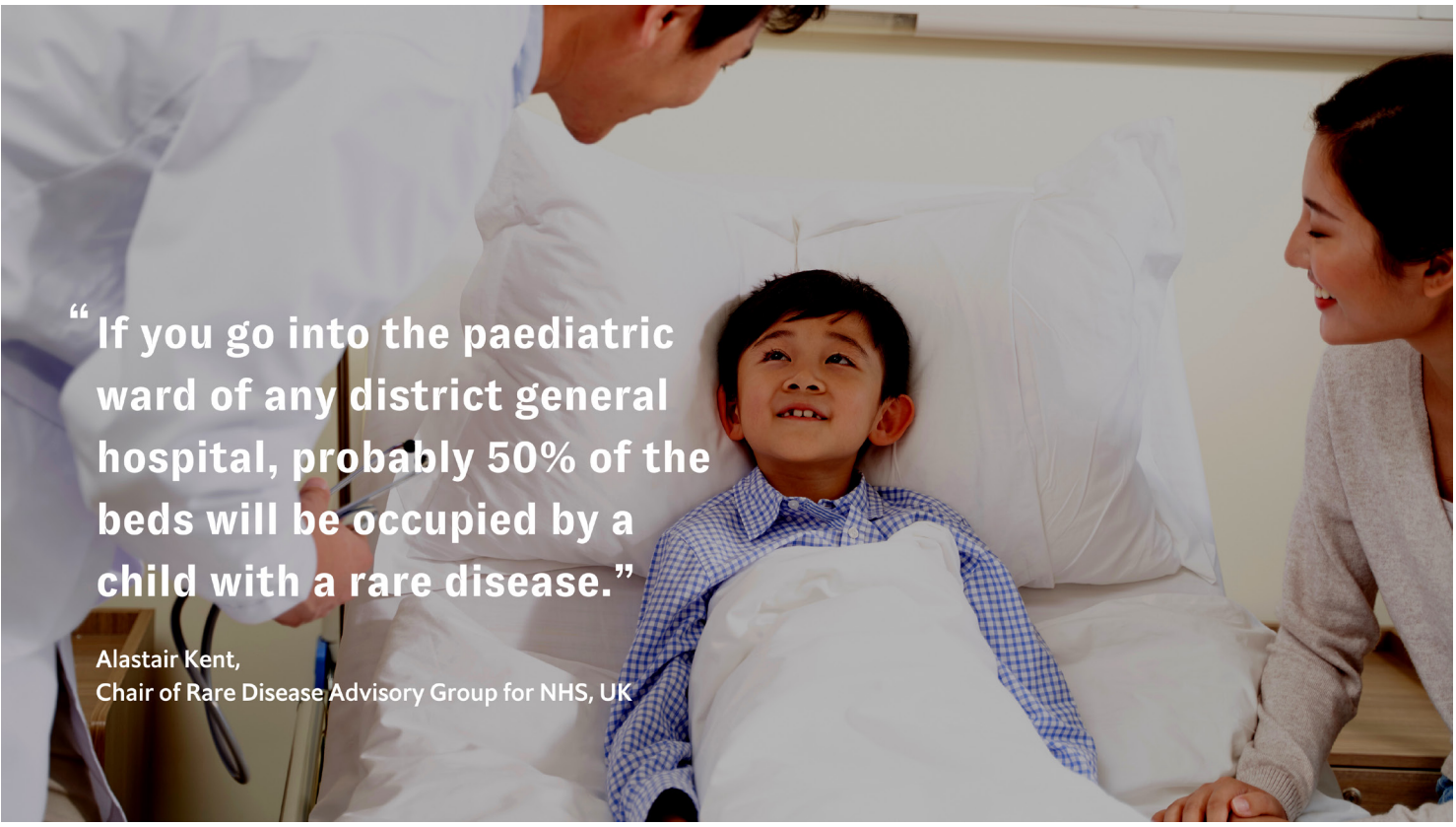
Rare disease: Learning to see a forest amid so many trees

A precise definition of rare disease is not essential to appreciate the toll of a given condition on an individual. Anne d'Andon, a medical doctor with extensive experience in drug development for rare disease, points to the impact, in terms of awareness, of an annual Muscular Dystrophy telethon that takes place in France: "In any little village [people] are aware that there are rare disorders, that they can be severe, that they affect children and adults, and that they are difficult to cure." However, to look beyond the specific struggles of particular patients, their families and carers, and to see the aggregate impact of thousands of rare diseases, requires a coherent conceptual framework.

This is harder than it might seem. Given the biological differences between rare conditions, an overarching category is defined by deciding on a measure of their single shared attribute: rarity. Any cut-off used is ultimately arbitrary. As a result, while the concept of orphan or rare disease as a group of conditions has existed for decades, convergence toward something like a consensus definition has been slow; even as late as 2015, a systematic review identified 296 definitions from 32 countries.[1]

In most major jurisdictions, national classifications are now at least similar. The orphan drug rules of the EU, the UK and Australia deem rare any serious condition with a prevalence of under five in 10,000 people. Other countries use upper limits on the absolute number of individuals affected within their total populations. In Japan and Korea, these work out to a little under four people in 10,000. In Taiwan, the number is lower—the incidence must be less than one in 10,000, and as Yin-Hsiu Chien, clinical professor in paediatrics at National Taiwan University explains, "this is the minimum requirement to be acknowledged as a rare disease—there are additional requirements, such as the disease having a genetic origin and being difficult to diagnose and treat."

Academic discussion gravitates toward the EU definition because it was adopted by Orphanet, a now 41-country network that maintains the most complete rare disease database in the world. Orphanet had information on 7,241 unique rare diseases as of May 2022. This number is steadily growing (it was 7,218 in March).[2] Some—for example, sickle cell disease, Down's syndrome, and cystic fibrosis—are common enough to be well known. Most, though, are extremely unusual: 85% of rare conditions affect fewer than one in a million people.[3] Such uncommon ailments could easily be missed by health systems. Even if noticed, as Alastair Kent, Chair of the UK Rare Disease Forum, recalls, "not so many years ago, rarity was indicative of not many people [affected], for whom probably nothing could be done anyway. Therefore they were not very important."



Looking at rare diseases in aggregate, however, shows that this would be a grave error. Although the precise prevalence figures for any given rare condition are frequently inexact, the overall picture is clearer.[4] The best estimate is that between 3.5% and 5.9% of the world population have one of these illnesses. Most rare diseases (57%) are known to appear initially only in children, while 9% present first in adults. The large majority (73%) also have a genetic origin, with the rest arising from a range of causes, including infections, environmental contaminants or auto-immune disorders.[3]

While the aggregate prevalence numbers are large, more striking is the human and economic toll of rare disease. “If you go into the paediatric ward of any district general hospital, probably 50% of the beds will be occupied by a child with a rare disease,” says Mr Kent. “Cumulatively, they have a huge impact on healthcare systems.” Any number of studies bear this out. Data from Ireland between 2006 and 2016 show that 59% of deaths among people under 16 arose from a rare disease.[5] In the UK, rare disease patients diagnosed in the year spanning April 2017 to March 2018 incurred healthcare costs of over £3.4bn (US$4bn)—double the expense per patient per hospital visit compared with those with other conditions.[6] In Taiwan, data from the National Health Insurance Research Database reported a 20-fold difference in average health expenditures between people with a rare disease and the overall population.[7]

The roots of efforts to deal with the challenges of rare disease

Our knowledge of the collective rare disease burden is relatively recent and still evolving. Orphanet’s database has existed for only around two decades, during which it has expanded from information on just a few hundred conditions in Europe to its current broader, global focus.

Probably the earliest effort that addressed rare diseases as a group was Japan's reaction to unexpectedly high levels of subacute myelo-optic-neuropathy (SMON), a severe neuro-degenerative disorder. Its 1972 "Outline of Measures against Intractable Disease" responded to the problems arising from unusual conditions in general, which the experience of SMON had made apparent.[8] From a global viewpoint, the bigger development in coming to terms with the rare disease burden was passage in the US of the Orphan Drug Act in 1983. It addressed a major impediment to research and development (R&D) of treatments for rare conditions: the lack of financial reward likely, given the inevitably small potential market. The act created a new orphan drug designation—under which products received a range of benefits—to make research into rare disease treatments more attractive. Several jurisdictions, including Japan, Australia, the EU, Taiwan and South Korea, followed the lead of the US over the next two decades. Since then, the existence of some form of orphan drug designation has spread to many developed countries.

Regulatory pathways have continued to evolve. Early developments marked the appearance of substantial patient influence on policy in this field, especially in the US, the EU and Taiwan, where patient groups played a key role in shaping legislation. Like regulation, patient influence has also evolved at different rates in various countries.

The initial orphan drug rules also involved the first national efforts to define rareness. This allowed early efforts to tackle another rare disease-related challenge for health systems: sparse data. It is no accident that in 2000—the year after the EU's orphan drug rules appeared—Orphanet went from being a unit within France's research body INSERM to one with European support.[9] Orphanet's arrival saw the beginning of the aggregation of research that gave a more overarching view of rare disease as a whole.

Soon after, national action plans and strategies began to address the challenges that health systems face in treating rare conditions. "These national plans are the best kind of vehicle for effective policy change around rare disease," says Eric Obscherning, an expert on rare disease and associate director for global health at Crowell & Moring International, a public policy consultancy.

European countries were the pioneers. Between 2005 and 2020, 25 EU states put in place national rare disease action plans.[10] Such policies have also appeared in the Asia-Pacific region. In 2017 South Korea's first plan came into effect after its 2016 Rare Disease Management Act required the Ministry of Health and Welfare to create one every five years; in 2018 Taiwan adopted the Rare Diseases and Rare Genetic Disorders Care and Services Plan; in 2020 Australia launched the National Strategic Action Plan for Rare Diseases. Meanwhile, Japan made rare diseases one of nine priority areas of its Agency for Medical Research and Development in 2015.

These action plans have not always resulted in a permanent policy focus. Most European ones were time-limited and, by 2020, had finished without renewal.[10, 11] Nevertheless, even a first strategy can have important effects. France, the most active in pursuing national health care plans, is currently on its third. Before such plans existed, Dr d'Andon says, "everything that was done was coming from the initiative of a local hospital or clinician, or from patient organisations." Now, with the national plans, new infrastructure is in place which, says Dr d'Andon, is growing more robust with each new iteration of France's plan.

Initiatives have also begun to appear at the international level. In 2018, Asia-Pacific Economic Cooperation (APEC) launched its own Rare Disease Action Plan. More recently, in December 2021, the UN adopted its first "Resolution on Addressing the Challenges of Persons Living with a Rare Disease and their Families".

Existing dots of progress—and the missing lines in between

Given today's higher level of knowledge about rare disease, it is an appropriate time to review the state of play. This report considers where the healthcare industry and health systems have made progress in helping those living with rare disease. In doing

so, our research finds some important areas of progress—the dots—amid a wider field of persistent problems, across which lines are needed to connect the islands of success. The current areas of most pressing priority include integrating treatment with diagnosis, dealing with reimbursement decisions, involving patients and collecting better data.

Inevitably, in a study of this size, some limitations are necessary. One is that, in discussing rare diseases, we focus on those of genetic origin. This is not to diminish the importance of other rare conditions: indeed SMON, which triggered initial changes in Japan, can be traced back to the use of an anti-fungal drug.[12] Instead, the greater commonalities between rare genetic disorders allow a more focused discussion within a piece of this length.

This study will largely rely on evidence from seven countries: Australia, France, Germany, Japan, South Korea, the UK and Taiwan. Where helpful, it will also bring examples from the EU as a whole and the US. (See the methods note in the appendix for more details of our research.) We acknowledge that this is far from a comprehensive global discussion: Africa, for example, lags behind in its efforts to address rare diseases.[13] Nevertheless, our restricted evidence base does give a good picture of the broader developed world overall.

"What patients are saying about the hurdles, the barriers, the problems, the issues, is all exactly the same," says Hugh Dawkins, former vice-chair of the International Rare Disorders Research Consortium. "It doesn't matter which health system you're talking about—be it Japan, South Korea, the UK, France, Germany, India, the Philippines, Malaysia, South America or African nations, to name a few. When you are talking about rare diseases, you are talking about the same thing. And it is important to remember there is, at any given time, an estimated 400m people globally living with a rare disease."

Dots of progress

In recent years, two areas have seen the biggest strides for those living with rare disease: the regulation of drug development and the diagnosis of conditions. Although no country has a perfect model for either, in both cases progress has come from finding new approaches to reshape traditional systems that were unfit to meet the specific needs of those with rare illnesses.

I. Drug regulation

In general, anyone wishing to sell a medical product needs to convince a given market's regulatory authorities that it is safe and effective. Frequently, this involves developers engaging in clinical trials, which ideally involve a large number of subjects and multiple arms that compare patients treated with the new product to a control group. The latter usually receive the current standard of care, a placebo or both.

This system impedes the creation of products to meet the needs of those living with rare disease. One issue is commercial: cost compared to likely return. Drug research and development is expensive. Although a contentious issue, the typical estimate for the cost of a new drug that reaches regulatory approval falls between US$1bn and US$2bn.[14] Here, orphan drugs have a big advantage. Comparisons vary widely, but the overall R&D cost per successful orphan product is on average anywhere between 21% and 57% of a non-orphan one, in part because phase III trials are often not needed. Moreover, if anything, the failure rate is slightly lower among orphan drugs.[15, 16]

The problem for developers is that treatments for a rare disease will have a much smaller potential market from which to recoup those costs—albeit still in the hundreds of millions of dollars for each product—than do drugs for other conditions. In the calculations of the National Institute for Health and Care Excellence (NICE), which is responsible for HTA in England, the average assumption for an orphan drug is 2.91 potential users per 50,000 population. For non-orphan products the equivalent figure is 102.57. In a market without blockbuster drugs, prices per QALY need to be higher to achieve the same return: according to a recent study, they need to be just under four times greater for rare diseases, and more than 48 times higher for ultra-rare conditions.[16] Another major barrier is a practical one: generating convincing evidence. Patient pools from which to draw for orphan drug trials are small, and meaningful outcomes measures are limited.[17]

Most jurisdictions have made little progress. "[Only] a small subset have well-defined, fit-for-purpose, orphan regulatory pathways," says Mr Obscherning. The countries in this study are part of this select group. As previously noted, all have had some orphan drug laws for a number of years. These laws bolster the development of relevant products through a range of incentives that either cut costs or increase potential financial benefits. They do this through some combination of several

elements: a period of market exclusivity, reduction or elimination of various fees in the application process, greater tax write-offs or subsidies to cover the cost of research, priority or accelerated review of applications, and scientific or regulatory advice.

The national variations in these benefits largely reflect the main barriers to bringing orphan products to the domestic markets in question. For example, while South Korea has a growing domestic pharmaceutical industry, it remains comparatively small, and Australia's is even smaller. Accordingly, both countries' strategies largely involve encouraging companies that have developed orphan drugs elsewhere to enter their markets. South Korea's main orphan drug benefits, for example, are up to 11 years of market exclusivity (for paediatric drugs where no alternative exists) and the possibility of accelerated approval; in Australia, the waiver of application fees has been a major element of its package for many years.[18, 19]

Europe and Japan, which have larger pharmaceutical industries, have a range of assistance to support orphan drug research and development. For example, the EU regulator, the European Medicines Agency (EMA), provides low-cost advice to companies so that they understand the kind of evidence that will eventually be needed to demonstrate the benefits of their product. Meanwhile, the EU's Framework Programme for Research and Innovation provides research grants.[20] Japan also gives subsidies through its National Institute of Biomedical Innovation and priority consultations through the Pharmaceuticals and Medical Devices Agency (PMDA).[21] The PMDA and EMA have created innovative new development pathways as well—Sakigake (2015) and PRIME (2015) respectively—which provide extra support for those working on innovative new drugs, including for rare diseases.[22]

Regulators have also been wrestling with the problems of limited evidence. In 2006 the EMA began to allow time-limited, conditional approval of medications that met a serious need where no alternative treatment was available, and where existing evidence indicated that the likely benefits outweighed the risks. In such cases, those selling the drug have to collect real-world evidence to monitor its effectiveness and present the results to the regulator. After a year, the EMA can either withdraw authorisation, approve the medication or allow another period of conditionality for the collection of further results. The EMA specifically includes orphan drugs as likely beneficiaries of this approach.[23, 24] Similar rules for conditional or provisional approval have become the norm in countries covered by this study.

Efforts toward regulatory innovation have led to a significant growth in the number of treatments for rare diseases. In the US, prior to the launch of the Orphan Drug Act in 1983, only 38 products for rare disease were available.[25] Under the new law, by 2019, 5,099 products had received orphan designation and 724 had been approved for 878 conditions.[26] Similarly, in 1999 Europe had just eight approved orphan products.[27] By 2022, 2,552 drugs had an orphan designation and 207 had been approved.[28] Countries trying to attract drugs developed elsewhere are also seeing some success. South Korean officials granted 165 designations between 2007 and 2019, of which 156 received market authorisation by April 2020—a ratio that indicates that a large number of applicant products had already proved themselves elsewhere (indeed, the vast majority of these treatments are imported).[29, 30] A similarly high ratio is observed in Taiwan. As of December 2021, 90 of the 120 drugs with orphan designations had been approved, and 58 of the 120 drugs had obtained licenses from the Taiwan Food and Drug Adminstration.[31] From 1993 to 2017, Japanese authorities granted 398 orphan designations and approved 307 products. Of the latter, 209 saw some development in the country, but 121 had already been approved in the US.[32]

The number of orphan treatments is likely to accelerate. A report by Evaluate Pharma estimates that 15% of global drug sales in 2021 were of orphan products, a figure that Evaluate says will rise to 20% in five years. The firm also expects that 29% of the global drug pipeline will consist of orphan drugs by 2024.[33] The benefits of orphan drugs are substantial. A review of approved orphan and non-orphan drugs found that the median health gain of the former, as measured in QALYs, is five times that of the latter.[34]

Conventional wisdom holds that over 90% of rare diseases remain untreatable. Yet this oft-repeated figure is at least five years old.[35] Research by the US National Organisation for Rare Disorders, a patient advocacy group, found that there were 599 approved orphan drugs in the US by mid-2020, and that these covered between 850 and 900 indications.[36] The data do not say how many of these indications are unique: presumably some drugs will be for the same condition. That said, certain rare diseases are treatable with devices: since 1990, the US Food and Drug Administration has approved 79 orphan devices.[37] Similarly, the impact of around 50 conditions can be ameliorated using vitamins, and at least 15 inborn errors of metabolism can be managed with diet.[38, 39]

Meanwhile, the number of drug indications for rare diseases with a prevalence of more than 50,000 within the US population is higher than that for conditions with a prevalence below 2,000.[40] Given that there are far fewer total diseases in the higher prevalence group, a greater proportion will be treatable. This, and the higher aggregate population of those living with these diseases means that the percentage of treatable patients is markedly higher than the number of treatable diseases. Based on these figures, it is reasonable to assume that health systems are now in a position to help between one in ten and one in five people who present with a rare condition.

This still falls far short of the ideal, but the more worrying figure is how few of these people get treatment. Evidence suggests that only around 10% of people for whom a treatment exists are getting it.[40] A major challenge is for health systems to get these new treatments to patients.

II. Better approaches to diagnosis

Healthcare has traditionally had a poor record in identifying rare diseases. Clinicians rarely, of course, come across rare conditions; and even if they

suspect something, they often lack clear referral pathways. Accordingly, many patients have had to endure the so-called "diagnostic odyssey".

"A lot of patients spend a lot of time being passed around different disciplines, different hospitals, different specialists, to try to get clarity on what their condition may be," explains Sheela Upadhyaya, rare disease strategic advisor at NICE. "It is a key challenge for those living with rare disease across many, many countries."

A correct rare disease diagnosis takes on average between four and five years, and requires seeing between five and seven doctors. In one study, the diagnosis for 10% of patients took 20 years or more.[41, 42] Dr Dawkins told us of one case in Western Australia where 70 years passed between the first appearance of symptoms and an accurate diagnosis.

It need not be like this. One way to short-circuit the diagnostic odyssey is to increase the number of diseases covered in national neonatal screening programmes. Taiwan has recently added three inherited metabolic diseases, Fabry disease, Pompe disease and Gaucher disease, to its panel reports. Since 2019 Germany has had national newborn screening for Adenosine deaminase deficiency, an inherited condition affecting the immune system, and spinal muscular atrophy has been included in the national screening panel since 2021. Meanwhile, rare disease action plans in France and England both call for screening for a larger number of rare diseases.[43, 44]

While certainly of benefit to the children identified with specific conditions, these efforts will have limited effect on the problem of under-diagnosis of rare disease as a whole. Many rare diseases are non-genetic. Indeed, an extensive study of the use of DNA sequencing for primary newborn screening, conducted at several US centres, concluded in 2019 that the technology was not yet available to improve on current methods.[45] Nor, the study found, would such screening address the needs of existing patients.

Instead, once again, reshaping existing processes can allow healthcare providers to serve these individuals much better. "If you talk to clinicians in the rare diseases space, they say that diagnosis is not such a big issue now," says Dr Dawkins. "This, however, sits in contrast to when you talk to the patients who say that having their rare disease recognised—for their complex symptoms and presentation to raise an index of suspicion of a rare disease for the doctor, and then having the referral to the appropriate clinical expert to progress to getting a confirmed diagnosis and right treatment and management—still takes far too long. In too many cases [this takes] five, ten or more years; it is a long time to live with the medical, physical and mental symptoms without getting the right care and treatment." No country has fully eliminated the diagnostic odyssey, but progress has come where health systems have combined a multi-disciplinary approach with broadly-focussed genetic testing, notably whole-genome sequencing. The potential of such testing is substantial: already the Online Mendelian Inheritance in Man, a catalogue of genes and genetic disorders, identifies 4,280 genes responsible for single-gene diseases, most of which are rare.[46]

One example of innovation in diagnosis is a model initially developed by the US National Institute of Health's Undiagnosed Disease Program. This dates back to 2005 and involves creating a specific network or facility to deal with all patients presenting with rare diseases that the health system has not been able to identify. Another national programme of this kind (and the one that serves the most patients) is Japan's Initiative on Rare and Undiagnosed Disease (IRUD).

IRUD began as a research effort in 2015 but is now fully integrated into the public health system. Local clinics can refer paediatric or adult patients if their condition's symptoms affect their daily lives, six months have gone by without a diagnosis, objective signs exist that more than one organ is affected and there is evidence that a genetic cause may be involved. Each referred patient goes to one of IRUD's 487 clinical centres and hospitals. The case is then reviewed by a multi-disciplinary diagnostic committee, which can consist of clinicians of various specialties and sub-specialities, clinical geneticists, genetic counsellors, and data scientists.

Teams can also draw on 469 experts from 21 clinical specialities to assist the local treatment teams where needed.

The committee may be able to make a diagnosis based on the patient's file alone. If not, the team orders relevant tests. These often including whole-genome sequencing, conducted in one of five regional analytical centres. The patient's situation is then reconsidered in the light of these results, which are compared to data in the growing body of information on rare disease cases held by the programme or available in international databases. Genetic abnormalities are examined to see if they reveal a known condition, or may be the cause of a previously undiscovered illness. The clinical centre provides genetic counselling and co-ordinates care with the local referring institution.[47, 48]

Genetic information arising from the IRUD process is kept and used in helping with future cases and for sharing internationally. A global approach is essential in rare disease diagnosis because a given patient population may number only a handful of individuals worldwide. To make such collaboration easier, rare disease programmes have increasingly contributed to multinational databases, such as PhenomeCentral. These use standardised data structures for cases that have allowed genetic matchmaking through the Matchmaker Exchange. In the past seven years, PhenomeCentral alone—one of eight current participants—has been involved in over 60,000 matches with other databases through the Matchmaker Exchange.[49, 50]

Other undiagnosed disease programmes in Asia-Pacific include Western Australia's Undiagnosed Disease Programme, dating from 2016. It is largely focused on children, and participants are invited rather than referred.[51] Efforts are now underway to roll out such a programme across the country. In South Korea, meanwhile, the pilot phase of the Korean Undiagnosed Diseases Programme finished in 2020 and it has now become permanent. It is similar to efforts in Japan and Western Australia, although most of its patients (over 80% in 2020) are self-referred.[52]

The effectiveness of such programmes is impressive, especially given that those enrolled—by definition—have not received a diagnosis from mainstream medical services. Between March 2019 and March 2020, IRUD gave a definitive diagnosis to 53% of patients referred to the service.[47] According to Takeya Adachi, an assistant professor at the Kyoto Prefectural University of Medicine who helped to establish IRUD, the programme has identified 40 new rare conditions since it was launched. At the level of the individual patient, the change can be huge. Dr Dawkins describes the case of Lily, the first patient diagnosed by the Western Australian programme. At nine years old, she had seen 150 clinicians and the physical width of her case files measured a metre and a half. Discussion of her case by a multi-disciplinary group, rather than by siloed experts, led to a potential diagnosis within 40 minutes. The suspicion was confirmed in 48 hours.

Nor is the cost great. Gareth Baynam, clinical professor in the Faculty of Health and Medical Sciences, University of Western Australia, recalls the early days of the Western Australian Undiagnosed Diseases Programme in 2015: "We just used clinics in the hospital system, got the clinicians together once a month, and paid for the extra time for a clinical genetic counsellor to pull together the patient notes and to send them out to the clinicians before the meeting." Meanwhile, the cost of even carrying out a whole-genome sequence for a human subject has dropped from over US$7,700 in 2011 to US$454 in 2021.[53]

Such integrated efforts exist in Europe as well, notably in Spain and regions of Italy.[54, 55] France and Germany, however, have taken a different approach. They have created a large number of specialist rare disease centres, most for specific groups of conditions but some with a broader remit. France's latest plan, which runs to 2022, recognises the ongoing diagnostic odyssey for patients. Its first listed action is that every patient undiagnosed after one year should be referred to one of the country's more than 600 competence or reference centres.[44, 56] Doctors at these centres are meant to make use of France's growing genetic testing

capacity in looking for a diagnosis. However, no analysis of the plan's effectiveness has been carried out. Germany has established three tiers of rare disease centre with those in Tier A given responsibility for patients who have lacked a diagnosis for a long time. Again, no data are available on how well this works.[57]

Although NHS England has now established its first rare disease centre, its biggest progress against the diagnostic odyssey has come from a major research initiative. The 100,000 Genome Project conducted whole-genome sequencing on 100,000 people who had childhood cancers, rare diseases or were family members of people who fit the first two categories. A pilot study of the data, which covered 2,183 undiagnosed rare disease patients, showed that it gave a diagnosis to 25% of patients, a quarter of whom had immediate clinical actionability, while 19 new gene-disease associations were also identified.[58]

England's 2022 Rare Disease Action Plan calls for expanded use of genomic medicine, with an increase in the number of genetic tests for rare disease that general practitioners can order (currently 387 genes are covered). The plan also commits the NHS to pilot Syndrome Without A Name (SWAN) clinics in 2022, where multi-disciplinary teams will examine patients in a way similar to that described for Japan, Western Australia and South Korea.[43]

Compared to just a decade ago, a markedly higher percentage of people living with rare disease can receive a reliable diagnosis if they reach the right kind of facility. Here, too, the challenge is integrating such programmes into healthcare provision as a whole.

Connecting the dots to improve patient access

Diagnosis and drug development for rare diseases have seen impressive leaps forward in recent years. However, lacking healthcare institutions that are better able to address the needs of those affected by these conditions, the impact of any progress will remain limited. Delivering accessible care, Mr Obscherning says, "is so complex and broad in terms of all of the different things that you need to address." The entire ecosystem of care goes beyond healthcare to include areas such as education and social care.[59] Here, we consider three particular areas within healthcare where, despite recent recognition of the challenge and some efforts, significant work remains.

I. Integrating rare disease care into the mainstream

"The biggest lag I hear about [for patients]," says Dr Dawkins, "remains that between the first presentation with a medical problem and getting somebody who suspects a rare disease to refer them to the appropriate clinical service or specialist clinician who can progress them to a confirmed clinical diagnosis and best care." Knowing to send such patients to diagnostic programmes is only the beginning. After that, clinicians—especially those in general practice—need to know how to treat people living with rare diseases.

In our study countries, the problem is not so much diagnostic services, nor is it a lack of specialist facilities. Serena Wu, founder of the Taiwan Foundation for Rare Disorders notes, for example, that her country has 14 rare disease centres. Australia is opening a new Rare Care Centre in Perth to provide integrated treatment. In Europe, 24 European Reference Networks (ERNs) now cover different categories of rare disease.[60] Germany itself has 37 centres that provide care for rare disease patients in general, and nine national reference networks for specific groups of rare disease.[61, 62] Meanwhile, England has 78 "highly specialised services" that provide care for one or more rare conditions.* The list could go on.

And formal referral pathways have become established around these institutions. Dr d'Andon believes that, as France has built up its rare disease infrastructure, "healthcare providers know to which centre they can refer the patient." Similarly, in Western Australia, says Dr Dawkins, "we have helped to create a seamless path for complex patients to be referred [to diagnostic services]". In Japan, meanwhile, Dr Adachi points out that referral mechanisms are an integral part of IRUD. Systems are not perfect—in many European countries, for example, they remain incomplete.[63] Nevertheless, formal pathways to rare disease care do exist.

* Economist Impact analysis of data from EuroBloodNet (http://www.eurobloodnet.com/best-practices/guidelines-repository/)

The problem is in integrating these facilities into wider health systems. In particular, problems exist with linking them to primary care. In Australia, for example, complaints about a poor healthcare experience among those with rare diseases remain common.[64] There, and in Japan, over half of clinicians and pharmacists surveyed by the EIU (a sister company to Economist Impact; formerly The Economist Intelligence Unit) in late 2019 said that something as basic as a lack of defined referral pathways was always or often a difficulty in treating those presenting with a rare disease.[65] In Taiwan, this figure was more than 40%. In Germany, meanwhile, a 2021 survey of rare disease patients revealed a substantial unmet need in getting necessary health system information.[66]

Indeed, the existence of rare disease centres, notes Axel Mühlbacher, professor of health economics and healthcare management at Hochschule Neubrandenburg, Germany, does not mean they are well-known within the health system. In a recent survey of German primary care physicians, 53% had no knowledge of any rare disease centre in the country. In the UK, meanwhile, "the vast majority of rare diseases don't benefit from a highly specialised service," says Mr Kent. "We need to look at how primary and secondary care are provided, and how patients are transitioned in a timely and user-friendly manner through the system." Finally, ERNs, while holding great potential, suffer from the need to create referral pathways from national to European services—a requirement that has never existed before and is running into institutional conservatism in several national health systems.[63]

Two major issues require attention to overcome these problems. The first is awareness raising about rare diseases within healthcare as a whole, and general practice in particular. Without this, clinicians within the system will not think to refer patients to specialist rare disease institutions.[63] In a survey of Australian paediatricians in 2017, fewer than half believed that their medical training had adequately covered rare diseases and 28% felt unprepared to treat these illnesses.[67] A 2019 survey EIU mentioned earlier, which covered five Asia-Pacific markets (Australia, China, Japan, South Korea and Taiwan) also found healthcare professionals self-reporting low levels of rare disease knowledge, with Taiwan scoring lowest.[65] Two years later, a 2021 survey of German primary care physicians found that the most commonly used source of information on rare disease (by 62% of respondents) was the internet, and only 12% felt confident in dealing with patients having these conditions.[68] That same year, in a small survey in Northern Ireland, 79% of GPs did not think themselves adequately prepared to treat patients with rare disease, and 93% wanted more training.[69]

Nor have these doctors been able to hide their shortcomings effectively. A study by Genetic Alliance UK reported that one of the challenges which rare disease patients reported was "a perceived lack of knowledge from the healthcare professionals, with some admitting that they don't know what to do."[70]

Healthcare systems are attempting to address this problem, with the current Australian, German, French, and English strategies committed to increasing awareness of rare disease across health systems. "There's quite a lot of awareness raising that goes on within the NHS [in England] to ensure that patients who may be bouncing around different specialists in the system can be diverted to the right service provision," says Ms Upadhyaya. The Korean plan (the first of its kind in the country, and which expired in 2021) concentrated on expert training.[71]

The second pressing need is guidance, especially for non-specialists working with patients who have a rare condition. In particular, clinical practice guidelines (CPGs) have an important role to play. A 2020 European survey found that 93% of experts in the field of rare diseases related to connective tissue and musculoskeletal systems thought that CPGs would be useful for them.[72] CPGs, however, are "scarce", to use the characterisation of Orphanet researchers. Across the field of rare disease, they found just 277 CPGs of good quality written within the preceding five years in any of ten major languages.[73] Since then, the situation seems little changed. A 2022 review found 26 CPGs for 29 high-prevalence, multi-organ rare conditions. However, it added, "many were based on lower levels of evidence, focused on a single body system,

"Access to orphan drugs is frequently thought of, in the minds of governments, as sort of that last step."

Eric Obscherning, Secretariat & Advisor, APEC Rare Disease Network; Associate Director and Lead for Rare Disease & Advanced Therapy, Crowell & Moring International

represented the position of a specific professional group, were over ten years old or were not written in English."[74] At the European level, efforts by ERNs to collect available CPGs have also shown the paucity of what is available. ERN Euroblood, for example, found only 20 evidence- and consensus-based guidelines for all rare blood diseases, of which just eight had appeared in the preceding five years.

Various organisations are trying to make what does exist available. Orphanet, in its searchable rare disease database, includes links to guidelines of sufficient quality.[75] The US National Institute of Health National Library of Medicine, on its GeneReviews site, provides information on diseases arising from mutations to 828 genes.[76] These include advice on the management of these conditions, but this content can be as short as just a sentence or two and rarely goes beyond several paragraphs. Things are slowly changing, and Dr Dawkins reports that, globally, "best practice guidelines have started to be developed." Meanwhile, many countries, including France, the UK, Japan and Germany, have committed to implementing rare disease CPGs.[77] European institutions have also recently begun publishing guidance on how to create and assess guidelines.[78] However, for those looking for advice on best practice in treating rare disease patients, the existence of help remains very much a hit and miss affair.

II. Adjusting HTA appraisals

"Fifteen years ago or so, there were just a few therapies for patients with rare diseases," says Ms Upadhyaya. "A lot of the support doctors gave was symptom management." On the one hand, she adds, the much greater variety of treatments today "is brilliant, given the unmet need that we've had so long." On the other, it has brought "an elephant in the room for all: how much these drugs cost."

Cost is not invariably an issue for every condition. Greater understanding of the genetics of rare diseases has sometimes allowed the repurposing of medications already approved for other indications.[79] In general, though, as Ms Upadhyaya points out, "all the challenges—small populations, collecting data and not fully understanding the natural history—[mean that] the research and development of these therapies becomes much more expensive." At an extreme, the costliest drug in the world may be Libmeldy, a gene therapy for metachromatic leukodystrophy, a rare brain disorder, which the makers plan to go to market with a list price of between US$3m and US$3.5m per treatment.[80]

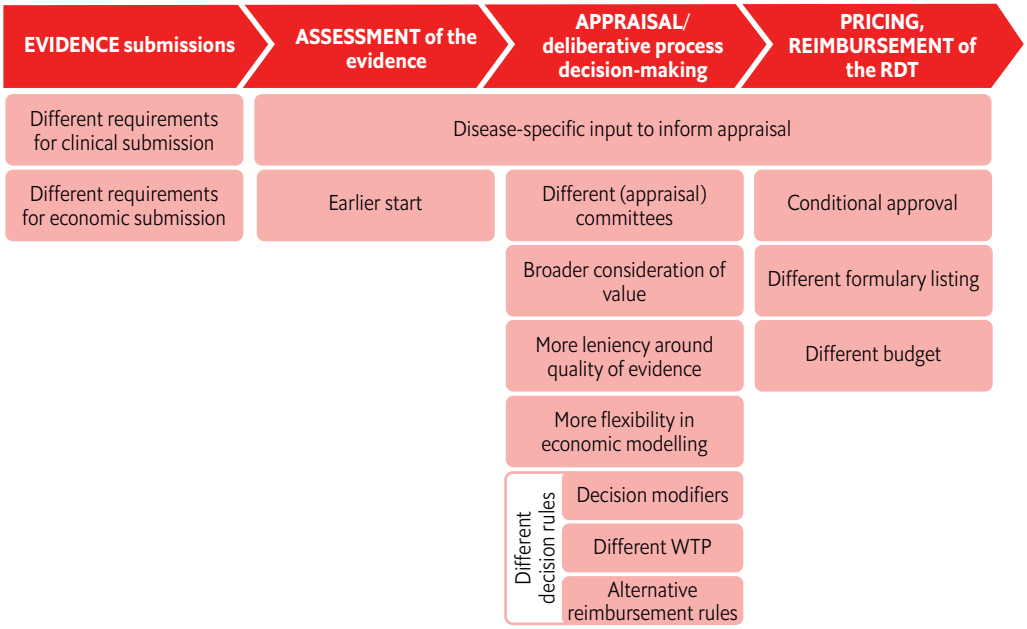
The substantial costs of rare disease interventions, even if not so stratospheric, pose a challenge for health systems. "In Australia," says Dr Dawkins, "the biggest hurdle [to access] is the reimbursement." In France, says Dr d'Andon, "the price negotiation is often very difficult in rare disorders: the companies would like a high price whatever the conclusions of the HTA and, of course, France is trying to reduce expenses and follow the rules, which are that the price is defined according to the additional value of a drug." Meanwhile, when it comes to reimbursement decisions in Taiwan, Ms Wu simply says, "It's about money." This is far from comfortable ground for health policymakers. "Access to orphan drugs is frequently thought of, in the minds of governments, as sort of that last step," says Mr Obscherning. "They'll do everything they can before they touch it because it's so challenging, so politically contentious and so financially intensive."

It is a nettle that governments must grasp. "The economic burden for these patients is huge," says Hye-Young Kwon, professor in the Division of Biology and Public Health at Mokwon University, Daejeon, South Korea. "It is probably the most challenging problem." Without low-cost or free provision within health systems, many of these new treatments will simply be out of reach.

In making reimbursement decisions, most health systems now rely on some form of HTA process. HTA bodies draw on analyses of a new treatment to determine the ratio of the increase in cost that it creates over existing care compared with any improved benefit over existing care. The latter is usually measured in QALYs but can conceptually include any individual or societal gain. The resultant incremental cost-effectiveness ratio (ICER) is then, in many jurisdictions, compared to a health system's normal ostensible willingness-to-pay figure, usually expressed as a single figure or range of currency units per QALY. Where the ICER is above the willingness to pay, it normally leads the HTA body to recommend against reimbursement, unless the process takes other relevant factors into account, such as, for example, a lack of alternative treatments.*

HTA is another health-related process that, while useful for more common medical needs, is problematic in the field of rare diseases. For example, for rare conditions there is often uncertain evidence of effectiveness because of a small patient population, making traditional assessment practices difficult to use. In addition, poor understanding of disease natural history impedes the selection of obvious endpoints in value assessment, and difficulties defining the direct and indirect burden of rare diseases make unmet need hard to measure. Collectively, all of these factors, and more, make any HTA analysis uncertain (see **Figure 1** for a fuller list of where HTA methodology needs attention to address the specific requirements of orphan drugs).[81]

Figure 1: Features included in supplemental processes for rare diseases across the HTA process (adapted from Nicod et al)[81]



RDT: Rare disease treatment, WTP: Willingness to pay

Mr Obscherning notes that very few countries have even begun to address the challenges of adapting HTA processes to the needs of rare disease assessment. He adds that it is regulators who have shown a willingness to first adopt innovations—such as use of real-world evidence—when dealing

* For a detailed discussion of HTAs, see Clifford Goodman, *HTA 101*, revised 2018, https://www.nlm.nih.gov/nichsr/hta101/ta10103.html

with orphan drugs. But HTAs are catching up. In 2022 NICE streamlined the processes for its Highly Specialised Technology assessment pathway for treatments for very rare diseases. Elsewhere, the French parliament has been examining legislation that would allow a new way of determining the value of products—called relative therapeutic value—which would apply where, as with many rare drug treatments, evidence is scarce.[82] One goal of Australia's rare disease action plan is better funding and pathways for reimbursement.[83]

In order to examine how far along these efforts are in our study countries, we have looked at the speed of reimbursement decisions for seven orphan drugs and one gene therapy: Lanadelumab, Pegvaliase, Obeticholic acid, Sebelipase alfa, Asfotase alfa, Elosulfase alfa, Nusinersen sodium and Voretigene neparvovec (**Table 1**).

Table 1: List of comparison treatments in Economist Impact's analysis of time between regulatory approval and reimbursement decision[84-86]

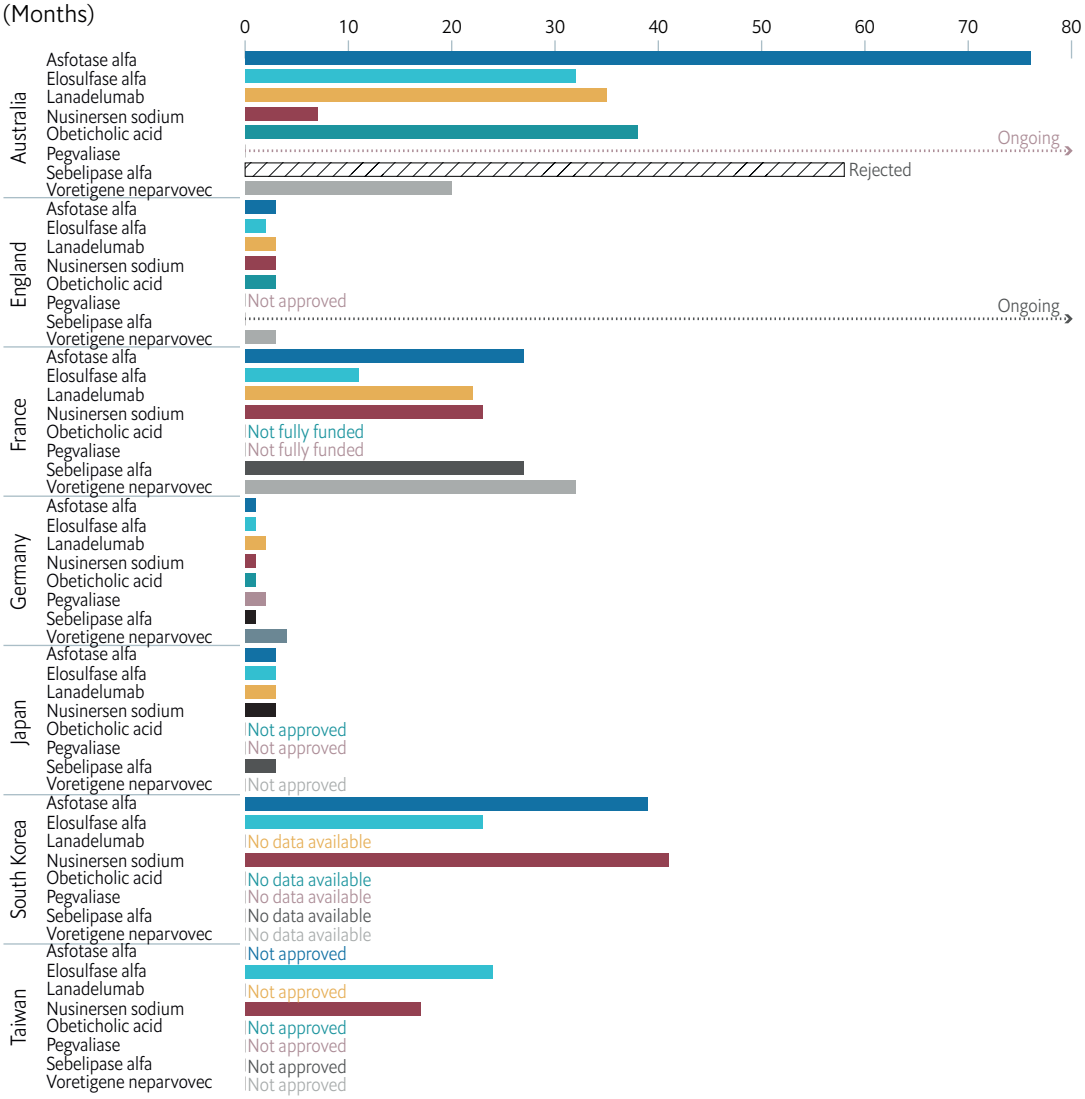
Medicine (brand name)	Disease/condition	Prevalence (per 100,000)
Lanadelumab	Hereditary Angiodema	5
Pegvaliase (Palynziq)	Hyperphenylalaninaemia	0.2
Obeticholic acid (Ocaliva)	Primary biliary cholangitis	21.05
Sebelipase alfa (Kanuma)	Lysosomal acid lipase deficiency	2
Asfotase alfa (Strensiq)	Childhood- or juvenile-onset hypophosphatasia	1
Elosulfase alfa (Vimizim)	Mucopolysaccharidosis type IVA	15
Nusinersen sodium (Spinraza)	Spinal muscular atrophy	10
Voretigene neparvovec (Luxturna)	Leber congenital amaurosis	2.5

The treatments selected for this analysis were chosen based on a range of factors to provide a proxy for reimbursement speed for treatments for rare disease. All appear in the "Essential list of medicinal products for rare diseases", produced in July 2021 by The International Rare Diseases Research Consortium's Rare Disease Treatment Access Working Group. To reflect more contemporary reimbursement processes in each market, we selected eight of the 204 treatments on that list based on whether they had been approved in the past decade. We also focused on treatments for diseases that had only one, or at least very few, treatment options. Data availability was also considered in the final selection process. See the methods note in the appendix for more details.

The marked differences between countries in the number of drugs available, and the time between marketing authorisation and reimbursement are striking (**Figure 2**). For example, Taiwan has two drugs on national formularies, South Korea has three, Japan has five, and the others between six and eight. Even where European countries have a common regulatory authority, they sometimes come to different opinions on reimbursement. Obeticholic acid is one such product. Despite the EMA granting marketing authorisation, France's Comité économique des produits de santé (CEPS) could not come to terms on a price with the producer.[88]

We describe below some important aspects of HTA that explain the differences in our results and, equally as important, how some countries reach similar results in distinct ways. Each has a distinct approach to making reimbursement decisions, and examples of movement beyond traditional HTA approaches are common. Nevertheless, continued

Figure 2: Time between marketing authorisation and when public health systems agreed to reimburse them for eight treatments across seven jurisdictions



Source: Economist Impact.

Note. Data on regulatory approval date, HTA submission date and reimbursement date were obtained from the MAESTrO database, developed by Wonder Drug Consulting Pty Ltd, along with grey literature searches. The data extraction was conducted between March and May 2022. Assumption for Japanese data made according to Pharmaceutical Regulations in Japan that requires the Reimbursement Pricing Process to be completed in 90 days the longest.[87]

Drugs that are labelled "Not approved" signify that there has been no regulatory approval date. "Rejected" drugs signify that a drug has been approved by a regulatory body but has not been denied reimbursement. "Ongoing" drugs signify that regulatory approval has been granted but the assessment for reimbursement is still ongoing. "Not fully funded" drugs are drugs that are not 100% reimbursed by the government. "No data available" signifies that data was not found during Economist Impact's research.

modifications, even by some of those already most advanced in funding these treatments, show that this field is still wrestling with finding the best ways to provide fair access to the increasing number of rare disease treatments available.

Germany

Germany began to reimburse all of our focus drugs very quickly after approval.[89-91] This apparent speed requires a caveat. In Germany, as Mr Mühlbacher explains, once a product receives EMA approval, "it is seen as ready to go to market. Then, we have a separation between reimbursement and price." Initially, for any medicine with newly-granted marketing authorisation, the producers set the price for a year. After that time, if the annual aggregate cost across the health system of the treatment is below €50m (US$49.9m), the asking price is made permanent. For more expensive drugs, the Gemeinsamer Bundesausschuss (G-BA), a statutory decision-making body representing physicians, dentists, hospitals and insurance funds, assesses the added therapeutic benefit provided based on evidence collected during the original clinical trials or real-world evidence generated during the first year of marketing authorisation.

Orphan drug evidence criteria, however, are less rigid than those for other products. Manufacturers do not need to prove comparative efficacy to an existing standard of care, for example, and non-randomised or non-comparative data are more likely to be accepted than for other products. Moreover, if insufficient data exist after a year, the drug is deemed to have an "unquantifiable benefit," although it must undergo subsequent regular benefit assessments. Once the initial G-BA analysis is complete, the national health insurers' association and the pharmaceutical company negotiate a price based on the benefits that the data reveal. This may be revised in the light of later assessments.

This system allows rapid reimbursement for new rare disease products—yet it also has potential drawbacks. A recent study by the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), which assesses the quality and efficacy of medical treatments, looked at 41 orphan drugs with annual sales of over €50m. All had been assumed to have an "unquantifiable benefit" during their initial assessment. During the regular reviews, conducted anywhere from one to nine years later, more real-world evidence was available. Just over half (22) were found to provide no benefit.[92] This should not be a surprise. These treatments are being used after only limited evidence is available, roughly analogous to completion of phase II trials. Most studies find that only 50% to 60% of products succeed at phase III.[93] It would be inhumane to deny potentially life-changing, or life-saving, medication to those with rare disease, but patients need to be aware that lower levels of evidence mean a higher proportion of orphan drugs that may simply not work.

England

NHS England ends up covering almost the same number of drugs as Germany—six out of eight—and nearly as quickly. Its process, though, is very different. Reimbursement decisions are not automatic. NICE conducts cost-benefit analyses for all products. Most are subject to a standard technology assessment but orphan drugs for very rare diseases can go through the Highly Specialised Technology (HST) pathway. Under the HST pathway, assessors are willing to consider a wider range of evidence, including observational studies. In addition, whereas NICE usually requires an ICER below £20,000-£30,000 (US$23,700-US$35,500) per QALY, for HST products, this is a minimum of £100,000. Moreover, where the treatment provides a very large benefit—greater than 30 QALYs—the willingness to pay cut-off can rise to £300,000.[81, 94-97] In early 2022 NICE further adjusted these guidelines to allow greater flexibility to relevant specialist committees to consider a wider range of evidence—including real-world and patient experience data—and to accept higher levels of uncertainty.[98, 99]

None of this necessarily lends itself to a speedy process. The apparently quick reimbursement decisions in the chart arise from the practice of allowing evaluation to begin before regulatory approval. For example, consideration of Lanadelumab, Elosulfase alfa and Nusinersen sodium began 10-15 months before they received marketing authorisation. This allowed reimbursement to begin two to four months later. Ms Upadhyaya explains that this early submission lets NICE work with the company and

stakeholders "to understand the remit of the drug and to understand the disease better." Meanwhile, she adds, in the case of delay, NICE's Innovative Medicines Fund provides conditional access while real-world data and patient experience outcomes are collected.

France

France may seem to lag behind its European neighbours, but the chart reflects the specifics of its assessment process rather than the speed of access. The country's Haute Autorité de Santé (HAS) is the HTA body that conducts a cost benefit analysis of the improvement over existing care.[100-103] As with HTA agencies in other countries, while demanding high-quality evidence, it understands the constraints when studying orphan drugs. "The gold standard is a randomised, double-blind clinical trial, but if that is not possible, the HTA committee adapts its assessment according to the feasibility of an RCT," explains Dr d'Andon. HAS may soon have a different option when a cost-benefit analysis is impossible—the proposed relative therapeutic value combines the quantity and quality of clinical impact of a drug, as well as the seriousness of the unmet need it could address.

"The price negotiation can take one month one year, we don't know. It varies. Everybody says it is too long."

Anne d'Andon—Consultant, former Medical Director of Conseils et études en Santé (CEMKA), former Head of Drug Evaluation Department of the Haute Autorité de Santé (HAS), France

HAS turns over its results to other officials at the Comité économique des produits de santé (CEPS). If the total annual cost of adopting the product in the health system is less than €30m, then the manufacturer's suggested price is accepted. Otherwise, CEPS negotiates with the producer. No ICER-based limit exists, but this does not necessarily speed things up. Whereas the HTA analysis normally lasts a few months, reports Dr d'Andon, "the price negotiation can take one month, one year, we don't know. It varies. Everybody says it is too long." Indeed, **Figure 2** shows how these talks can drag out.

Patients are not, however, simply left to wait. Since 1994, France has had a series of temporary early access schemes, collectively known as Autorisation temporaire d'utilisation (ATU). This is another area relevant to rare disease that has seen recent reform. In 2021, the government combined six programmes into two: Autorisation d'accès compassionnel and Autorisation d'accès précoce. In general, these permit access to as yet unapproved drugs, and pay their costs, when they address serious conditions, the apparent risk outweighs the benefit and nothing else is available.[104, 105] The programmes can even kick in even before marketing authorisation from the EMA—on average 19 months before for orphan drugs under the old ATU programmes.[106] As a result, in practice, access in France is as early as in our other two European study countries.

Australia

In Asia-Pacific, Australia's health system pays for the highest number of our focus drugs—six of eight—but it takes noticeably longer than other healthcare systems to agree to reimburse them. Unlike France, where the ATU provides access for patients during the administrative processes, in Australia those affected have to wait until the formal determination is made. New drugs normally need to undergo an HTA process conducted by the Pharmaceutical Benefits Advisory Committee (PBAC) for inclusion in the country's Pharmaceutical Benefits Scheme (PBS). Although sympathetic to the challenges of assessing rare disease treatments, the PBAC does not have special rules in assessing their value. Moreover, orphan drugs are frequently turned down for PBS inclusion on the first application, leading to more delays in access and increased costs from fees for repeated applications.[107-109] The process leads to a certain level of frustration. "There are only a few economists in Australia that have really learned how to think about rare diseases and the health impact on the community across health services, health and care resources, family and carers, and workforce," says Dr Dawkins.

If the PBAC turns down an application for inclusion in the PBS, rare disease treatments are sometimes eligible for inclusion in the country's Life Saving Drugs Plan (LSDP). Rather than cost-effectiveness, this programme considers evidence of increased

life expectancy from use of the drug in question, whether alternatives exist, if direct purchase would put an unreasonable burden on the patient, the similarity of the proposed price to that charged in other countries, and if the applicant pharmaceutical company will be collecting data to address uncertainty in outcomes. Although the LSDP to date reimburses just 15 medications, it does fund two of the six drugs on our chart that Australia covers: Afotase alfa and Elosulfase alfa.[110, 111]

A 2014 report found that reimbursement decisions in Australia can take two to four years more than in comparable developed nations, a problem that the National Strategic Action Plan for Rare Diseases said remained in 2020.[83, 112] However, in September 2021 the Australian government announced a new five-year strategic agreement with Medicines Australia, which included commitments to supplying affordable medicines, earlier patient involvement in PBAC processes and the first independent review of Australia's HTA system in almost 30 years. This independent review will examine methods for evaluating medicines for rare diseases, the use of real-world evidence and international work-sharing.[113] "The rare disease community is very excited for these changes," says Durhane Wong-Reiger, chair of Rare Disease International, president of Asia Pacific Rare Disease International, and president and CEO of the Canadian Organization for Rare Disorders. "For many years, the use of traditional HTA cost-effectiveness assessment in Australia has denied and delayed patient access."

Japan

Japan reimburses five of our focus drugs. Four of them gained this status before 2019, when the country's drug pricing regime underwent a major revision. Previously, all drugs that received marketing approval were eligible for reimbursement at a price set by the Ministry of Health, Labour and Welfare. The ministry used formulae that took account of the price of any comparator drugs as well as offering a premium based on factors such as the extent of innovation, the utility of the new product and whether it could be used in paediatric care.[114]

Since 2019, the country has adopted a system very similar to Germany's. Within 60-90 days of marketing authorisation, the national health insurance covers the drug at the manufacturer's requested price. Any drug that exclusively treats a rare disease is exempt from further economic evaluation and, therefore, from price adjustment. However, products that can be used for both a rare disease and at least one more common condition must go through the HTA process.

The price assigned by the health ministry is based

Figure 3: Government and compulsory health expenditure per capita in 2019, for the seven study countries[116, 117]

(US$)

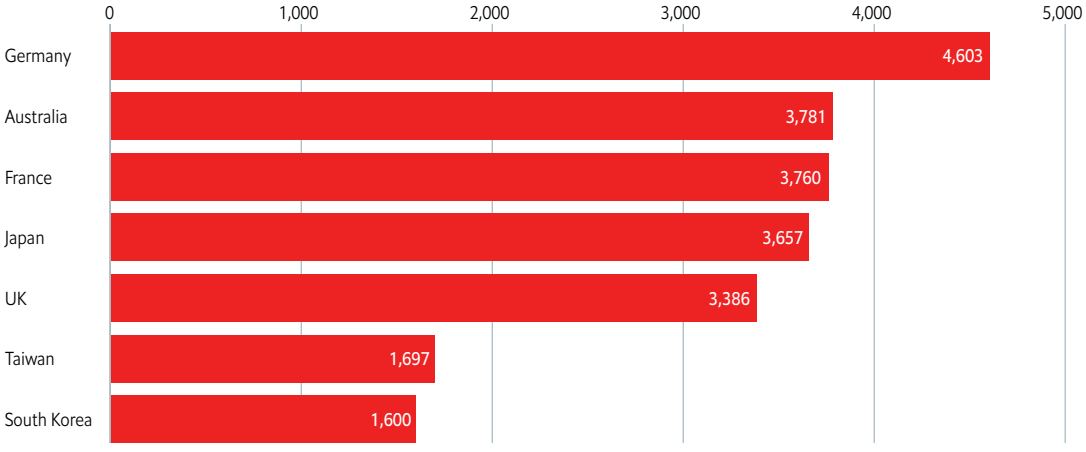


Figure 4: Government and compulsory health expenditure as a percentage of GDP in 2019, for the seven study countries[116, 117]

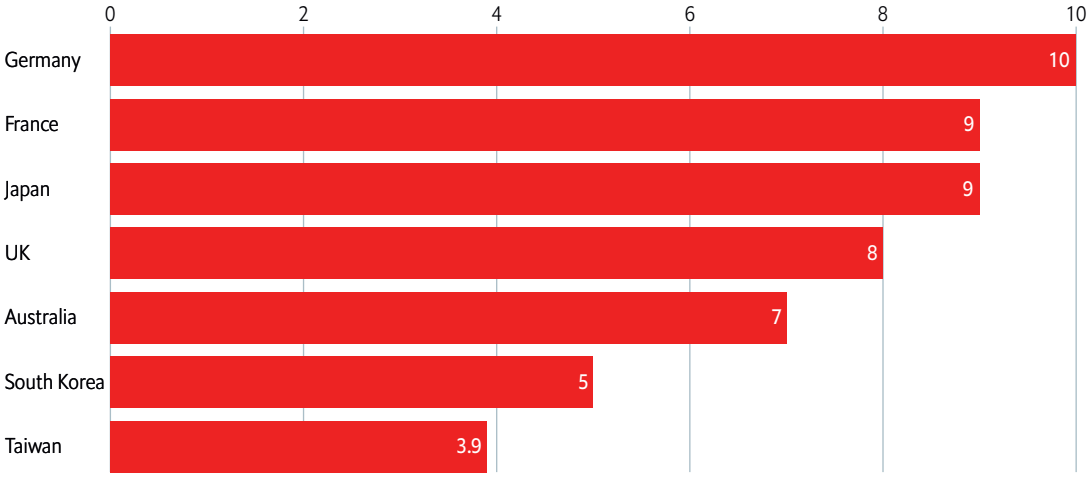
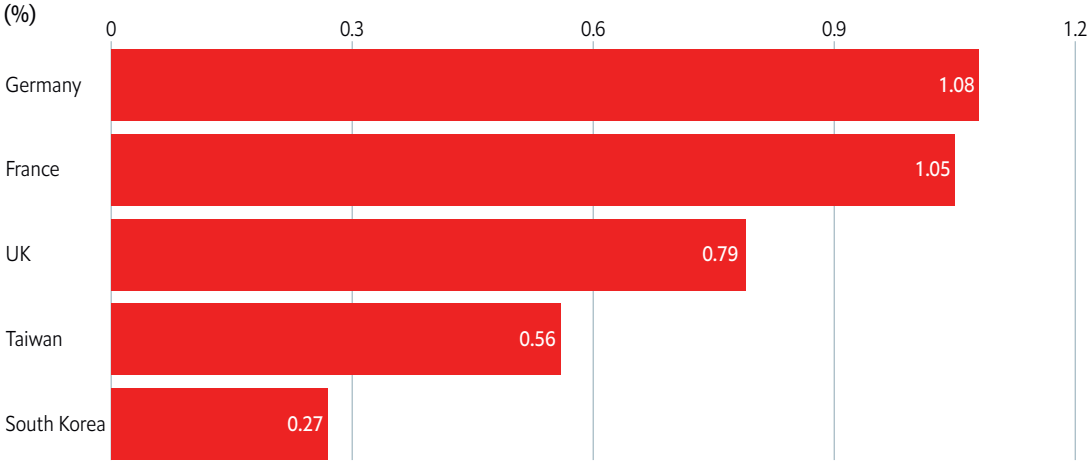


Figure 5: Expenditure on orphan medicinal products as a percent of total healthcare expenditure in 2017 (latest available data), for five of the seven study countries (data unavailable for Australia and Japan)[29, 117-120]



on complex calculations that depend on the cost of making the drug and any improvements over any given comparator. The results may then be adjusted downward based on the ICER level. The difference for orphan drugs is that, when evaluated, the ICER point at which price reductions occur is 1.5 times higher than for other therapies. Japan also has a conditional early access programme but, between 2017 and 2020, only one rare disease drug qualified.[115] How this will work out in practice remains to be seen. Approved rare disease drugs will presumably get reimbursement quickly, like the German system, but any downward price adjustment might lead to withdrawal from the market in the future.

South Korea

The two countries that offer reimbursement for the fewest of our focus drugs are South Korea and

Taiwan. Both face similar challenges of finding ways to square the circle of attracting drug makers to relatively small markets where healthcare spending per capita is smaller than elsewhere (**Figures 3, 4 and 5**). In addition, despite often successful orphan drug legislation in both countries, some companies may simply not be interested in markets of this size. Moreover, in both, reimbursement is not straightforward.[121, 122]

Before 2014, South Korea's HTA procedures made it very difficult for rare disease treatments and certain other kinds of drugs to demonstrate cost-effectiveness. This led to frequent refusal to reimburse treatments. A series of reforms in 2014 and 2015 effectively split rare disease drugs into two categories. Those for serious diseases where no other treatment is available and that can demonstrate substantial clinical effectiveness are classified as essential drugs. These are reimbursed at a price based on that charged in seven other major jurisdictions (France, Germany, Italy, Japan, Switzerland, the UK and the US).

Where, as is frequently the case, insufficient evidence of clinical effectiveness exists, but three of the seven major jurisdictions have listed the drug, then it can be reimbursed, so long as the producer and health service can negotiate an expenditure cap. Sometimes, refunds are also necessary if the product does not meet agreed clinical outcomes on a patient. These kinds of agreements fall under the broader category of managed entry agreements. To date, good data is simply unavailable on how effective or ineffective they are at improving access or patient outcomes.[123]

South Korea's approach has had mixed effects for access. The reforms of 2014 and 2015 did increase the success rate of rare disease drugs seeking reimbursement—between 2014 and 2018, spending on orphan drugs by the health system more than quadrupled, compared with growth of 43% for all pharmaceutical expenditure.[124] This has caused substantial concern among policymakers. On the other hand, by 2018, orphan drugs still represented only 1.4% of all pharmaceutical spending, which is a low ratio internationally, even after taking into account the higher proportion of health spending that goes to pharmaceuticals in South Korea compared to other study countries.[125-127] Moreover, just 56% of orphan products with marketing authorisation are covered within the South Korean health system.[125]

The barriers to improved access are various. On the supply side, pharmaceutical companies are not always interested in seeking to be listed for reimbursement quickly, or even at all, notes Dr Kwon. She adds as an example that, for one of the three of our focus drugs that the health system now covers, the pharmaceutical company took over two years after approval to submit the data needed to start the process to consider reimbursement. On the government side, once an orphan drug reimbursement application is in the system, it can take one to three years before a decision.[125] Even after the 2014 reforms, 30% of rare disease drugs are still rejected by the country's Pharmaceutical Benefit Coverage Assessment Committee.[124] With policymakers concerned about the rise in spending on orphan drugs, any change to the status quo is likely to be slow.

Taiwan

Taiwan, though a leader in rare disease policy in some ways, has become increasingly stringent in its attitude toward orphan drugs.[65] As with South Korea, the problem is fear of cost. Spending on rare disease drugs grew by 29.7% per year in 2005-12, and by 12.5% per year in 2013-21, compared with just 3% annually for all pharmaceutical spending.[128] However, rare disease accounted for only 2.3% of all drug spending that year, again a low figure low by international standards.[7, 119, 127]

This overarching concern, explains Dr Chien, has led to the reimbursement authorities creating "a lot of restrictions in order to control the number of patients who can get those treatments." Ms Wu agrees: "Now we have a lot of drugs and more patients, so [the reimbursement authorities] came up with a lot of unreasonable restrictions and limitations. The budget is never enough and there is a long queue of so many rare diseases."

Previously, the Expert Advisory Meeting (EAM), whose members are mainly medical specialists and clinical pharmacists, conducted professional

drug evaluations with support from the HTA division of the Center for Drug Evaluation. These evaluations formed the basis for consideration of the National Health Insurance Administration. However, this process was reformed in 2013. With it, the Pharmaceutical Benefit and Reimbursement Scheme (PBRS) Joint Committee was established to encourage participants of different stakeholders (i.e. health professionals, manufacturers, government officials and members of the public) in the drug evaluation process. In the revamped process, the EAM continues with its past role in providing evaluations and recommendations to new drug applications, but these are then reviewed by the PBRS Joint Committee, which is the final arbiter of a drug's suitability to the National Health Insurance system.[129]

Stakeholders in Taiwan reported that too much focus is placed on the cost-effectiveness analysis, and not enough attention is paid to the patient perspective, nor ethical and social considerations. "Using the same evaluation process for treatments for common and rare diseases is not fair," says Dr Chien. "For common medications, it's said that if one QALY should be less than 3 times the GDP [per capita], it is cost-benefit. For rare diseases, they [evaluators] will say "we are so generous, we already give you ten times the GDP per QALY", but we don't have a consensus on a number that is fair to use in a rare disease situation."

While treatments for rare diseases go through a similar assessment process to treatments for common conditions, Taiwan has a separate, ring-fenced budget dedicated to rare disease treatments. However, for medications to qualify, the disease itself must be one of 236 currently designated under the Rare Disease and Orphan Drug Act.[130]

As of June 2022 61 of the 90 approved orphan drugs had been reimbursed for 36 rare diseases.[128] This number grew, on average, by only five per year over the previous eight years.[131, 132] Not only are the numbers small, the process is lengthy. According to a study of 17 drugs undertaken by the Taiwan Foundation for Rare Disorders, the average time between approval and a positive reimbursement decision was 2.5 years between 2013 and 2021.[133] Here, then, **Figure 2** accurately reflects the access challenges involved for orphan drugs.

III. The need for better, more integrated information

Simply changing HTA reimbursement or healthcare delivery platforms in a vacuum will have limited effect. "You have to think about this in a broader context," says Mr Obscherning. One important element of meeting this need, he adds, will be the creation or improvement of rare disease registries, "so that you're collecting sufficient data that then informs decisions." Registries are structured collections of information on patients that can include a potentially wide range of data, including items such as clinical information on an individual's case and how it changes over time, outcomes of medical interventions, or patient self-reported data on quality of life. Registry data can improve understanding of the burden of a disease, offer insight into when an intervention is most effective, and provide outcomes to use as endpoints in a clinical trial. Although, in theory, registries can cover every affected individual in a population, for rare disease they have typically been less comprehensive collections of cases pulled together by patient organisations, researchers or clinicians.

Registries for individual rare diseases are far from new. For example, EUROGLYCANET, which covers congenital disorders of glycosylation, dates back to 1999.[134] As interest in rare disease has grown, so has the number of these data repositories. By 2017, 703 distinct registries existed in Europe, Turkey and Israel, according to Orphanet.[135] By 2021 this had risen to 812—average growth of 26 per year. Most have only national or regional coverage (639), but a few are European or multinational.[136] In Japan, meanwhile, a collection maintained by RADDAR-J, a project funded by the Agency for Medical Research and Development, has data from 88 highly focused research projects. Some of these are being turned into registries for individual conditions or groups of conditions, such as deafblindness.[137, 138] In Australia there are 55 disease registries, with an additional 19 international registries accepting information on people from the country.[139] Although South Korea

has a National Genetic Mutations database, it is small.[140] In practice, information on the rare diseases burden comes, as in Taiwan, not from registries but from national health insurance data.[7, 141, 142]

Even where the information that they hold is substantial, these registries face a challenge common across the rare disease field: fragmentation. The 812 European registries, for example, cover only 736 specific conditions.[136] Moreover, most of these registries have a size reflecting the patient population, making the data less able to yield insights compared with national cancer or other disease registries. Accordingly, efforts have begun to allow the aggregation of rare disease registry information.

France has seen the most progress. In March 2022, after roughly a decade of development and data collection efforts, France's Banque Nationale de Donneés Maladies Rares (BNDMR), issued its first prevalence report on rare disease. As of June, 98% of rare disease facilities in the country were reporting case information, and BNDMR had information on roughly 950,000 patients affected by around 5,600 conditions.[143-146]

UK efforts are further behind. In 2015 NHS England established its National Congenital Anomaly and Rare Disease Registration Service. Congenital anomaly registration has seen great progress since, and this has implications for data on any number of rare diseases, such as Down's, Edwards' and Patau's syndromes. Nevertheless, the plan to have widespread recording of all rare disease cases remains mostly an aspiration. Accordingly, building a sustainable rare disease programme is a major part of the service's current work plan.[147-149]

The EU has also seen progress, albeit slow. As early as 2013 the EU funded the Building Consensus and Synergies for the EU Registration of RD Patients initiative. Its aim was to create a model registry.[150] The results sank with little trace. In 2019 the EU instead created a Registries Task Force and began funding its ERNs to create EU-wide registries for the collection of patient data in their areas of expertise.[151] We reviewed a random selection of these registries' websites and found that many are still being rolled out or in a pilot phase. According to Orphanet, as of December 2021 some were not yet functional.[136] In order to tackle interoperability issues, various European bodies have collaborated to create the European Platform on Rare Disease Registration to cope with the fragmentation of patient data across hundreds of registries.[152] So far, the platform has organised discussions among the various ERN registries on common elements to include in their data entries.[153] In short, these European registries remain a work in progress.

Other study countries are even further behind. Japan's RADDAR-J programme offers a way for government-funded researchers to make project data available. So far, though, under 100 of roughly 300 eligible projects have done so.[137, 138, 154] Meanwhile, Australia's umbrella rare disease patient group, Rare Voices, recently published an initial scoping audit of the registries that exist.

Overall, although France's BNDMR has come on stream, and some large registries in Europe may do so in the coming years, health systems need to find better ways of collating what data are available on those living with rare disease, and on the progression of their conditions, in order better to shape policies and planning.

Those working to improve registration have come across another important data-related challenge. The predominant disease recording system—the International Classification of Diseases (ICD) codes—was not built with rare diseases in mind, and fewer than one in five rare conditions has a specific ICD-10 code.[155] This plays a large role in obscuring the picture around rare diseases. In looking specifically at inherited metabolic diseases, NHS England's National Congenital Anomaly and Rare Disease Registration Service found that existing codes were insufficient. Accordingly, clinicians provided text diagnoses that had to be assessed before entry into the registry and hence may be inaccurate.[147]

Health system management is also affected by the lack of ICD coding. "What we're doing is diagnosing the patient, but then we don't have a specific ICD-10 code for them," says Dr Dawkins. "So, we then

bury them back in the system with a code which says 'other'. So a health economist, for example, can't track them. There are standardised coding and classification systems available, such as Orphanet RD codes and the draft ICD11s, and embedding them in existing systems through addition of adding a single data field; it is not an onerous task for health records to have a specific unique rare disease code added, and the impact on cost and efficiency would be enormous." Unfortunately, he says, in healthcare databases, rare diseases are "under-recognised and under-counted".[155]

Countries are free to adapt the ICD-10 codes to their particular circumstances. Several have done so in order to monitor rare diseases better. Germany is the most advanced in this regard. In 2013 the German Institute of Medical Documentation and Information began integrating every condition listed in Orphanet's rare diseases database into ICD-10-GM, the German version of the ICD codes. Health authorities continue to add new diseases as they are entered into the Orphanet database.[156, 157]

Dr Dawkins reports that the results have been impressive. "Because they did that nearly ten years ago now, they've got data that enables them very quickly to ascertain the potential benefits and the costs." He believes that this helps to explain the "incredible" success of German healthcare on rare disease in many regards.

Eventually, the world will catch up. The latest iteration of the global ICD codes (ICD-11) went into effect at the start of 2022. Taking a cue from the German innovation, it includes 5,500 diseases found in the Orphanet database.[158, 159] However, as of February 2022 only 35 countries were using ICD-11.[160] When others do so, they will get much better information on burden and the effectiveness of treatments. In the interim, many will continue to stumble in the dark.

The benefits of better connections with patients

Ultimately, better healthcare provision is to help those living with rare diseases and their loved ones. What health systems can forget is that the best way to do this is through collaboration with patients and families rather than simply trying to do the best things for them.

The value of more effective collaboration with patients in health delivery has been extensively discussed.[161] Better engagement is also important for both HTA processes and information gathering. Those living with rare disease already play some role, but strengthening those connections will be essential to further progress.

Enhancing the patient role in HTA appraisals and reimbursement decisions

HTA bodies are meant to assess value. Ultimately, this is impossible without reference to patient preferences and priorities. "The patient and their family live with the condition 24 hours a day, seven days a week, 52 weeks of the year," says Mr Kent. "That experience and the experience of identifying the change brought about by a novel intervention, as well as its value in terms of improvement in the quality of life of the affected individual, the rest of the family, and carers—these are all an essential contribution to the determination of value." This is far from special pleading of a specific interest group. "I am an economist, so maybe that explains my narrow-mindedness, but value cannot be defined without the consumer," says Mr Mühlbacher. Broadly speaking, two implications for HTA processes arise from this insight. First, patients and related parties must be involved directly in discussions and decision-making. Second, HTAs need to look at non-clinical evidence that such individuals consider pertinent.[162]

Such thinking has only begun to reshape HTA processes relatively recently. Most European states, along with many wealthier Latin American and Asian ones, had HTA bodies by the end of this century's first decade.[163] However, in 2010 patient perspectives were still "rarely included" in assessments and perceived as "anecdotal, biased views."[164] Indeed, as late as 2016, France's HAS debated whether it should publish submissions received by patients because the latter potentially have a conflict of interest in supporting medications that might help them.[165] Similarly, controversy remains over patient participation in South Korea's Pharmaceutical Benefit Coverage Assessment Committee (PBCAC), a committee under the Health Insurance Review and Assessment Service (HIRA) that reviews drug reimbursement, including HTA assessments, for the same reason.[166] Moreover, a cultural chasm has been revealed over what information is relevant for decision-makers: in 2015 an Australian study found that medical experts on HTA committees saw clinical outcomes and patient preferences about treatments as the crucial data; patient groups wanted to expand this to the social, economic and emotional aspects of living with a disease.[167]

Despite ongoing reservations, the last dozen years have seen a sea-change toward acceptance of the importance of incorporating patient views into HTAs.[168, 169] Nevertheless, patient involvement, and consideration of the patient experience, in HTA processes overall remain limited.[170] Once again, our study countries are further ahead than most, but still short of the destination. “Governments agree that there should be—for orphan drugs in particular—some way to better involve patient groups in decisions on reimbursement,” says Mr Obscherning. “Whether there’s a process and system for doing so, is another story.”

A range of common strategies exist, including statistical research into patient preferences, elicitation of input from patient groups, and formal membership—either participatory or voting—of patients on committees and bodies involved in the HTA process. The extent to which these and other mechanisms are used varies widely between countries. In all, however, important barriers to patient participation in the HTA process remain.

Our Asian states have seen the least progress. The Japanese HTA system, which dates only to 2019, has no role for patients.[171, 172] In South Korea patients are not involved in reimbursement decision-making or included in the PBCAC. Dr Kwon says that, in practice, the bigger impact which patient groups have on HTA decisions is outside the process—“They always raise their voices politically,” she says. Rather than patients being meaningful stakeholders, a 2019 academic study found that, in practice, the PBCAC is “primarily…an intermediary between clinicians and government.”[173]

In Taiwan, meanwhile, the National Health Insurance Act requires that patients, among others, be invited to voice their opinions on which drugs are covered by the health system. In practice, this involves submitting opinions over

a web portal and then, possibly, being invited (with just one week's notice) to give a ten-minute presentation to the committee making reimbursement decisions.[174, 175] After speaking, the patient representatives are asked to leave.

There is no indication of how much attention officials may pay to limited patient input in either country. Ms Wu says that it is "a totally untransparent process." If anything, she adds, patients are getting less attention now than in the past. In South Korea, a recent analysis reports that, for published PBCAC decisions, "evaluation results and summarized evidence…are not detailed enough for stakeholders to understand the reasoning behind [them]."[166]

In France, patient representatives have been part of the Transparency Committee, the specific part of HAS which conducts HTA work and makes recommendations, since 2015.[176] They currently make up three out of 29 members, including one of the vice-presidents.[177] In 2016 HAS also began publishing weekly a list of medications under consideration, for which patient groups could send submissions. The body is particularly interested to hear about matters related to the lived experience of the disease and how the intervention is likely to benefit.[165]

In Germany, the G-BA by law has patient representatives on its various committees. These can participate in deliberations but not vote.[178] IQWiG, meanwhile, for its HTA work conducts oral consultations with affected persons to better understand the impact of a potential intervention. It usually finds these individuals through the G-BA patient representatives. It can approach relevant patient groups directly, but rarely does.[179, 180]

Australia has more extensive structures. Two patient—or consumer, to use the Australian term—representatives sit on the PBAC, one of whom is its vice-president. One is on the expert panel of the LSDP as well.[181] Patients are able to submit written assessments during the HTA process and can also be called on to give testimony and answer questions at PBAC committee meetings. In 2019 the PBAC established the HTA Consumer Evidence and Engagement Unit, to support broader consumer participation strategies, and the Health Technology Assessment Consumer Consultative Committee, which brings together patients involved in various HTA and drug regulation committees to advise the Department of Health and Aged Care.[182]

The "transparency" problem

France, Germany and Australia, then, have formalised some role for patients in HTA. Yet a common criticism arises in each. Professor Mühlbacher believes that one of the biggest challenges in the area of orphan diseases is "untransparent decision making about reimbursement pricing." Similarly, several representations by Australian rare disease groups to a recent Parliamentary Inquiry into pricing of new drugs raised the lack of transparency at various points in the HTA process.[182] The complaint is heard in France too.[183]

The general criticism of a lack of transparency in practice relates to at least three distinct problems. First, patient groups find it difficult to work within the system. MS Australia, for example, told the above-mentioned Australian enquiry that the HTA process "remains mysterious to most consumers." Duchenne Australia added that "there needs to be a clear and transparent pathway to provide patient experience data through the HTA process."[182] Existing efforts at transparency may simply be insufficient. The publication of upcoming assessments by the HAS in France, for example, in practice requires patient groups to monitor developments. This might help to explain why, in the first two years during which the HAS was open to patient submissions, it received input on only a quarter of the drugs assessed.[184]

Second, existing structures are not always fit for purpose. This is particularly relevant to patient participation in formal bodies, which is essential but not necessarily sufficient for meaningful patient engagement. As Dr d'Andon reports, because members of the HAS Transparency Committee are chosen for three years, their level of expertise in assessing any given treatment is, to some extent, a matter of chance.

Although committees cannot have infinitely flexible memberships, Mr Mühlbacher characterises the situation in Germany as representation "by professionally organised patients sitting at the table, but not allowed to vote." He says that there is no certainty that the views of these individuals represent the patient community. Meanwhile, patients are not always happy with the point at which their voices are heard. For its part, Australia's Patient Voice Initiative, a coalition of patient groups seeking to improve their role in HTA, is pushing for earlier participation in assessment activities.[185]

Beyond individual patient committee members, another way to improve patient input is through patient preference studies. Such research has been around for some years, and it has been used by both IQWiG and NICE.[186] The problem is that good practice on its integration into HTA decisions is still being worked out. Despite IQWiG's ostensible openness to such instruments, a group of German HTA officials told researchers in 2021 that they could not see how information from patient preference studies could be used in current HTA reports for medications.[187] Here, NICE is the most advanced—it has published recommendations on how to carry out patient preference studies.[188] In 2020 it also reported on the results of a two-year study considering the potential contributions that such research could make at various stages of HTA, including when technologies have important non-health benefits.[189, 190] However, the results are still at the recommendation stage.

The third transparency-related problem is a lack of clarity on how—if at all—patient input has an impact on decisions. In Germany, says Mr Mühlbacher, "there is no formal process documenting how patient preferences went into the equation." Similarly, an analysis of patient submissions to the HAS in France, covering the first six months after they were permitted, found that the Transparency Committee looked at only 65% of them. A review found that the biggest challenge remained the cultural one for evaluators of understanding the potential benefits of patient-contributed information. It recommended a formal definition of the processes around their use.[165] Meanwhile, the Patient Voice Initiative is also pushing for HTAs to "take account of patient input and patient-based evidence in their documented procedures and terms of reference."[185]

Probably the most advanced HTA body in terms of patient engagement is NICE. Members of patient groups and other affected individuals serve on, and participate in, decision-making of boards and committees at every stage. It considers patient submissions and oral statements, and is willing to look at a range of different kinds of evidence in making its decisions.[172, 191] "In the UK, the potential contribution to sensible decision-making that patient engagement can make is being recognised," says Mr Kent.

That said, NICE's patient engagement efforts remain a work in progress. Mr Kent notes some of the same problems that exist elsewhere. "The overriding challenge for patient advocates, particularly for those interventions targeted at extremely rare conditions, is understanding how the decisions are made and knowing where they can have an input." More generally, he adds, "I'm the last person in the world to say everything in the garden is rosy. There is clearly a lot more progress that we need to make." Ms Upadhyaya agrees: "I won't say it's perfect, I'm sure there are lots of things the system could do better." Nor is the organisation sitting on its hands, as the 2022 changes to the HTA process and research on patient preference surveys show.

The nature of rare disease patient groups: small, and in need of support

The relative progress of NICE makes clear another barrier to effective rare disease patient involvement in HTA processes—the nature of patient groups themselves. Mr Kent explains that, for extremely rare conditions especially, many patient organisations "are tiny and run by volunteers for whom participation in the process is a huge challenge. In an HTA evaluation programme, everybody else is a professional who understands the system. For the patient or patient advocate, often the only unpaid person in the room, this may be the first and only time they participate. It can be intimidating; it can be baffling; and they carry with them a huge sense of responsibility for speaking on

"Helping patients understand the basics of the HTA process, so that they can participate in an effective and constructive way, is becoming more popular."

Eric Obscherning, Secretariat & Advisor, APEC Rare Disease Network; Associate Director and Lead for Rare Disease & Advanced Therapy, Crowell & Moring International

behalf of their community." Finding ways to help these organisations, he adds, is necessary.

The problem is common in all our study countries, but efforts to help patient groups certainly do occur. For example, the G-BA has a patient involvement specialist team that provides advice and training, the HAS telephones a representative of every patient organisation that submits information during an HTA assessment to go over the impact of their input and how it might be improved, and Australia's Consumer Evidence and Engagement Unit holds workshops and fora for patient organisations and is developing a mentoring programme.[178 165 185] "Helping patients understand the basics of the HTA process, so that they can participate in an effective and constructive way, is becoming more popular," says Mr Obscherning. Even here, though, he adds, governments are not sure what to include in such efforts. "What are the sort of facts that you need to have lined up? How do you talk about these issues?"

The need for more help in developing expertise certainly remains. In Australia, for example, the Patient Voice Initiative is asking for better patient group training around HTAs. Meanwhile, in France, Dr d'Andon reports that the willingness of patient groups to submit information to HAS varies by condition and the idiosyncrasies of the organisation.

Every country in our study, then, needs to find ways to enhance the role of patients in the HTA process. Statements from the International Network of Agencies for Health Technology Assessment and Health Technology Assessment International have served as starting points for change and could provide further ideas for best practice in individual jurisdictions.[168]

Perhaps an Australian initiative points in the most useful direction. Whereas many countries have, in different ways, added patient participation to existing systems in a piecemeal fashion, for the first time in 30 years Australia is conducting an independent, comprehensive review of its entire HTA system.[192] If other countries step back to take such a broad view, it would be valuable to consider holistically how patients could be involved across all HTA activities. Doing so will only strengthen the HTA process by engaging with an essential partner: those people living with a rare disease who can talk about real-world outcomes. As Dr Dawkins puts it, patient groups "represent the quietest and the loudest voice in the room. They're not usually adversarial. They're just looking for the best outcome for their family members and the other people worldwide living with a rare disease."

Patients and registries

Registries contain data on patients. Whether this specific information is of the most interest to patients themselves depends on the registry. The databases that are likely to have the most beneficial impact on issues that matter to those living with rare disease therefore require active patient participation in governance.

In some cases, this involves patient groups founding such facilities themselves. For example, cystic fibrosis associations in Australia, France, Germany and the UK have all started registries.[193-196] Others look at the rare disease field as a whole. In Japan, the Advocacy Service for Rare and Intractable Disease (ASrid) has organised various patient groups to work together on J-RARE, a registry into which patients enter their own information including medication, test results, economic costs and outcomes of importance to them. It has specific data collections for six diseases—distal myopathy, Isaacs' syndrome, Marfan syndrome, relapsing polychondritis, Silver-Russell syndrome and mitochondrial disease—as well as a general collection for those with other rare conditions. Patients can use the information for self-management and better informed interaction with clinicians. The data is also available, after anonymisation, for ASrid's own investigators and for

others approved researchers.[197] In 2020, drawing on data from patients in the registry, ASrid produced a leaflet on "Progressive muscular disease patients' need for assistance and care" for distribution to clinicians in Japan.[198]

However, undertaking any kind of registry requires expertise and resources that may be lacking for groups concerned with conditions that are even rarer than cystic fibrosis. One solution is to create programmes that support interested patients, such as the Rare Diseases Registry Programme (RaDaR) operated in the US by the National Centre for Advancing Translational Sciences.[140]

Ultimately, though, patient group registries are likely to form a minority of those databases tracking rare diseases. According to Orphanet's latest figures, 88% of rare disease registries in Europe are run by public bodies or for-profit organisations. Some of the remaining will be run by non-profit groups of expert clinicians, meaning that patient-group-led registries are very much in the minority.[136] The solution to effective collaboration should therefore involve a patient role in the governance of all registries. However, a survey of rare disease registry managers published in 2021 found that, while 71% agreed that patients should have some role in registry governance, a number of respondents felt that this involvement was likely to be minimal. Of the international registries covered by the study, only 55% had a patient group active in governance.[199] Similarly, a review of registries in Europe in 2022 found that the non-involvement of patients and patient groups in the development of registries led to "insufficient consideration of the patients' view and experience".[134]

The Australian umbrella patient group Rare Voices appears to have found a way around this difficulty. In 2018 it founded the National Alliance of Rare Disease Registries, which currently brings together 25 organisations. Alliance members are committed to a range of best practice sharing, including collecting person-centred quality-of-life data. They are also jointly working on forward-looking goals, such as greater interoperability, agreed minimum data sets and the development of national operating principles.[200] By convening this conversation, Rare Voices has ensured that patient interests will be central to the dialogue. It has proposed, as the basis for discussion of national operating principles, a set of principles put together by European, Canadian and US patient groups, which include that registries should: "involve patients equally with other stakeholders in governance; and serve as key instruments for building and empowering patient communities."[200]

Working with patient groups on registries will not only provide health systems with the information that they think they need. It will also help them to obtain the best data needed to help patients, and for patients to help themselves.

The policy implications of bringing it all together across health systems

It is no longer possible to miss the huge health and economic burden that rare diseases collectively represent, whatever the differences in national definitions of the category. These conditions are a leading cause of childhood mortality and create a serious economic burden for health systems.

However, those same systems were originally designed in ways that poorly serve individuals living with rare diseases. Slowly, though, officials have found ways to modify parts of the health ecosystem in order to overcome barriers to care. We have explored how orphan drug laws have created an environment in which rare disease treatments are now a leading part of pharmaceutical research and development. Similarly, new diagnostic programmes are able to identify diseases in a growing number of cases. These dots of excellence are far from perfect; nevertheless, they have changed the environment for those living with rare disease.

In order to deliver on their full potential, these advances need to be better connected into the healthcare environment as a whole. This study has identified several basic areas where, although some improvements have occurred, more needs to be done. These are:

- *Integration of rare disease awareness and care into the health system mainstream.* To make the most use of the growing number of diagnosis programmes, and in some cases specialist treatment centres, clinicians across health systems need better information. This is especially the case for general practitioners. Healthcare workers need more knowledge of the basics of rare disease identification, awareness of referral pathways and clinical guidance on their role in treating patients once diagnosed.
- *The comfort of HTA programmes with the evidence-related challenges of assessing the value of rare disease treatment.* Like regulatory bodies before them, HTAs are wrestling with the challenges of determining value and deciding on reimbursement when evidence of treatment effectiveness is hard to determine. Most have made some progress. Yet continued process modifications, even among those bodies with the most advance understanding of these issues, show that best practice is still being worked out.
- *Better patient registries and health system information to mine for real-world evidence.* Rare disease registries are burgeoning but remain fragmented. Efforts to aggregate the data that they hold will, when complete, inform policy and healthcare much better. A very basic step in this direction needs to be rapid adoption of the new ICD-11 codes, which are the first built with rare disease in mind.
- *Empower the patient voice.* Patients and patient organisations are eager to contribute towards improving the healthcare eco-system that they exist within, including rare disease registries and HTA decision-making processes, but more often than not, they are left on the sidelines. If enabled,

patients can play a key role in strengthening registries, ensuring that the data collected is most relevant to them and their unique disease.

The majority of study countries have some level of patient involvement in their HTA processes, although this varies between countries. What is common across countries is the uncertainty about whether patient input has an impact on HTA decisions. Some ways to empower the patient voice include involving patients and their organisations earlier in the evaluation process, building capacity and understanding of the HTA process through training, and providing patients and their organisations with feedback on the impact that their input has on the decision-making process.

Progress in these ways would help people living with rare diseases to receive better care, as well as reduce the high health system costs for this group of patients. Although both goals are worth seeking, they represent only a starting point for the broader health system advances that the suggested improvements are likely to bring.

Already, changes to address rare diseases are benefitting much wider parts of the population. For example, drug pathways and assessment procedures that grew out of those created for orphan drugs are being used to help to assess products from the rapidly developing field of cell and gene therapy. Although rare illnesses have acted as a major proving ground for such interventions, certain cell and gene therapies can now treat a growing number of conditions that are not rare, including certain previously intractable cancers.

In the same way, the lessons being learned in rare disease look capable of revolutionising primary care. Among our study countries, for example, both the UK and France are working to make whole genome sequencing a standard tool at this level of medicine. Not all diseases are genetic, of course, but the wider understanding of the risks inherent in different abnormalities in DNA could create highly personalised prevention, advice and treatments in many cases.

In short, connecting the dots for those living with rare disease is not simply a matter of providing better care to the significant minority of the population with such conditions—as important as that is. The results of these efforts will mean better healthcare for all.

Appendix: methods note

This research explores the HTA and reimbursement processes for orphan drugs, which treat rare diseases. The countries of interest are Australia, France, Germany, Japan, South Korea, the UK (specifically England) and Taiwan.

We conducted a literature review that focused on how different countries respond to the challenge of improving access to effective treatments for individuals with rare diseases, particularly focusing on how reimbursement decisions are made.

The purpose was to obtain a broad overview of the regulatory environment and reimbursement policies in the countries of interest, rather than insight into a single narrow research question. To identify the relevant literature, a structured database search was conducted, making use of the following information sources:

- Bibliographic database searches via Embase.com (MEDLINE and Embase)
- Grey literature searches to identify information not published in scientific journals

These combined searches yielded over 2,900 results, which were then screened to include articles that were the most relevant for the research question. The literature review was followed by an expert advisory meeting to build on its insights.

For the analysis of the speed of reimbursement for the selected orphan drugs, data on regulatory approval date, HTA submission date and reimbursement date were obtained from the MAESTrO database, developed by Wonder Drug Consulting, along with grey literature search. The data extraction was conducted between March and May 2022.

The nature of the data gathering process and the gaps in publicly available material made this a challenging task. Although 100% accuracy can never be guaranteed, we have made every effort—including triangulation and extensive data checking—to ensure that the data presented are correct and up to date.

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