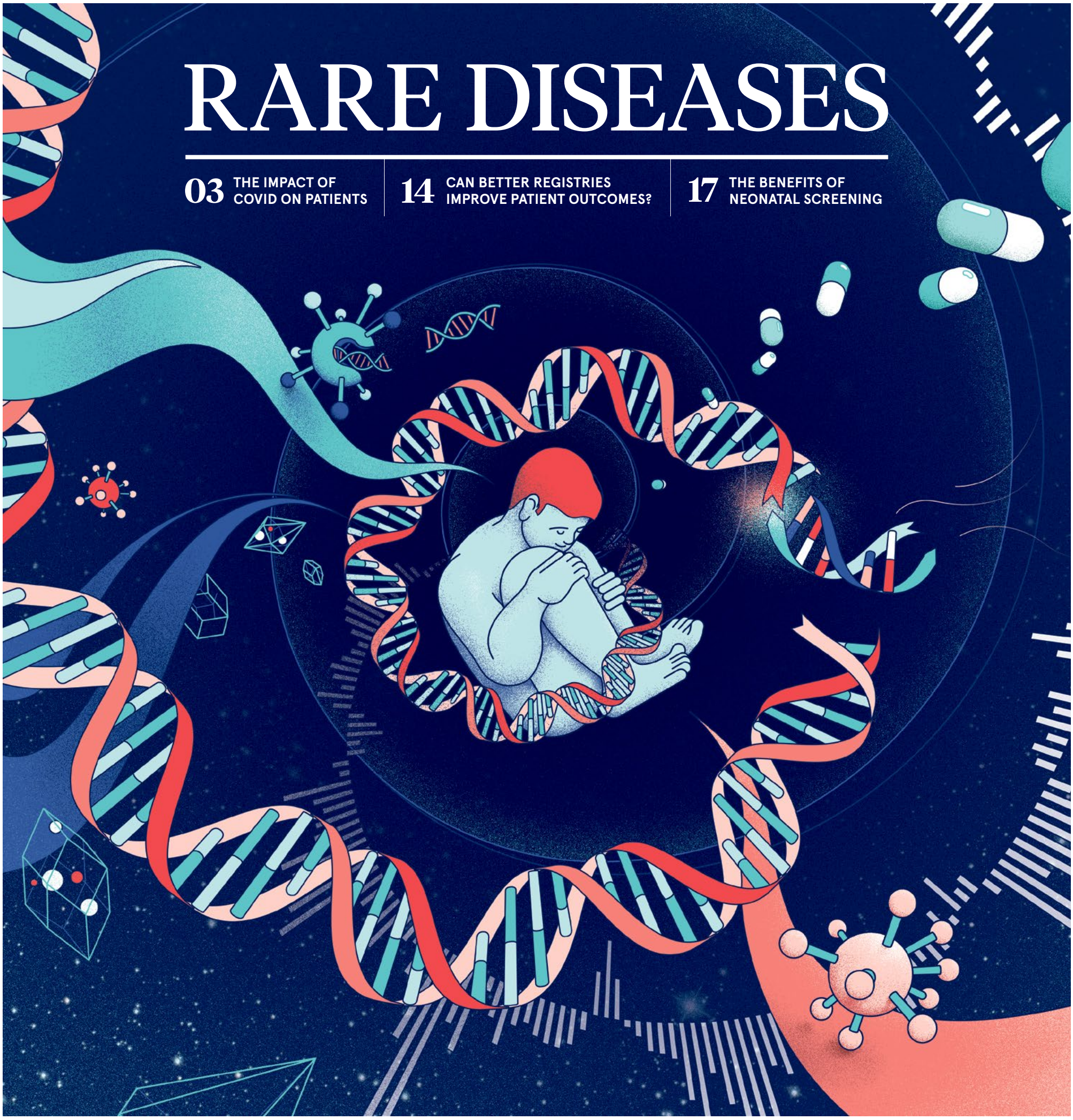
RARE DISEASES



RARE DISEASES

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IMPACT

How Covid-19 rocked the rare disease community

People living with rare and complicated health conditions have experienced more challenges than most during the pandemic. However, emerging remote health services offer new opportunities

Natalie Healey

The prime minister's message to the UK on 23 March 2020 was clear: stay home, protect the NHS, save lives. Most of us will never forget the moment the country locked down to fight the spread of Covid-19. But although the rules might have been the same for everyone, lockdown affected some people more negatively than others.

Amanda Mortensen from Brighton was terrified her teenage daughter Livvy would catch Covid-19. Livvy has Phelan-McDermid syndrome, a rare illness that causes multiple daily seizures. At the start of the pandemic, the nearby care centre that Livvy attended five days a week had to close its doors. For several months, Mortensen and her husband provided all of Livvy's care, while both working full time.

"It was quite intense," she says. "We weren't leaving the house, we weren't going to the shops. We isolated ourselves completely."

Rare diseases – conditions that affect fewer than one in 2,000 people – are more common than most people realise. Collectively, approximately 3.5 million people in the UK live with a rare condition, from well-known illnesses such as cystic fibrosis and Huntington's to ultra-rare disorders such as glycogen storage diseases. Because each condition is individually rare, this large population is often overlooked, even during better times.

Rare disease patients and their families consistently report significant care inadequacies, unmet clinical needs, and feeling 'left in the dark' about their condition. These challenges intensified at the height of the pandemic as it became more difficult to access the usual health and care support.

"We were all in the same storm, but we were not all in the same boat," says Dr Gemma Chandratillake, who is the chair-elect of The British Society for Genetic Medicine and education, and training lead for the East Midlands and East of England NHS Genomic Laboratory Hub.

In some ways, the wider population got a taste of what it feels like to experience a rare condition at the start of the pandemic. Suddenly everyone had to isolate themselves, conduct a risk assessment before even the most banal activity, and deal with the uncertainty of potentially catching a little-understood illness for which there was then no treatment or vaccine.


FG Trade via Getty Images

But while the majority of people have been able to enjoy a return to normality as lockdown rules eased, some rare disease patients are living with the long-term effects of the disruption caused by Covid-19. These range from everything from diagnostic delays to reduced clinical services, says Mortensen, who is also chief executive of the Batten Disease Family Association (BDFA), a charity that offers guidance to families affected by Batten disease, a group of rare neurodegenerative diseases.

Obtaining a quick and accurate diagnosis can be challenging for somebody with a rare disease, even when the NHS isn't dealing with a pandemic. In the UK, patients can expect to wait several years for the right verdict and often receive several misdiagnoses along their journey. It is such a challenge that many rare disease patients call the arduous process a 'diagnostic odyssey'.

Livvy is now 20. She only received her diagnosis of Phelan-McDermid syndrome at the end of last year after participating in the 100,000 Genome Project, an initiative set up in 2012 to sequence 100,000 whole genomes from NHS patients with rare diseases or cancer. Such delayed diagnosis is frustrating, but it can also have serious consequences. Delays are inked to fewer treatment options and worsening illness, as well as shorter life expectancy.

Earlier in the pandemic, diagnostic rates for rare diseases slowed because of reduced access to health services, suggests the Making the Unseen Seen report from advocacy organisation Action for Rare Disease Empowerment (ARDEnt). For families dealing with a mystery condition, the first port of call is usually their GP. But primary care appointments fell from 6,026,140 in the first week of March 2020 to 4,225,502 in the last week of the same month, according to NHS data.

The appointments that did occur were largely conducted by telephone and video consultation, which aren't always suitable for spotting indicators of certain rare conditions, such as dermatological diseases. Referrals to specialists – who perform the tests to confirm a diagnosis of a rare condition – were also negatively impacted by the pandemic. In some areas of the UK, GP referrals to specialist services fell by more than half during April to June 2020, the ARDEnt report suggests.

Even rare disease patients who had received an accurate diagnosis for their condition by March 2020 faced significant challenges during Covid-19. Many of the NHS medics who usually looked after rare disease patients were redeployed to Covid wards. A survey by Rare Disease Europe (EURORDIS) found that 83% of patients experienced delays and cancellations to healthcare appointments during the first wave of the crisis. The findings also suggest that pandemic-induced pauses in treatment might have led to severe deterioration for some patients. Three in 10 individuals who experienced disruption to their care reported it was 'definitely' or 'probably' life-threatening.

Services that many patients view as vital to manage their conditions, such as speech therapy and physiotherapy, were considered 'non-essential' during the lockdown and forced to stop operating. Restricted access to support has often led to family members taking a much greater role in their loved one's care, says Amy-Jayne McKnight, a professor and molecular epidemiologist at Queen's University Belfast. "Parents were left on their own with no access to support."

Feeling shut out of health and care systems and faced with confusing guidance about protecting vulnerable people during the crisis, patients and their families often turned to small charities for advice. These frequently serve the needs of specific rare disease communities. However, they also faced pressure caused by the pandemic.

Many non-profit organisations are staffed by volunteers (often themselves affected by a rare disease)

21% of patients were unable to access rare disease treatments during Covid

3 in 10 rare disease patients and/or family carers perceive Covid-related interruptions to care to be 'probably' or 'definitely' life-threatening

2 in 3 rare disease patients suffered from depression or a feeling of not being able to overcome their problems since the beginning of the pandemic

EURORDIS, 2020

who had to try to juggle work, home-schooling and greater care responsibilities, leaving them with fewer resources to respond to patient concerns. Because very few fundraising events took place during the first lockdown, 38% of medical research charities reported a loss in income during March-May 2020.

The mental health impact of the pandemic on rare disease communities has also been considerable, says Dr Rick Thompson, CEO of rare disease charity Findacure. Some vulnerable patients were so worried about catching a deadly virus that they didn't seek medical help when it was needed. Others avoided trips to the grocer or even going outside.

"Many patients were more scared of catching Covid than other people given the potential additional complications. That has led to increased isolation in an already isolated population," says Thompson.

Cancelled clinical research dashed the hopes of some rare disease sufferers. Worldwide, more than 2,500 trials were terminated or suspended between the end of 2019 and May 2020. Studies that had been years in the making were abruptly halted as research funding was repurposed to fight the Covid crisis and many trial clinicians called to the frontline.

Clinical trials are sometimes the only hope of developing a treatment for patients with ultra-rare diseases, so it is heartbreaking when they're shut down, says Chandratillake.

"For particular rare diseases, there might be a clinical trial that's taken years to get together. And then overnight, it's just gone." In 2020, investigators terminated the only clinical trial of a treatment for Alström syndrome due to the constraints of the pandemic. This rare disease causes heart problems and progressive loss of vision and hearing. There is currently no approved treatment.

No one would choose to repeat the last 20 months. For many rare disease families, Covid-19 caused additional heartache, anxiety and strain.

However, advocates think lessons can be learned from this tragic period. For example, the NHS embraced remote patient monitoring as well as wearable devices. Patients no longer had to travel miles to visit specialists – instead, they could have a virtual consultation via video link.

"Having to drive for three hours to sit in hospital for a 10- to 15-minute appointment and then drive three hours home again is not the best use of anyone's time," says McKnight

Now that remote monitoring is more common, it is important to make sure test results can be embedded in electronic healthcare records so that medical experts can quickly access an up-to-date account of a patient's condition.

More focus on remote care could also present opportunities for clinical research into rare diseases. Even before Covid-19, conducting clinical trials for rare conditions was challenging due to the small numbers of people in each country living with any particular illness. Patients with a rare disease often had to travel long distances to participate in research.

However, 'decentralised clinical trials', which rely on virtual collaboration between researchers, medical teams and patients, are now more common. Collecting patient data using digital technology, rather than in-person tests, might attract and retain a wider pool of trial subjects. That could mean treatments are approved faster.

The pandemic has accelerated the adoption of such strategies, with many arguing that decentralised trials will only grow in popularity as they help to improve representation and access across geographical locations, says Dr Tim Guillams, CEO of Healx, an AI drug discovery platform for rare diseases. "By allowing people to complete the trial from the comfort of their own home, patients can also feel more at ease throughout the process, reducing drop-out rates significantly."

Dr Jenny Rivers, deputy director of research and innovation at Great Ormond Street Hospital, in London, says the pandemic has made more people aware of clinical research and how they can get involved, which could also potentially boost recruitment rates for future rare disease treatment trials.

"More people now understand what medical research is and the power of clinical trials," she says. She would like to see research automatically embedded into all aspects of clinical care and believes remote monitoring tools and services could one day make this possible. "Remote consultations mean we will be able to potentially offer more treatments and access to clinical trials in areas we haven't been able to before."

> **Many rare disease patients were far more scared about catching Covid than other people**

Some experts are optimistic that Covid-19 has made political leaders more aware of the challenges of living with a rare illness in the UK. In January 2021, the Department of Health and Social Care released its vision for improving the lives of people with rare conditions, aiming to speed up diagnosis and increase awareness, as well as improve treatment and care.

The UK Rare Disease Framework suggests four key pillars for improvement: helping patients get a final diagnosis faster; increasing awareness of rare diseases among health professionals; better coordination of care; and improving access to specialist treatment and drugs.

Dr Lucy McKay, is a paediatrician and the CEO of Medics4RareDiseases. She thinks the framework is a positive step towards addressing the needs of patients, many of whom were disproportionately impacted by the pandemic.

She suggests the second priority is of particular importance. "Making sure every healthcare professional understands the role they have to play in rare disease diagnosis and management has to underpin the framework for it to actually make real change," she argues.

Thompson thinks the report is encouraging, but it's what happens next that will have the most impact. "There's definitely been a real and-serious push to engage with the rare disease community. However, until we can see what the implementation plan is going to be, it's hard to judge," he says.

He hopes for a big push around care coordination, the third of the framework's four priority areas. The success of the 100,000 Genomes Project has led to the NHS Genomic Medicine service, which aims to sequence 5 million genomes in England between 2018 and 2023 and means more rare disease patients, like Livvy, are finally getting the answers they need.

But infrastructure and investment must be in place to support newly diagnosed patients, says Thompson. "We're sleepwalking into a trap if we're not careful," he says. All four UK nations will now develop their own action plans to address the framework's four priorities.

Despite the colossal challenges rare disease communities faced in 2020 and 2021, opportunities have emerged for better access to specialist medical services and more convenient participation in clinical research, which could make a real difference to patients' lives.

"As we've learned with Covid, if there's a will there's a way," says McKay. "We'll see in the next few years if there's a will when it comes to rare diseases." ●

THE LOCKDOWN EXPERIENCE OF RARE DISEASE PATIENTS

83% of rare disease patients experienced disruptions to care during the Covid pandemic. They identified the following problems:

6 in 10 did not have access to diagnostics such as blood testing and medical imaging

6 in 10 were unable to access medical therapies such as infusions and chemotherapy

7 in 10 had medical appointments cancelled or postponed

6 in 10 had psychiatry follow-up sessions postponed

8 in 10 had rehabilitation therapies such as physiotherapy postponed or cancelled

6 in 10 had surgeries or transplants postponed or cancelled

EURORDIS, 2020

OPINION

'The small steps will be the ones that improve the lives of people with a rare condition'

The biggest disconnect we see for people living with rare conditions is between the headlines and the day-to-day. We are in an era of great technological leaps forward, where gene and cell therapies are available on the NHS to treat some rare conditions. Inconceivably large amounts of genomic data are analysed everyday in NHS labs to find diagnoses for people with conditions that had not been identified even a few years ago.

We welcome these developments - they represent ambition, investment, talent and hard work. But they don't match up with what we see when we speak to people who work with the one in 17 people in the UK living with a genetic, rare or undiagnosed condition.

When we hear from people who have been diagnosed with a rare condition, we hear that they cannot get their local healthcare service to provide them with physiotherapy because their condition is too complicated. Our members help people who have had a diagnosis but do not have a clinician to treat their condition. We also get calls from people who have been told by their GP that they couldn't possibly have that condition because it is so rare.

The UK Rare Diseases Framework offers us the opportunity to correct these contrasting sides of the rare disease world; it's an opportunity for us to fill in all the gaps. We need to build the connections to take a patient from a GP - who cannot be expected to know all the details of every rare condition - to the clinicians who have access to the labs that can read genomes and make accurate diagnoses.

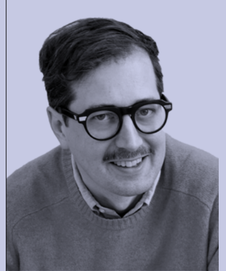
Then, once they've had their diagnosis, we need to bridge the gap to the expertise in the NHS that can keep them as healthy as possible. We need to make sure they access the right clinical trials, or can access the best and the newest medicines.

We need to connect all of the headline-grabbing initiatives with the hard-working bits of the system that are just as crucial for the best outcomes. With each new leap forward there are prosaic requirements for the NHS to adapt its approach and build or change care pathways.

We're in an era where life expectancies for people with certain rare conditions can suddenly grow by an order of magnitude. We must get the implementation of the new therapy that delivers that step change in outcomes right. But we also need to follow up with new care pathways for patients to help them transition to adult care for the first time and to start addressing care needs in later life that will never have been a concern before.

As the four nations of the UK write their action plans to implement the UK Rare Disease Framework commitments, the temptation might be to put the spotlight on the high technology big ticket investments of priority one - diagnosis - or priority four - access to therapies. There is a reason these are the areas of focus, they have the potential for the biggest leaps forwards.

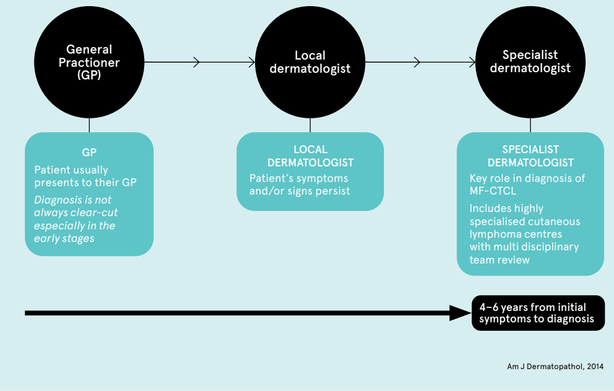
But we must be sure not to miss the smaller steps in priority two - ensuring healthcare professionals are aware of rare conditions - and priority three - coordination of care. These might be where we find the changes that can connect patients with innovative treatments and genomic diagnostic technologies. And especially for those who aren't lucky enough to get those breakthroughs, the small steps will be the things that improve the lives of everyone living with a rare condition in the UK. ●



Nick Meade
Joint interim chief executive and director of policy, Genetic Alliance UK

A PATIENT'S JOURNEY

Patients interact with many healthcare professionals on their journey



Am J Dermatopathol, 2014

Empowering patients to understand skin lymphoma

Lymphoma Action is amplifying the voices of skin cancer patients to produce better results for patients

Patient voices are helping build a brighter future for people living with the chronic condition, T-cell skin lymphoma.

Their powerful advocacy reveals there may be psychological effects from the disease being misdiagnosed as psoriasis or eczema, causing uncertainty and impacting quality of life.

This slow-progressing condition, also called Cutaneous T-cell Lymphoma, is a cancer of the lymphocytes, a type of white blood cell, that multiply abnormally in the skin. Across the UK people are living with this rare condition, and it's time for individual action.

It is not hereditary but mycosis fungoides, the most common type which is initially characterised by a scaly red rash or patches, and/or plaques, can occasionally run in families.

Skin lymphoma diagnosis can take years particularly as dermatology resources in the UK may be stretched. The symptoms can appear common to other conditions and the diagnosis requires staff from different hospital departments who work as part of a multidisciplinary team.

"People with skin lymphoma can suffer severe discomfort, itching, pain and fatigue with subsequent effects on employment, leisure activities, relationships and day-to-day living," says Dallas Pounds, director of services at the charity Lymphoma Action.

> **People with skin lymphoma can suffer severe discomfort, itching, pain and fatigue**

"In addition, the psychological impact of the condition is significant. People report feelings of uncertainty, frustration, embarrassment, helplessness, confusion, worry, anxiety and depression.

"People also report feeling frustrated and isolated during the period of waiting for a diagnosis. It is draining to have to attend repeat appointments that might feel as though little progress is being made."

T-cell skin lymphoma is usually diagnosed in those aged 50 to 74 years and is slightly more common in men than women. The symptoms can resemble those of common conditions such as eczema or psoriasis and they can respond well to some of their standard treatments which can prolong the time to reach an accurate diagnosis. Most patients need several GP visits and face a long period of monitoring before skin lymphoma is finally diagnosed.

Research is making progress in understanding the disease journey and its genetic characteristics and the PROCLIPI study is starting to identify factors that could help predict the outcomes in skin lymphomas, mycosis fungoides and Sézary syndrome.

"People with skin lymphoma have a poor quality of life. They have to live with a certain level of disease and knowing they have a cancer diagnosis," says Prof. Julia Scarisbrick, consultant dermatologist at University Hospital Birmingham, who leads the Cutaneous Lymphoma Service and is chief investigator for the PROCLIPI Study.

This evolving study collates and analyses data from more than 1,700 patients around the world. Results have already established critical information about both early onset and advanced stage patients while also revealing that some patients have a delay of more than four years before a diagnosis is made and they can receive appropriate therapy.

It is hoped these data will help build a prognostic index – a group of factors – that will enable patients at risk of disease progression to be identified allowing for improved survival and quality of life.

Lymphoma Action provides information and support for people with lymphoma from pre-diagnoses through treatments and remission

"People with skin lymphoma usually live with their condition for many years, and experience symptoms flaring up from time to time. Everyone diagnosed with lymphoma, and those close to them, will have their own unique experience, and individualised needs for information and support," adds Pounds.

She continues: "We can support people affected by lymphoma to feel informed to talk to their GP or healthcare team by giving them information, and providing practical and emotional support."

To learn more about lymphoma conditions and support: Patient association: lymphoma-action.org.uk

SUPPORT

Building connections: uniting against an uncommon foe

Digital communities have become support networks for patients of rare diseases, as well as professionals. They boost access to research, encourage advocacy and aid evidence-gathering

Magda Ibrahim

When Lucinda Andrews learnt that her newborn son was only the 16th person in the world known to be diagnosed with an ultra-rare genetic disorder, she felt completely lost. Testing had revealed a mutation in baby Leo's TBCD gene, affecting his brain, central nervous system and muscles.

"There was nowhere I could turn to ask questions as even the experts don't have the answers, because of the rarity of the disease," Andrews explains. "While my family is great for support, I didn't have another parent I could talk to who knew what it felt like to have a child affected with this condition."

After trawling through research and sending thousands of emails and social media messages, Lucinda pieced together a jigsaw of families with the same TBCD gene mutation, which causes a neurodegenerative disorder. Discovering a network of cases in the US, Germany, Turkey, Peru, Israel, China and Japan, the UK-based mum reached out in the hope of finding support and information that could help Leo.

It brought an "enormous sense of relief" when Lucinda made these connections and found other parents who "knew exactly what I was going through". A small online chat group means emotional support is on tap, while Lucinda has benefited from more experienced parents demystifying medical jargon.

"There have been times when I've been really low and it makes all the difference," she adds.

By their very definition, rare diseases can easily cause patients and their families to feel isolated. Their low prevalence means there is often a large geographical spread between patients. This is exacerbated further for those with ultra-rare diseases, informally defined as conditions affecting fewer than one in 50,000.

The need to connect and find support means growing numbers of rare disease patients are turning to digital platforms for valuable insights. Social media breaks down the barriers of borders, time zones and even language, as translation tools mean patients can easily share experiences with someone on the other side of the world.

Social media also opens a channel where patients can speak about the challenges they face, access and share expert research that was previously held in libraries, and develop advocacy plans to fundraise and campaign for greater awareness.

For Amanda Cordell, who has two children diagnosed with eosinophilic-associated diseases affecting the gastrointestinal system, creating an online community helped with the daily "battle".

She launched the EOS Network as a Yahoo support group in 2005 to connect with others dealing with these chronic rare diseases, which can affect as few as three in 100,000. The charity network has grown to thousands worldwide across multiple social media channels and within a closed Facebook group.

"You are battling every day, whether you are living with it, campaigning for it or trying to treat it," she explains. "You are exhausted and you can feel alone. There is a true strength when you come together."

It is not just patients and their families who need support. Recognising the isolation felt by medical teams working with rare diseases, a second community runs parallel to the patient group, with more than 240 healthcare professionals in 34 countries now connected.

"They are also battling for research and investment to get drugs developed," says Cordell. "It goes hand in hand: healthcare professionals need insight and better understanding, while patients need doctors."

Rare disease groups exist across all the major social media channels, from Facebook and Instagram, to Twitter and TikTok. The latter has clocked up almost 290 million views of videos posted using the hashtag #raredisease.

Rare disease groups have also turned to digital communities that sit outside the major social media sites. Healthcare-specific platforms focusing on rare disease communities include closed-access groups on sites like Inspire and Smart Patients.

Another example is RareConnect, created by EURORDIS, a European alliance of rare disease patient organisations.

RareConnect launched in 2010 with a single community for a rare auto-inflammatory disease. There are now more than 260 disease-specific online groups on the continually expanding network, says manager Sandra Pavlovic. Posts are available in 13 different languages on the moderated groups, which are translated to meet each patient's pre-selected language preference.

"Patients and their families use the platform to share their experiences, exchange disease management techniques, better identify symptoms and empathise with one another," says Pavlovic. "But for all of them the common ground, especially those living with an ultra-rare disease who feel isolated, is in finding any available resource anywhere in the world or a connection with another patient."

FACEBOOK IS A MAJOR PLATFORM FOR RARE DISEASE SUPPORT GROUPS

6,398
rare disease support groups exist on Facebook

69%

of those are private groups

826
diseases are covered by rare disease support groups on Facebook

23,414
members are included in the largest of these support groups

JMIR Pediatrics and Parenting, 2020


FG Trade via Getty Images

In a study published in March 2021, researchers from the University of Salford found social media to be a powerful tool in helping to understand unmet patient needs when it comes to rare diseases. The team was granted ethical approval to anonymously analyse almost 2,000 posts over two years from patients in a closed UK Facebook group for people with the chronic kidney disease IgA nephropathy.

Probing the posts, the study found a large number of information gaps and unanswered questions covering themes that "differed significantly" from those identified in traditional patient focus groups. It highlighted the data as "a reminder to clinicians that acknowledgment of patient concerns is fundamental to their role".

That priority is recognised by the group Medics4RareDiseases, which connects healthcare professionals who are early in their career across channels including Twitter, Facebook and Instagram. The aim is to raise awareness of rare diseases and ensure patients can be "heard and understood", says its chief executive Dr Lucy McKay.

However, while the benefits of digital connections with rare disease patients can be vast, a "pinch of scepticism" may be needed, according to Thomas Smith, a member of the NHS Health Research Authority's Ethics Review Advisory Group.

> **There can be as much disinformation among rare disease communities as on any other platform**

"While there is unity around a singular cause, we have the same pitfalls as with other social media interactions," says Smith, who was diagnosed with cystic fibrosis at six weeks old. "It can be toxic, encourage comparison or run the risk of over-simplifying. There can be as much disinformation among rare disease communities as on any other subject, so it is a tool that must be used correctly."

For Samantha Ernst, it is crucial to avoid these dangers. She has a strict evidence-based policy for the digital network she launched eight years ago to help those with twin anaemia polycythaemia sequence (or TAPS), which affects twins sharing a placenta in the womb. Starting with just 10 members, the forum has grown to almost 700 people who come together to share their experience of the condition.

Ernst's two daughters Emilie and Mathilde were born at 31 weeks old at the Leiden University Medical Center (LUMC) in the Netherlands. When the TAPS diagnosis was made, "I was 16,000 kilometres away from any close family apart from my husband and I felt so alone," she says.

Practical support can include community webinars as well as expert Q&As, while the group's focus on evidence means offering access to the latest research.

"There is a real power in sharing, especially when some people in our community have very tragic losses," says Ernst. "We really see the benefits of the friendships and of providing that moment of clarity for people through peer-to-peer support."

The group has a "unique collaboration" with the medical and research team at the LUMC, which is a world leader in treating TAPS. Ernst says this allows information-sharing that bridges the patient-doctor divide.

Researcher Dr Lisanne Tollenaar is a silent member of the group. She believes being part of this community helps her clinical team to "better understand TAPS patients and their perspective and understand their needs", which helps improve care. "We also use this to refine our information both during our daily clinical work and online."

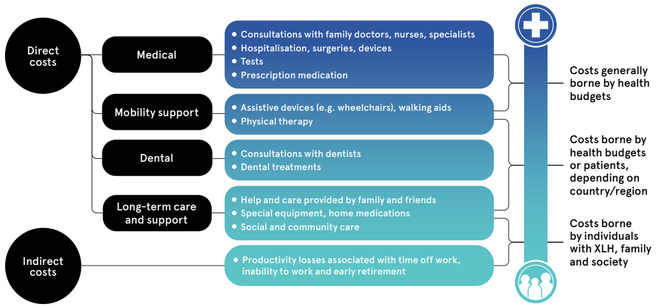
Although collectively rare disease patient numbers and the body of evidence and research is vast, the fragmented nature of information about individual conditions can be a hurdle not just for patients, but for medical professionals.

Digital groups allow for dedicated conversations, social listening and evidence-gathering. These can then help to advance our understanding, empower patients and professionals and ultimately have the potential to further research. ●

Commercial feature

THE HIDDEN COSTS ASSOCIATED WITH RARE DISEASES

Costs associated with X-linked hypophosphataemia (XLH), a rare and debilitating metabolic bone disease in adults



Kyowa Kirin, The Unrecognized Burden of XLH in Adults, 2020

Working to improve the lives of people with rare diseases

More attention is turning to caring for and treating those with rare diseases but more still needs to be done, says a Japan-based global specialty pharmaceutical company Kyowa Kirin

In the UK, across the EU and globally, a strong momentum is building to improve the lives of people living with rare diseases. This includes the UK Rare Diseases Framework, Eurordis's #30millionreasons for European action on rare diseases campaign and the global community's call for a UN resolution on the issue. Patient groups are pressing for better access to care and treatments, and for a greater understanding of the corrosive and all-encompassing impact conditions have on their lives as members of society.

In the UK, around 3.5 million people have to cope with the debilitating effects of rare diseases, according to the Department of Health and Social Care. The vast majority wait years for an accurate diagnosis and then struggle to access effective treatment - if it even exists.

Promising policy initiatives have launched that support the progress of research into and access to rare disease therapies. The current focus on addressing health inequalities is encouraging. However, implementation will be key and consistency between policies the litmus test. For instance, how can the UK be a leader in genomics and still lag its European partners for newborn screening? How can health inequalities within the rare community be fully addressed if medicines approval criteria are often failing to consider fully the implications on all affected?

"There is so much uncertainty for people living with rare conditions," says Victoria Hayes, director of public affairs, Northern Cluster, for Kyowa Kirin, a Japan-based global specialty pharmaceutical company involved in rare diseases. "Inequality exists all along their journey from diagnosis to access to treatment and care, with hidden costs to society."

The National Institute for Health and Care Excellence (otherwise known as NICE) has just carried out a consultation on its evaluation methods to support the ambition of the NHS to provide high-quality care that offers good value to patients and to the NHS.

"Kyowa Kirin believes the proposed changes – to be confirmed when the outcome of the consultation is made public – are a step in the right direction. We welcome the work being done but want to see more because people with rare diseases are hugely disadvantaged," says Richard Johnson, Kyowa Kirin general manager, Northern Cluster.

Research in this area poses specific challenges. The small number of patients and the fewer treatment options mean, for example, that to ethically recruit in a clinical trial finding the right comparator is arduous.

"Most importantly, all of us need to have the right mindset to meaningfully listen and engage with people living with rare conditions. Rare conditions can come with the risk of downward social mobility. People can be stifled in their career aspirations, while their personal relationships and family life are affected. Research suggests that, in some cases, there is a downward social spiral for families where the disease is hereditary," says Johnson.

The UK Rare Disease Framework sets out the basis for each of the four UK nations to draft their action plans, expected to be published shortly.

"The devil will be in the detail; we hope these plans will be an important step forward. Access to multi-disciplinary teams that can see the whole person will be crucial," says Hayes. "Like the patient groups we work with, we want to see the uncertainty taken out of the system and greater flexibility introduced when considering rare conditions in terms of clinical trials and drug approval. At the end of the day what matters is people and their lives; the full picture not just the medical notes."

For more information please visit international.kyowa-kirin.com/uk/products

KYOWA KIRIN

Between **291 – 578**

adults live with XLH in the UK

R. Keen et.al, Estimated prevalence of adults with X-linked hypophosphatemia (XLH) in England based on burosumab early access experience from five sites, Bore Research Society Abstracts, 2021

GENOMICS

Designer genes: a price worth paying?

There is optimism that gene therapy could cure many of the 5,000-plus known rare diseases caused by single-gene disorders, but the associated costs and risks are formidable

John Illman

A life-saving gene therapy with a reported 'list price' of £1.79m per dose became available on the NHS in March after NHS England struck a confidential pricing deal with Novartis for what is said to be the world's most expensive drug.

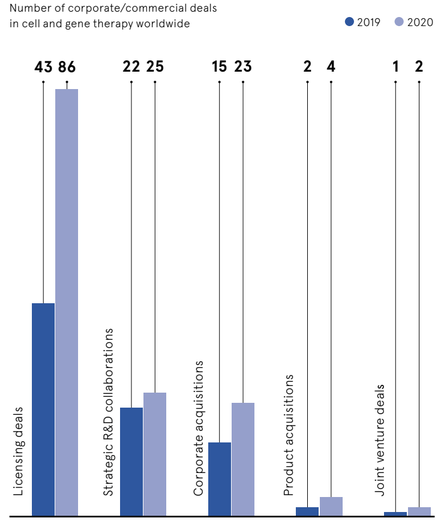
Zolgensma treats spinal muscular atrophy (SMA), a rare and all too often fatal genetic disease that causes muscle weakness and progressive movement loss, as well as paralysis. Severely affected babies have a life expectancy of just two years.

What makes this therapy so exciting is that it is delivered in a single dose. It contains a replica of the missing SMN1 gene, helping babies to breathe without the aid of a ventilator, sit up on their own and crawl. By contrast, many traditional drugs for rare diseases need to be taken permanently, often several times a week. Some of them have painful side effects. Moreover, they usually treat only the symptoms.

More than three-quarters of the approximately 7,000 rare diseases known to science are linked with just one faulty or missing gene, according to the National Center for Advancing Translational Sciences, which is based in the US. The hope is that many such disorders can be cured with one-off treatments.

THE GENE THERAPY MARKET IS BOOMING KPMG, 2021

Number of corporate/commercial deals in cell and gene therapy worldwide



But the typical costs incurred in producing gene therapies are huge. The Innovative Genomics Institute at the University of California estimates that developing one treatment can require an investment of up to $5bn (£3.7bn) – more than five times the R&D cost of the average conventional drug – which puts Zolgensma's price tag into perspective. SMA is thought to affect up to 10,000 babies annually worldwide, but the drug is highly unlikely to be affordable in many countries outside England, where about 80 babies are born with the disorder each year.

Patients with lipoprotein lipase deficiency, an inherited disorder affecting about one person in 1 million and causing severe pancreatitis, have already been denied the drug Glybera. In 2012, it became the first gene therapy to be approved in the EU, but was withdrawn just five years later because it was unprofitable, even with a price tag of $1m.

Cost is not the only problem. In the high-risk game of pharma roulette, there are many more losers than winners. The 50-year history of gene therapy has been marked by failure and controversy.

For instance, of several hundred trials that were started before 2002, not a single one was completed successfully, according to research published in *Value in Health*, the journal of the US Professional Society for Health Economics and Outcomes.

In 1999, studies were almost ended in the US after the death of Jesse Gelsinger, an 18-year-old student in Tuscon, Arizona. He had a rare metabolic disorder called ornithine transcarbamylase deficiency syndrome, which causes ammonia to reach dangerous levels in the body.

Having managed his condition on a low-protein diet and nearly 50 pills a day, Gelsinger joined a gene therapy trial. Previous participants had experienced flu-like symptoms after taking the treatment. However, he developed an intense inflammatory response that proved fatal.

Gelsinger's tragic case illustrates some of the risks of gene therapy. Genes cannot be inserted directly into patients' cells, so they are usually delivered using a vector. The most common vectors are viruses with the original 'bad' genes substituted by 'healthy' ones. Such treatments could target the wrong cells and lead to other illnesses, such as cancer; generate infections if the virus recovers its disease-causing abilities; or prompt the patient's immune system to overreact in attacking the virus.

Nonetheless, there is increasing optimism that gene therapy will become part of mainstream care. In October, the first patient to undergo such treatment at Great Ormond Street Hospital (GOSH) celebrated his 21st birthday.

Rhys Evans, who is from Cardiff, was born with severe combined immunodeficiency, a rare condition leaving him vulnerable to even the smallest infection. He was a year old when his parents made the brave decision to write him into medical history. Evans is one of more than 100 young patients to have received gene therapy at GOSH, which is a leading international research centre. Without it, many would have died before their second birthday.

Paul Gissen, professor of metabolic medicine and head of the genetics and genomic medicine department at GOSH, says: "The original research was sponsored by academic grants from bodies such as the Medical Research Council and charities.

"The success of these has led to an explosion of industry-sponsored trials by companies such as Alexis and Spark Therapeutics."

More than 120 clinical trials testing cell and gene therapy – 10% of the global total – are ongoing in the UK. Any success stories arising from these will inevitably raise the hopes of the 500,000-plus Britons who are believed to be currently living with a genetic disorder.

Laurence Woollard, who is 32, has haemophilia A, a disease caused by defects to the F8 gene. Haemophilia impairs the blood's ability to clot and can cause arthritis and joint damage, as well as painful internal bleeding.

He has extensive joint damage despite the fact he injects himself up to five times a week with a synthetic version of Factor VIII, the clotting protein encoded by F8.

"In England, we have one of the cheapest Factor VIII products in the developed world," says Woollard, who is the founder and director of On the Pulse, a consultancy providing guidance on the management of rare diseases.

humonia via Getty Images

> **Because people like me were under-treated for haemophilia when we were children, we developed significant physical disabilities. Yet children are still being treated suboptimally today, with the same bad outcomes**

"Because people like me were under-treated for haemophilia when we were children, we developed significant physical disabilities. Yet children are still being treated suboptimally today, with the same inevitable bad outcomes."

Gene therapy could free Woollard from a lifetime of painful maintenance therapy and even save the NHS money in the long term, despite speculation that the cost of treating haemophilia this way could exceed £1.8m per patient.

Research published in 2017 estimated that the combined annual cost of looking after people with severe haemophilia in France, Germany, Italy, Spain and the UK was €1.4bn (£1.2bn), equating to an average of just under €200,000 per patient.

Health economists are proposing alternative payment models for gene therapy. One suggestion is that the health service or insurer should pay annuities to meet the costs, as long as the treatment works, until these have been met in full.

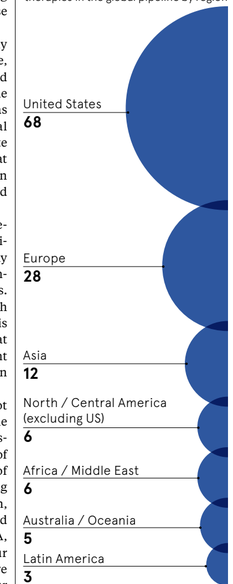
The UK continues to invest heavily in this area. In March, for example, an £18m programme was announced by the LifeArc charity and the Medical Research Council, as well as the Biotechnology and Biological Sciences Research Council, to create 'gene therapy innovation hubs' at NHS Blood and Transplant in Bristol, the University of Sheffield and King's College London.

But Woollard and others with haemophilia fear that increasing optimism around gene therapy may encourage people to join trials without fully understanding the risks. The current process through which a patient gives informed consent is inadequate, they argue, saying that it should involve an independent adviser, not a one-off discussion with a researcher.

That's a radical proposal, but not nearly as revolutionary as gene therapy itself, which could transform the treatment not only of many rare conditions, but also of several other diseases, including some cancers. As James Watson, one of the scientists who discovered the molecular structure of DNA, put it: "We used to think that our fate was in the stars. But now we know that, in large measure, our fate is in our genes."

GENE THERAPY AROUND THE WORLD

Number of active trials for gene therapies in the global pipeline by region



EFPIA, 2021

INTERVIEW

Peer review: a political champion for rare disease patients

Baroness **Nicola Blackwood** is on a mission to raise awareness of and improve treamtment for rare diseases, informed by her own health history

Nick Easen

Rare diseases don't often get the attention they deserve in the halls of Westminster, even though they are collectively common. Baroness Nicola Blackwood is an exception – one who speaks from personal experience.

Blackwood is one of the youngest members of the House of Lords and a former Conservative MP for Oxford West and Abingdon. The 42-year-old also has Ehler's-Danlos syndrome, which can cause heart problems, chronic migraines and severe joint and muscle pain. It took 30 years for Blackwood to receive the correct diagnosis, which came in 2013.

"I felt strongly that I had to hide being sick for years because I was undiagnosed," she says. "How do you explain to someone that you have a condition that fluctuates, which you or doctors cannot understand and affects you all the time, but you cannot describe because it doesn't have a name?"

A key moment came in 2019, when she fainted at the despatch box. This had its positives, helping to shine a light on her specific condition and highlighting that many people live with uncommon diseases, too.

"I've worked hard to communicate the issues because for many people living with a rare disease, it's hard for them to explain the impact it has on their lives," Blackwood explains.

For many years, Blackwood's condition affected friendships, relationships and work, she says.

"It wasn't until I had a diagnosis that I was confident to go out publicly and say this is who I actually was," she says.

"There were two Nicolas. The 'well' Nicola, who was pretending that she was this healthy, energetic person. Then there was the person I actually was – someone who was quite ill. When I was sick I closed the doors of my flat and I shut the curtains."

Blackwood is not alone. One in 17 people in the UK suffer from a rare disease: that is more than 3.5 million people. On average, it takes between four and seven years to diagnose a condition, but for some it takes much longer. Nearly 6,000 children are born each year with a syndrome without a name.

> **There is a huge risk that impetus will get lost with the pressures that are on the NHS**

It can be very challenging for people suffering with rare diseases to receive diagnoses. Now, with the tremendous pressure on the health system caused by Covid, there is a tendency to focus on obvious conditions such as cancer, diabetes, heart disease or strokes, she says.

"I don't want the treatment and awareness of rare diseases to go backwards and for it to become more difficult again for patients to access the services they need," she stresses.

And while there has been an increase in political awareness at the leadership level, that doesn't mean there's capacity in the health system, she warns.

"There is a huge risk that impetus will get lost with the pressures that are on the NHS. Rare disease patients could suffer the most. We need a call to action to make sure this doesn't happen."

The global pandemic has been a double-edged sword for those with rare diseases. Covid has sucked up resources, meaning efforts to catch back up will likely focus on the diseases that are easiest to treat.

But at the same time, the healthcare system's ability to innovate to tackle the virus has shown the general public and the healthcare profession what can really be achieved in tackling novel diseases at speed.

"One thing that we've learnt over the past 18 months is that there's been huge public support for medical research and for some of the requirements for this, such as health data sharing. We can now do huge clinical trials at pace and scale, safely and ethically, and have seen that UK regulators are some of the best in the world," says Blackwood.

This should be translated effectively into non-Covid trials, she says, ensuring we can find diagnostics as well as treatments for patients with rare diseases.

Covid-19 also shone a spotlight on genomics, the study and mapping of genetics. The UK has uploaded more than 1 million genome sequences of SARS-CoV-2 – nearly a quarter of all sequences published globally. This provides a better understanding of how the virus evolves and informs the global pandemic response, with implications for rare diseases.

"The genomics ability here in the UK is extraordinary; we say we are world leading in many things but in genomics we are right at the front of discovery," Blackwood says. "What's really exciting is that we don't only have the scientific capability, we have the infrastructure and research, innovation and clinical capability within our medical teams across the country, and we have political support."

Genomics is always supported in budgets or health funding, "because it is recognised for its transformational potential", Blackwood says. "It's not just theoretical, it's being translated into patient outcomes on the ground. This means it will be able to deliver for rare disease patients in the future."

Blackwood is the chair of Genomics England, an organisation set up to deliver the 100,000 Genomes Project. It sequenced the genetic codes of 85,000 NHS patients affected by rare diseases.

Recently and for the first time ever globally, whole genome sequencing was used in a healthcare system and applied to large numbers of patients with rare diseases. This can deliver life-changing results – one in four participants who live with rare diseases received a diagnosis for the first time.

Patients without a diagnosis after six months or who have experienced repeated referrals without a diagnosis should be offered full genome sequencing, Blackwood says.

"Already many rare diseases are eligible for whole genome sequencing in the NHS through the Genomics Medicine Service – our goal is to extend this to all rare diseases as soon as possible," she says. "This is going to be transformational for early diagnosis, directing patients towards precision therapies."

In the UK Government's autumn spending review, money was set aside for a new national new-born screening programme. A pilot will use genome sequencing to detect rare diseases in 100,000 babies, allowing families to find out about conditions early.

> **For many people with a rare disease, it's hard for them to explain the impact it has on their lives**

"We are at the start. This has enormous potential for cutting the diagnostic odyssey for the very sickest of children. Too often they aren't supported with the care they need because clinicians simply do not have the medical insights. That is why this programme has incredible potential," explains the peer.

Another area that still concerns Blackwood is the price of new treatments for rare diseases. Many gene therapies, for instance, are extremely expensive. They're also slow to be approved, which creates issues for their use in the NHS.

"The problem is yet to be solved," Blackwood says. She points to a pilot model for tackling antimicrobial resistance, under which new drugs will be paid for by the world's first 'subscription-style' payment model. This pays companies upfront for access to their antibiotic based on a product's value to the NHS, rather than how much is used.

Learning the lessons of the pilot and being open to innovative funding models also holds potential for rare disease treatments.

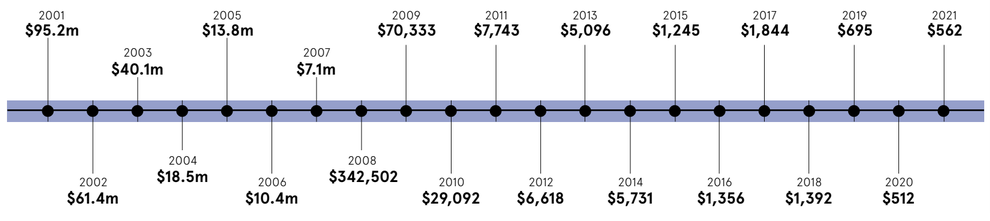
"There are creative ways to think about solving the problem. We need to make sure there are still incentives in the market for companies to make the drugs.

"We aren't there yet," she admits. "But you can always find a solution if you look hard enough."

THE PRICE OF A HUMAN GENOME

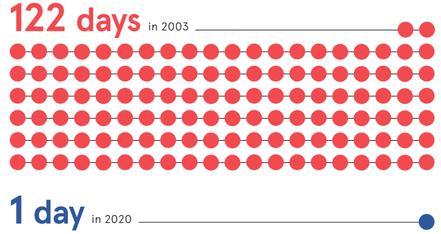
Cost of sequencing one full human genome

NIH, 2021

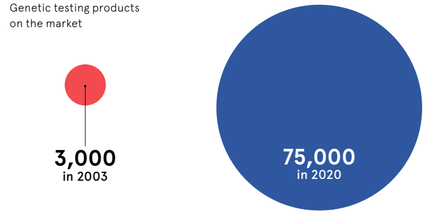


GENOMIC TESTING HAS BECOME FASTER AND EASIER

Time to generate a human genome sequence



Genetic testing products on the market



Personalized Medicine Coalition, 2020

Commercial feature

Decentralisation unlocks new possibilities for rare disease research

The Covid-19 pandemic accelerated innovation in medical research. The growth of decentralised studies is set to improve rare disease treatments

The way clinical trials are conducted has not traditionally favoured the rare disease community. Typically conducted at medical centres in large cities, where specialist clinicians are located, participation in clinical research has long been a challenge. Patients with rare diseases are, by definition, limited – although collectively, many are affected (approximately 5% of the world population) – and often experience debilitating symptoms which make clinical trial participation challenging.

Almost 40% of rare disease patients travel over 60 miles for healthcare. Clinical research sites are often much further away. Even if they can reach clinics, participation can be long and tiring. Participants must adhere to strict visit schedules over the treatment period – anywhere from six months to many years. Each visit requires substantially more testing and time than a normal doctor's visit. Time required in a research study adds a commitment burden to participants and their families and is a key barrier to participation.

"Rare disease research has historically been very challenging, but new solutions are now available to make participation easier" says Joyce Moore, head of rare disease solutions at THREAD, a leading provider of decentralised clinical trial technology that has supported over 50 global rare disease trials. "The number of patients available with a rare disease is inherently small, and requirements for frequent long-distance travel to research clinics may discourage many otherwise motivated patients. When you consider that 50% of rare disease patients are children, this adds additional complexities."

3.5m

people in UK are affected by rare disease

50%

of patients with rare diseases are children

The solution, to many in medical research, is clear: decentralisation. Advances in healthcare technologies like telemedicine, mobile surveys and digital communications, mean many clinical trial procedures can take place in a patient's home and clinical assessments can be reported securely online. While the technology to enable this experience has been available, the biopharmaceutical industry and regulators (MHRA, FDA, EMA) have been slow to adopt these new solutions.

That is until COVID-19. The pandemic required the biopharmaceutical industry and regulators to support new ways of engaging participants. The combined effort ensured that crucial clinical trials could continue to take place during national lockdowns. The result was a tipping point.

"While the biopharmaceutical industry was developing new vaccines, there remained a significant effort and need to maintain safety and data integrity in all clinical trials. Patient safety was of the utmost importance," Moore says. "It was an important moment for rare disease sufferers as regulators supported the biopharmaceutical industry to incorporate decentralised elements in studies and by doing so increase inclusion, patient choice and flexibility."

THREAD is playing a key role in this shift to decentralised studies. THREAD helps biopharma and life science organisations capture data from participants and sites remotely during, between, and in lieu of in-clinic visits. The company's mission seeks to make trials five times more inclusive and 30% more efficient through one comprehensive technology platform. Driven by this mission, THREAD has become a reliable partner for an industry looking to help people with rare diseases.

"Our experience over the last six years taught us how important it is to give people with rare diseases more opportunities for their care. For a large rare disease registry, we implemented new data dashboards that provide real-time information to participants so they could compare their experience with others. This, along with the platform's ease-of-use and features, led to a 50% increase in registry participation and successful patient recruitment across 12 new clinical trials," notes Moore.

DCT approaches like these are already helping researchers conduct more efficient studies and bring new therapies to market faster.

"There is still a large unmet need for new rare disease treatments in the UK, where 3.5 million people are affected," Moore says. "THREAD has a large rare disease portfolio, including trials in the UK. By speeding up the clinical trial process, and making it more accessible, we can get vital rare disease treatments to those that need them quicker."

For more information visit, threadresearch.com

THREAD™

THE DIAGNOSTIC ODYSSEY

People with rare diseases often face a long and emotional search for a diagnosis. They'll typically see several clinicians, undergo myriad tests and, all too often, spend years in pursuit of the answer. While genetic testing has offered hope to many, the average time from the onset of symptoms to an accurate diagnosis is about five years, according to the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease. Some patients still face the prospect of never getting one. 'Odyssey' is clearly an apt metaphor for what many patients and their families experience.

Start of symptoms

With more than 7,000 recognised rare diseases, there are countless symptoms that may indicate one. For instance, sickle-cell disease could begin with fatigue or swelling in the extremities. Cystic fibrosis might start with salty sweat and poor growth.

70%

of rare diseases begin to present during childhood

Eurordis, 2020

First primary care visit

Initial visits may include comprehensive blood work, X-rays and other scans.

94%

of physicians rate their knowledge of rare diseases as 'insufficient' or 'very poor'

***Orphanet Journal of Rare Diseases*, 2021**

Patient research

While awaiting the results of the various tests, patients or their families might start doing their own research. This can be a period of intense anxiety for patients and their loved ones.

Referral to a specialist

If the referral is deemed urgent, a patient can hope to be seen within

2 weeks

For non-urgent referrals, the waiting time will be closer to

18 weeks

NHS, 2019

More primary care visits

4 primary care physicians will routinely see a patient before referring them to a specialist. This includes more testing and further attempts at diagnosis.

1 in 17

people will be affected by a rare disease at some point in their lives

European Commission, 2020

1 in 13

people are estimated to be living with an undiagnosed rare disease

Mayo Clinic, 2019

Misdiagnosis

It's not uncommon for rare disease patients to be misdiagnosed. Most of these will be spotted early, but in some cases a misdiagnosis means weeks, if not longer, of unsuccessful treatment.

44%

of rare disease patients will be misdiagnosed at least once

***Orphanet Journal of Rare Diseases*, 2019**

No diagnosis

Similarly, the first visit to a specialist may yield no answer at all. In this scenario, clinicians might treat the patient's symptoms without addressing the underlying cause.

50%

of people with rare diseases are estimated to be undiagnosed

***Genetics in Medicine*, 2021**

4-5 years

the average time taken to obtain an accurate diagnosis for a rare disease in the UK

Rare Disease UK, 2019

Another specialist visit

Still lacking an accurate diagnosis, the patient might visit another specialist, who could then refer them on to yet another specialist.

Genetic testing

Incredible advances have been made in genetic testing over the past decade. But rare diseases are still difficult to pin down and genetic testing may still not provide an accurate diagnosis.

80%

of rare diseases have a genetic component

NHS, 2020

Diagnosis

After between four and five years, the patient might finally receive an accurate diagnosis for their disease.

25%

of patients report a diagnosis timescale of between five and 30 years

NHS, 2020

Finding (or establishing) a support community

There are more than 6,000 rare disease support groups on Facebook alone. The UK is also home to more than 3,000 patient organisations.

More specialist referrals

7 is the average number of physicians that a rare disease patient will see before receiving an accurate diagnosis.

Genetic testing or genome sequencing

If there's still no reliable or accurate diagnosis, more genetic testing might be conducted. The patient could undergo genome sequencing if it's available.

Genetic tests lead to no diagnosis

Genetic tests can be hard to interpret and they cannot detect every possible disease. Even at this stage, there's a chance of ending up with no diagnosis.

More patient research

Patients and/or their families are likely to start researching the condition, looking into innovative treatments and the availability of support systems.

Genetic counselling

With a diagnosis in hand, it is common for patients and their families to attend genetic counselling. There are more than 300 genetic counsellors in the UK.

Patients' ratings of the top challenges during the diagnostic process

30% Obtaining the right diagnosis	**19%** Awareness of rare disease among healthcare professionals	**17%** Access to specialist care	**16%** Coordination of care	**18%** Other*

Department of Health and Social Care, 2021

* including access to drugs, information and wider support

Healthcare professionals' ratings of the top challenges during the diagnostic process

18% Diagnosis	**14%** Awareness among healthcare professionals	**11%** Access to specialist care	**18%** Coordination of care	**39%** Other*

Department of Health and Social Care, 2021

*including training for diagnosis and opportunities to collaborate with other experts


Andrew Brookes via Getty Images

REGISTRIES

Crowd control: deploying data against rare diseases

Rare diseases are highly complex, but data can help overcome the challenges of small population sizes. However, it must be treated with care

Danny Buckland

Data is a saviour in many settings. For rare diseases, its value is immense, with a power to accelerate understanding and advance treatment.

Rare diseases – conditions that affect fewer than one in 2,000 people – are at a disadvantage when it comes to drug development. Their small population sizes create logistical, legal and economic roadblocks to clinical trials.

Registries collate patient histories and responses across aspects of a particular disease. They can play a vital role in understanding disease trajectory, leading to clinical trials that meet safety and efficacy criteria despite their low enrolment: many have fewer than 100 patients.

But, as is the case with most healthcare datasets, there are concerns around how data is curated, stored and used, with campaigners calling for greater transparency.

EURORDIS, an alliance of patient organisations representing 974 rare disease patient organisations in 74 countries, believes registries are a vital component in improving the lives of the 30 million people affected by rare diseases in Europe.

"They are a core part in advancing knowledge and care, and the development of treatments," says Anna Kole, EURORDIS's public health policy director.

"Because these conditions are so rare, data is scarce and it is a struggle to reach thresholds for clinical trials and care standards, as well as health policy decisions."

Pooling data for clinical and epidemiological research and stratifying patients improves the design of clinical trials, she explains, and the chances of finding eligible patients. It also means researchers can follow a cohort of patients over time to track the natural history of a disease, helpful both for clinical trials and developing standards of care, she explains.

"It may not lead to a curative treatment, but it can track what is working and what doesn't work to inform care for people."

A EURORDIS Rare Barometer survey among rare disease patients found 100% approval of data sharing for research, with 80% wanting to keep a level of control.

"But control simply means people who share their data want to know the who, how and why their data might be shared – being informed, engaged and involved in where the data is helping research," says Kole.

A lot of patient organisations are starting registries themselves, she adds, because they can be pivotal to advance prospects for their particular condition. Research shows that conditions with a registry combined with a well-connected community of clinical specialists and a threshold of publications have more potential to improve care, create clinical trials and the opportunity to ultimately develop treatments.

"They are seen as a way of getting past a bottleneck," she adds.

Data is protected by a range of relatively new legislation including the General Data Protection Regulation (GDPR), but these were not designed with patient registries in mind.

"Good and clear regulatory controls are also key to patient registration and GDPR can be hard to navigate," says Kole. "There should not be unnecessary hurdles and in this rapidly changing area we need a wider discussion so that patient data can be collected and shared more efficiently, but without risking the privacy or expectations of patients."

The benefits are clear. Patient registry data successfully acted as the control arm in a clinical trial for a new enzyme replacement treatment for Pompe's disease, according to a paper in the Orphanet Journal of Rare Diseases. Pompe's disease is a glycogen storage condition that's currently diagnosed in less than 200 patients in the UK. Without the registry, the drug would not have made it to a clinical trial and subsequent approval.

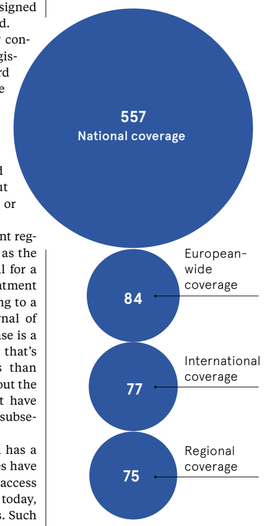
But the use of patient data has a difficult past. Landmark cases have stoked fears over commercial access to data that still reverberate today, tainting data safety promises. Such cases include the NHS's abandoned care.data scheme and the Royal Free Hospital's decision to share kidney patient information with DeepMind, a subsidiary of Google, without consent

Likewise, a research study into the genetic and environmental factors of autism ran into trouble earlier this year when protestors said the DNA data could be misused by researchers wanting to cure autism rather than advance understanding.

MedConfidential is an independent organisation that campaigns for privacy and consent in health and social care. It believes more work is still needed to ensure patient data is stored correctly and used ethically.

DISEASE REGISTRIES' COVERAGE

Number of rare disease registries by coverage, worldwide



"Every patient should know where their data is being used; there should be no surprises," says Sam Smith, MedConfidential co-ordinator.

Smith advocates tighter consent protocols, greater transparency and the ability for people to check a central database to see where their data is being used.

"The NHS can act as honest broker here," he adds. "We want to see a system where a legitimate researcher can log into a computer to analyse the data and take just the analysis away, not the data as well.

"This gives researchers access to more data, as well as offering more accountability and confidence."

EURORDIS is itself campaigning for better patient registry practices, including shared quality assurance and data security standards.

"In recent years, registries have been cross-linking clinical data, confirming genetic mutations and underlying symptoms, that helps speed this along," adds Kole.

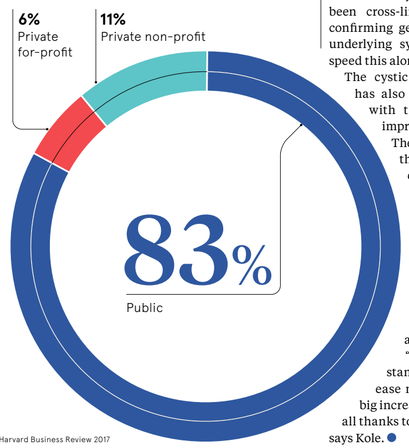
The cystic fibrosis community has also benefited, she says, with the registry used to improve standards of care.

The life expectancy of those living with the disease was improved because people could get care in accredited health centres that were part of a network, making it possible to monitor and share information on aspects such as dosages and how to avoid infection.

"As a result, improved standards of care and disease management led to a big increase in life expectancy, all thanks to the patient registry," says Kole. ●

MAINTAINING RARE DISEASE REGISTRIES

Share of rare disease registries by affiliation, worldwide



Harvard Business Review 2017

OPINION

'We must commit to investment in a world-leading patient registry'

Considerable effort has been made in the UK by patient advocacy groups and representatives such as Findacure, M4RD and the Genetic Alliance UK to develop the UK Rare Disease Framework. However, there is a risk that we repeat the mistake that plagued the government's 2013 Strategy for Rare Diseases – that no funding is allocated to underpin the many excellent recommendations in the paper. Following the 2013 strategy, new proposals followed in both 2018 and 2019, yet eight years on we still witness rare disease patients suffering from the same diagnostic odyssey, a lack of coordination of care and treatment, and poor outcomes.

National action plans that are formulated in conjunction with delivery partners will be hamstrung unless funding is now bid for, but this should have accompanied release of the 2021 plan. Of concern are witness comments that say things such as "to be achieved from within existing resources" or "that's all I can commit to presently". The fact that the Action Plan for England, which is being published to coincide with Rare Diseases Day on 28 February, 2022, will be "reviewed and updated annually over the five-year course of the framework" is also a worry.

In particular, the strategic importance of the comprehensive use of a patient registry for the rare disease community needs to be grasped by senior decision-makers within government, the Department for Health and Social Care (DHSC), and respective NHS departments and funded accordingly. This means investing on the same scale as initiatives such as the 100,000 Genome Project, which received more than £310m from the UK Government, and BIOBank, which has received £133m in core funding.

This requires a broader vision, rather than tinkering in the margins. The Covid-19 pandemic has taught us the significance of capturing data and sharing it appropriately for the wider good, as Health Data Research UK and Public Policy Projects will testify.

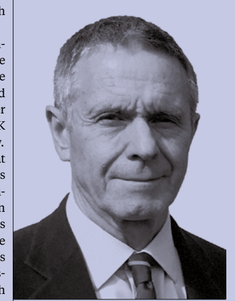
Having trodden the same path that so many frustrated patient advocates have within the rare disease community, I swiftly reached the conclusion that to truly help patients a Behçet's Patient Registry was required. The 2021 Rare Diseases Framework offers the potential, but the whole rare disease community in the UK, which numbers 3.5 million people, needs it.

Behçet's is a particularly nasty, painful and debilitating autoimmune and autoinflammatory condition that can affect any organ in the body, has no known cause and is only treatable, to a degree, with off-label drugs. Those suffering from long-Covid will have some idea of what the Behçet's community, of about 3,000 people in the UK, go through because many of the symptoms are similar – but with Behçet's there are more and they are for life. Why shouldn't members of this community be treated with the equity and equality that other more well-known conditions are?

Disease registration was previously declared "central to public health and healthcare" by (the now defunct) Public Health England. If that is really the case, it needs appropriate funding and investment.

The National Disease Registration Service includes both the National Cancer Registration and Analysis Service, and the National Congenital Anomaly & Rare Disease Registration Service. The first shows how the model can work, offering one of the largest, most advanced and complex cancer data curation services anywhere in the world. It optimises the importance of the data journey and, in particular, patient registry, which requires the inclusion of real-word data, such as quality of life information, from patients.

The rare disease community now calls on the UK Government and the DHSC to truly treat rare disease patients equitably and thus reduce health inequalities. This means committing to investment in a world-leading patient registry that academics and scientists can access, to improve the quality of life and prognosis for all rare disease sufferers. ●



Tony Thornburn
Chair, Behçet's UK

Commercial feature

Shining a light on the inequalities around sickle cell disease

Sickle cell disease is a challenging existence for many. It is the most prevalent of rare diseases and the most commonly inherited blood condition in the UK, yet it's still poorly understood and supported

Sickle cell disorder patients start their lives with the knowledge that they have an unpredictable and serious condition for which there are limited treatments. There is the expectation of painful episodes, chronic tiredness, anaemia, eventual organ damage and risk of infection.

"There is a massive lack of national understanding around this disease," explains Dr Emma Drasar, a consultant haematologist at the Whittington Hospital. "This is why there is an issue with sickle cell being taken seriously. There is also a lack of funding opportunities and research."

Because it affects predominantly people of African, South Asian and Caribbean descent, this condition exacerbates already existing health and social inequalities in British society. People with sickle cell disease are at greater risk of a serious covid infection. The genetic illness also primarily affects socio-economically vulnerable groups. The majority of patients who access NHS services for this condition are also from relatively deprived areas.

"Due to the fact that patients are from minority groups they have all that stigma on top of having this chronic disease. It's a condition that can cause intense pain that we currently have no disease-modifying acute treatment for and limited preventative treatments. Patients with sickle cell also have the potential for worse outcomes if they become unwell with Coronavirus," explains Drasar.

Studies show that people with sickle cell disease face four times the risk of hospitalisation and twice as much risk of dying from Covid-19. Sickle cell starves you of oxygen. Red blood cells become deoxygenated, crescent-shaped and rigid. The so-called sickling process leads to low haemoglobin levels and red blood cell destruction, as well as blockages in blood vessels.

"Sickling goes on all the time, 24-7. Patients are consistently anaemic, you and I might have 140 grams of haemoglobin per litre, I have patients that have 50 grams, a third of what you should have," details Drasar.

This is why over time patients can experience damage to the brain, heart, lungs, liver, kidney, eyes and joints, due to a lack of oxygen to the tissues. The genetic condition is complex. "The problem with this disease is that it is exceedingly unpredictable. You might be fine one day and the next in agonising pain. Recurring episodes are a constant worry that can interfere with every aspect of daily life," states Drasar.

Sickle cell is the UK's most prevalent genetic disorder; around 15,000 people in the UK have the condition, 52,000 people across Europe, and double that in the US. The prevalence of this disease is also on the rise. There's more migration from areas where it is prevalent in the Global South, where it is an adaptation to combat malaria. There is also a rise in the number of babies born with sickle cell.

Even though the lifespan of patients has increased down the generations, those with this chronic genetic condition still live 25 to 30 fewer years than the general population. Since the damage is being done from the day someone is born, the sooner patients can receive treatment the better, the longer they will live and the better quality of life they will have.

It helps that the first new treatment in 20 years for sickle cell anaemia became available on the NHS in October, making headline news. An oral drug called hydroxyurea, which has been licensed for a long time, can also help to reduce pain by preventing the blood cells from going out of shape. Moreover, regular blood transfusions can be deployed to replace destroyed and distressed blood cells.

"The issue of race still plays a part in why sickle cell has so many health inequalities and why it has taken so long for a second disease-modifying treatment to be licensed," points out John James, chief executive at the Sickle Cell Society.

"Compare this with a similar genetic blood condition such as cystic fibrosis, which is equally challenging. Cystic fibrosis has hundreds of licensed treatments in the UK. It has a lot of funding. Yet more people suffer from sickle cell than cystic fibrosis, which is predominantly a white person's disease. Race is definitely a factor as to why sickle cell disease over decades has been underserved, under-researched and under-invested compared to similar conditions."

It doesn't help that a recent All-Party Parliamentary Group inquiry has found serious care failings in acute services and evidence of attitudes underpinned by racism with respect to sickle cell patients.

Calling out substandard care, low awareness of the disease among healthcare professionals and clear examples of inadequate training and insufficient investment in sickle cell services, can only drive change and social justice.

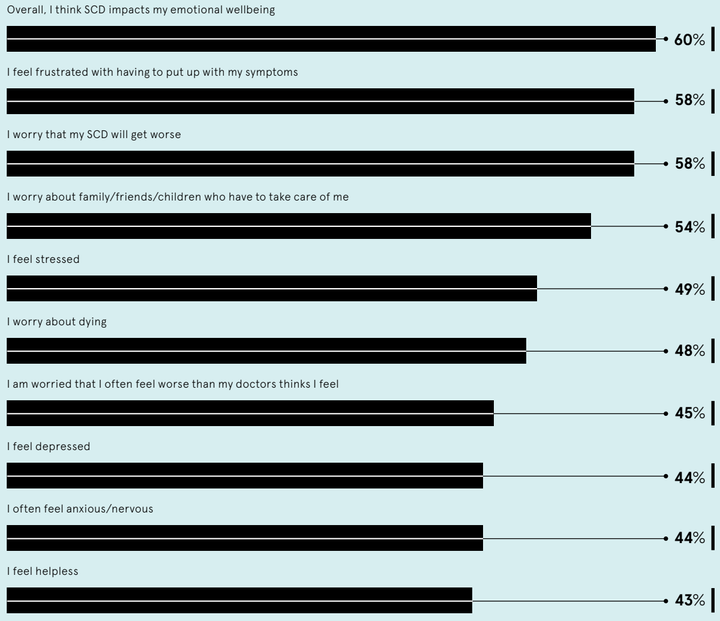
"We now need a more joined up, holistic approach to tackle this disease and the care needed, the whole system needs to work better otherwise people will die," points out James.

Despite these issues. The future does look more hopeful for patients. Spending on sickle cell services has increased in recent years albeit from a low baseline. The licensing of a new drug in the UK gives hope for other novel therapeutics in the future.

"There is light at the end of the tunnel. In the last five years it's been very promising. Now there are new options in the pipeline with new gene therapies emerging. This gives patients hope. They feel now there are more people on their team that will help them make their lives better," explains Drasar.

"The quantity of life, the longevity of sickle cell patients has certainly gotten better, but it's the quality of life that counts. I want better wellness for my patients and people with this condition. This can be achieved over time."

IMPACT OF SCD ON EVERYDAY LIFE



Osunkwo, 2021

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Global Blood Therapeutics (GBT) is dedicated to the discovery, development and delivery of life-changing treatments that provide hope to underserved patient communities. GBT's goal is to transform the treatment and care of sickle cell disease: www.gbt.com

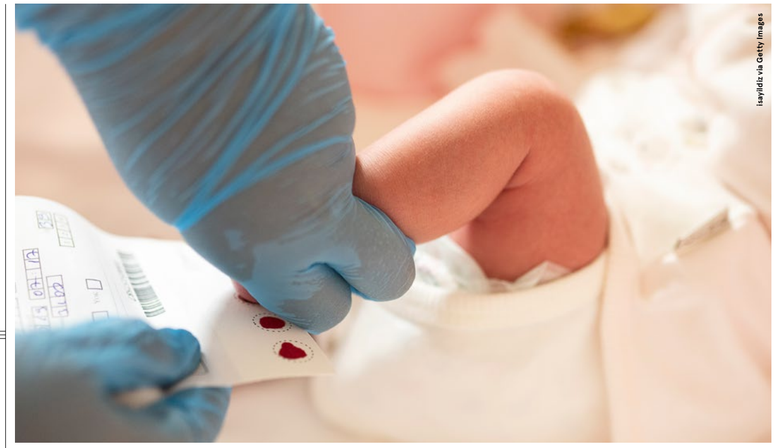
GBT
Hope + Science + Community

NEWBORN TESTING

A measured revolution in infant screening

Major advances in genomics are set to boost the number of conditions that the NHS could test for in neonates. But ethical considerations mean this process cannot be hurried

Peter Archer



Isavidiz via Getty Images

The early diagnosis of a rare disease can help people with such conditions to improve their quality of life. When this happens shortly after birth, it can enable life-saving interventions and prevent severe disabilities from ever developing.

All babies in the UK are offered newborn blood-spot screening on the NHS, also known as the heel-prick test, which is ideally conducted when they're five days old.

This test screens for nine rare but also serious conditions, including sickle-cell disease, cystic fibrosis, congenital hypothyroidism and six inherited metabolic diseases. (In some parts of England, it also covers severe combined immunodeficiency.) But Professor Jim Bonham, who is president of the International Society for Neonatal Screening, says that the "genetics revolution" means that between 300 and 400 more conditions could be covered.

"We should explore the potential that genetics offers, but do so in a way that serves patients' interests," he says. "We need clear evidence to demonstrate that, by intervening early in life, we are going to offer real benefits for the child."

Bonham explains that newborn screening is best applied to treatable diseases where early diagnoses would offer improved outcomes.

"It is very important to maintain public confidence," he says. "Some parents may not wish to know about a condition if no treatment for it is available. Others may wish to know, even if there is no treatment, to enable them to plan effectively for the future of their family

"But all would agree that the early diagnosis of a serious disorder that leads directly to life-changing treatment is to be welcomed. This is the central remit of newborn screening."

A pilot programme backed by NHS England is set to explore the potential for extending the scope of the heel-prick test. With support from UK Research and Innovation's Sciencewise programme, the UK National Screening Committee and Genomics England (the body behind the 100,000 Genomes Project), have invited the public to comment on their proposed use of whole-genome sequencing in newborn screening. The findings of the consultation so far show widespread support for the move, providing that the right safeguards and resources are in place.

The UK National Screening Committee, which reviews its recommendations on testing for different conditions as new research findings become available, advises the NHS on which screening programmes to offer. When considering whom to test and which conditions to test for, the benefits of offering such a scheme are weighed against the potential harms. The committee recommends screening only when the benefits to those being screened will outweigh the harms.

The ability to sequence and analyse a newborn's entire genetic code could help clinicians detect many more conditions and transform the NHS into a more prevention-focused healthcare system. But the proposal raises ethical and societal questions, which is why the committee and Genomics England are seeking the public's input before considering its use in the NHS. There will also be extensive engagement with clinicians and patients to shape the final programme.

"The difficult areas concern how predictive the results are; which conditions it would be acceptable to screen for; what information to give to whom and when; and, finally, how to help parents make informed choices about tests that could have important implications for their child, themselves and others," says Professor Bob Steele, chair of the UK National Screening Committee.

Professor Sir Mark Caulfield, who just recently stepped down from Genomics England after eight years as its chief scientist, adds: "This work is a fantastic foundation from which to take forward the exploration of a pilot newborn scheme."

The next step of this project will be to design and run an ethically approved research pilot embedded in the NHS to explore whether and how to offer whole-genome sequencing to all newborns to accelerate diagnosis and access to treatments for rare genetic conditions. Up to 200,000 babies' genomes will be sequenced and analysed for a set of actionable conditions that may affect their health in infancy.

With the consent of their parents, babies' genomes will be de-identified and added, alongside their health data, to the National Genomic Research Library, which Genomics England manages. This information will help academic, clinical and commercial healthcare researchers, who have all been vetted, to improve their knowledge; develop new tests and treatments; and understand how therapies can be improved as well as repurposed.

Storing babies' genomes securely, regardless of their screening outcome, could enable these to be reanalysed, potentially enabling access to new developments in genomics throughout their lifetimes.

The scale and delivery quality of newborn screening programmes can vary drastically from one country to another. Testing for more than 50 diseases, Italy leads the way in Europe, with Austria, Hungary and Spain testing for 20 or more.

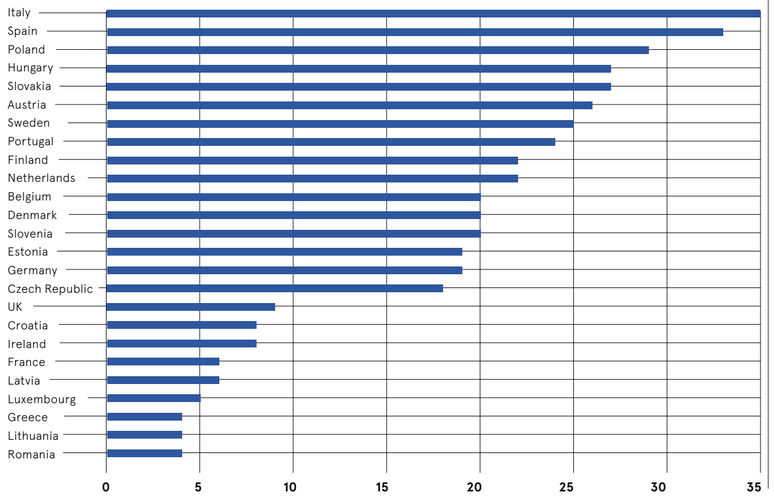
Eurordis, an alliance of 1,000 patient organisations in the UK and 73 other nations, advocates a harmonised approach to newborn screening as the way to ensure as many babies as possible are covered by the most comprehensive tests available.

This would "guarantee the human right of achieving the highest standard of health for all newborns, regardless of their country of birth", says Eurordis board director Simona Bellagambi, who has a teenage niece with tuberous sclerosis, a rare and currently incurable genetic condition. "If you could help your baby by reducing the severity of their disease, or possibly even help them to be healthy, wouldn't you try your best? Screening is an effective way to obtain a diagnosis – and all newborns deserve it."

ITALY LEADS THE EU IN NEWBORN SCREENING

International Journal of Neonatal Screening, 2021

Number of rare diseases screened for in selected European countries



> All would agree that the early diagnosis of a serious disorder that leads to life-changing treatment is to be welcomed

FUNDING AND RESEARCH

Rare disease research points the way to common benefits

Research into rare diseases doesn't just help these small patient populations. The health benefits are felt across common conditions thanks to the genomics revolution

Katrina Megget

In the 1970s, two researchers at the University of Texas Southwestern began studying a rare metabolic disorder known as familial hypercholesterolemia. The patients presented with intriguing symptoms, including extremely high levels of blood cholesterol. They often suffered heart attacks at a young age.

Through this rare disease research, the two biochemists, Dr Michael Brown and Dr Joseph Goldstein, discovered cholesterol was regulated through the LDL receptor. The findings earned the researchers a Nobel Prize in 1985 and formed the basis for the development of one of the world's most prescribed class of drugs: statins.

What started as research into a rare disease ended up revolutionising the treatment of cardiovascular disease, the number one cause of death in the world.

"These rare disease studies opened up the whole pathway of cholesterol metabolism and led to some of the most profitable drugs in history, which have saved millions of lives treating and preventing cardiovascular disease," says Dr Anne Pariser, who is director of the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences, part of the US National Institute of Health.

This is not a standalone case. Rare disease research has the potential to shine a light on a range of common health conditions and normal body functions, from blood clotting and ageing to autism and cancer.

"The study of these rare diseases is incredibly important for identifying cellular and molecular pathways that lead to the development of the disease," explains Dr Fuki Marie Hisama, who is professor of medical genetics at the University of Washington School of Medicine in Seattle, US.

That benefits rare disease patients, she notes. However, many rare diseases are severe forms of a common disease, while other common conditions, such as cancer and dementia, can be broken down into rare subtypes. Such research "could yield new insights into understanding and then treating the [common] disease", Hisama says.

This is because about 80% of rare diseases are genetic, with many arising from a mutation in a single gene. Understanding the gene, the protein it encodes and the function that protein performs in the cell can provide insights into the molecular pathways that control the biology of our cells.

In turn, this can help us understand normal biological processes like metabolism, cell growth and division – important in cancer development – and even ageing. Common diseases can also share many of these genetic pathways, shedding light on the disease processes and providing targets for the development of new drugs.

That has been true of research into the rare disease tuberous sclerosis complex (TSC), which causes non-cancerous tumours to develop in different parts of the body. Research into the disease found that the genes involved in TSC normally control a cell growth pathway, which is overactive in TSC because of the faulty genes.

"It was the linking of the TSC proteins to mTOR signalling, a key regulator of cell growth, that helped advance research and treatments for TSC patients," says Dr Elaine Dunlop, TSC researcher at Cardiff University in Wales. That includes the mTOR-targeted drug rapamycin,

The mTOR pathway is also activated in cancers, making things interesting from a broader health perspective. There's been a lot of interest in using rapamycin as a cancer therapy, says Dunlop.

"The importance of the TSC/mTOR pathway in cell growth has meant there are a number of scientists working in the field, which has been beneficial for a better understanding of the molecules controlling cell growth, which in turn helps us to understand both TSC and cancer better."

Another rare disease with the potential for broader health benefits is Hutchinson-Gilford progeria syndrome, which is characterised by premature ageing, such as wrinkled skin, hair loss, hypertension, hardening of the arteries and heart failure. Understanding the function of a faulty protein in the disease could provide insight into the ageing process in the general population, as well as helping identify targets for the treatment of cardiovascular disease.

Rare disease research is also benefiting health more broadly through the acceleration of drug innovation. The first chemotherapies, for example, were for rare blood cancers. Now, as genetics and genomics improve, rare diseases are at the forefront of personalised or precision medicine because their single genetic mutations allow for precisely targeted drugs.

"Rare disease research leads the way for drug innovation in gene therapy and cell therapies," Pariser says, with the two approved gene therapies in the US both for rare diseases. The same principles can now begin to be applied to more common conditions, she says.

But the path forward has its challenges. Perhaps most importantly, there is still a limited understanding of the underlying biology for many rare diseases.

"There are more than 7,000 rare diseases that have been discovered but many are not yet known to be linked to common diseases," says Hisama. That makes it harder to discern the broader potential benefits, she adds.

The picture is further complicated by the complex nature of genetics and genomics, says Hisama. The same mutations can sometimes result in different diseases, while common conditions can actually be rare subtypes with mutations affecting multiple genes, she explains. In both cases there may be no single common pathway to target for drug development.

Dr Richard Thompson is chief executive of the UK rare disease charity Findacure. He is concerned that there are not enough researchers conducting rare disease research because of the lack of incentives.

Thompson thinks the skills and understanding exist to find links between rare diseases and more common conditions through examining the scientific literature and the use of artificial intelligence. However, he wonders if the appetite exists to do this work.

> **The study of rare diseases is incredibly important for identifying cellular and molecular pathways**

Part of this comes down to funding. Rare diseases are often considered a poor relation when compared to more common conditions with larger patient populations.

However, while rare diseases might appear, well, rare at first glance and therefore lacking relevance for the majority of people, Dunlop thinks that emphasising the links between rare diseases and common health conditions can help pull funding into the sector.

"Many funders want their money to go towards research that will benefit as many people as possible, but there are opportunities for funding more rare disease work to help our understanding of some fundamental biological pathways and develop targeted treatments that could have an even wider impact."

> **Many funders want their money to go towards research that will benefit as many people as possible**

Dunlop's TSC research is a case in point, where the link to cancer has seen more money invested in studying the biology than would have been available through TSC-focused charities alone.

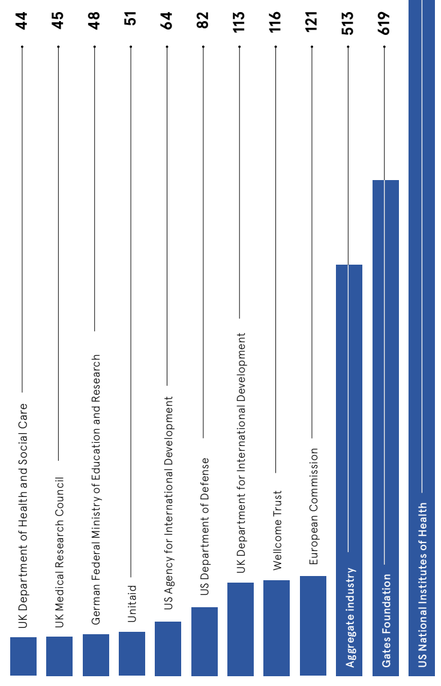
Greater creativity and collaboration are key to encouraging a more permissible funding environment, says Thompson. Research should "look at pathways in common between diseases and then fund research for the pathway, which would help both rare diseases and common health conditions."

The future of medicine lies in a genomic revolution and rare disease research can lead the way. We all have DNA in common and we all have mutations, even if we're not aware of them, says Pariser. That's why some people have severe side effects to drugs and some suffer from Covid, yet others have no symptoms at all.

Building up our knowledge of rare diseases would benefit everyone, she believes. "Understanding rare diseases, mutations and pathways is important to all of us."

WHO IS FUNDING RARE DISEASE RESEARCH? Policy Cures, 2021

Leading organisations for funding of R&D in neglected diseases (in $m, 2019)



Commercial feature

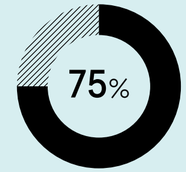
Why clinical trials for rare disease treatments must embrace digital innovation

Brendan Buckley, chief medical officer at Teckro, describes how a digital-first approach can transform rare disease clinical trials

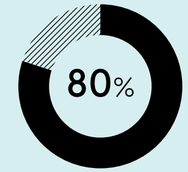
RARE DISEASES ARE NOT THAT RARE

About 6% of the population suffer a rare disease so most people know somebody with one

3.5million people in the UK and 300 million worldwide suffer from a rare disease



of those affected by rare diseases are children



of rare diseases have a genetic component

88% Between 2006 and 2016 there was an 88% increase in the number of clinical trials in rare diseases

The potential of new and emerging treatments in the rare disease field offers real hope for the 3.5 million people in the UK and 300 million people worldwide who will be affected by a rare disease at some point in their lives. It's a positive sign that between 2006 and 2016 there was an 88% increase in the number of clinical trials in rare diseases. But innovation in clinical trial operations needs to be prioritised, so that the study of rare diseases in human subjects is simpler and more modern, paving the way to get potential treatments to patients faster. For those living with rare diseases, it's highly frustrating that drug development is such a slow process. It can take years to develop new treatments, which means efficiency of clinical trials for rare diseases is essential.

Despite their collective name, rare diseases are, paradoxically, quite common overall. About 6% of the population suffer a rare disease, so most people know somebody with one. Of the 7,000 or so rare diseases that we are currently aware of, some are well known due to the raised media profile they have. For example, cystic fibrosis and motor neurone disease, have more notoriety than other rare diseases thanks to actors such as Jenny Agutter who has the cystic fibrosis gene, and sportspeople such as ex-rugby player Doddie Weir and ex-footballer Stephen Darby who both have motor neurone disease. Sadly, 75% of those affected by rare diseases are children. For example, Duchenne muscular dystrophy is a horrible, life-limiting disease of boys that often starts very early in childhood.

One of the challenges of any clinical trial – especially for rare diseases – is the recruitment phase. This is when researchers must find enough people who match the characteristics to be eligible to participate in the study. This means it is essential for physicians to have immediate access to determine whether the person in front of them meets the eligibility criteria of a rare disease clinical study. The fact that study documents are stored on paper away from the clinic is not conducive to the real-time decision making necessary to enrol candidates in complex studies.

> **It is essential for physicians to have immediate access to determine whether the person in front of them meets the eligibility criteria of a rare disease clinical study**

We should also consider that 80% of rare diseases have a genetic component. Hope now rests on some of the new advanced therapies, such as gene therapy and cell therapy. We already have a gene therapy for a rare form of blindness helping to transform people's lives. In addition, we are moving closer towards being able to alter genes in people with genetic rare diseases through CRISPR-Cas9 gene editing. This involves changing a single letter, or base, in a gene. Furthermore, CAR T-cell therapies which use gene-replaced autologous T-cells, have been approved in the last couple of years as part of treatment for some rare types of cancer.

These approaches offer real promise for future progress in rare disease treatment. But modern medicine also requires more sophistication in clinical trials. A digital, mobile-first approach to clinical trials equips investigators and other research staff with the information they need to make informed decisions and properly carry out complex procedures. This makes real-time communication with experts even more critical to preserve the data integrity of the clinical trial and more importantly protect the safety of the human beings in the study.

A person living with a rare disease has a basic human right to not have their condition overlooked, no matter how rare. It's important that such patients are not marginalised and that we respect those with rare diseases. Clinical trials, especially for rare diseases, need to be done in a modern way that avails of the mobile digital tools that we all use in our everyday lives. Otherwise, they will continue to be slow and delay effective treatments.

Teckro clinical trial software provides a hub of communication and collaboration for clinical trial study teams and researchers, ensuring accurate, current study guidance is always available at the point of care. For more, visit teckro.com

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Commercial feature

Q&A

Call to arms: how can we improve access to rare disease treatments?

Fleur Chandler, head of market access at Sanofi UK & Ireland and parent to Dominic, a child with a life-limiting disease, Duchenne Muscular Dystrophy, has called on the government and industry to improve how new rare disease treatments are assessed and made available

Q What is it like to have a child with a life-limiting rare disease?

A My child has a life-limiting, disabling, progressive rare disease that has no treatment – exhausting is the overarching sentiment. Three quarters of rare diseases affect children and 30% of patients with rare diseases will not live to their fifth birthday, according to the Department of Health and Social Care. When you're treating adult diseases, by and large you are treating an individual. When you're treating a child with a rare disease, you're treating a whole family. If the progression of the illness can be slowed or stopped, the exhausting experience of children and families like mine would also be slowed or avoided.

For my family, the cost, both financially and mentally, has been enormous.

My husband had to give up his job to help us manage the myriad of hospital appointments and necessary care. We have had to make significant adaptations to our house, to enable wheelchair access, with minimal support. We had to buy a wheelchair-adapted vehicle. As it is difficult to travel, and accessible options are limited, we are unable to go on typical family holidays. Our daughter also makes sacrifices to enable us to function as a family.

Some of that might sound like first-world problems but as somebody who works in the pharmaceutical industry, ensuring the value of Sanofi's medicines are articulated well to groups like the National Institute for Health and Clinical Excellence (NICE) and Scottish Medicines Consortium (SMC), it can be frustrating to know that treatments could be available for certain rare diseases if we approached testing and access in a more innovative and pragmatic way.

Q Why is the current way rare disease treatments are assessed not working?

A There are many medicines in development across a wide range of paediatric progressive conditions. But the UK system for looking at the evidence and saying 'yes' to those medicines is just not set up to accommodate rare diseases, which it is much harder to gather evidence for. This is in part because there are very small patient populations and the type of evidence being sought is difficult to gather in these diseases. As companies go about trying to gather that evidence, they're fishing in the same small pool, which is ultimately a set of patients and families who already have a huge emotional load to contend with, in addition to potentially participating in the clinical trials that help pharma companies generate the right evidence. The approval process is lengthy, particularly when evidence is sparse, and sadly during the time taken to assess a medicine's value, many children become ineligible for treatment as their diseases have progressed beyond the point at which treatment is potentially impactful.

> **Ultimately, we need to see more governmental will towards treating rare diseases. Families don't have the time to wait**

Q What needs to happen for more rare disease treatments to become available?

A We need the government to acknowledge the current system isn't working. I'd like to see more emphasis on access to medicines for rare paediatric progressive conditions, and a clear commitment that the UK will make available those medicines that are developed for paediatric patients. It would also mean the UK demonstrating its commitment to being a global life sciences leader, which the current government has articulated as a priority.

Ultimately, we need to see more governmental will towards treating rare diseases. Families don't have the time to wait. Statistics show one in 17 people in the UK will be affected with a rare disease, which is noted in the Department for Health and Social Care's UK Rare Diseases Framework, and may cause alarm at how much it might cost to tackle. But not all rare diseases are fatal or even impactful – they're just rare – and it wouldn't be difficult to identify the ones which really need attention, particularly in paediatric care.

In a BIA survey earlier this year, 79% of respondents said patients with a rare disease should be able to access medicines on the same basis as people with more common conditions, and 78% agreed the NHS should ensure access on the basis of clinical need even if it is more costly.

Q Which organisations are leading the way in rare diseases?

A It's a fascinating space. There's room for everybody and there are lots of small biotechs and exciting developments coming out of university research. But it's especially important to have larger pharmaceutical companies working in this area. You need the muscle of these companies, which have the expertise in running clinical trials and health technology assessments. The biggest impact, however, will be through collaboration; bringing all stakeholders together to generate the evidence so desperately required.

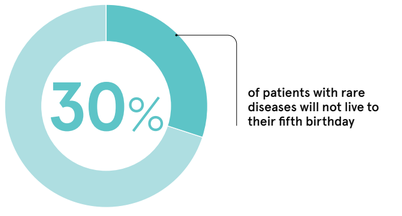
Q How are you seeing organisations collaborating to improve rare disease treatment?

A One thing I've done outside Sanofi, though Sanofi has been very supportive of it, is set up Project HERCULES, a collaborative project in Duchenne evidence generation across ten pharma companies, led by the patient organisation Duchenne UK. This initiative has created a disease-level evidence base that all companies can use when it comes to decisions around access. There is room for that model now in other rare diseases. We need people and policies to work together better to support the rare disease community.

Q What else needs to change to improve rare disease outcomes in the UK?

A Education, support and commitment. I've got the head of a health economist but the heart of a rare disease mum, so I'm in a unique position to help patient organisations understand the needs of those assessing new medicines, and how the pharmaceutical industry meets those needs. I don't know if there will be a treatment available in UK in my son's lifetime, so I'm extremely passionate about ensuring as few UK parents as possible end up in the same situation. We must ensure the voices of patients and families like mine are heard in a way that assessors can understand. For example, there are standard ways of collecting quality of life data, which is a key part of the decision, but they don't address what you're feeling as a family. They don't touch the burden or the psychological hardship. We need to see much more specific methods of data collection to articulate the ultimate value of treating these diseases. It's a privilege to use my professional knowledge and personal experience to support all paediatric progressive conditions, as my experience is similar to many parents of children with rare disease. It's time that access to treatment for rare diseases – especially in paediatric progressive, life-limiting diseases – is prioritised in the UK.

3/4 of rare diseases affect children



of patients with rare diseases will not live to their fifth birthday

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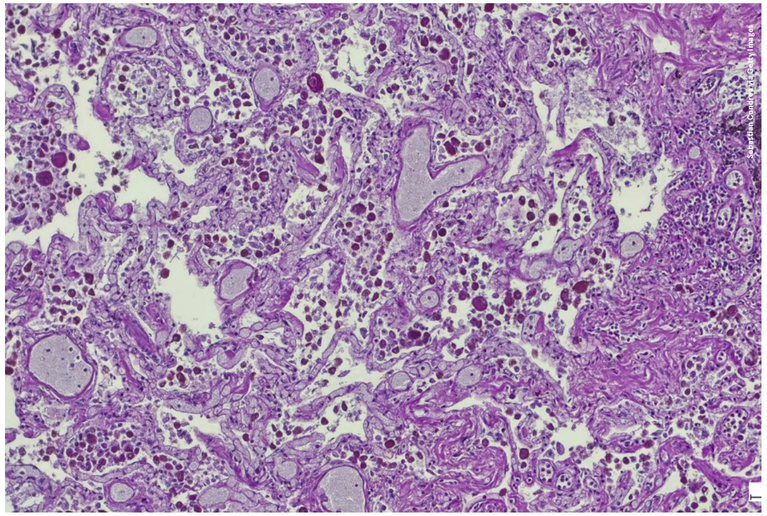

Sebastian Kaulitzki/Getty Images

CANCER TREATMENT

Rare cancers: how genetic medicine is improving treatment

Genetic sequencing is challenging our understanding of many types of cancer, breaking them into subtypes. There could be benefits – but who will pay?

Martin Barrow

When most people think of rare diseases, cancer probably doesn't rank high on the list. It's not hard to see why, with one in two people born in the UK after 1960 likely to be diagnosed with the disease in their lifetime.

However, many cancers are considered rare, including anal, stomach, and laryngeal cancer. About one in five cancer sufferers in the UK have a rare cancer, and around one in three of these are very rare types, meaning they affect fewer than one in 100,000 people each year. Rare cancers disproportionately affect some demographic groups, based on ethnicity, age or gender.

There are different reasons why cancers are considered rare. For example, while skin cancer melanoma is the fifth most common cancer in the UK, melanoma that starts in the eye is much less common. Similarly, non-Hodgkin lymphoma is one of the 10 most common types of cancer, but there are many subtypes, some of which are very rare.

Scientists are identifying multiple subtypes at great pace by harnessing advances in genetic sequencing. These advances are constantly challenging our view of cancer and other diseases as single entities.

In November, a report published in the *British Medical Journal* said that whole genome sequencing can diagnose an extra 31% of rare disorders in patients in the NHS. But we are not just discovering new rare diseases; we are also discovering mutations that turn 'common' diseases such as breast cancer into rare diseases, with each new discovery affecting an ever-smaller population of patients.

These developments have the potential to transform treatment and care. The 'one size fits all' approach is being replaced by personalised care, with targeted drugs known to be effective. In September the NHS became the first health service in Europe to offer Sotorasib, a tumour-agnostic drug, to patients in England with non-small cell lung cancer. The drug targets a mutation on the KRAS gene, binding to it and making it inactive, stopping cell division and cancer growth.

Under an early-access deal agreed with the National Institute for Health and Care Excellence (NICE) and Amgen, the drug's manufacturer, NHS England said it expected to begin providing the drug within weeks. Around 600 lung cancer patients per year will be offered the treatment initially, who have locally advanced or metastatic non-small cell lung cancer (NSCLC) with the KRAS G12C mutation.

Similarly, the tumour-agnostic drug Larotrectinib – which targets a specific genetic abnormality called an NTRK gene fusion – has been approved for use in Europe. The Royal Marsden was the UK centre for trials of the drug.

Dr Julia Chisholm, consultant in Paediatric and Adolescent Oncology at The Royal Marsden, is the main investigator for the ongoing SCOUT study, which tests the safety and efficacy of the drug for treating tumours with NTRK gene fusion in children. "The beauty of this drug is that it targets the abnormality in the tumour, and it is a step towards treating cancers based on genetics rather than site of origin in the body," she says.

> **It is a step towards treating cancers based on genetics rather than site of origin**

Dr Alasdair Rankin is director of research development (health) at King's College London. He says: "Tumour-agnostic treatments hold real potential to deliver kinder targeted treatments to people with rare blood cancers, including children, where evidence of the effectiveness of drugs can be built up more quickly in trials of people with different types of cancer."

New treatments mean better outcomes for patients who previously faced an uncertain future. But they also bring with them some of the challenges that are well known to patients with rare diseases and their advocates. Targeted drugs have much smaller patient populations, making it more difficult for pharmaceutical companies to recover the costs of research and development.

These costs are substantial, averaging around $1bn, according to research published by JAMA last year. By therapeutic area, oncology and immuno-modulatory drugs were the most expensive to develop, coming in at a median of $2.8bn. When the drugs come to market, they are often expensive relative to other drugs, making it difficult for NICE to ascertain whether they represent value for money.

Sotorasib, which is known as Lumykras in the UK, was licensed through Project Orbis, the partnership between medicines regulators in countries including the UK, US and Australia to speed up the approval process for promising cancer treatments. But there is frustration at slow progress with Trodelvy, which is used to treat triple negative incurable secondary breast cancer.

Gilead, which developed the drug, failed to reach an agreement with NHS England to provide the drug free-of-charge to eligible patients ahead of a NICE decision next year. Gilead has offered a pre-reimbursement access scheme, but critics say it falls short of what is needed. The temporary scheme limits numbers and imposes conditions on who can receive the drug until it is approved by NICE.

Baroness Delyth Morgan, chair of the charity Breast Cancer Now, says: "These women don't have time to wait. Gilead must urgently do the right thing for breast cancer patients by reaching an agreement with NHS England so that all eligible women are granted access to Trodelvy without delay."

The NHS is in a strong position to harness the power of genomics, building on the legacy of the 100,000 Genomes Programme and the strong links between scientists, the pharmaceutical industry and the health service in the UK. This ecosystem gave the UK a head-start when it came to developing a vaccination for Covid-19, while the NHS is the first national healthcare system to offer whole genome sequencing as part of routine care.

The challenge for health providers like the NHS is to make a new generation of personalised drugs available to those who need them while avoiding the dispiriting battle for funding that patients with rare diseases have fought for years. ●

WHERE IN THE BODY DO RARE CANCERS DEVELOP?

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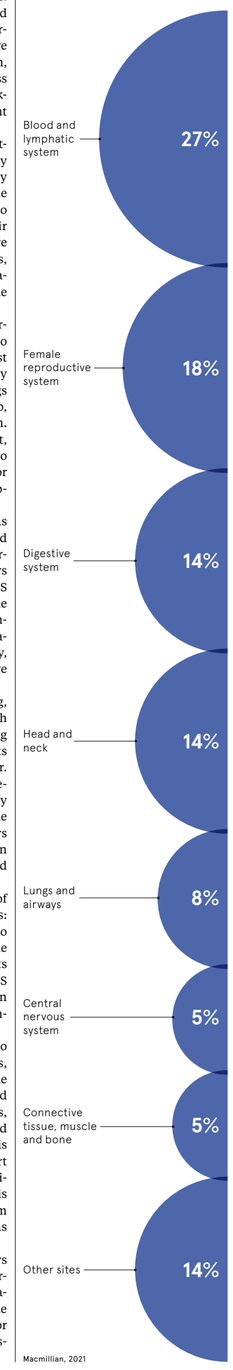


Macmillian, 2021

CASE STUDY

Mother of reinvention

Duchenne UK is both boxing clever and punching above its weight in the fight against muscular dystrophy. For the charity's CEO, Emily Crossley, it's a very personal – and urgent – battle

John Illman

In effect, Emily Crossley's 10-plus years as a broadcast journalist served as an apprenticeship in advocacy for her current role as CEO of an innovative healthcare charity. The former anchor for Channel 4 and CNN believes that her background in TV news reporting gave her a solid grounding in how to communicate with large, diverse audiences and engage with policy-makers.

"I thought that I didn't have the qualifications to lead a charity. And, of course, I had much to learn – I took a crash course in drug development, for instance – but being a journalist does enable you to cut through the noise," Crossley says. "We're laser-sharp in our focus."

She co-founded Duchenne UK in 2011 after her eldest son, Eli, then three, developed Duchenne muscular dystrophy (DMD), which is the most common fatal genetic disease in childhood. Boys with DMD (it very rarely affects girls) cannot produce dystrophin. This is a protein that Crossley likens to a coat hanger holding the muscles intact. About 300,000 people worldwide, and 2,500 in the UK, have this progressive condition. Without effective treatment, people with DMD often become wheelchair users in their teens. Thanks to improvements in care and treatment, some patients can survive into their early 30s, but treatments remain limited.

The diagnosis initially left Crossley in despair for her son. She found herself crying "on the Tube, at the shops, on the bus". But then she drew on the same steely determination that had helped her to succeed in the tough world of TV.

"The turning point was when I met other Duchenne mums who felt as I did," she recalls. Among them was Alex Johnson, who would become Duchenne UK's other co-founder. "Alex and I wanted to be defined not by DMD, but by our response."

They chose not to follow the traditional charity model of raising money and leaving other people to decide how to use the funds. They wanted – with the guidance of in-house research director Dr Alessandra Gaeta – to control DMD studies themselves and thereby avoid taking the fragmented approach that can often hold back projects of this type. Stakeholders in disease research normally include patients, charities, the pharmaceutical industry, academics, clinicians, the NHS and the government's Medicines and Healthcare Products Regulatory Agency. The number and diversity of interested parties can make it hard even to agree on a project's criteria for success.

"We don't start by thinking about 'the market' for a drug. We start with the patient," Crossley stresses. "We can then work out how to develop a drug to meet the patient's needs."

> **We don't start by thinking about 'the market' for a drug. We start with the patient**

This philosophy is changing perceptions of DMD in both academia and the pharma industry.

Clinical trials of new drugs are guided by quality-of-life (QoL) questionnaires that help to evaluate treatments and determine whether the NHS will pay for them or not. Crossley was disturbed to find that the standard questionnaire failed to capture "the full reality" of living with DMD, especially its debilitating social and psychological effects.

As the Association of Medical Research Charities notes: "Only patients, their families and carers really understand what matters when a disease is diagnosed and, hopefully, treated or managed."

For this reason, Duchenne UK worked with researchers at the University of Sheffield to design a bespoke DMD QoL questionnaire. Said to represent a new benchmark in rare disease research, this serves as a better indicator of the condition's progression and the effectiveness of new treatments.

This was not the first time that Duchenne UK has challenged establishment practice. Crossley explains: "When Eli was diagnosed, the doctors told me: 'Forget gene therapy.' They considered it too far off. But we invested $1m in a US biotech firm, Solid Biosciences, which is now testing a treatment on boys with DMD."

Last month, Solid Biosciences reported that the treatment had been benefiting patients 12 to 24 months after their first doses

The charity is also researching Tamoxifen. Developed in the 1960s, this became one of the world's best-selling hormonal breast cancer drugs. It is now being tested for DMD.

One of a growing number of so-called repurposed drugs found to have additional therapeutic potential, it is highlighting concerns that the traditional big-pharma model for developing new therapies may be financially unviable. This is especially true in the case of rare diseases such as DMD.

The Association of the British Pharmaceutical Industry (ABPI) has estimated that it typically costs £1.5bn to develop a prescription drug. Requiring extensive safety tests, this process can take anything up to 20 years. A repurposed drug, which already has an established safety record, will be much quicker and cheaper than a new one to test. The ABPI has claimed that, for each marketed medicine that makes enough money to recoup its development costs, 25,000 are tested.

Repurposed drugs are also usually cheap because they are out of patent. A 20mg Tamoxifen tablet has been available for as little as 10p – although that was in 2011, before profiteering drove the price back up.

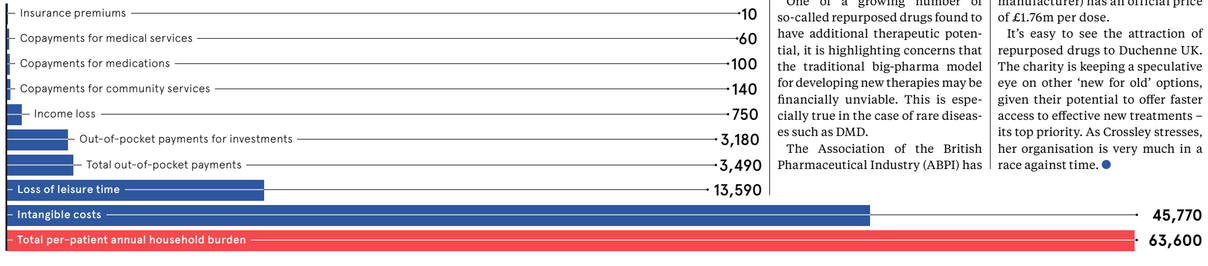
The Tamoxifen trial is one of about 150 ongoing research projects that have funding from Duchenne UK. This may seem a lot for a small charity, but Gaeta notes that "very few of these – perhaps one or two – will result in licensed treatments. This is why, as a small charity, we are robust in what we invest in."

In only eight years, the charity has raised more than £11m for research. Again, this may seem a lot, but Zolgensma, a gene therapy now available on the NHS (thanks to a confidential deal struck with the manufacturer) has an official price of £1.76m per dose.

It's easy to see the attraction of repurposed drugs to Duchenne UK. The charity is keeping a speculative eye on other 'new for old' options, given their potential to offer faster access to effective new treatments – its top priority. As Crossley stresses, her organisation is very much in a race against time. ●

QUANTIFYING THE COSTS OF DUCHENNE MUSCULAR DYSTROPHY Neurology, 2014

Mean annual household burden of Duchenne muscular dystrophy per patient (in 2012 international dollars)



OPINION

'Improving the rare disease care pathway now will maximise its impact and benefit'

The UK's drive to bring genomic medicine into the heart of the NHS is unequivocally a good thing for those living with the world's rarest diseases. However, it is not the full solution to addressing the challenges faced by rare patients - who lack treatments, care pathways and often access to doctors with an understanding of disease progression.

It is crucial that we train clinicians to understand both genetic medicine and rare disease. It is crucial that more treatments reach patients and that care is coordinated, guiding people into meaningful treatment. Without these changes, we are simply diagnosing our way out of one problem and right into another.

To the government's credit, the rare disease strategy published this year lists these as major themes that will help deliver more effective and equitable rare disease care. But how change will be implemented and how much investment will be delivered remains to be seen.

Care coordination is particularly challenging. Due to the complex, multisystem effects of many rare conditions, patients frequently have to manage multiple appointments with multiple specialists in multiple cities across the UK. Stories of poor communication between these specialists are rife, and the burden of receiving even basic monitoring and advice from clinicians is huge.

The rare disease community has been calling for dedicated care coordinators for years. This healthcare professional could manage rare disease cases, ensuring access to services, coordination of appointments and communication between specialists. While such roles exist in some places, wider rollout remains a distant prospect.

This must change. The rare disease framework offers an opportunity to capitalise on the huge strides made in genomics. Improving the rare disease care pathway will maximise its impact and benefit. If we delay, we will build a backlog of genetically diagnosed patients with no meaningful access to care.

But where to start with such a large undertaking? There are two areas that would have a significant impact on a swathe of rare patients. First is diagnosis. At the point of receiving a genetic diagnosis there needs to be somewhere for patients to turn and a pathway to ensure effective genetic counselling and a coordinated plan to access specialist advice and care. Post-diagnosis coordinators would be a logical development of the new genomic medicines service, delivering huge impact and demonstrating commitment to the community.

Second is a better transition from child to adult services. Patients typically experience a change of clinical team at the same time as becoming responsible for their care decisions for the first time.

This process varies widely between hospitals. Good transitions are managed gradually over time, allowing patients to build a new relationship with doctors and ensuring effective handover of complex medical histories. Others happen in an ad hoc fashion, with different specialisms transitioning at different times, no discussion and little planning.

Dedicated rare disease transition coordinators could help to manage patients through this key change in their care, ensuring all patients could access available services in a coordinated manner, at a time and pace that works for them. Ultimately, this will improve both the care they receive and their wellbeing.

The introduction of genomic medicine to the heart of the NHS will lead to more rare disease diagnoses and better understanding of rare conditions. But without time and investment into the professionals and services that serve both newly diagnosed individuals and young people, rare disease patients will be left isolated and disenfranchised by the health system.

It is crucial we act to provide more coordinated pathways for patients at the key stages of their rare disease journey. The rare disease framework presents a fantastic opportunity to make that happen. ●

Dr. Richard Thompson
CEO, Findacure

DARE TO THINK RARE

In the UK

3.5 million

people live with a rare condition

Lifetime risk

1 in 17

of being affected by a rare disease

individually rare

collectively common

Take a crash course in rare disease and become an ally by joining Medics4RareDiseases at The Royal Society of Medicine for The Unusual Suspects: Rare disease in everyday medicine on 9th February 2022, held in association with The Medical Genetics Section.

MEDICS 4 RARE DISEASES

To book your place at this online, evening event or to register for M4RD's online crash course, Rare Disease 101, visit M4RD.org