GENETIC ALLIANCE UK

Stats behind the stories

ABOUT GENETIC ALLIANCE UK

Genetic Alliance UK is an alliance of over 200 charities and support groups working together to improve the lives of people in the UK with lifelong and complex genetic and rare conditions.

We advocate for fast and accurate diagnosis, good quality care and access to the best treatments. We actively support progress in research and engage with decision makers and the public about the challenges faced by our community.

We run two long standing projects:

Rare Disease UK: A campaign focused on making sure the new UK Rare Diseases Framework is as successful as possible, and to ensure that people and families living with rare conditions have access to a final diagnosis, coordinated care and specialist care and treatment.

SWAN UK: The only dedicated support network in the UK for families affected by a syndrome without a name – a genetic condition so rare it often remains undiagnosed.

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FOREWORD

Although rare conditions are individually rare they are collectively common, affecting 3.5 million people in the UK.

This means that millions of people living with different rare conditions are experiencing the same difficulties. Delivering timely diagnosis, better coordinated care, more awareness among health professionals, and improved access to treatment and care – the ambitions set out in the UK Rare Disease Framework – could improve the lives of millions.

It is currently estimated that there are over 7,000 rare conditions, with new conditions regularly identified through scientific progress. Eight out of 10 rare conditions are caused by a change to someone's genetic code.

Some conditions are so rare that there may only be one or two families in the UK affected by them. Other conditions are so new to science that they affect just one person, which means their condition remains undiagnosed and we can't give it a name.

These statistics are simple and memorable. For Rare Disease Day 2024, our campaign has focused on raising awareness of these numbers among the public and healthcare professionals, and sharing some of the stories behind the statistics.

However, for this year's Rare Disease Day policy report we're turning this approach on its head and exploring the statistics behind the stories. As Rebecca Middleton, CEO and Founder of Hereditary Brain Aneurysm Support says: "It's often said in the rare disease world that if you can't be counted, then you don't count. And of course, counting data is counting people. Each data point has a person and a powerful story behind it."

We would like to thank our member charities HBA Support, Superficial Siderosis Research Alliance, The Aplastic Anaemia Trust alongside members of the Better Together for Healthy Marrow Alliance, and Neurological Alliance for contributing their expert views and experience to this report. We would also like to thank our industry partners who have generously supported Rare Disease Day 2024 to help us raise awareness of the challenges facing people living with rare conditions.

We know surprisingly little about the 3.5 million people in the UK who are estimated to be affected by rare conditions. Which conditions affect them? What is the prevalence of these conditions? What causes these conditions? What services and treatments are available for people living with these conditions now, and how can we build on and improve the care that they receive in future?

Our report argues that we need to segment and better understand UK data about who has rare conditions, and which rare conditions they have, so that the NHS can provide the right services and support. As Rebecca rightly says: "Our community counts. It's time we were counted."

EXECUTIVE SUMMARY

In the UK, rare conditions, though individually rare, collectively impact 3.5 million people. We know surprisingly little about the 3.5 million people in the UK who are estimated to be affected by rare conditions. Which conditions affect them? What is the prevalence of these conditions? What causes these conditions? What services and treatments are available for people living with these conditions now, and how can we build on and improve the care that they receive in future?

We have started the process to address these questions by analysing the portion of the rare condition spectrum with the highest frequency, the 163 conditions in the Orphanet database with a prevalence between 5 in 10,000 and 1 in 10,000, which together could account for 80% of people with rare conditions.

Why do we need to examine this data? Our four case studies give the perspective of four of our member organisations on the value of better understanding the rare condition population in the UK.

Hereditary Brain Aneurysm Support, describes the absence of comprehensive data on familial brain aneurysms, pointing to the urgent need for awareness and improved data collection. Recording incidence of the condition would allow us to better understand its natural history and generational impact, which can lead to tailored treatment guidelines and screening protocols and bring visibility and understanding to the partially hidden condition.

Rhys Holmes from **Superficial Siderosis Research Alliance** describes his slow diagnosis of superficial siderosis, which was the consequence of surgery for a childhood brain tumour. Early detection could have prevented or slowed progression of the condition, limiting the damage that Rhys lives with. An earlier link between his health challenges and his surgical history could have made the diagnosis sooner.

The **Better Together for Healthy Marrow Alliance** is a coalition of six charities focused on rare and ultra-rare bone marrow conditions, whose study revealed stark contrasts in available services. Some benefit from funded specialised services, 24/7 emergency support, and expert care at multiple locations. Whereas others face fragmented care lacking coordination and leading to altered care plans and delayed specialist appointments. The alliance is concerned that Integrated Care Boards (ICBs) could potentially widen these gaps.

More than half of rare conditions are neurological. The **Neurological Alliance** explains that most neurological services will shift to Integrated Care System (ICS) level. It is not known to what extent neuroscience services will be prioritised by Integrated Care Boards (ICBs) and how accountability frameworks will function. Despite the challenges, there is a chance to improve care within the new framework, with collaboration, patient involvement, and comprehensive service specifications to address unwarranted variation.

The data: Our Orphanet data sample contained the 163 most prevalent in the database. All with prevalences between 1 in 10,000 and the limit for a rare condition, 5 in 10,000. We categorised these into the following sets:

- Cancer and pre-cancer conditions (15 of 163)
- Complications of more common conditions (9 of 163)

- Infections (8 of 163)
- Injuries (5 of 163)
- Rare conditions or outcomes, potentially a symptom or consequence of multiple rare conditions (25 of 163)
- Unusual health outcomes from treatment or surgery (8 of 163) and
- ‘Conventional’ rare conditions (93 of 163)

The ‘conventional’ rare condition set was found to be more complex in terms of body system involved, have earlier onsets and have a greater proportion of genetic, neurological, and developmental Orphanet classifications than the other sets of conditions.

UK provision for the most prevalent rare conditions We present our findings as an introductory insight as to what would be possible with a well resourced robust study, though this information was not always easily accessible.

- Only a minority (44 of 163) conditions were supported by NICE guidance, the majority of this as part of guidance with wider scope.
- For those conditions where a commissioner for England could be easily defined, 9 of 79 had a nationally commissioned specialised service, 26 of 79 had a specialised service commissioned jointly with ICBs and 44 of 79 did not have a specialised service.
- Genetic tests were available for 80 of 163 conditions, mapping closely to the genetic condition Orphanet classification.

Recommendation - identify segments of the rare community
Systematic assessment of the prevalence of rare conditions and symptoms in the UK by the registration services would identify groupings of rare conditions or symptoms of rare conditions that combine to a significant health challenge, allowing the NHS to commission and organise services accordingly.

Recommendation - identify new solutions
Investigation into the prevalence and cause of rare conditions in the UK would lead to new avenues to improve diagnosis, raise awareness and potentially prevent them or reduce their incidence.

Recommendation - identify clear commissioning routes for all rare conditions
A review of rare conditions, starting with the most prevalent, should indicate the commissioning level for all rare conditions, clearly and with a stated rationale.

Recommendation - provide clear information for patients and their supporters
Commissioning and access decisions should be clearly accessible for rare conditions, starting with the most prevalent. Positive and negative decisions should be clearly recorded.

Recommendation - expand to cover all rare conditions
An inclusive approach to future provision will allow the rarer conditions to benefit from progress for the more prevalent rare conditions.

Genetic Alliance UK will work with its membership in the coming months to discuss this work with policy makers and UK Rare Disease Framework delivery partners with a view to building on the thinking behind this work.

INTRODUCTION

Although rare diseases are individually rare they are collectively common, affecting 3.5 million people in the UK. It is currently estimated that there are over 7,000 rare diseases, with new conditions regularly identified through scientific progress. However, it is hard to find data that breaks down this number in a usable way. Many rare diseases are life-long and complex which means that people can be diagnosed at any age, and under the care of a wide range of medical specialities. NHS data is fragmented and poorly coded making it difficult to collect information about how many people have a particular condition and how they are currently being supported by the health service. There is an urgent need for a central source of data about rare diseases in the UK, that can be built on over time to advance our knowledge and drive improvements in care and treatment.

In 2024 we aim to use Rare Disease Day to start the process to create and raise awareness of a central source of data about rare diseases in the UK. Ultimately we would like to see the creation of a 'map' characterising rare diseases in the UK. This year, we began the endeavour, informed by our analysis of the data held within the Orphanet database based on a previously published peer-reviewed analysis. We will publish this report's findings together in one place with existing data about rare diseases in the UK (for example data relating to screening, diagnosis, care coordination, management and treatment) on our new website. Our aim is for information on rare conditions to be easy for everyone to find, use and reference. We have also put together a series of accessible factsheets on the key issues affecting people living with rare conditions.

On Rare Disease Day 2024 itself we are raising awareness of facts and figures about rare diseases in the UK with NHS staff, healthcare professionals, people living with rare disease and the public. We will also maximise this opportunity to make specialist charities, Royal Colleges, NHS trusts and wider stakeholders aware that a new central source of data about rare diseases in the UK is being developed and can be used to inform their work.

For this year's Rare Disease Day policy report we are exploring the statistics behind the stories. What do we already know about the 3.5 million people in the UK who are estimated to be affected by rare conditions. Which conditions affect them? What is the prevalence of these conditions? What causes these conditions? And what services and treatments are available for people living with these conditions now?

WHY DO WE NEED TO EXAMINE THIS DATA?

Genetic Alliance UK is an alliance of over 200 charities and support groups working together to improve the lives of people living with genetic and rare conditions.

We have asked four of our member charities to share their perspectives on why we need to segment and better understand UK data about who has rare conditions, and which rare conditions they have, so that the NHS can provide the right services and support.

CASE STUDY 1

Who's counting the heartache? The missing data story of hereditary brain aneurysms

By Rebecca Middleton, CEO & Founder of Hereditary Brain Aneurysm Support
References: (Brain Aneurysm Foundation) (HBA Support) (Kim et al.) (Mathieu et al.) (Schievink et al.)

When talking about Hereditary Brain Aneurysm Support, the patient organisation I founded two years ago, I often encounter people who have been impacted by a brain aneurysm. Whether it's a family member, a friend or someone they know, this silent condition affects many of us. Often, too, they tell me the story that they are worried it may 'run through the family' or have been told by a clinician 'not to worry' but would like to explore further.

I also often get asked how common it is. That's where I draw breath and say, the real answer is that we don't know – we can only guess. The data isn't there. No one is counting the disease. And no one is counting the devastating impact this condition is having on generations of families.

Brain aneurysms, ruptured and non-ruptured, are mostly sporadic and caused by environmental and other risk factors. However, some do cluster in families and these cases are known as familial. When an individual has been diagnosed with an aneurysm, ruptured or non-ruptured, and they have a confirmed, strong family history of aneurysms, they are given the diagnosis of 'familial cerebral aneurysm syndrome'.

Hereditary Brain Aneurysm Support (HBA Support) was launched in 2022 to support families with this rare condition, one which has blighted my family for at least three generations. It has killed two loved ones and, around five years ago, caused me to have life-saving brain surgery for a growing brain aneurysm.

The launch coincided with the publishing of HBA Support's first ever piece of research – a Targeted Literature Review. Produced on a pro-bono basis by Costello Medical, the review looked at three key areas; genomic research, the national and international guidelines on how to treat the condition, and the prevalence and incidence rates. It showed that prevalence and incidence data on brain aneurysms was patchy, that data on the familial cases is not consistent globally and completely lacking in the UK. In the US, the Brain Aneurysm Foundation estimates that 1 in 50 US citizens have an unruptured aneurysm. HBA Support's research identified three studies in the US and Canada which reported 20% of ruptured and unruptured cases and 20-29% of ruptured cases were likely familial. So how rare is the condition really?

Familial brain aneurysms are listed on ICD 11[1] and Orphanet as Familial Cerebral Saccular Aneurysm. However, this is counting the symptom and not the disease or condition.

Why does this matter? Because it means this 'silent disease' will remain so, unless we build awareness and grow our data knowledge. We know that those who have the familial condition and have a diagnosis of an aneurysm are likely to develop more aneurysms as they age. Do we then count another symptom and still not see the disease? It's often said in the rare disease world if you can't be counted and then you don't count. And of course, counting data is counting people. Each data point has a person and a powerful story behind it. And unfortunately, with familial brain aneurysms, there is often heartache attached to that story that is left unsupported and unseen.

We can only change this situation and get better support and screening and treatment pathways with better data. If we don't count the condition, how can we start to understand whether we are 'rare' or 'common', get a better understanding of the natural history of the condition, the generational impact, and the social and emotional toll too.

Our literature review told us that characteristics of familial aneurysms differ from those that occur sporadically. They have a higher risk of rupture - which often leads to death or disability. Tailored treatment and screening guidelines from NICE are needed to reflect this. At the moment, these don't exist.

The genetic foundation of the disease has so far not been confirmed. Although over 80% of the research studies looked at gave evidence to implicate several genetic variants, no standout gene was identified. Until we find the genes responsible, screening for at-risk family members through brain scans – suggested for those with two or more first degree relatives with a confirmed aneurysm or have been through a subarachnoid rupture - is the only way we can save lives.

At HBA Support, we're committed to working with our partners in the NHS and across the clinical and research landscape to address these urgent challenges and better support families. Conversations are already underway but, like nearly every rare condition organisation, we urgently need more research and clinical and scientific support. As one researcher told us, 'we have a mountain to climb' – and tracing the condition back through generations will be virtually impossible as family health records are not linked in adulthood. Instead, we need to try and change the narrative going forward, one data point at a time. Our community counts. It's time we were counted.

To find out more or start a conversation, please get in touch: rebecca@hbasupport.org
linkedin.com/company/hbasupport/
facebook.com/HBASupport/
For HBA Support's Targeted Literature Review and further information, please visit: hbasupport.org

HBA Support

Acquired aneurysmal subarachnoid haemorrhage is on our most prevalent rare conditions list (appendix).

[1] The International Classification of Diseases (ICD) is a global medical classification system maintained by the World Health Organisation. The latest version of the ICD, ICD-11, was adopted in 2019 and came into effect on 1st January 2022.

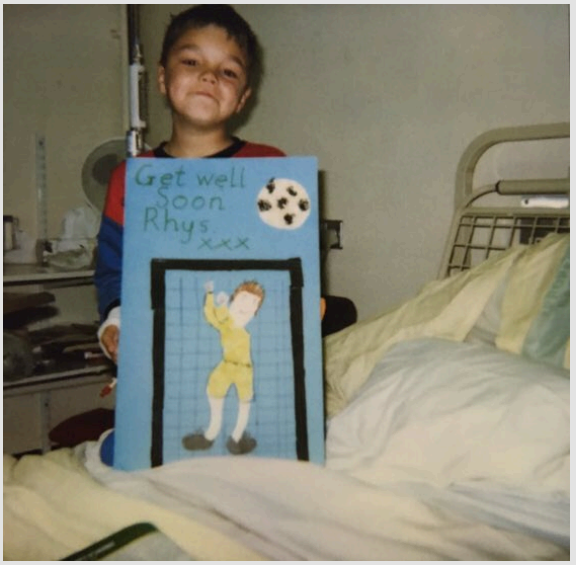
CASE STUDY 2

A ‘Raregular’ Occurrence. Living with superficial siderosis, a consequence of childhood surgery

By Rhys Holmes, UK Director of Superficial Siderosis Research Alliance

The early days

Football was always my passion and dream when I was growing up, and along with all my friends in the local area, I was, and of course still am an avid Liverpool FC fan. I played as a goalkeeper for my local club and attended Cardiff City AFC Soccer school of excellence. Things would change when I was 8 years old and diagnosed with a brain tumour which had to be surgically removed. Unfortunately for me it wasn’t the end of it, as I had problems with the pressure in my head and needed a shunt fitted to drain the excess brain fluid that had built up. The bad news was I was no longer able to play football due to the fragility of my head.



Rhys Holmes, aged 8

A new hobby

Fast forward to 2010 and I was now in university studying my new passion and hobby, which was music. I’d had a bout of meningitis in 2009, and in 2011 had noticed I was struggling to hear the TV and had high pitched ringing in my ears. My doctors attributed the hearing issues to the meningitis, and I was prescribed hearing aids which helped to manage it at the time. The hearing aids allowed me to continue playing music, and my hearing remained stable for the time being.

An unwanted surprise

It wasn’t until autumn 2015 that I knew something was seriously wrong, when I woke up in the middle of the night and the hearing in my right ear had dropped to virtually nothing. I saw my audiologist who tested my hearing, noting a sudden 20 decibel reduction on my right side. He wrote to my GP to make a referral to the ear nose and throat department at the hospital, but before this happened, I had become dizzy and lost my balance whilst at work. My manager told me to go to A&E, which I did. The next year was very bumpy and included brain surgery and countless appointments whilst new symptoms started appearing. Numerous lumbar punctures followed by an MRI scan, and I was told that I have superficial siderosis. A condition caused by a long-term bleed at the back of my head from the brain tumour removal when I was eight years old, 18 years prior.

Coming to terms with it

Only a year or so after my diagnosis, I had come to the realisation that continuing with music was not plausible, especially as my left sided hearing declined. Symptom management of superficial siderosis is a full-time job, and having a strict routine is key for me to make the most of each day. I’ve had many more bouts of brain surgery due to pressure issues caused by the condition, and the bleed that caused the superficial siderosis has been stopped, but I’ve been left with permanent disabilities. I work my weekdays

around the medication I take to aid the removal of the toxic iron from my brain and spine. I attend physiotherapy once a week, and do home exercises every day, it was such a huge mental boost to get back on my feet again after my neurosurgeon had advised I use a wheelchair.

Empowered to drive change

When my neurologist told me I was the first person in Wales to be diagnosed with superficial siderosis, it was quite daunting; but it's also strangely empowering to know that I'm teaching him about the condition. Education is a huge matter with rare diseases, and due to how rare superficial siderosis is, I can understand to an extent how it was never in question from brain tumour removal, an operation that is routinely performed. This however does not change the fact I want surgeons to be aware of the potential consequences of a brain tumour resection, especially as it can take decades for superficial siderosis to develop.

Rhys Holmes

A 'common' theme amongst the rare

I've met others both in the UK and abroad who have acquired superficial siderosis from surgery at the back of the head. Removal of the bone leaves the dura (the membrane that surrounds the brain and spine) unprotected. It's essential to catch superficial siderosis early on to limit the damage caused by the toxic iron that accumulates from the bleeding. Hearing loss is usually the first symptom of superficial siderosis, and I strongly feel that asking about previous history of surgery or trauma to the head and spine is a must to catch the condition as early as possible.

My name is Rhys Holmes and I'm 33 years old. In my spare time I enjoy watching my favourite football team, Liverpool FC and advocating for superficial siderosis through the Superficial Siderosis Research Alliance. You can find me on X @RhysHolmes

SSRA SUPERFICIAL SIDEROSIS RESEARCH ALLIANCE

Superficial siderosis does not appear on our list of most prevalent rare conditions (appendix), however we classified eight conditions as unusual health outcomes from treatment or surgery and five as injuries.

CASE STUDY 3

Why is there such great disparity in care for rare bone marrow conditions?

By Stevie Tyler, CEO, The Aplastic Anaemia Trust alongside members of the Better Together for Healthy Marrow Alliance

Our alliance of six charities represents a variety of rare and (mostly) ultra-rare conditions affecting the bone marrow. Our work together has uncovered glaring disparities between those conditions which have available medicines – bringing specialised services provision and clinical pathways – and those serious, life limiting conditions which do not have treatment and do not have the accompanying services and pathways. For example, paroxysmal nocturnal hemoglobinuria (PNH) has a funded Highly Specialised Service which is renowned worldwide:

'The PNH service considers it a privilege to be able to offer patients a gold standard service for rare disease. With a centralised team available 24 hours a day in case of emergency, and a wider team available during working hours, patients are supported by telephone in between appointments by staff with specialised knowledge to 8 different locations around the UK to try and reduce travel for patients when accessing expert care, has been appreciated by patients and clinicians. The model of care delivery is considered an example of excellent care by other PNH services worldwide and can be used as a template for other rare diseases with similar patient numbers as PNH.'
Dr Morag Griffin, Consultant Haematologist

For patients with some of the other conditions we represent, the story is different. Children are under several different services, care is not coordinated and families need to repeat themselves. People are treated by doctors who are not experts in the condition, which means care plans are regularly changed and appointments with specialists often come too late to avoid crises. This reduces confidence in clinical teams which has knock-on consequences for day-to-day anxiety. People living with these conditions need to take on duties to collate information about their medical history and are left hoping their next clinician takes an interest and chooses to support them.

We saw some evidence of this disparity in the results of our national survey, published in our 2023 Rare Voices report. 50% of PNH respondents know where to access the information needed to help manage their condition, compared to 39% of all other condition respondents (percentages for 'strongly agree'). The survey also showed that a higher proportion of people with PNH (77%) feel supported by services (healthcare and/or charity/patient groups) than people living with the other rare conditions affecting the bone marrow (63%). Thinking about care more broadly, 66% of PNH respondents report being very satisfied with the level of care they receive from their core medical professional team for their condition, compared to 60% for all other conditions.

Our alliance of charities is concerned that these disparities in care could grow wider as a result of the proposed role of Integrated Care Boards (ICBs) in commissioning specialised services. As discussed, the few conditions that are covered by a specialised service specification are presently managed in specialist centres. For the others, how will the multi-disciplinary care these patients need be managed in local hospitals with limited expertise? Those conditions that are not recognised by 'the system' (i.e. have no

ICD-10[2] code, no service specification, referral pathway or evidence-based treatments) will continue to be overlooked.

'We believe it is time to listen to people who live with rare diseases and who care for them, develop formal pathways that mean they have access to specialist care and advice. Properly coordinated care would provide opportunities for clinicians to specialise in rare diseases and open up possibilities for clinical trials and studies using repurposed treatments that currently do not exist, giving hope to patients and their families.'
Dr Jane Paxton, Scientific Advisor, DC Action

Our alliance is calling for:

1. Existing Specialised Services Specifications for those health conditions supported by our member charities to be protected and remain commissioned directly by NHS England.
2. Service specification provision to be urgently made (which is at least equivalent to the service specifications currently commissioned directly by NHS England for Specialist Haemoglobinopathy Services) for the following conditions that do not yet have service specifications: aplastic anaemia, dyskeratosis congenita and telomere biology disorders, Fanconi anaemia and Shwachman Diamond syndrome.

We need clearly defined services and support for all rare diseases and investment in coordinated care. It is because of inequalities like this that we formed the Better Together for Healthy Marrow Alliance.

The member charities of our alliance are: Aplastic Anaemia Trust, Congenital Anaemia Network, DC Action, Fanconi Hope, PNH Support and SDS UK

To read more about the recommendations that were made in the Rare Voices report, visit Recommendations – Super Rare – But not alone (super-rare.org)

To join in with Super Rare around Rare Disease Day to support people living with rare conditions connected to bone marrow, visit Super Rare – But not Alone (super-rare.org)

None of the conditions covered by the Better Together for Healthy Marrow Alliance appear in our list of most prevalent rare conditions. They are included for the perspective of the less prevalent rare conditions.

[2] The International Classification of Diseases (ICD) is a global medical classification system maintained by the World Health Organisation. ICD-10 was superseded by ICD-11 in 2022 but is still used in many contexts.

CASE STUDY 4

Will rare be a priority for Integrated Care Systems?

By Georgina Carr, Chief Executive, Neurological Alliance

One in six people across the country live with a neurological condition. Neurological conditions, conditions which affect the brain, spine or nervous system, can affect anyone at any age. More than half of rare conditions are neurological, and people with rare neurological conditions often report long waits for care, being unable to access support for their mental health and poor care coordination.

To be frank, many people with neurological conditions will not know, or care, about whether an acute Trust, Integrated Care Board (ICB),Clinical Commissioning Group (CCG) or NHS England funds or delivers their treatment and care. What people want to know is how to access specialist advice, treatment and support quickly and that they can speak to health and care professionals who know about their condition and their experiences. Our collective challenge, then, is how commissioning can facilitate these things, enabling seamless and timely support.

This is no small feat in neuro - neuroscience services face many systemic challenges. At the end of 2023, neurosurgery had the longest waits of any specialty. Adult neurology has the fifth largest medical outpatient waiting list and is in the top ten specialties for non-elective admissions. A third of the adult neurology workforce is based in the South East. 4% of primary care consults are for headache alone. Clearly, we need to change how we plan and deliver services, if we are to deliver equitable, high-quality support now and in the future.

Changes are now in motion and going forward the majority of services for people affected by neurological conditions will be commissioned at an Integrated Care System (ICS) level. This includes adult and paediatric neurology, neurosurgery, neurorehabilitation and neurophysiology. These services were all previously commissioned nationally by NHS England.

There are potential opportunities we should and could explore, through delegation, to address these systemic challenges. A shift to population health, backed by quality data to support good decision-making, could help us join the dots, delivering more personalised, comprehensive care. Closer local collaboration between NHS systems and frontline providers helps to plan and deliver integrated support and, possibly, innovate together to address common challenges. Provided, of course, local decision-makers truly have the autonomy to innovate (and that other systems are able to learn from these innovations too).

But, and it is a big but, there are risks to delegation. On average, a quarter of a million people with a neurological condition live in an Integrated Care Board (ICB) area, with many more impacted as friends and family. Despite this, improvements to neuroscience services are rarely at the top of the priority pile for ICB's. There are 27 specialist neuro centres, spread across 42 ICBs – many ICBs simply do not see neuroscience services as their 'problem' to tackle. Neuroscience is seen as too niche, or too complex.

ICBs will have to work together to provide care, across multi-ICS footprints. This will be particularly important for people affected by rare neurological conditions with smaller numbers of people (and a lack of specialist expertise) necessitating services and support to be delivered at a multi-ICS level or nationally. This presents a significant unknown for services, staff and people with neurological conditions and so far, we are yet to see how this will work in practice.

What is clear is that more support and thinking is needed to fully involve people affected by neurological conditions in designing and delivering these new processes too. There are pockets of good practice - the South West London Neurosciences Network is an ICS-based clinical network with multiprofessional leadership and membership from community, primary, secondary and tertiary care. With funding from the SW London ICS, the network co-designed a public and patient involvement (PPI) strategy which reflects the diversity and complexity of the needs of people living with neurological conditions and their families, working in partnership with neurosciences staff at all levels in the system. Led by and for people affected by neurological conditions, the network has had buy-in from the highest points of the ICS which has meant that those involved have the power to achieve what they are setting out to achieve.

The accountability framework for ICS's also remains unclear. There is a particular issue in neuroscience services, where limited NHS service specifications, underpinned by poor quality data, do not allow for sufficient scrutiny. Work is underway to rapidly review service specifications across neuroscience, and this cannot come a moment too soon. To make the most of new NHS structures, specifications must represent a whole pathway approach. Without comprehensive, outcome driven specs in place, delegation risks exacerbating unwarranted variation in services.

We are, however, optimistic that improvements to care can be made in the new delegated framework, despite these challenges. The neuro sector is a motivated partner, keen to work with systems to improve care and ensure people affected by neurological conditions are at the heart of this work. With new National Clinical Directors in post for neurosurgery and neurology, as well as national transformation programmes in tow, there is a collective drive to make the most of NHS reforms. The daily battles for access to treatment and care will not be improved by further NHS reorganisation.

The Neurological Alliance harnesses the energy and passion of the neurological community to ensure public policy in health reflects the realities of living with a neurological condition, so that everyone can access treatment, care and support whenever they need it. Learn more about our mission on the Neurological Alliance website.

35 of the conditions on our list of 163 most prevalent rare conditions have been the 'neurological' classification by Orphanet.

HOW HAVE WE EXPLORED THE DATA?

Our starting point

This report is based on an analysis of the most frequently occurring rare conditions. In 2020, we read the fascinating finding that just 149 rare conditions accounted for 80% of people living with a rare condition. This came from a paper by Wakup et al (Wakap 2020), 'Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database'.

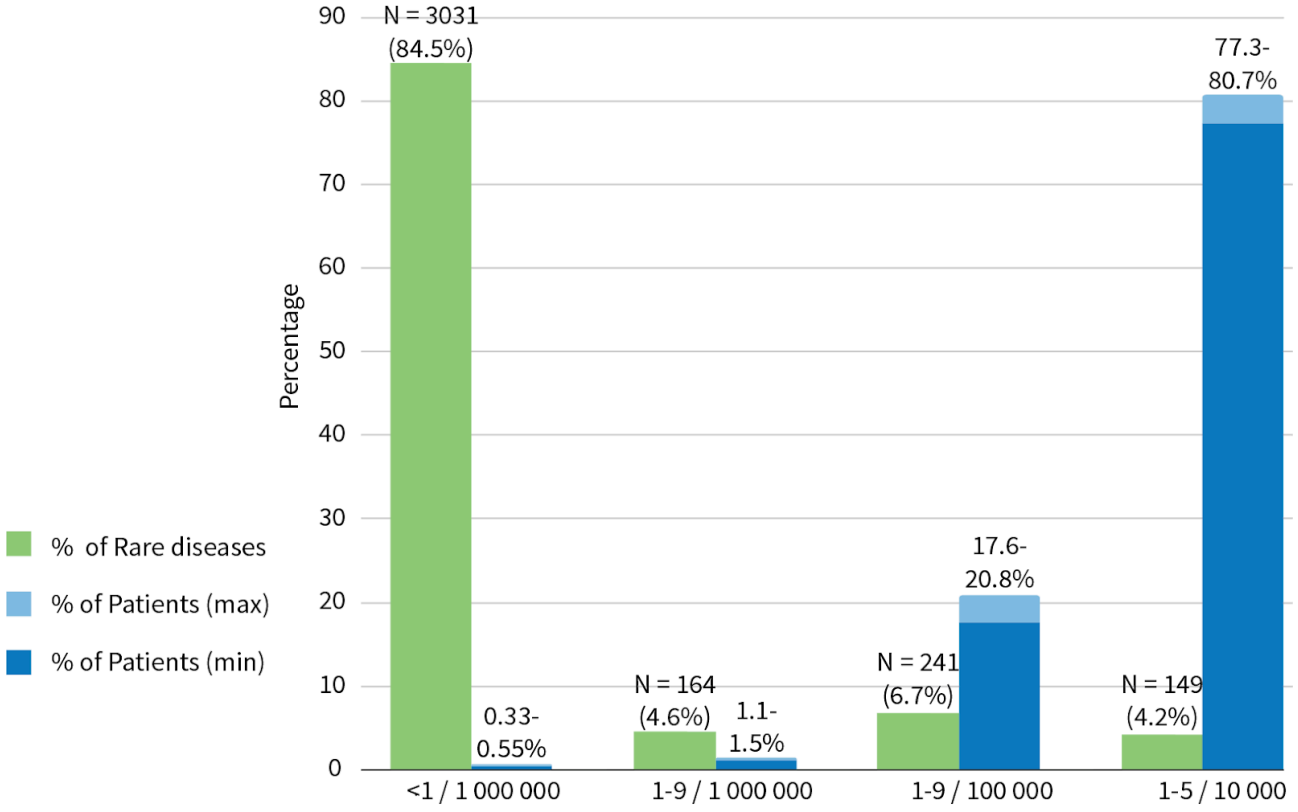


Figure 1: Distribution of rare diseases and rare disease patients according to the point prevalence class. For each prevalence class both the number of rare diseases and the range of patients with rare diseases are shown.
Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020).

The key chart from the paper is reproduced above. The paper became a topic of regular discussion for the Genetic Alliance UK team and for some of our member organisations. There are many different perspectives and conclusions that can be drawn from this view of the rare condition population. Those conclusions could help us shape our thinking and our advocacy for the estimated 3.5 million people living with a rare condition in the UK.

At the more prevalent end of the spectrum (the right-hand side of the chart), 149 rare conditions account for such a large proportion of people living with a rare condition - 77.3% - 80.7%, that they are an attractive target for effective action to improve the lives of people living with rare conditions. This first tier includes conditions that fall just inside the definition of a rare condition in the UK, that is conditions that

affect fewer than 5 in 10,000 people, (this statistic is sometimes represented as fewer than 1 in 2,000, which is equivalent) and more than or equal to 1 in 10,000 people.

The second tier is a further 241 rare conditions, which have prevalences below 10 in 100,000 and more than or equal to 1 in 100,000. This tier affects a further 17.6% - 20.8% people living with a rare condition. Taken together, all rare conditions between 5 in 10,000 (equivalent to 50 in 100,000) and 1 in 100,000, amount to 390 conditions, affecting more than 99% of people living with a rare condition.

If we take this data as representative of the population of people affected by rare conditions in the UK, our first conclusion from these discussions is that focused attention on comparatively few rare conditions could have a high impact on the vast majority of people living with rare conditions. Understanding more about these most frequently occurring rare conditions would tell us a lot about the community Genetic Alliance UK represents. When taken as a whole, the enormous numbers of rare conditions are very challenging to analyse as a population, perhaps a smaller cohort of the most frequently occurring would be less complex to examine, and might lead us to some important conclusions about how to approach rare conditions in the UK.

The chart also shows another side of the picture. The left-hand side of the chart shows the vast majority of the rare conditions on the Orphanet database (once the exclusion rules of the Wakap et al study had been applied) - 3,031 conditions. (In fact there are many different ways to count rare conditions: as we publish this report, Orphanet records 6,313 rare conditions on their database, the UK Rare Diseases Framework references ‘over 7,000’ rare conditions.) The prevalences here are very low, less than 1 in a million, and so the population affected is very low too, around 0.5% of people living with rare conditions.

There are many challenges that people living with rare conditions face, such as lack of awareness of conditions among healthcare professionals, slow or challenging diagnoses, scarce information and difficulties accessing comprehensive treatment. If many of these challenges increase with rarity, then surely it is this large group of very rare conditions that face the greatest challenges. Would we be neglecting those most in need if we focus on the other end of the rare conditions spectrum?

With a view to ultimately examining the whole spectrum of rare conditions, the Genetic Alliance UK team chose to examine the portion of the rare condition spectrum with the highest frequency. This was a task that seemed feasible for a small team with limited resources to undertake, and we predicted this analysis would prompt insights that could be applied more broadly, potentially delivering learning points for the wider rare condition community.

Our questions were about how well the UK supports these communities. What are the diagnostic tools available to us, which services are available, are there treatments and what support is there? As well as being the most manageable start to a broader process, there was a strong chance that our learnings would benefit those living with a less frequently occurring rare condition too.

Our data source

We are grateful to Moï Yamazaki of Orphanet INSERM for providing the download of 2022 Orphanet data, on which this report has been based. To try to replicate the approach of the 2020 paper that inspired the

work, we applied our own filter to the download to exclude any entries that were labelled by Orphanet as groups of disorders or subtypes of conditions. The total number of rare conditions with prevalences ranging from the upper bound of rare (5 in 10,000) to our cut off point (1 in 10,000) was 163 conditions. We list these conditions at the back of the report for your reference. This is slightly more than the 149 conditions identified in the paper of 2020. It is unsurprising that the number changes over time as the database reflects new scientific findings as they are published.

What did we expect to find?

At the beginning of this process, we expected to be able to categorise the 163 conditions we were working with, and assess them against a series of key objective measures:

- Is there a commissioned service for the condition?
- Is there a genetic test for the condition?
- Is there a medicine for the condition?
- Is there clinical guidance on the condition?
- Is there a support group for the condition?

Though we weren't expecting a clean sweep, our thinking was that this group of 163 conditions are the most likely of all rare conditions to have positive answers to those questions. We would then be able to shine a light on any gaps we found as some of the most effective actions to take that would benefit the largest cohorts of people living with rare conditions.

The next useful outcome that we expected was that we would be able to examine the services, guidance and support available to see whether these include similar conditions with much lower prevalences within their scope, or could be adjusted to do so. In this way, our findings might indicate a route forward to expanding existing services to support the very rare conditions that might be falling through the cracks.

Of course, we were also expecting to learn about the community we serve, and to identify gaps in our knowledge of the rare condition world that this exercise might begin to fill.

WHAT HAVE WE LEARNED FROM THE DATA?

How complex are these rare conditions? What categories are the conditions in?

The Orphanet database allocates rare conditions into categories which generally describe the body system affected. Each condition can have multiple categories. The most in our list was Noonan syndrome, which is labelled with 14 categories, and 50 out of 163 conditions were labelled with just one category.

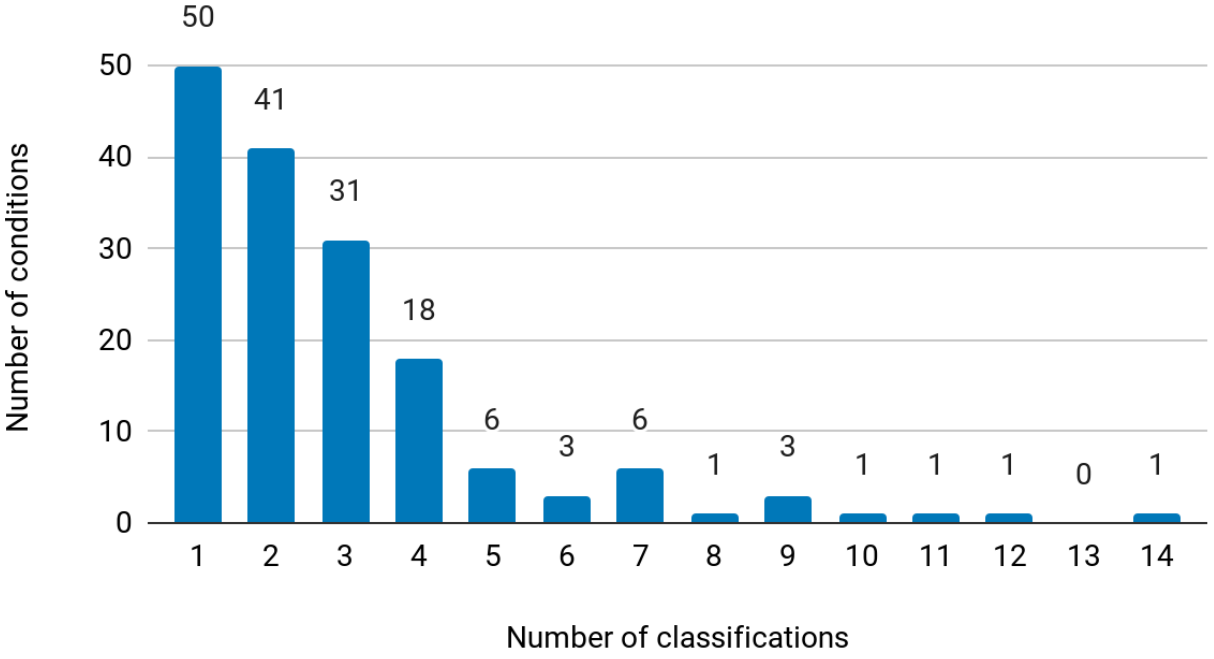
To understand these categories a bit more, we've taken sickle cell anaemia as an example, which is listed with seven categories: (in alphabetical order) bone diseases, genetic diseases, haematological diseases, neurological diseases, renal diseases, systemic and rheumatological diseases, transplant-related disorders. If we compare this with the introduction to the condition by the Sickle Cell Society:

> 'The main symptoms of sickle cell disorder are anaemia and episodes of severe pain. The pain occurs when the cells change shape after oxygen has been released. The red blood cells then stick together, causing blockages in the small blood vessels.
>
> These painful episodes are referred to as sickle cell crisis. They are treated with strong painkillers such as morphine to control the pain.'

We can see that there is overlap with the term 'haematological' conditions, but this is not emphasised by Orphanet in the way many describing the condition would. The other categories are mentioned in later sections of the Society's description.

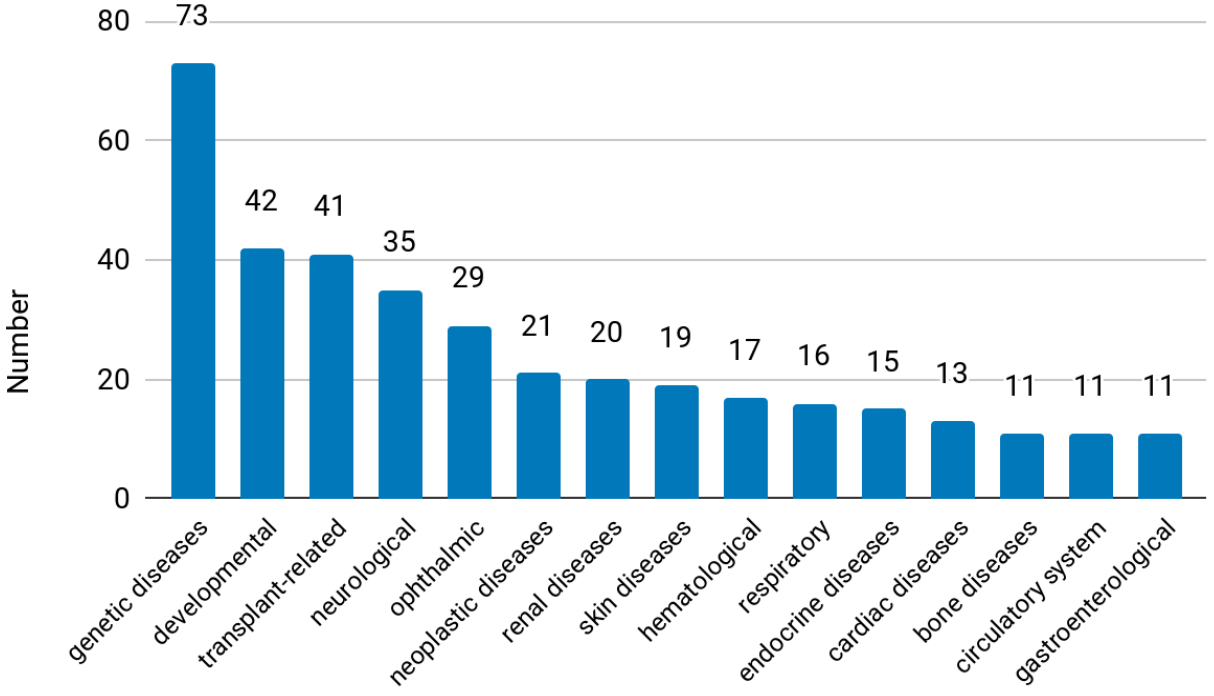
Even with these limitations, we can use the categories as a measure of complexity, and to understand which categories the 163 rare conditions we are examining fit into.

Figure 2: Complexity of conditions by number of Orphanet classifications



We found that more than half (91 of 163) of the conditions were only labelled with one or two categories, and that three quarters (122 of 163) were labelled with three or fewer categories. This was a surprise to us, as a characteristic of rare conditions is the complexity, and our expectation was that a much greater portion of the conditions in our list would be labelled with a higher number of categories. Just 25.1% (41 of 163) of the conditions had four or more categories attached to them.

Figure 3: Most frequently occurring classifications by number of conditions



In terms of which categories were occurring most frequently, developmental anomalies (42 of 163), neurological conditions (35 of 163), ophthalmic conditions (29 of 163) and renal (kidney) conditions (20 of

163) are some of the most frequently occurring categories. These category breakdowns, showing which organs are affected, and which clinical specialism is responsible for treating a condition are helpful. Alongside these, we can also see that 73 of 163 (45%) of the conditions are given the 'genetic disease' category, 41 of 163 (25%) are given the 'transplant-related disorder' category, and 21 of 163 are given the 'neoplastic disease' category. While these categories are also very helpful to understand the group of conditions, they are some of the first signs of surprises in the set of 163 conditions.

One of the most frequently used statistics about our community is that 80% of rare conditions are genetic in origin. The much lower proportion in this group of conditions shows that conditions caused by a genetic change are not evenly distributed through the prevalence spectrum of rare conditions. Genetic rare conditions, on average, are more rare than non-genetic rare conditions. This is an interesting and unexpected finding.

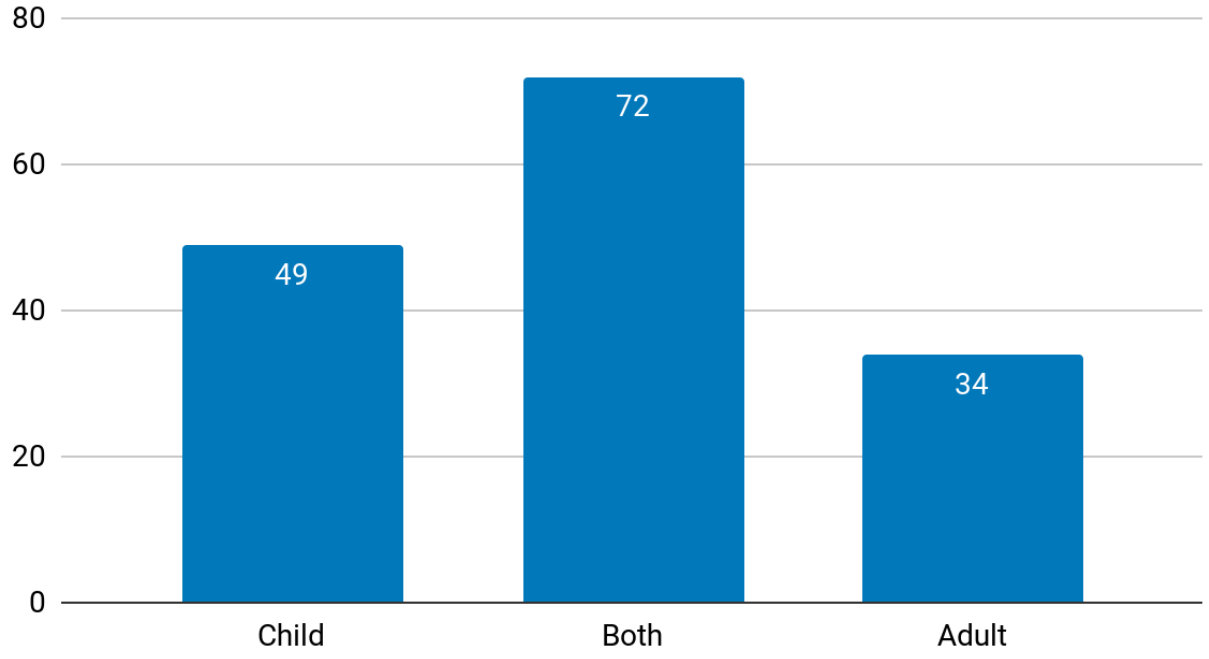
Neoplastic conditions include cancers, so this category shows the rare cancers within the data set. This category also includes non-cancer tumour conditions, as well as inherited cancer risk conditions. Though Genetic Alliance UK does not exclude cancer support groups within our membership, we do not have a large cohort of rare cancer groups as they are well supported within other support networks such as Cancer 52, Blood Cancer UK and the many organisations supporting children and teenagers with cancer.

The 'transplant-related disorder' category (41 of 163) groups together 40 conditions that might be treated by transplants and one condition which is a potential outcome from some transplants: post-transplant lymphoproliferative disease. We were surprised by the number of conditions that were in this category. The high count is certainly an indication of how important transplants are as treatment for this group of rare conditions, but it should be noted that for many of the conditions in the list, transplant is the treatment only for very severe cases of certain issues in the condition, such as conditions causing congenital heart defects.

What is the age of onset for these conditions?

Another often-quoted, key statistic for all rare conditions is that 75% of rare conditions affect children. Does that hold true for this cohort of the most frequently occurring conditions? Ignoring the eight conditions that do not have this attribute, we found that this does hold true, 77.1% (121 of 155) had an onset listed of childhood or adult and childhood.

Figure 4: Number of conditions with child or adult onset



Examining the most prevalent rare conditions further - expanding the view of the rare condition world

We decided we needed to look more closely at this list to understand which conditions were collected in the set of 163. Our review found five groups of conditions that were helpful to separate out and examine in more detail:

Cancer and pre-cancer conditions (15 of 163) - examples include small cell lung cancer and neuroblastoma. It is worth acknowledging these groups as a separate cohort, because they are not included within the UK Rare Diseases Framework, on the grounds that they are included within strategic cancer policy. This group does not include the condition 'hereditary breast and ovarian cancer syndromes' (a single condition in our data source) or non-cancerous tumour syndromes (such as tenosynovial giant cell tumour) because we chose to categorise these as 'conventional' rare conditions as that is how they tend to be treated in the context of rare condition policy.

Complications of more common conditions (9 of 163) - examples include conditions arising from premature birth, and dermatitis herpetiformis, which is an unusual skin complication of coeliac disease. These are worth distinguishing, as they may not be rare in their respective communities at risk.

Infections (8 of 163) - examples include Boutonneuse fever (transmitted by dog ticks) and hepatitis D. We draw these conditions out, as they are not usually a consideration in rare disease policy development.

Unusual health outcomes from treatment or surgery (8 of 163) - examples include complication in haemodialysis, post-transplant lymphoproliferative disease and scarring in glaucoma filtration surgical procedures.

Injuries (5 of 163) - examples include spinal cord injury and acute lung injury.
Though these types of conditions are not usually our focus, we do not exclude people with these conditions from our work, nor the organisations that support them from our membership.

Taking 'unusual health outcomes from treatment of surgery' and the post-transplant lymphoproliferative disease (PTLD) as an example we can see the value in acknowledging these groups. PTLD is a consequence of transplant, a treatment itself for many rare conditions. What does this mean for our analysis of the most frequently occurring rare conditions? As Lymphoma Action explain, *'post-transplant lymphoproliferative disorder (PTLD) is the name for types of lymphoma that sometimes develop in people who have had a transplant. It can affect people who are taking medicines to suppress their immune system: after an organ transplant to prevent rejection; after an allogeneic (donor) stem cell transplant to prevent graft-versus-host disease.' (Lymphoma Action)* A 20 year analysis of solid organ transplants in two UK transplant centres found that after a median follow-up of 7.7 years, 142 of 5365 (2.6%) patients have developed PTLD (Santarsieri 2022). Though this is not a likely outcome from transplantation, among people who have had a solid organ transplant it is not rare according to the definition of rare conditions.

Examining the list from Orphanet further, we found a total of 8 of 163 conditions that we categorised as unusual health outcomes from treatment or surgery. Other examples were complication in haemodialysis and scarring in glaucoma filtration surgical procedures.

The eight conditions we categorised as 'unusual health outcomes from treatment of surgery', though rare in the general population, are not typical rare conditions. Their existence within the data set poses challenges. Some are unusual outcomes of treatments for other rare conditions, this means that we should be careful when including incidence of these conditions alongside other rare conditions. They are also potentially not rare within the populations at risk - just as PTLD is not rare among people who have transplants. Only a subset of the UK population receives haemodialysis or glaucoma filtration surgery, and only they are at risk of these conditions. We say this not to marginalise or ignore those affected, but to acknowledge that the challenges faced by people with these conditions with respect to diagnosis and access to information and treatment (and the opportunities to address these challenges) are not necessarily the same as rare conditions unrelated to surgical procedures.

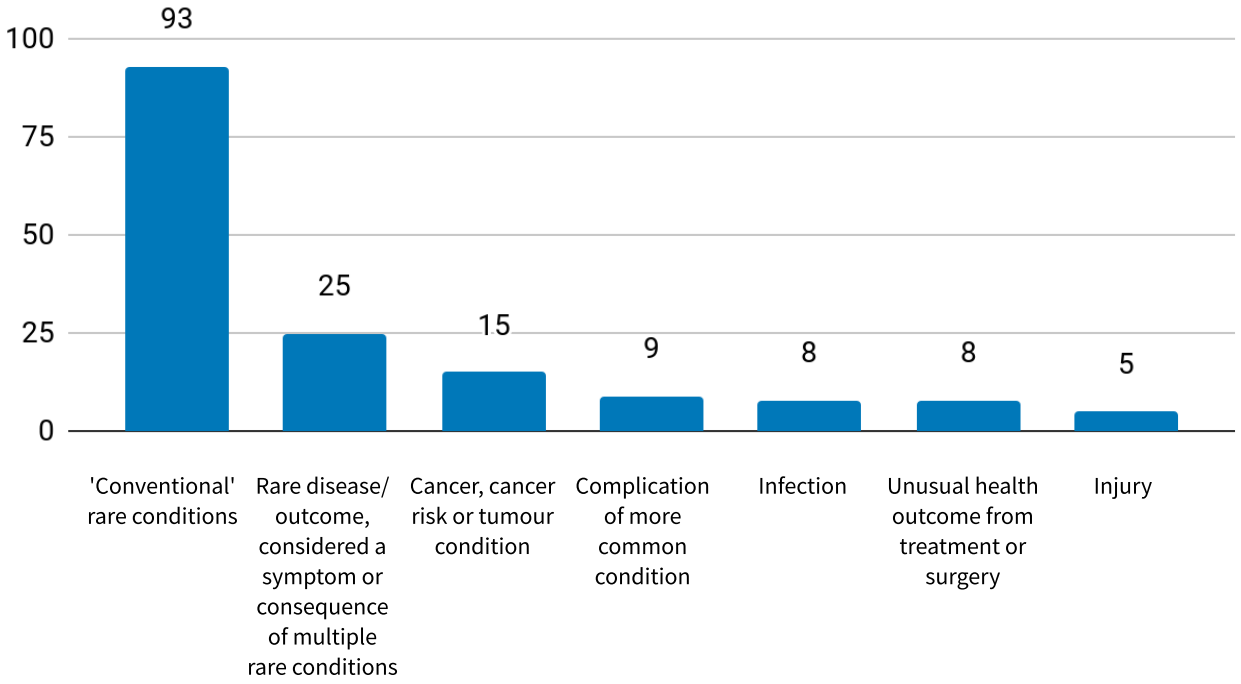
Our examination led to another important finding about this cohort of conditions: the remaining 118 of 163 conditions included both rare conditions with a single identified cause and rare conditions that are or can be symptoms of other conditions. An example of the former is sickle cell anaemia - this is a condition that encompasses a series of symptoms and prognoses for affected individuals. An example of the latter is cleft lip/palate - this is a valid diagnosis for people affected, but it is not an explanation of the cause of the condition. In fact there are many syndromes which include cleft lip/palate as a symptom.

The distinction is clear when you ask the question 'is there a genetic test for this condition?' For the former group including conditions such as sickle cell anaemia, the answer is 'yes, there is a genetic test that will diagnose people with sickle cell anaemia'. For the latter group including conditions such as cleft lip/palate, the answer is 'yes, there is a genetic test that can define whether the cleft lip/palate has a genetic cause, and identify it.' These are two different forms of rare condition within the Orphanet data, and again here there is the potential for overlap between conditions.

We therefore identified another category:

Rare conditions or outcomes, potentially a symptom or consequence of multiple rare conditions (25 of 163) - examples include Hirschsprung disease (a bowel condition affecting newborns), microtia (small or absent ears), and cleft lip/palate (a gap or split in the upper lip and/or roof of the mouth).

Figure 5: Our categorisation of the most prevalent Orphanet rare conditions



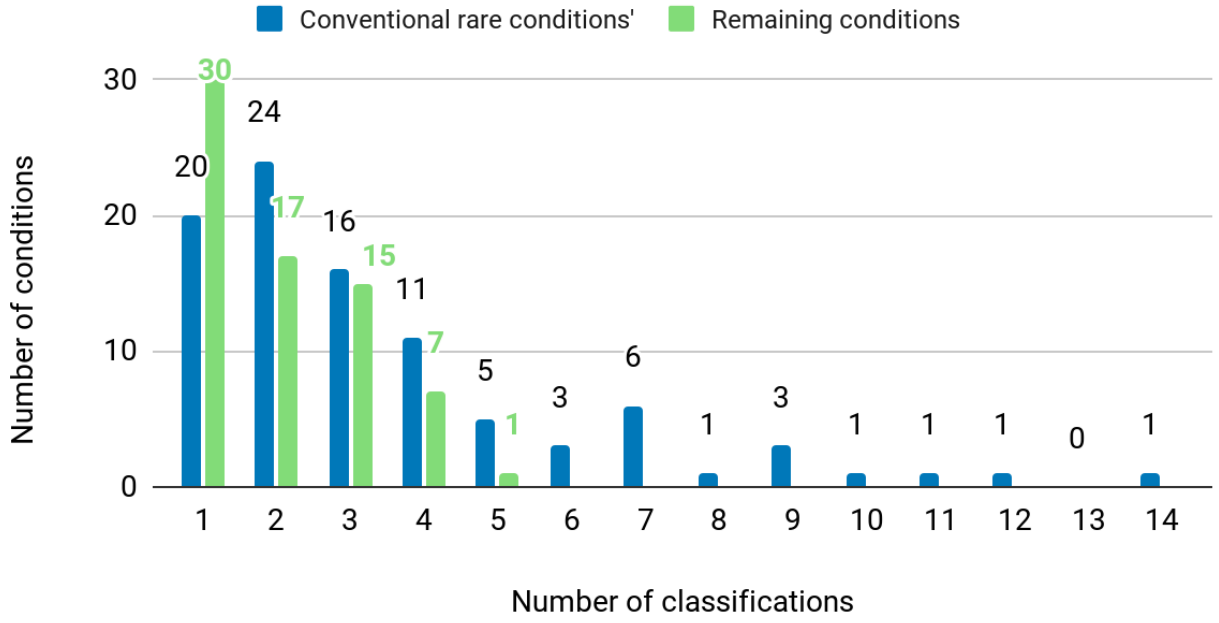
Analysing the 'conventional' rare conditions

We will discuss the implications of the categories we have identified further in our conclusions.
Ninety-three of 163 conditions were not selected as one of the subgroups identified above. These rare conditions have a relatively clear cause established and represent distinct groups of patients. We will call these ‘conventional' rare conditions.

We acknowledge that the Genetic Alliance UK team developed an ad hoc protocol for making this distinction, and that better resourced and more rigorous studies could develop a more thorough approach. However we are confident that these distinctions exist in the dataset, and that we have good estimates of their proportions here.

How do the patterns we have seen in the whole dataset change when we examine the 'conventional' rare conditions?

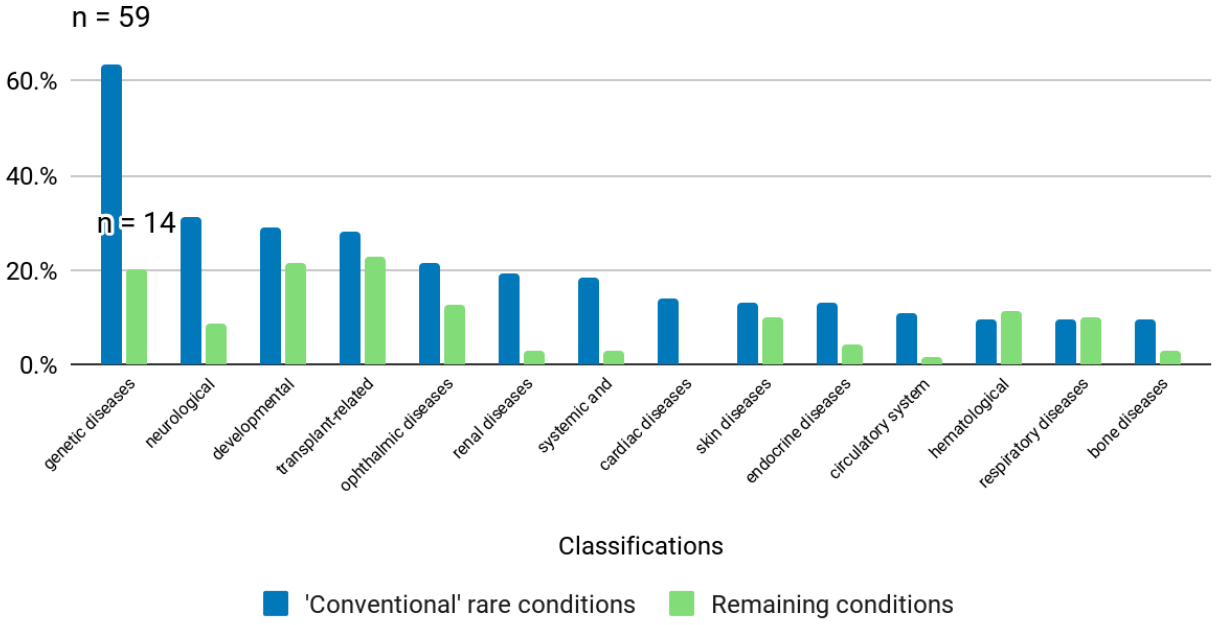
Figure 6: Complexity of 'conventional' rare conditions against the remainder by number of Orphanet classifications



The 'conventional' rare conditions are more complex in terms of how many Orphanet categories are assigned to them. The mean number of categories assigned by Orphanet to this group is 3.5, and the proportion of conditions that have four or more categories assigned to them is 36% (33 of 93), whereas the mean number of categories assigned by Orphanet to the remaining conditions is 2.0, and the proportion of conditions that have four or more categories is 11% (8 of 70), with the most categories being five assigned to one condition.

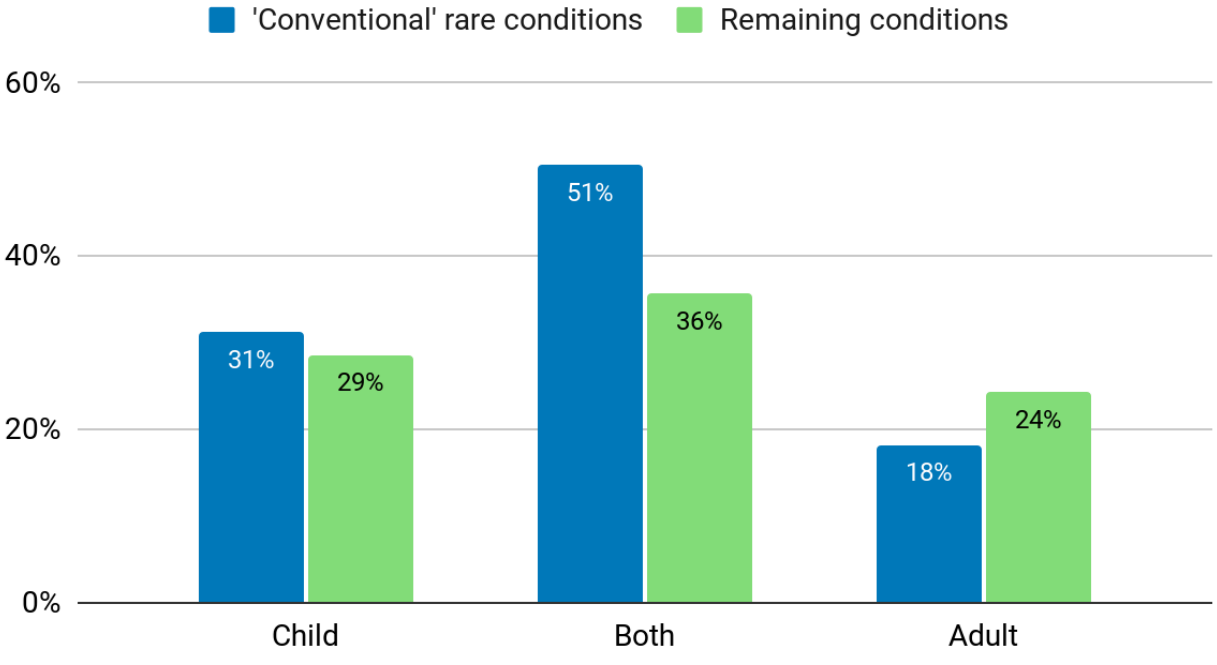
This shows that at least one characteristic of the conditions we have separated out is clearly different from the rest of the set of conditions. This group conforms more to the expectation that rare conditions will be complex because they affect multiple body systems and require care from multiple medical specialties. With respect to the remaining set of conditions that are composed of the categories discussed above, these appear to be less complex by this measure. This could mean that this cohort of rare conditions will face some of the hallmark challenges of rare conditions, such as poor care coordination, to a lesser extent.

Figure 7: Proportion of 'conventional' rare conditions (n = 93) and proportion of remaining conditions (n = 70) with each Orphanet classification ordered by frequency for 'conventional' rare conditions (showing classifications seen in 8 or more 'conventional' conditions)



The most commonly assigned category for the 'conventional' rare conditions continues to be ‘genetic diseases’, though ‘neurological diseases’ is now assigned to a greater proportion of the conditions than it is in the whole group of 163 conditions. The genetic conditions in the remaining conditions group are predominantly those conditions which we have assigned to the ‘rare conditions or outcomes, potentially a symptom or consequence of multiple rare conditions’ category (25 of 163).

Figure 8: Proportion of conditions with child, adult or 'both' age of onset



A smaller portion of the ‘conventional’ rare conditions have onset in adulthood.

UK PROVISION FOR THE MOST PREVALENT RARE CONDITIONS

Overview

This study was adapted to enhance our understanding of the Orphanet dataset, shifting the focus away from answering questions about service provision for individuals with these conditions. A significant finding was the feasibility of addressing some of our straightforward research questions. Certain essential information is not readily available, raising concerns for individuals seeking these services and requiring self-advocacy. Other questions, such as around commissioning arrangements, have complex answers that are challenging to categorise at a population level. A robust analysis would need work to develop a comprehensive taxonomy of categories of commissioning provision.

We present our findings as an introductory insight as to what would be possible with a well resourced robust study, and we discuss the challenges of accessing this information.

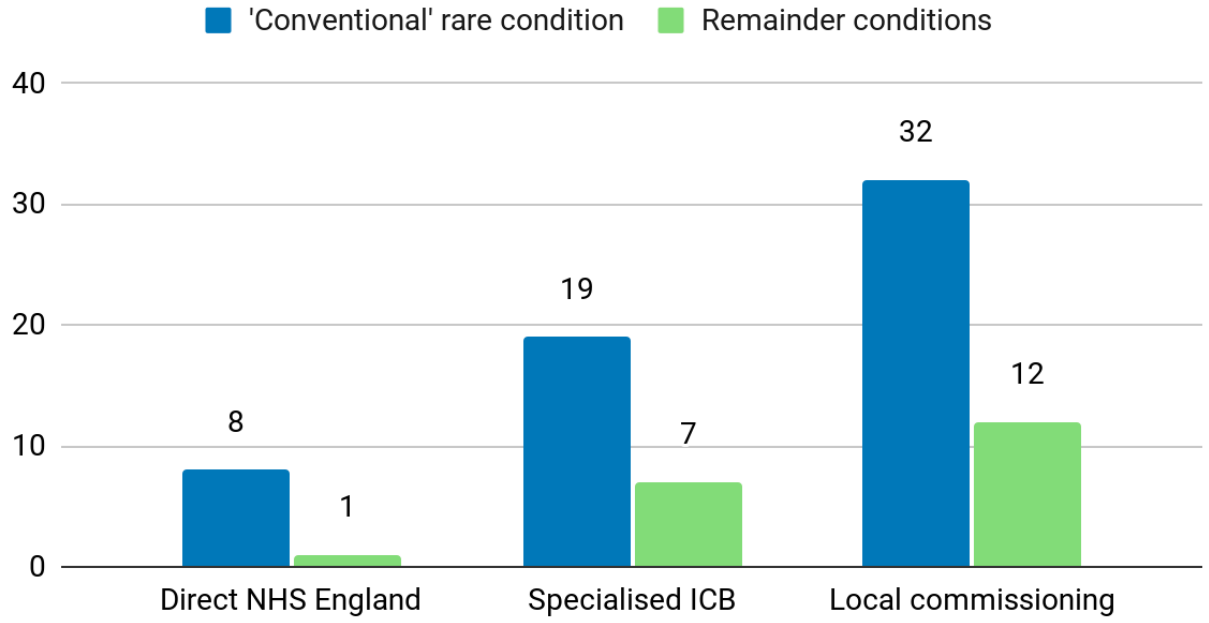
Availability of services

Though we carried out some exploratory searches in Wales and Scotland, we will focus our comments and findings on England. Evaluating the availability of services for the rare conditions on our list posed a range of challenges. NHS England's Specialised Service Specifications are a large suite of documents which were all created in parallel, originally in 2013 (and some have not been updated). These define specialised services, but do not have a consistent structure or approach to set their scope.

Some use relatively general terms to rule conditions in or out of scope. An example of this is 'ocular genetic disorders', which is part of the list of conditions covered by the service specification for specialised ophthalmology. Inclusive scope definitions are a positive way to ensure everyone living with a rare condition is entitled to appropriate care. When new conditions are identified through research, they can be included without adjustment to the specification. However some terms may be so general as to risk differences in interpretation which may disadvantage those less able to advocate or create differences in practice between centres providing care.

When taken alongside the Prescribed Specialised Services Manual (NHS England 2023) these sources can demonstrate that services for a particular individual should be provided by specialised commissioners. However where a rare condition does not appear in these documents or cannot be reasonably placed within the scope of a service, the rationale is not clear. It could be a deliberate decision placing a rare condition outside of the scope of specialised commissioning because local commissioning is the correct choice, or it could be the default position because the correct commissioner not been considered for people with this condition and no commissioning decision has been made.

Figure 9: Key commissioner for the most prevalent rare conditions where a clear key commissioner can be defined



The Prescribed Specialised Services Manual (NHS England 2023) defines three levels of commissioning: direct commissioning by NHS England, which includes the most specialised Highly Specialised Services; commissioning by Joint Committees (NHS England and Integrated Care Boards (ICBs)) commission in 2023/24 in line with national standards; and local commissioning according to local policies (also by ICBs).

We have only included a key commission in our data presented here where we could be confident of our allocation. This was only possible for 79 of the conditions in our list. Part of this is because it was challenging to access enough information to be confident with the answer. Other conditions were not categorised because their commissioning arrangements were too complicated to be categorised in this way, for example where diagnosis of a condition is a different service from treatment, and where there is a specialist single intervention that is commissioned at a different level from day to day care.

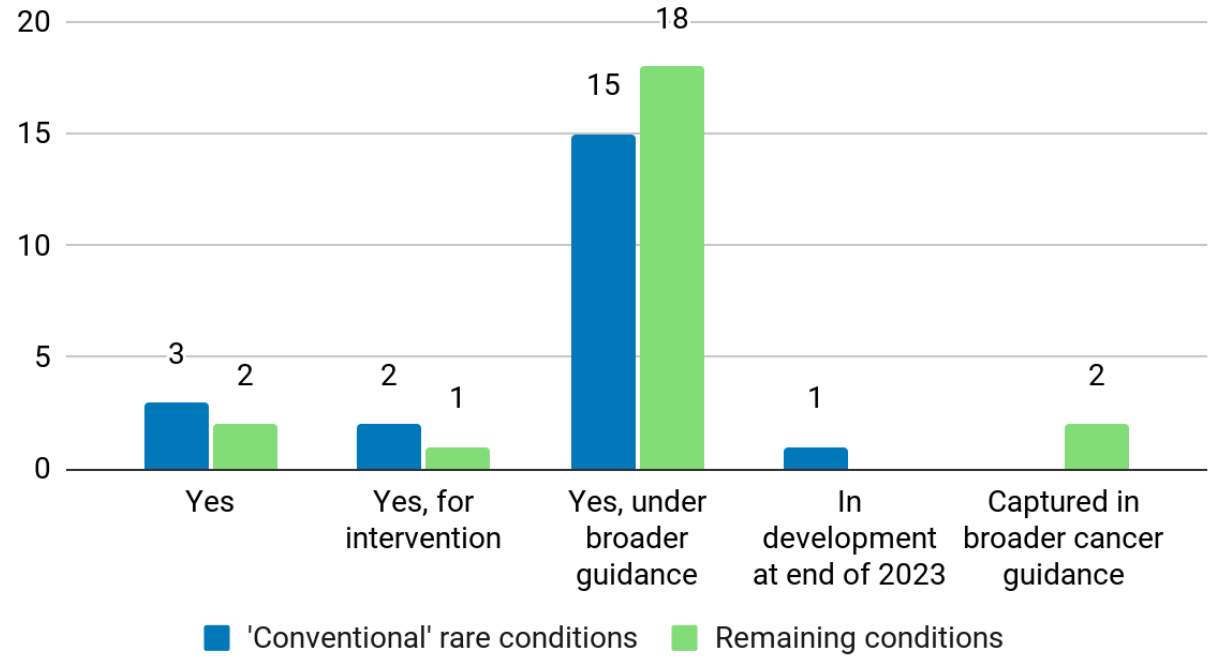
For the most prevalent rare conditions, a spread as indicated here is not unexpected. Perhaps the most surprising element of these findings is that within the nine conditions for which services are commissioned directly by NHS England, three of these fall within the scope of a highly specialised service. These were Aicardi-Goutières syndrome (which falls into the scope of the inherited white matter disorders diagnostic and management service), AL amyloidosis (the diagnostic service for amyloidosis [adults and children] is a Highly Specialised Service) and Fabry disease (which falls into the scope of the lysosomal storage disorders service [children and adults]). This is surprising because Highly Specialised Services are usually ‘provided to a smaller number of patients compared to specialised services; usually no more than 500 patients per year’ (NHS England 2023).

This is surprising and interesting, but not a cause for criticism. Commissioning is a complex process and there are many reasons to decide to use the Highly Specialised Services commissioning process to establish a service, population is just one factor. It is important that flexibility is applied to deliver the most appropriate service.

NICE information support

We assessed whether the conditions in our list were supported by NICE with substantial guidance or information. There are many conditions on these lists whose names appear within NICE Guidelines or other information products, for example retinopathy of prematurity, but they are not accompanied by significant advice or recommendations specific to the condition. We marked these conditions as lacking substantial guidance or information. It is valuable for retinopathy of prematurity to appear within the NICE Guideline on developmental follow-up of children and young people born preterm, but there is no specific information on how to identify it, or how to treat it.

Figure 10: Conditions with substantive NICE information provision



The pattern we found with respect to NICE's information provision for the most prevalent rare conditions was as expected, that there is scarce focused information tailored to specific rare conditions. This is not a surprise, as the prioritisation of NICE's guidance is based on utility within the population and added value to the NHS. It is encouraging to see that this gap is being filled with references to rare conditions within guidance with wider scope. We are also aware that NICE is supporting work to examine the possibility of a broad scope Quality Standard for rare conditions, as part of a programme of work arising from the UK Rare Disease Framework Stakeholder Forum.

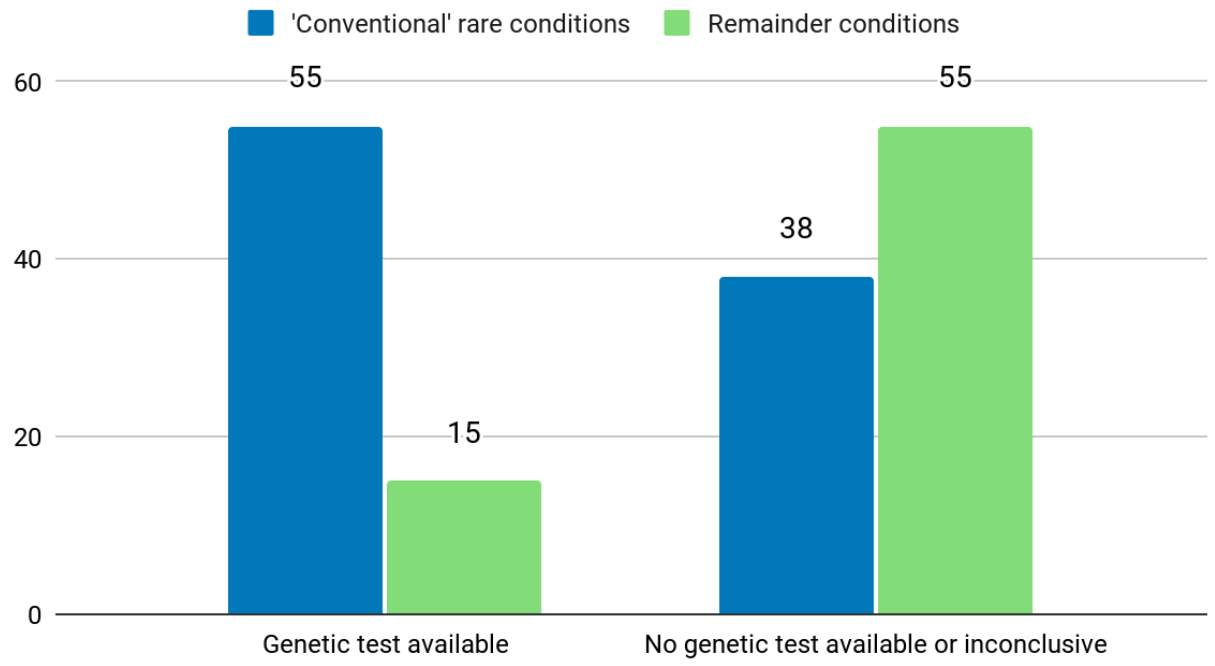
In Scotland the pattern is similar, there are no specific current SIGN guidelines for the conditions on the list, although some fall within the remit of wider guidelines. Two older outdated SIGN guidelines which are no longer published do exist for two conditions on the list. The Right Decision Service of digital tools could be adapted to provide information for rare conditions.

Availability of genetic testing

In England, to assess the availability of a genetic test for a particular condition requires consultation of three resources: the national genomic test directory for rare and inherited disease (a list of tests and

panels available), rare and inherited disease eligibility criteria (the criteria for accessing the tests), and PanelApp (specification of what the test will identify genetically). All of these are accessible from the NHS England website, but the process is complex and this means it is not a simple process to answer questions about genetic tests available on the NHS in England. We are aware that NHS England has started a process to unify these sources in a more accessible tool, this would be valuable when the work is complete.

Figure 11: Genetic tests in England for the most prevalent 163 rare conditions on Orphanet



The numbers we found matched quite closely against the Orphanet classification of genetic condition (total of 73 as per figure 3). As discussed previously, the question as to whether there is a genetic test 'for' a condition changes depending on the condition concerned. Genetic tests for those conditions which we classified as 'rare conditions or outcomes, potentially a symptom or consequence of multiple rare conditions (25 of 163)', such as cleft/lip palate or Hirschprung disease will be identifying the genetic cause for the condition. Whereas genetic tests for 'conventional' rare conditions such as fragile X or sickle cell disease are confirming a diagnosis made based on characteristic signs of the condition. Understanding this distinction will help us examine genetic test availability for comprehensive coverage, potentially increasing rates of diagnosis.

When we examined the availability of tests in Scotland we found very similar availability of tests, but similar challenges in accessing this information in a transparent manner.

WHAT SHOULD HAPPEN NEXT?

It is vitally important to understand more about the rare conditions affecting the UK

This project was conceived as the beginning of a piece of work that would lay the groundwork for a central repository of information about rare conditions with further information about services and support available for those affected. The work has reinforced our view that a resource would be valuable. We found answering the questions 'is there a specialised service for this condition?', 'is there a genetic test for this condition?', etc harder to answer comprehensively than we had expected. Some rare conditions are not named in the relevant service specification, others do not have their whole care pathway defined as a specialised service.

Our source of information for this work is Orphanet, an internationally recognised source of information about rare conditions. Its scope is all health issues that have a prevalence lower than 1 in 2,000. It records all rare diseases, including both rare symptoms of other rare conditions, syndromes, injuries, genetic conditions, and adverse effects from surgery. It includes cancer. Orphanet is not UK focused, and the UK does not have an equivalent data set.

We value the commitment of the governments of the UK to the UK Rare Diseases Framework, but in making this commitment, the governments have committed to solving an unknown problem. While it might be quite clear why we can't have accurate prevalence figures for the rarest conditions, our brief examination has shown that institutionally we know little about the more prevalent end of the spectrum too. It can be very challenging to access some information, or it may not be clear whether an overt planning decision has been made about a condition.

Without wishing to criticise Orphanet, as it depends on the collective efforts of scientists and clinicians worldwide, it should be noted that there are many conditions on the database that do not have a prevalence recorded. These are beyond our ability to examine. Our case study from Hereditary Brain Aneurysm Support (HBA Support) shows how better understanding and systematic data collection could combine to account for a non-rare health issue (brain aneurysm) which encompasses a group of rare conditions, some with genetic causes. It also considers how better knowledge about prevalence could allow the NHS to make decisions about screening for the condition in adult populations.

The four rare disease registration services of the UK: National Congenital Anomaly and Rare Disease Registration Service (England), Congenital Anomaly Register and Information Service (Wales), Congenital Conditions and Rare Diseases Registration and Information Service for Scotland, and the Northern Ireland Rare Diseases Registry, are the ideal hosts for this work.

Recommendation - identify segments of the rare community

Systematic assessment of the prevalence of rare conditions and symptoms in the UK by the registration services would identify groupings of rare conditions or symptoms of rare conditions that combine to a significant health challenge, allowing the NHS to commission and organise services accordingly.

Understanding all the possible causes of rare conditions

This project has been a learning experience for Genetic Alliance UK. Our remit is both rare conditions (those affecting fewer than 1 in 2,000 people in the UK) and genetic conditions (those with a clear genetic cause). We know there is a large intersection between these two groups; almost all genetic conditions are rare, and around 80% of all rare conditions have a genetic cause. This work has taught us more about the non-genetic causes of rare conditions, bringing infection, and unusual health outcomes from treatment or surgery more clearly into the scope of our work.

Of the 163 conditions we have examined here, only 58 (35.6%) of them have a genetic cause - much lower than the statistic applied to all rare conditions that about 80% have a genetic cause. Despite our health warning about drawing firm conclusions from our analysis, there is an indication that the proportion of rare conditions with a genetic cause might vary by prevalence, with the rarer conditions more likely to be genetic. Understanding which categories of rare conditions make up the rare condition population will help drive policy development.

One of the focus areas of the 2023 England Rare Diseases Action Plan is on support for people with non-genetic rare conditions. The plan acknowledges that there is a lack of epidemiological data on non-genetic rare conditions, though the National Congenital and Rare Disease Registration Service (NCARDRS) delivered 10 relevant papers under action 9 during 2022. There has also been further work on identifying individuals with non-genetic rare conditions, including an exploration of the recommendations of 'Resetting the balance', by RAIRDA – The Rare Autoimmune Rheumatic Disease Alliance (2022) which outlines the needs and challenges facing people living with non-genetic and late-onset rare conditions.

We categorised eight of the conditions we examined as 'unusual health outcomes from treatment or surgery'. These are rare conditions, but their prevalence *among* the population who have experienced the relevant treatment or surgery must be higher. This opens up opportunities for diagnosis and identification of people living with these conditions, and potentially prevention or reduction in occurrence of these rare conditions. The examples we gave for this category were complication in haemodialysis, post-transplant lymphoproliferative disease and scarring in glaucoma filtration surgical procedures. For these examples, one would expect that the procedures having taken place would be key to the diagnoses, and in fact for some procedures these outcomes are planned for or mitigated from the start.

This is not the case for all rare conditions that fall within this definition, as our case study from Rhys Holmes shows. Rhys had a diagnostic odyssey of seven years to diagnose his superficial siderosis. This condition is rarer than the cohort that we examined for this study, but was chosen because it illustrates two important points for rare conditions in this group. Firstly, diagnosis is not always straightforward: Rhys's medical procedures would have been known to his doctors, but the connection was not made at the first signs of superficial siderosis. Secondly, this condition is preventable: changes in surgical procedures to reduce the chances of post-operative bleeds, or better surveillance to identify post-operative bleeds, could have prevented or reduced the impact of Rhys's superficial siderosis. With more work to identify examples of this group of rare conditions, we could improve diagnosis and begin to prevent cases of these types of rare conditions.

Recommendation - identify new solutions

Investigation into the prevalence and cause of rare conditions in the UK would lead to new avenues to improve diagnosis, raise awareness and potentially prevent them or reduce their incidence.

Breaking down rare conditions to achieve equity

One of the key practical issues we could address with a better understanding of the spectrum of prevalence of rare conditions is equitable commissioning of health services for people living with rare conditions. Our examination showed that different conditions with similar prevalences experience differing levels of provision within NHS England's specialised commissioning structures. To illustrate this we asked the Better Together for Healthy Marrow Alliance to describe the disparity they see in NHS provision for rare bone marrow conditions and explain their concerns.

NHS England Specialised Service Specifications define the scope of the care that should be delivered to people with rare conditions by NHS England and the ICSs. In practice, many rare conditions fall through gaps in these Service Specifications, or the proposed care is extremely brief or non-specific. Many Service Specifications are unchanged since their publication in 2013 (for example, rare mitochondrial disorders service, haemophilia, metabolic services). In the context of the 18-month-old Integrated Care System arrangements, we asked the Neurological Alliance to discuss the risks for rare neurological conditions.

The choice of commissioning level for different rare conditions is a complex decision; prevalence is a factor, but there are many other key issues at play. However the rationale behind a choice to commission at a certain level is only clear and transparently accessible when the level is within specialised commissioning. It is not always clear whether local commissioning is a choice or a default.

Recommendation - identify clear commissioning routes for all rare conditions

A review of rare conditions, starting with the most prevalent, should indicate the commissioning level for all rare conditions, clearly and with a stated rationale.

Empower patients and their supporters with accessible information on service provision and decision-making

When the whole set of more than 7,000 rare conditions is considered, certain ideas or initiatives seem insurmountable. When we segment the population and ask the question about a much smaller number of conditions affecting a significant population, these ideas or initiatives become more realistic. Through this lens we can reconsider the tools we have available to us to access information about services for people living with rare conditions.

It would not be realistic to expect there to be accessible information about services for thousands of conditions to be available transparently on the NHS website, but when we examine the service provision for a set of the most prevalent rare conditions, we can see that the tools we have to access this information are complex and in some cases uncertain or incomplete. Improvements to these tools to make information more accessible to the most prevalent rare conditions would have a knock on effect on all rare conditions.

Recommendation - provide clear information for patients and their supporters

Commissioning and access decisions should be clearly accessible for rare conditions, starting with the most prevalent. Positive and negative decisions should be clearly recorded.

Include all rare conditions

The process we've discussed here is focused on the most prevalent rare conditions, as the largest population is the correct starting point. This work can be expanded to further tiers of rare condition prevalence in two ways.

Tier by tier - if examination of sets of rare conditions by prevalence is a valuable undertaking this can be repeated for less prevalent tiers of conditions. Rare conditions with a prevalence between 1 in 100,000 and 9 in 100,000 number 241 according to the Wakap et al paper referenced earlier.

Through inclusive definitions of services - where clinically appropriate - definitions of services for people living with rare conditions could be designed to be inclusive of rarer similar conditions. This approach could lead to a more consistent level of service quality for a broader range of rare conditions. The Inherited White Matter Conditions Service is an example of this approach.

Recommendation - expand to cover all rare conditions

An inclusive approach to future provision will allow the rarer conditions to benefit from progress for the more prevalent rare conditions.

CONCLUSION

We maintain the view that the analysis we set out to undertake is valuable. Examining cohorts within the rare condition population instead of taking the population as a whole would make learning about our population more feasible. Some of this knowledge will benefit the whole rare condition community.

Whereas some questions about rare conditions are insurmountable for more than 7,000 rare conditions, questions like 'is care available and equitable?' become much more feasible for a smaller set of rare conditions.

APPENDIX List of conditions

Conditions are listed as per their title in Orphanet

22q11.2 deletion syndrome
47,XYY syndrome
Acquired aneurysmal subarachnoid hemorrhage
Acute liver failure
Acute lung injury
Acute peripheral arterial occlusion
Acute sensorineural hearing loss by acute acoustic trauma or sudden deafness or surgery induced acoustic trauma
Addison disease
Adenovirus infection in immunocompromised patients
Adult acute respiratory distress syndrome
Aicardi-Goutières syndrome
AIDS wasting syndrome
AL amyloidosis
Alopecia totalis
Alopecia universalis
Alpha-1-antitrypsin deficiency
Anal fistula
Aplasia cutis congenita
Asherman syndrome
Atopic keratoconjunctivitis
Autoimmune hepatitis
Autosomal dominant polycystic kidney disease
B-cell chronic lymphocytic leukemia
Beckwith-Wiedemann syndrome
Boutonneuse fever
Bronchopulmonary dysplasia
Brugada syndrome
Buerger disease
Bullous pemphigoid
Cardiogenic shock
Catecholaminergic polymorphic ventricular tachycardia
CD4+/CD56+ hematodermic neoplasm
Central retinal vein occlusion
Charcot-Marie-Tooth disease type 1A
Chronic actinic dermatitis
Classic Hodgkin lymphoma
Cleft lip/palate
Cleft velum
Complication in hemodialysis
Congenital bilateral absence of vas deferens
Congenital primary aphakia
Congenital sucrase-isomaltase deficiency
Cystic fibrosis
Cystinuria
Cytomegalovirus disease in patients with impaired cell mediated immunity deemed at risk
Dentinogenesis imperfecta
Dermatitis herpetiformis
Dermatofibrosarcoma protuberans
Double outlet right ventricle
Down syndrome
Duane retraction syndrome
Dysbetalipoproteinemia
Esophageal atresia
Essential thrombocythemia
Fabry disease
Familial cerebral cavernous malformation
Familial isolated dilated cardiomyopathy
Familial Mediterranean fever
Familial or sporadic hemiplegic migraine
Fetal and neonatal alloimmune thrombocytopenia
Fetal cytomegalovirus syndrome
Follicular lymphoma
Fragile X syndrome
Gastrointestinal stromal tumor
Gastroschisis
Giant cell arteritis
Hemorrhagic fever-renal syndrome
Hepatitis delta
Hereditary breast and ovarian cancer syndrome
Hereditary elliptocytosis
Hereditary hemorrhagic telangiectasia
Hereditary spherocytosis
Hereditary thrombophilia due to congenital antithrombin deficiency
Herpes simplex virus stromal keratitis
High-grade dysplasia in patients with Barrett esophagus
Hirschsprung disease
Huntington disease
Hypermobile Ehlers-Danlos syndrome
Hypocalcemic vitamin D-dependent rickets
Idiopathic hypersomnia
Idiopathic intracranial hypertension

Idiopathic pulmonary fibrosis
Immune thrombocytopenia
Indolent systemic mastocytosis
Infant acute respiratory distress syndrome
Interstitial cystitis
Isolated cleft lip
Lennox-Gastaut syndrome
Limbal stem cell deficiency
Marfan syndrome
Mayer-Rokitansky-Küster-Hauser syndrome
Microtia
Moderate and severe traumatic brain injury
MODY
Mucolipidosis type III
Multiple myeloma
Myasthenia gravis
Narcolepsy type 1
Necrotizing enterocolitis
Neovascular glaucoma
Neuralgic amyotrophy
Neuroblastoma
Neurofibromatosis type 1
Neurotrophic keratopathy
Non-acquired isolated growth hormone deficiency
Non-functioning pituitary adenoma
Non-papillary transitional cell carcinoma of the bladder
Non-syndromic metopic craniosynostosis
Noonan syndrome
Oligoarticular juvenile idiopathic arthritis
Omphalocele
Osteochondritis dissecans
Osteogenesis imperfecta
Partial atrioventricular septal defect
Partial chromosome Y deletion
Partial deep dermal and full thickness burns
Pemphigus vulgaris
Phenylketonuria
Placental insufficiency
Pleural empyema
Pneumonia caused by Pseudomonas aeruginosa infection
Polycythemia vera
Post-transplant lymphoproliferative disease
Pouchitis
Preeclampsia
Primary biliary cholangitis
Primary lymphedema
Primary membranoproliferative glomerulonephritis
Primary Sjögren syndrome
Progressive supranuclear palsy
Proximal 16p11.2 microdeletion syndrome
Pulmonary fungal infections in patients deemed at risk
Radiation proctitis
Recessive X-linked ichthyosis
Retinitis pigmentosa
Retinopathy of prematurity
Rett syndrome
Romano-Ward syndrome
Sarcoidosis
Scarring in glaucoma filtration surgical procedures
Secondary hypoparathyroidism due to impaired parathormon secretion
Sepsis in premature infants
Serrated polyposis syndrome
Sickle cell anemia
Small cell lung cancer
Spinal cord injury
Stargardt disease
Steinert myotonic dystrophy
Supravalvular aortic stenosis
Syndactyly type 1
Systemic lupus erythematosus
Systemic sclerosis
Tenosynovial giant cell tumor
Thyroid ectopia
Thyroid hemiagenesis
Trisomy X
Turner syndrome
Uremic pruritus
Vernal keratoconjunctivitis
Von Willebrand disease
Vulvar intraepithelial neoplasia
Wild type ATTR amyloidosis
Young-onset Parkinson disease

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