PUBLIC POLICY PROJECTS

INSIGHTS

A Fairer Future

TOWARDS A MORE EQUITABLE DELIVERY OF CARE FOR THOSE WITH RARE DISEASES AND CONDITIONS IN THE UK

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About

ABOUT PUBLIC POLICY PROJECTS

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Cognitant Group is an Oxford-based business that uses immersive technology to provide people with accessible, personalised and trustworthy information about health and treatment. The company works with life science companies, patient advocacy groups, the NHS, health insurers and care providers to empower people to manage their health more effectively. Cognitant Group's data-driven information prescription platform, Healthinote saves clinician time, improves patient reported outcomes and reduces unnecessary complications across many care pathways.

Acknowledgements

This report is the culmination of over 10 hours of discussion, between February and May 2022, amongst over 60 participants, and case study submissions. The discussions addressed the contents of the Action Plans published at the time. The Wales Rare Disease Action Plan was not a part of the discussions but has been included in the body of the report as it was published in June 2022. Scotland's Rare Disease Action Plan was not published at the time of writing.

In addition, special recognition is awarded to the patients and advocates who contributed their time and experiences to the programme. We would like to thank you for your vital input.

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ALASTAIR KENT OBE, INDEPENDENT PATIENT ADVOCATE

Alastair Kent was the executive director of Genetic Alliance UK (GA-UK) the national alliance of over 200 patients support organisations helping those with rare and genetic disorders for almost 25 years. He founded and chaired Rare Disease UK, the campaign managed by GA-UK until January 2018. In April 2017 he stepped back from the campaign to take on a new role for the organisation, namely that of Ambassador, promoting awareness of the needs and expectations of all those affected or at risk from rare and genetic conditions. He retired from Genetic Alliance UK at the end of April 2018, but remains active in the field, working as an independent consultant.
Alastair was made OBE for services to healthcare in 2011. In 2017 he became a Fellow of the Royal Society of Arts for his work on behalf of genetic patients and families, and was named Healthcare Advocate of the Year at the Communique Awards ceremony. In 2018 he received a lifetime achievement award from Eurordis, the European organisation for rare diseases.

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Dr Shehla Mohammed is a paediatric clinical geneticist with 26 years' experience predominantly in rare genetic conditions and in the care of children and families with complex life-limiting disorders. Until 2017, Shehla had been Head of Service of the Guy's Regional Genetics Service for 20 years. She has a special interest in translational research and is involved in Phase III clinical trials. Her experience in the implementation of robust technology platforms and their rapid translation into a clinical setting has enabled the successful delivery of multidisciplinary, patient-focused and integrated services. She has developed and leads national Highly Specialist Services with colleagues from the dedicated Rare Diseases Centre at Guy's and St Thomas NHS Foundation Trust.
Dr Mohammed has Committee experience with a number of external organisations, either in the capacity as Chair or member of a number of national committees or working groups. She is currently a member of the Highly Specialist Technology Committee of NICE, Trustee of patient support groups and had a past role as Expert Clinical Advisor to the UKGTN.

Foreword

Alastair Kent OBE

Dr Shehla Mohammed

In January 2021, the UK Rare Disease Framework was published by the Government. This identified four key priorities to be addressed if continued improvement in services and support for the approximately 1 in 17 UK citizens affected by a rare disease is to be realised in the lifetime of this Framework.

The four priorities are:

1. Helping patients get a final diagnosis faster
2. Increasing awareness of rare diseases among healthcare professionals
3. Better coordination of care
4. Improving access to specialist care, treatments and medicines

The Framework itself is a high-level document, aspirational in tone rather than a detailed route map. The details are the responsibility of Implementation Groups in each of the four UK nations. It is clear that successful delivery of the Framework will depend on engagement with and commitment from a wide range of key stakeholders. Of these, the voice of those most directly affected - the individuals and families living with the daily consequences of a rare disease - is crucial to the achievement of this goal.

As a contribution to the evolution of the delivery plans by the four nations, PPP convened a series of workshops, each targeted at a key framework priority. To ensure that any proposals for change were pragmatic, achievable and addressed the expressed needs of the rare disease patient community each workshop was undertaken in two parts.

The first of these comprised leading patient advocates drawn from across the spectrum of rare disease support organisations. Their expertise and lived experience informed a clear frame for the issues and priorities that are important from the perspective of patients and families and equally helped in evaluating any proposed responses to the needs.

This framework was then used to set the scene for the second part, where a multi-stakeholder panel of experts drawn from clinical medicine, research, policy, industry and other groups was able to develop responses to the challenges posed. At each stage, ideas were developed between patient and family representatives and other expert stakeholders to ensure they remained relevant and responsive to the views of the patient community.

This report is the culmination of this process. Whilst the proposals reflect the knowledge and first-hand experience of relevant stakeholder groups, they will inevitably need to evolve in the light of new knowledge, new opportunities to intervene and any changes in the organisation and delivery of health care across the UK. Sharing knowledge and good practice across institutional and disciplinary boundaries will be key to the effective realisation of the Framework's key priorities and to meeting the needs of those with rare diseases and their families. This report is offered as a contribution to support this aim.

Alastair Kent OBE & Dr Shehla Mohammed, Project Co-Chairs

Recommendations

DIAGNOSIS

Recommendation 1: As the Genomic Medicine Service is rolled out it is essential that healthcare professionals, including the anti-natal and neo-natal workforce, be informed on the impact this may have on newborns and those exhibiting symptoms. This is to ensure expecting mothers and new parents, are provided with appropriate time to familiarise themselves with the service and potential options available to them.

Recommendation 2: While the Newborn Screening Programme aims to focus on including actionable genetic conditions which may affect their health in early years. It is essential that, once implemented, this be periodically reviewed to ensure the system is flexible enough to accommodate conditions for which new treatments are later developed and approved.

Recommendation 3: The list of conditions currently screened for, using the heel-prick test, should be expanded by the National Screening Committee to include those such as Spinal Muscular Atrophy (SMA) Type 1, for which a gene therapy exists. This should occur in addition to the ongoing Newborn Screening Programme. It should be a commitment that this aim be met before the completion of the Newborn Screening Programme, run by Genomics England (GEL), in 2025.

Recommendation 4: Whole Genome Sequencing (WGS) in newborns may result in a potential 3000 more patients entering the healthcare system every year. It is essential that in ongoing consultations the system be prepared to absorb those diagnosed. The implications upon clinical services to respond and develop timely care plans must be considered, to ensure newly diagnosed patients and families to not end up on disproportionally long waiting lists.

CLINICAL DEVELOPMENT

Recommendation 5: To level up the delivery of care, building upon the lessons learned from the Covid-19 pandemic and the commitment to develop a toolkit for virtual consultations, a hybrid approach to clinical assessments must be adopted. This should form a core part of the patient's care plan which enables, where suitable, all patients and NHS trust with the flexibility to build care and monitoring plans which make use of both in-person and virtual consultations.

Recommendation 6: The increase in collected data as a result of the Newborn Screening Programme in England, could play a central role in deepening understanding of rare diseases. Building a federated dataset, available across the UK, which accounts for and records those identified by WGS would begin to build the foundations on a UK rare disease patient registry. While it may not initially account for existing patients, it would serve to deepen understanding and build a platform into which they may later wish to submit their data.

ENGAGEMENT, EDUCATION AND AWARENESS

Recommendation 7: Rare Disease Multidisciplinary Teams should be established, beyond the remit of Rare Disease Collaborative Networks, to promote the raising of education levels and awareness amongst current healthcare professionals. The need for an effective education and awareness programme for members of clinical teams involved in the care of rare disease and condition patients is evident. Cross-pollination of expertise is at the core of furthering professional education.

Recommendation 8: To harness widespread engagement and raise awareness of rare diseases beyond the healthcare ecosystem, the conversation must be rephrased. A collaborative and cross-sectoral recasting of public perception and understanding through the lens of 'population health impact and intervention', should work towards harnessing an understanding of the health impacts of rare diseases beyond those directly affected.

Recommendation 9: Universities, Royal Colleges, Health Education England, and other professional bodies and academic institutions should promote the upskilling and further education of their students and healthcare professionals. It is also essential that these be completed by key decision-makers within the health service, for example those allocating resource for commissioning services, to ensure impact is felt across the health ecosystem. These may be delivered through virtual and in-person workshops.

COORDINATION OF CARE

Recommendation 10: The key findings and recommendations from the CoOrdiNated Care of Rare Diseases (CONCORD) study should be viewed as a foundation upon which the basis for the planning and delivery of coordinated care is established.

Recommendation 11: To deliver the maximum possible health gain to the patient and utilise resources to the highest level of efficiency possible, an interdisciplinary and holistic health economic evaluation must be undertaken of current services and resource allocation. To truly analyse the economic impact upon the patient, their family and carers, the health service, as well as the societal cost of lost opportunity and productivity, enabling evidence-based decision-making on the use of financial resources.

Recommendation 12: Living with a rare disease places substantial strain on mental health. In anticipation of the reforming of the Mental Health Act, a focus on effectively integrating mental health services and support into rare disease services is essential. Not only for the individual living with the rare disease or condition, but for their family and carers as well.

Introduction

Living with a rare disease or condition poses many challenges. Over the past decade, improving the delivery of care for the 3.5 million people living with rare diseases or conditions within the UK has been the central focus of the work of many. The formation of participant panels, policy boards, the publication of frameworks, and most recently, the Action Plans, reflect the commitment both from Government and the wider health service to improve the lives of those living with rare diseases and conditions in the UK.

With committed long-term funding into Genomics England's Newborn Genomes Programme for instance,[1] and the creation of the NHS Genomic Medicine Service (NHS GMS),[2] the ambition to deliver faster diagnoses, deepen understanding of conditions, and increase the development of treatments and drugs, is unquestionable. However, with not all rare diseases and conditions being genetic this is just one side of the coin.

The experiences however of those living with rare diseases and conditions reflect a comprehensive standard of care that is below what it should be. The insights provided by the Patient and Advocate Group address both the breadth of excellent and world leading care, as well as outline a system that is too often disjointed.

In considering how to improve services for those living with rare diseases, owing to the number, variety and intricacies of the diseases and conditions, it would be easy for this task to appear overwhelming. However, the discussions held frequently echoed with the shared sentiment that 'if you can do it for cancer, do it for rare disease.' While by no means a copy and paste exercise, the intent behind the messaging is clear: the space and capacity exist to do more.

This report builds directly upon Public Policy Projects (PPP) past reports, most recently Rare Diseases Coalition: Implementing the UK Rare Diseases Framework, and Reflections on Rare Diseases; both of which made clear recommendations on how to improve the delivery of care to those with rare diseases and conditions.

Policy must reflect the populations it serves, and collectively the rare disease and condition community could make up the second most populated city in the UK behind only London. Therefore, while there is no roadmap for innovation; we can stive to build a framework in which its achievement is not disjointed. The time to act is now.

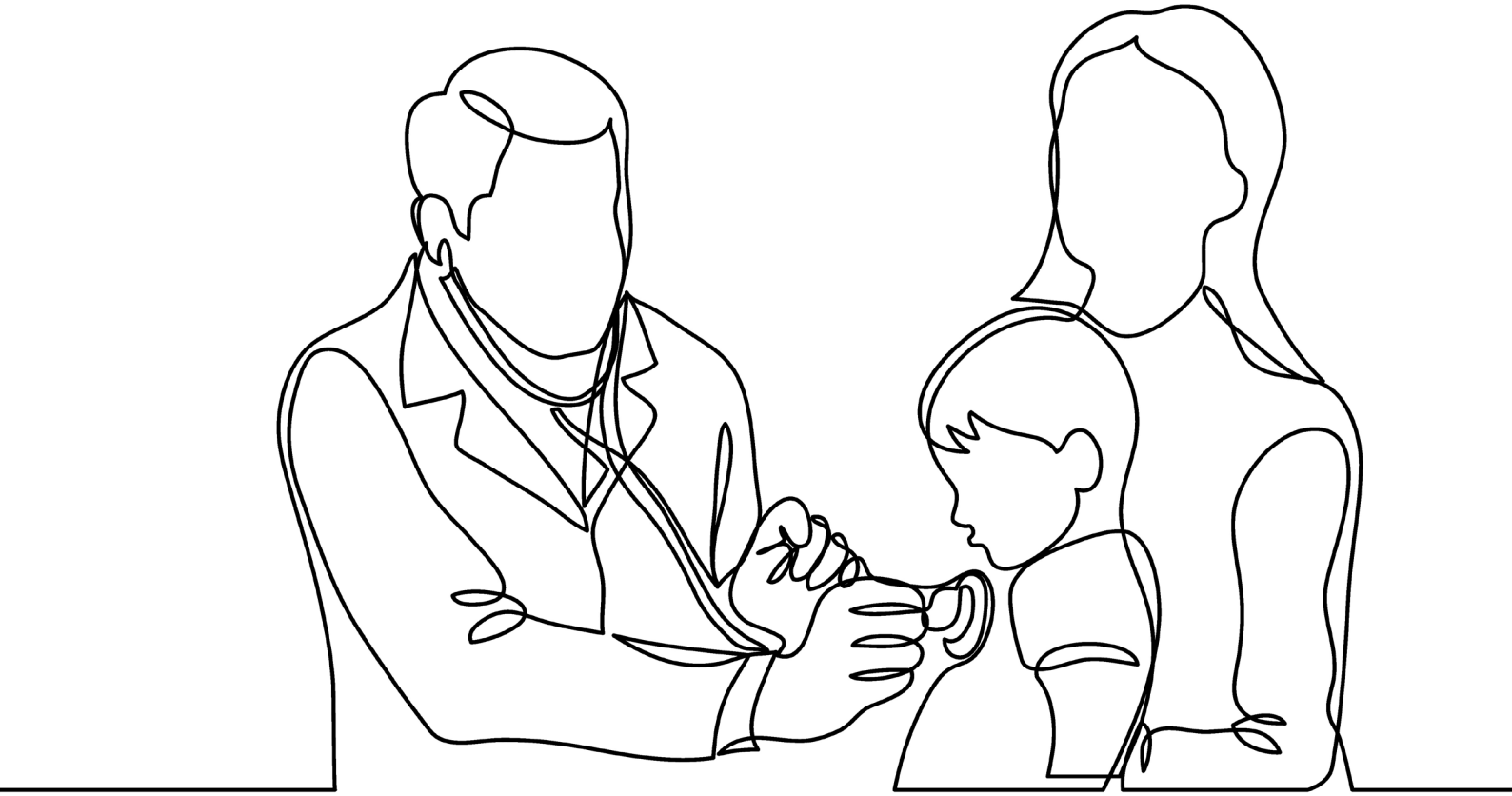
Source: Statista

In building upon existing literature, including the Rare Disease Framework, England, Northern Ireland and Wales' Action Plans, (those published at time of writing) and Genome UK; this report provides evidence-based and actionable recommendations which can feed into the work of the Department of Health and Social Care (DHSC), and the Devolved Administrations, as they review the Action Plans and their progress, over the coming months and years.

The subjects covered within this report are by no means reflective of the experience of every individual living, or caring for someone, with a rare disease; nor those who are healthcare professionals or decision-makers. However, this does build directly off of the contributions and lived experiences of all of those who participated across both the Patient and Advocate, and Stakeholder and Expert tracks. To those who shared their stories, experiences, insights, and opinions; thank you.

Chapter One

DIAGNOSIS



Collectively people living with rare diseases are numerous, however, in isolation numbers of people per rare condition can vary from tens of thousands to single digits. Many patients and patient advocates speak of the drawn-out diagnostic odyssey they face as they seek answers for complex multi-system conditions. As a result, patients and their families are forced to navigate the system at great personal, financial, and emotional cost.

Diagnosis can be described as the cornerstone of the patient's journey through the healthcare system. Until the point of diagnosis, many swing from appointment to appointment, specialist to specialist, hanging by a thin thread of hope that the next one will 'solve' what is 'wrong' with them. While the UK can boast of one of the most highly developed healthcare systems in the world, for those with rare conditions and diseases the system is disjointed. With a few exceptions, it doesn't function as well as it should.

The Rare Diseases Framework, England's Rare Diseases Action Plan, the Wales Rare Diseases Action Plan, and Northern Ireland's Rare Diseases Action Plan reflect a pan-national commitment from governments,[3] regional and national, and the NHS to address the disparities and failings within the system for those with rare diseases and allied conditions.[4] Diagnosis, and detection, are articulated as the first priority in all.

For many, the first point of contact with the healthcare system is normally with their local GP or community service. It is essential to recognise that the successful diagnosis of a rare disease or condition may involve many different professionals in the healthcare workforce. This can range from GPs, to nurses, to specialised clinicians, and beyond, everyone has a role to play in the patient's diagnostic odyssey.

The focus upon improving the system for those with rare diseases and conditions is evident, and over the last decade much progress has been made. However, with the introduction of the Genomic Medicine Service across England, and a renewed focus upon the newborn screening programme, including the consideration being given to whole genome sequencing (WGS) that is being piloted by Genomics England, it is time now to ensure that the potential of the system is maximised to improve care and outcomes for all patients with rare diseases and conditions.

"If you know what you have, you know what to expect. Even if you knew from before and there is no treatment available, at least you know how to deal with it and how to make their life (the patient's) more comfortable."
Prof. Dian Donnai, Consultant and Clinical Geneticist, Manchester Centre for Genomic Medicine

FIRST POINT OF CONTACT: PATIENTS AND THEIR PRACTITIONER

With more than 7,000 recognised conditions, a number which is ever-increasing, countless symptoms may indicate that an individual could have a rare disease or condition. For instance, SMA may present as a 'floppy' newborn or infant, with limited mobility. Bardet-Biedl syndrome (BBS) may present as delayed development of core motor skills, impaired speech and a constellation of other problems. Ehlers-Danlos syndromes (EDS), for which there are 13 subtypes, may present as joint hypermobility or dislocations, fatigue and fragile skin that breaks or bruises with ease.

Knowing what to look for, spotting the indicators of symptoms presenting themselves, is crucial. Participants in the Patient and Advocate Group spoke about incredibly negative experiences with their local GPs, describing instances in which symptoms and fears were dismissed, often labelled as simply an "anxious parent" or a "fussy child"; which can have long-term mental health implications upon patients and their families. It must be appreciated however, that every physician cannot understand every condition.

Before the Health and Social Care Committee, in March 2022, the average GP appointment was estimated as being around 12 minutes in length.[5] Using a traditional approach of looking for specific signs for specific conditions, little can be expected to be achieved in less than 15 minutes, especially when initial symptoms can present as multiple conditions. However, with four to five years being the average time frame in which to receive an accurate diagnosis,[6] the gap between 12 minutes and four years must be bridged.

Therefore, a pragmatic expectation from primary care and one that embraces the unique role that GPs play as generalists in the community, must be adopted. If we move away from expecting GPs to diagnose specific conditions or come up with a differential diagnosis but rather to suspect that a rare condition is afoot, arguably 15 minutes is long enough to make a big difference. Especially when they're provided guidance on rare disease (as a disease group) and triaging tools.

With the Covid-19 pandemic, the accumulation of a significant backlog, and long waiting lists, it is becoming more common for people to go to their GPs for repeat visits, which achieve very little. However, the GP may not know the particular patient in the required level of detail, so that is the first barrier faced by the patient. Additionally, the GP may not have the power to refer or if they do refer the referral may be rejected for instance by the speciality or at a review level put in place by the primary care network. There are a multitude of reasons why a patient presenting to a GP with signs and symptoms of a rare disease may not then receive adequate follow-up that lay outside of the individual GP's control. Without clear referral pathways for "possible rare condition" GPs are left without meaningful options for action.

> *"Parents are often being accused of fabricating illness in their child because their child (externally) looks fine."*
> **Dr Kay Julier, Managing Director, The Ehlers-Danlos Support UK**

The current set-up of the system is not optimised to ensure those with rare diseases, or symptoms presenting as such, are identified quickly. While addressing issues pertaining to education, awareness and engagement across the healthcare ecosystem and wider civil society will be further explored later in this paper, it is important to 'set the scene'.

WORK IN DEVELOPMENT - MEDICS4RAREDISEASES: RED FLAGS OF RARE DISEASE

Medics4RareDiseases carried out a study amongst rare disease patient groups to attempt to qualify how patients may present when they're on a diagnostic odyssey caused by a rare disease. It is important to remember that when looking back after diagnosis it can seem obvious that the patient had clues to their underlying condition on first presentation. However rare diseases often present initially with vague symptoms that then develop overtime. It is appropriate to rule out other, more common diagnoses, during the diagnostic workup. Therefore, time passing, with meaningful observation and review, can be an important part of the diagnostic process. The critical next step is ensuring that healthcare professionals are equipped to prevent that process from becoming an odyssey due to a lack of understanding about rare disease.

There are tools in the medical literature that suggest when to suspect rare genetic conditions e.g., FamilyGENES or specific conditions e.g., cherry red spot in Tay Sachs Disease. However, these often rely on clinicians already being open to suspect that when a rare condition. The Red Flags of Rare Disease is based on the significant findings from a survey that combined both qualitative and quantitative data about what the diagnostic odyssey looks like in 81 different conditions. The results paint a picture of how a person living with a rare condition might present as a whole and therefore when to be suspicious.

For example, their symptoms may have started years ago, in childhood, affecting multiple body systems which is evidenced by multi-specialist input. The family and patient may have experienced a downturn in their mental health as a result and suffered from difficulties in school or employment. And despite investigation there is still no convincing explanation for what the patient is experiencing, and problems have been refractory to intervention.

Using educational tools such as this one, alongside general rare disease education and existing clinical decision-making tools for both genetics and individual diseases has the potential to help healthcare professionals #daretothink rare and stop the diagnostic process from being an odyssey.

AT THE BACK OF THE QUEUE: THE IMPACT OF THE COVID-19 PANDEMIC

The notion of a fractured system is reinforced when considering the impact of the Covid-19 pandemic on the patient backlog. While this will not solely affect those with rare diseases and conditions, they are more likely to have been required to shield, and access to care will subsequently be inhibited. As rare diseases often require multi-disciplinary care, the accumulative impact could only be assumed to have been greater.

As recorded by the British Medical Association (BMA) in February 2020, prior to the pandemic around 4.43 million people were on a waiting list for care. As of January 2022, this number has increased to a record of over 6 million.[7]

The data shared in Raconteur's 'Rare Diseases' report, articulated that "if the referral is deemed urgent a patient can hope to be seen within 2 weeks" and "for non-urgent referrals, the waiting time will be closer to 18 weeks."[8] Research by The King's Fund, showed that by March 2022, over 300,000 patients waiting more than a year for routine planned care.[9]

The true impact to be suffered by those with rare diseases and conditions, both with and without a diagnosis, as a result of this is unknown. As the national dialogue predominately focuses on the addressing and reducing of the cancer backlog,[10] it must be ensured that rare diseases are not overlooked. This must be of paramount national importance.

"If you can do it for cancer, do it for rare diseases."
Dr Lucy McKay, CEO, M4RD

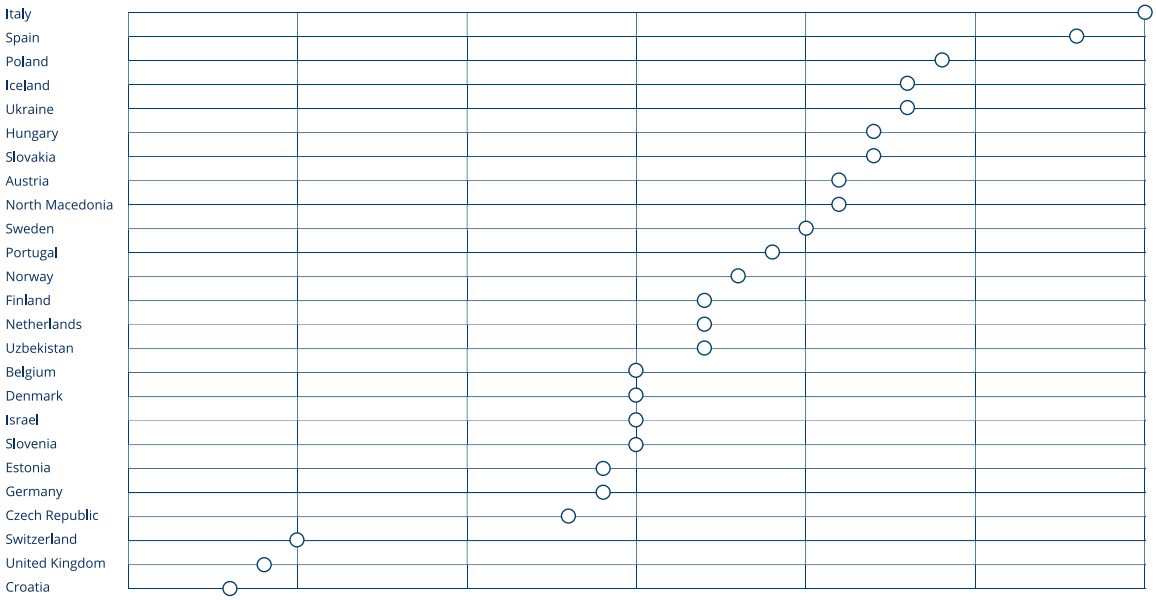
WHOLE GENOME SEQUENCING AND THE NEWBORN SCREENING PROGRAMME

Present conditions screened for in the heel prick test in the UK:

1. Sickle cell disease
2. Cystic fibrosis
3. Congenital hypothyroidism
4. Phenylketonuria
5. Medium-chain acyl-CoA dehydrogenase deficiency
6. Maple syrup urine disease
7. Isovaleric acidaemia
8. Glutaric aciduria type 1
9. Homocystinuria

While it may have one of the most developed healthcare eco-systems in the world, the UK currently falls outside of the top 20 European countries by number of conditions for which it screens for, with the heel prick test only screening of nine conditions. Presently, Italy leads by screening for 36 conditions.[11]

NUMBER OF RARE DISEASES SCREENED FOR IN SELECTED EUROPEAN COUNTRIES



Source: Int J Neonatal Screen. 2021 March 7 (1): 15

GEL's 'Newborn Genomes Programmes' explores the possibility of offering whole genome sequencing (WGS) to all newborns in England. An estimated 3000+ newborns per year could benefit from lifesaving or life-changing interventions as a result of WGS.[12] The GEL research programme runs until 2025 and aims to gather evidence to inform whether or not this technology could be incorporated into current newborn screening (NBS).[13] This holds the potential to present a solution to the diagnostic odyssey many are confronted with. The Programme aims to focus on actionable genetic conditions which may affect their health in early years.

For certain rapidly progressive neuromuscular disorders or immunodeficiency conditions, such as SMA Type 1 for example, "everyday counts"; and for many, knowledge is regarded as power; placing great emphasis upon the need and value to be derived from the NBS programme. In the case of SMA Type 1, the gene and cell therapy Zolgenzma,[14] which has the most benefit if administered before the child's second birthday, emphasises the importance of early diagnosis or being able to intervene before symptoms arise. This could also empower those impacted by such conditions through giving them time to familiarise themselves, to the best of their ability, with the condition, the potential treatments or long-term care requirements. Ensuring more are able to benefit ultimately from a timely diagnosis.

While early diagnosis presents the opportunity to parents to prepare for providing support for the child to live the best and most comfortable life possible in some cases, this should not be regarded as something that would be universally welcomed. In some case, for example, families have enjoyed the first few years of life without anxieties looming over them with regards to when symptoms may present and how they might do so.

Therefore, in reviewing the progress of the Newborn Genomes Programme, it could be worthwhile and potentially most beneficial to the patient and their family to screen for conditions which are apparent from birth, or soon after, rather than those for which symptoms do not present until a few years, if not later, into the child's life. It is crucial that GEL and other key stakeholders continue to consider this with appropriate consultation with patients, advocates, patient organisations and clinical experts.

It must also be considered, when the most appropriate time to introduce the concept of NBS and WGS may be. It could be argued that it would be of high value for health professionals to introduce parents to the concept of WGS and NBS during pre-natal appointments. This would create an approach which would share the responsibility and need for resources more fairly across the health-care ecosystem, rather than relying overtly on patient groups, clinical specialists and genetic counsellors. This would facilitate obtaining adequately informed consent at the appropriate time.[15]

CASE STUDY 1
GENOMICS ENGLAND: THE NEWBORN SCREENING PROGRAMME

Initiatives such as the 100,000 Genomes Project and the NHS Genomic Medicine Service have expanded access to genomic testing, including whole genome sequencing, and increased the potential of finding a diagnosis for families with rare conditions. There has also been growing recognition of the potential for technologies, including genome sequencing, to enhance newborn screening by identifying a larger number of rare conditions that may benefit children and their families.[16] Research indicates that nine children are born in the UK each day with a treatable genetic condition.[17] Identification of these conditions through genome sequencing therefore has the potential to reduce or avoid harm in early life.

Following a nationwide public dialogue in 2021, Genomics England, and NHS England and NHS Improvement, developed a vision for the Newborn Genomes Programme.[18] This research Programme is comprised of three parts:

Part 1: focuses on evaluating the utility and feasibility of using whole genome sequencing to screen for a larger number of childhood-onset rare genetic conditions than is currently looked for in the UK.

Part 2: aims to understand how babies' genomic and health data could be used for discovery research – with a focus on developing new treatments and diagnostics for NHS patients.

Part 3: explores the potential risks, benefits, and broader implications of storing a baby's genome over their lifetime.

Initial engagement with the public and experts have highlighted six emergent themes for the Programme to address:

1) Communicating the benefits, limitations, and unknowns of whole genome sequencing as a screening tool;

2) Co-developing principles for including conditions in the screening panel with relevant stakeholders;
3) Enabling person-centred consent across screening, research, and reanalysis;
4) Designing a supportive and inclusive experience for all families through the process of recruitment, and after receiving results;
5) Ensuring processes for data storage and use are trustworthy and future-proofed; and
6) Considering requirements for a sustainable and scalable programme for the NHS, should the evidence generated from the Programme support a future clinical service.

To develop the Programme, Genomics England is committed to being open and transparent, and engaging with stakeholders from a wide range of backgrounds including expectant parents, young people, families with rare conditions, healthcare professionals, and other experts. The Programme has established working groups which focus on conditions should be screened for; how the Programme should approach recruitment; ethics; education and training; and evaluation. In addition, the NHS Steering Group is supporting and monitoring the Programme through its development. Genomics England's in-house Participants' Panel, and Ethics Advisory Committee are also key to inputting into the development of the Programme.

The Newborn Genomes Programme is committed to embedding ethics in the design and delivery of the programme. This includes ensuring that ethical issues relating to consent, equity, data governance, and broader societal implications are carefully considered and addressed through meaningful engagement with the public and other stakeholders.

The Programme's ambition is that, by 2025, it will have:

- Sequenced the genomes of up to 100,000 newborns in the UK
- Established an evidence base on what the screening of those babies means for future treatment and research with newborns
- Begun to establish the data needed to evaluate the programme's outcomes, to inform future UK policy

BEYOND GENOMICS: A SOLUTION NOT THE SOLUTION

According to the NHS, "the sad truth is that babies and children are most likely to be affected by a rare disease with as many as 30 per cent [of those presenting with symptoms] dying before their fifth birthday."[19] While the introduction of WGS may begin to address this, it can only be foreseen that as a result of its widespread use the number of those with diagnosed conditions will gradually increase. It is thus essential that the workforce is prepared for the need for extra capacity, resource and learning to efficiently provide this service and suitable levels of care.

Doctors are taught "when you hear hoofbeats, think horses not zebras", and breaking away from this mindset is essential in identifying an individual who presents with symptoms of a rare condition. This idea and desire to provide better care for those with a rare condition, combined with scientific advancements has led to the plan to introduce WGS for newborns in England. However, if genetic testing alone was able to solve the diagnostic odyssey, the system would already be identifying and providing care for individuals much sooner.

For newborns with rare diseases, such as SMA Type 1, the first few days aften birth can be the difference between the ability to walk or not, or in some cases between life and death. Slow progress can therefore miss life-saving opportunities. If both tests and treatments are available, diagnosis should not be left up to 'chance' that a healthcare professional will pick it up within the first few weeks.

GEL's WGS research project will surely be a great advance, but it is an aside to the expressed needs of the community, that need to be actioned now. Newborn screening does not just consist of a blood test. The newborn and infant physical examination (NIPE) takes place at 72 hours and 6-8 weeks, in which data on heart, eyes and hips is collected. Audiology tests are also collected. These should feature in the review of strategies and Action Plans to improve speed of diagnosis. Owing to this, adding new conditions to the list of those screened for would not be complicated, especially if treatments for them exist.

> *"Only 80 per cent of rare diseases and conditions are genetic. Whole genome sequencing presents a tangible solution to the diagnostic odyssey for many. But genomics is not the panacea and we cannot forget this."*
> **Alastair Kent OBE, Independent Patient Advocate; Program Co-Chair**

Therefore, the Newborn Screening Project presents a solution but not the solution. This is especially key when taking into consideration the impact of the Covid-19 pandemic, which has resulted in many children not being seen by a healthcare professional in almost three years.[20] It is difficult to assert how many will require specialised consultations and treatments if children have been unable to access more basic and routine health consultations for so long.

Lastly, it will be essential to determine a shared understanding of what is implied by WGS. It is crucial that it is not just a headline that seemingly offers more than it actually can deliver. Hence, the limitations of newborn screening must be clearly articulated. The public must understand that the integration of WGS and NBS is not going to test every single sequenced gene, it will only target specific ones. The potential future use of the collected data must also be a core part of the discussion to harness public trust. Bridging this knowledge gap is essential.

THE ROLE OF DATA IN SUPPORTING DIAGNOSIS

It must be acknowledged that there are many patient and community groups for which the healthcare system, and beyond, does not yet have sufficient data to provide the necessary insights. The lack of data in the UK equates to a whole set of people who will not, as a result, benefit from current developments. The benefits will not be equitably reaped if sections of the population are not accounted for from the outset. This must be rectified. Providing access to international datasets could therefore play a crucial role in attempting to fill such gaps. This is where technologies such as Artificial Intelligence (AI) could play a role, if deployed in the right manner.

The need to learn from not just what is going on in the devolved administrations but also from overseas is essential. The European 'Screen4Care' pilot is one example, which is working on linking WGS and AI to spot and help highlight indicators that will enable an early diagnosis and also provide guidance for next steps after this has been undertaken.[21]

While it is evident in England's Action Plan that there is a commitment to investing further in technologies to enable and support faster diagnosis, any potential benefits are unlikely to be fully realised if the lack of suitable data is not addressed. If the data does not reflect those the technology is deployed for, its usage will be uneven across the patient community. Investment in rare diseases cannot result in an unintended exacerbation of health inequalities without this safeguard being in place.

THE FUTURE OF THE FOUR-NATION APPROACH

Genomics, NBS, WGS, data and the Covid-19 backlog have all been identified and addressed as key factors which impact the diagnosis of patients with rare diseases and conditions. A conscious effort has been made to ensure the nation-specific action plans, which are presently being developed, reflect a delicate balancing of the health and care needs of those with rare diseases and conditions in each nation and the Government's commitment to avoiding health disparities between nations.

The UK Rare Disease Framework Board was assembled to address concerns regarding such disparities and the 'post-code lottery' many have experienced between and within nations. A commitment to ensuring the devolved administrations are represented throughout the development of Government led policies and strategies is evident. Nonetheless, more could be done.

While the commitment is evident to coordinate the approaches across the four nations, ensuring they are as aligned as possible where needed. As reflected by the action plans published at the time of writing, the approaches adopted reflect a clear difference in priorities. Across the four nations, the approach must strive to support those with rare diseases and conditions as they venture through the health service, irrespective of where they do so. For instance, Northern Ireland's Rare Disease Action Plan 2022/2023 articulates Action Points which are not recognised within England's equivalent plan.[22] While it must be appreciated that the regional priorities will change across the four nations, the differences in priorities between England and Northern Ireland's [NI] plans alone highlight the need for a more coordinated UK wide approach.

> *"While some action points will be specific to a nation there are also actions that could be adopted across all for nations as a UK-wide standard, that could then be measured to ensure the plans are truly delivering equitable change. And if not, we can analyse why not."*
> **Dr Lucy McKay, CEO, M4RD**

BEYOND DIAGNOSIS: NOT A SINGULAR FIX

Addressing diagnosis in isolation will not fix issues regarding equity of care. While it is essential, ultimately a rapid diagnosis is not enough on its own. Patients need to be supported throughout the journey and beyond. It is therefore crucial to consider that within the NHS, currently, the continuity of care can be very disjointed or even non-existent. Patients are seen by various professionals in different locations and, sometimes, even for the same issue.

Minimising the diagnostic odyssey experienced by patients, and their families, will not solely benefit them. Research conducted by Imperial College Health Partners (ICHP) in 2018 revealed that during the diagnosis period, patients "have cost NHS England in excess of £3.4 billion" over the last 10 years.[23] While it is beyond the remit of this white paper to evaluate the Government's funding and

spending into health research, successfully addressing the diagnostic odyssey would reduce such excess in spending, enabling that funding to be redirected towards other research supporting those with rare diseases and conditions.

Therefore, to prevent patients being forced to navigate the system, processes need to be put in place to provide a more holistic understanding of the patient and their health and needs. This then leads into issues surrounding lifelong care and the situation where many individuals become lost in the system at the point of transition between childhood to adulthood care. This will be addressed in an appropriate amount of detail in a later Chapter of this paper.

CASE STUDY 2 - PERKINELMER

PerkinElmer's pharma sponsored program is a good example of how we are enabling access to diagnostic services to those that needs it at no cost to the patient. The pharmaceutical company is paying for the cost of testing. One example is the Latern Project. The Lantern Project aims to change that by providing a no-cost testing program for patients in the United States who suffer from specific types of lysosomal storage disorders (LSDs). Physicians will be able to use the Lantern Project to arrange for biochemical enzyme testing of certain suspected LSDs as well as confirmatory DNA testing (single gene and gene panels) and phlebotomy services for their patients.

Launched by Sanofi Genzyme with PerkinElmer Genomics, The Lantern Project will assist patients whom physicians suspect may be suffering from Gaucher disease, Fabry disease, Pompe disease, mucopolysaccharidosis type I (MPS I), or acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick disease types A and B.

Several leading genomics companies and laboratories, including Illumina, Fulgent Genetics, Invitae, GeneDx, and PerkinElmer Genomics, have formed the CardioGenomic Testing Alliance (CGTA), a collaborative group aimed at raising awareness and utilization of genomic testing in cardiology. CGTA seeks to educate healthcare providers and other stakeholders about the value of such testing to assure adherence to existing guidelines from professional medical societies, to inform medical management and cascade testing, and to improve clinical outcomes.

According to the American Heart Association, "genetic testing is informative and useful for the clinical management of various inherited cardiovascular diseases such as cardiomyopathies, arrhythmic disorders, thoracic aortic aneurysms and dissections, and familial hypercholesterolemia."

PerkinElmer collaborates with patient groups for example in Facioscapulohumeral Muscular Dystrophy (FSHD) testing where we lead globally to offer advance testing for this rare disease. We work to provide support to FSHD society and provide not only access to PerkinElmer Genomics FSHD testing but also educational and scientific support.

The Neuromuscular Disease Foundation (NDF) – the world's leading non-profit organization focused on the rare genetic disease called GNE Myopathy (GNEM, also known as HIBM) is

currently collaborating with PerkinElmer for Whole Genome Sequencing (WGS) paired with metabolomics for analysis of 100 samples.

This WGS project will help us better understand the molecular pathways for this rare genetic muscle disease, and lead to finding effective therapies for GNEM.

Recommendations

Recommendation 1: As the Genomic Medicine Service is rolled out it is essential that healthcare professionals, including the anti-natal and neo-natal workforce, be informed on the impact this may have on newborns and those exhibiting symptoms. This is to ensure expecting mothers and new parents, are provided with appropriate time to familiarise themselves with the service and potential options available to them.

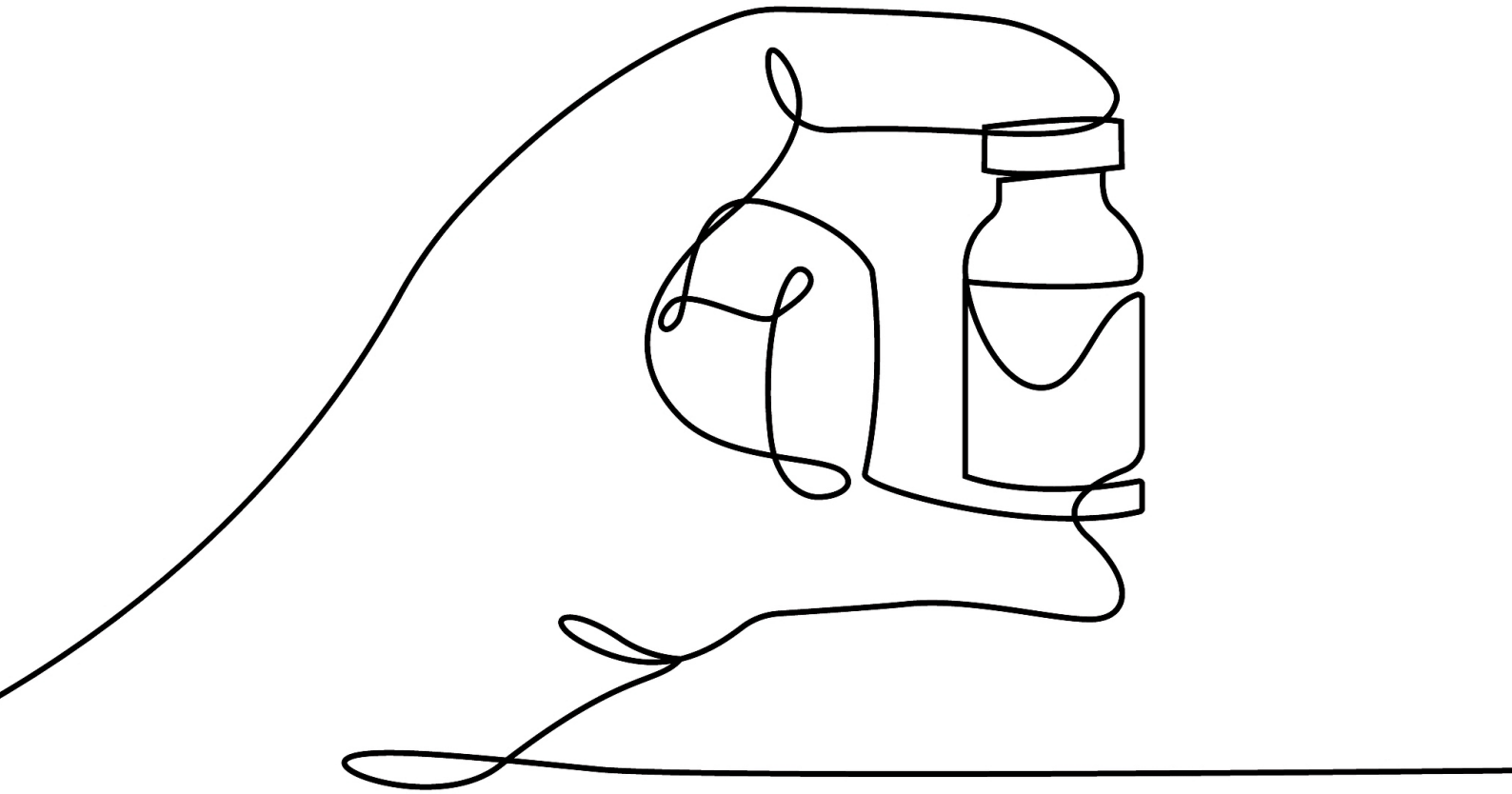
Recommendation 2: While the Newborn Screening Programme aims to focus on including actionable genetic conditions which may affect their health in early years. It is essential that, once implemented, this be periodically reviewed to ensure the system is flexible enough to accommodate conditions for which new treatments are later developed and approved.

Recommendation 3: The list of conditions currently screened for, using the heel-prick test, should be expanded by the National Screening Committee to include those such as Spinal Muscular Atrophy (SMA) Type 1, for which a gene therapy exists. This should occur in addition to the ongoing Newborn Screening Programme. It should be a commitment that this aim be met before the completion of the Newborn Screening Programme, run by Genomics England (GEL), in 2025.

Recommendation 4: Whole Genome Sequencing (WGS) in newborns may result in a potential 3000 more patients entering the healthcare system every year. It is essential that in ongoing consultations the system be prepared to absorb those diagnosed. The implications upon clinical services to respond and develop timely care plans must be considered, to ensure newly diagnosed patients and families to not end up on disproportionally long waiting lists.

Chapter Two

CLINICAL DEVELOPMENT



Rare diseases and conditions are, by nature, complex; and providing access to safe, high-quality specialised care, condition specific management, treatment and support is essential. Benefitting from such access can present many challenges to both the patient and their family. These can include travel, cost, time away from work, accessibility, and the need to plan for other family members amongst others.

It is essential that patients have access to expertise in the management or treatment of their disease or condition. As highlighted by the Rare Disease Framework, it is crucial that "there are opportunities to develop innovative models of care across the healthcare system so that patients have their care delivered as locally as possible."[24] These must combine the benefit derived from specialist oversight as well as local clinical support.

Presently only about five per cent of rare diseases and conditions have an approved treatment, which is an estimated 400 of the 7000 which are currently identified. At this rate, it will take an estimated 2000 years until treatments are available for all rare diseases and conditions.[25] Clinical development plays a core role in the provision of access to specialist care, treatments and drugs for patients living with rare diseases and conditions. This is precisely articulated under 'priority 4' of both the UK Rare Diseases Framework and England's Rare Diseases Action Plan.[26]

While Wales Gene Park have begun to establish dedicated clinics for undiagnosed patients through a SWAN UK (Symptoms Without a Name) pilot;[27] for the majority of patients or those living with unnamed or undiagnosed conditions, established clinical care pathways do not exist. Patients can be treated symptomatically, but this can result in their care being siloed across the health care system, leaving them and their families feeling as though they are 'bouncing around'. Combined with the estimation that the average rare disease patient receives at least three misdiagnoses;[28] this can render living with, and managing, a rare disease or condition incredibly taxing for the patient and also for their family. This impacts on their physical wellbeing, and also, in many instances on their mental health.

The development of specialist care, and necessary treatments and drugs lies at the heart of what was articulated in Chapter One of this report as the Government's commitment to creating a thriving life sciences sector within the UK. The second chapter of this report will therefore focus on how a strategic approach to clinical development is constructed.

Over 7,000 plus conditions have been identified to date, but very few possess established treatments. The development of treatments is complex and time consuming, and owing to the time, resources and cost that goes into the clinical research, may result in high costing drugs and treatments. Such as, for example, the £1.7 million price tag (prior to the confidential deal between NHS England and the manufacturer) on the innovative gene therapy,[29] Zolgensma, developed for those with SMA Type 1, which made national news headlines in summer 2021.[30]

Once developed however, the assessment of, and access to, such medicines can bring to surface further challenges due to the limited data pool available and allocated resources within the NHS. Though some of these challenges reflect, and are the result of, the access criteria that by default have to be met to optimise the clinical utility and safety of a treatment, to be approved by NICE for NHS patients.

While the vision, articulated by both the Rare Disease Framework and England's Rare Disease Action Plan, "is for rare disease patients to have improved access to specialist care, treatments and drug", the road to delivering such a vision is a turbulent one.[31] The provision of rapid access to drugs and treatment may be revolutionary for some patients, however, this won't be the case for all, especially when some may spend months, if not longer involved in clinical trials which do not result in the development of a novel therapy.

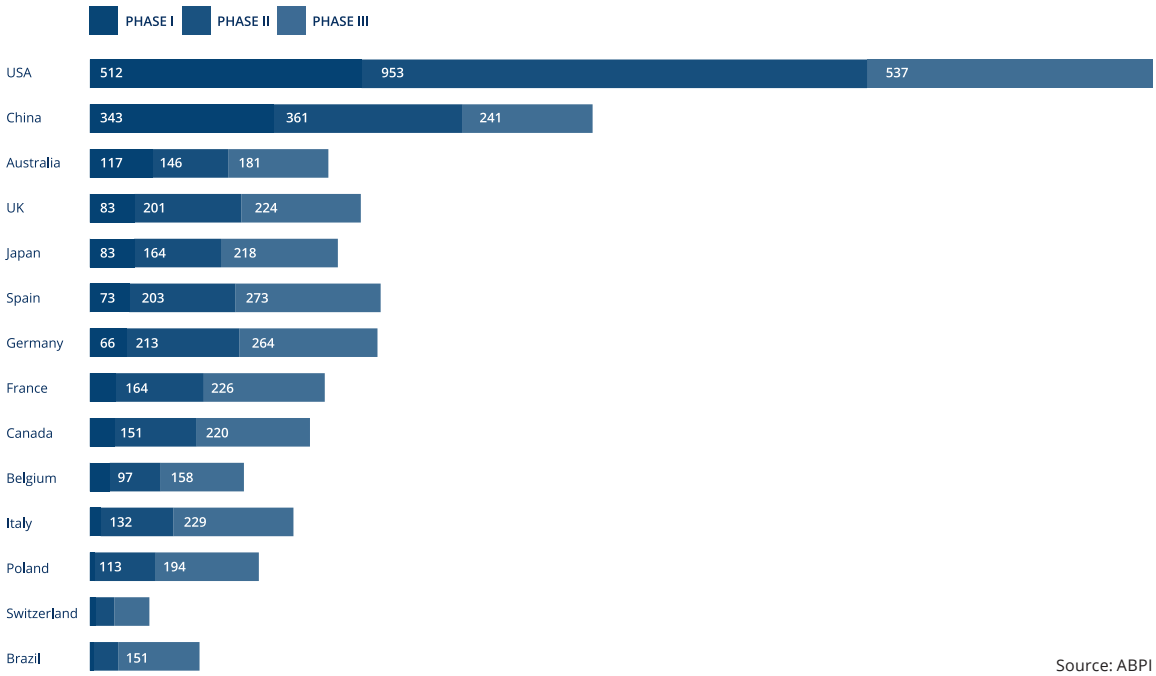
SETTING THE SCENE: THE CLINICAL RESEARCH AND DEVELOPMENT LANDSCAPE IN THE UK

Innovation lies at the heart of improving the delivery of care to patients and those living with rare diseases and conditions. The ambition has been set for the UK to become the destination of choice for such innovation. This is one of the core messages detailed in the Life Sciences Vision, and frequently reinforced by George Freeman MP, Minster for Science, Research and Innovation. However, it must be ensured that the health service has the capacity to undertake and deliver such clinical innovation, through research and trials.

Despite the UK boasting of world leading clinicians and researchers and leading the development of many unique interventions, as detailed by the calibre of participants in this report, it is lagging behind other nations in truly becoming the ideal destination for clinical research. As detailed by the below chart, the UK falls behind both European and global competitors in the number of trials ongoing.

While this data, provided by the Association of the British Pharmaceutical Industry (ABPI),[32] outlines a pre-Covid 19 and non-rare disease specific research landscape, it can only be assumed that the pandemic hindered further development of trials and research. As research practices begin to return to their previous rates, it is essential that the Government weave the conduct of clinical research into the heart of the health service. The Health and Social Care Act 2022, for instance,[33] presents the ideal opportunity for this to be realised.

GLOBAL RANKINGS - NUMBER OF CLINICAL TRIALS INITIATED IN 2020 BY COUNTRY BY PHASE



Source: ABPI

THE ROLE OF PATIENTS, PATIENT REPRESENTATIVES AND PATIENT GROUPS

Providing access to necessary and high-quality specialist care, treatment or drugs, plays a defining role in managing a patient's rare disease or condition. Monitoring the extent to which this impacts their quality of life is essential if resources are to be used efficiently. However, as articulated above, disease modifying treatments are missing for 95 per cent of conditions. The continuation, investment in, and promotion of clinical development is therefore essential and is dependent upon clinical research and trials.

Building upon the exploration of the benefits awarded by early diagnosis in Chapter One, a diagnosis opens the door for the patient and their family to engage with the rare disease and condition community, and as a result, with relevant patient and support groups. Through such engagement, awareness regarding ongoing clinical trials and research is increased. Consider for example, Duchenne Muscular Dystrophy's Clinical Trial Finder.[34]

"What we have found that has been really helpful is that we invite the clinical researchers into our patient annual workshops and conference and very often we have also gone into the laboratories. For example, some have gone to Bonn in Germany where they have got a major centre, then very often the BBS patients will go in and meet the researchers. The feedback we get from the researchers is that they find that incredibly helpful because it brings real meaning to the work that they are doing on a day-to-day basis when they can see the impact their research is having and how much it means to the patient community."
Margarita Sweeney-Baird BEM, Founder and Chair, Inclusive Skating; [Former] Trustee, Bardet Biedl Syndrome UK

The role of patient groups and organisations must not be overlooked. While this will not be applicable to all groups and organisations, many have played a crucial role in building data sets, finding patients for trials, and bridging the gap between patients, and their families, and the clinicians regarding how trials will operate.

Our discussions served to shine a light upon the role patient groups wish to adopt in order to ensure the needs of the patients are at the heart of all clinical developments. These include participating from the outset in trial design and developing the eligibility and inclusion criteria. Developing trials and clinical research through one singular perspective is not enough, and often overlooks key needs of those involved. It is thus crucial that a methodological triangulation approach (using more than one kind of method to study a phenomenon) is adopted. This further supports the early scoping workshops conducted by the National Institute for Health and Care Excellence (NICE) in which patients and patient advocacy groups are included from the outset.

This would enable the perspectives of the patients, clinicians and external bodies, such as Medical and Healthcare products Regulatory Agency (MHRA) or NICE, to support in the development and running of trials and research. Involving patients, patient representatives and patient organisations in research is essential. It is crucial this is done from an early a stage to maximise the advice and unique insight they can provide. This will serve to ensure that the ratio of potential benefits, the limiting of the burden of trial participation, and the measurement of derived outcomes are maximised.

Building upon the experience of conducting clinical research during the Covid-19 pandemic, we have seen renewed commitments to "increase diversity and patient involvement" as well as to update the "national legislation and associated guidance", to ensure any learnings are evaluated and incorporated in the future.[35] It is thus essential, that in order for such commitments to be achieved, the above considerations are directly addressed.

THE ROLE AND VALUE OF HEALTH TECHNOLOGY ASSESSMENT

The debate regarding whether the role played by health technology assessment (HTA) organisations results in higher quality delivery of care for patients and those living with rare diseases and conditions is not a new one. In 2019 for example, before the House of Commons, Liz Twist MP spoke regarding the felt and experienced shortcomings of the NICE appraisal processes upon those with rare diseases and conditions.[36] In 2017, almost 200 rare disease patient groups and organisations came together to call on NICE and NHS England (NHSE) to revaluate the cost-effectiveness threshold for drugs and new medicines for rare diseases and conditions.[37]

"My constituent Archie McGovern is 12 years old. He is bright and lively, and full of beans now, but it has not always been like that way because Archie has PKU— phenylketonuria. Putting it simply, PKU is a genetic condition that means Archie and others are unable to handle phenylalanine, which is found in protein—so no meat, no fish and no dairy products. There is a whole range of other things that we would not think had protein in them: the list is endless. On top of that, he has to take a protein substitute drink—if we can call it that, as it is very unpleasant—to keep the balance right.

At present PKU is not curable, and a hugely restrictive diet is the only way of controlling the condition throughout childhood and adult life. The condition is picked up by the pinprick test at birth, and for those identified as having PKU that is the start of a difficult lifetime of dietary control. For children that is especially difficult, but it is also very important because failure to control the condition can lead to serious neurological problems.

That is how it was for Archie until quite recently, but there is a treatment that can help to control PKU. It is called Kuvan, and although it was licensed 10 years ago and is widely available in many countries in Europe, and further afield, it is not available to patients in the UK. Not everyone with PKU responds to Kuvan, but it is believed that more than 20% of people will respond well and see a significant improvement in their life."
Liz Twist MP

While it is not the purpose of this paper to evaluate the role of bodies such as NICE, it is essential to consider the role they play under 'priority 4' of both the UK Rare Diseases Framework and England's Rare Diseases Action Plan.[38] For many conditions the patient pool is small. As a result, drugs and new medicines can be of considerably higher cost than those for more common conditions, which will most likely fall upon the health service.

Nonetheless, the role of such bodies must be considered as the methods and frameworks used to evaluate new drugs and medicines are observed internationally. Therefore, the UK's regulatory regime will have a wider impact – beyond the patients and those living with rare diseases and conditions – on how the UK's investment in medicines, and by association research and development (R&D), are viewed internationally.[39]

For example, in January 2022 NICE published the review into their health technology evaluation.[40] While the publication represents a significant milestone in working towards improving patient access to new medicines, drugs and health technologies, it received mixed responses. Consider for instance, responses from the BioIndustry Association (BIA) and the Association of the British Pharmaceutical Industry (ABPI), regarding the review as failing to deliver on the promise of a more ambitious review.[41]

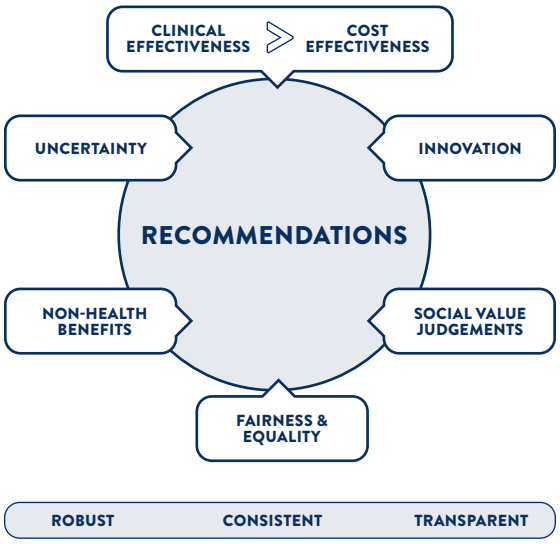
WHAT IS NICE?

- An independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health
- Aims:
  - To reduce inequalities and variation
  - To ensure quality and value for money for the NHS in England

CORE PRINCIPLES OF NICE AND GUIDANCE DEVELOPMENT

- Based on the best available evidence
- Expert input
- Patient & carer involvement
- Independent advisory Committees
- Consultation
- Regular review
- Open & transparent process
- Social values and equity considerations

APPRAISING THE EVIDENCE – STRUCTURED DECISIONMAKING



SO, WHAT FOR RARE DISEASES

A broad package of support for rare diseases

- earlier access to valuable new innovative treatments
- more equitable access for people with severe diseases that can also be rare
- Revised HST topic routing criteria - provide clarity and efficacy in routing decisions
- improved ability to embrace the full evidence base and new data sources
- increased clarity, predictability and transparency into how we develop guidance and decision-making approaches
- an approach for continuous improvements in methods and process developments to support innovation.

Source: NICE

"I think there is willingness there and a greater degree of integration than has perhaps traditionally been the case between MHRA and NICE in the rare disease field because historically the rare disease interaction would have been with the EMA than the National competent authority, let's push the envelope and see how far we can take it."
Alastair Kent OBE, Independent Patient Advocate; Project Co-Chair

Our discussions highlighted the key questions and principles regulatory bodies such as NICE aim to address when evaluating new technologies. Does the technology work? And how? How good is it for patients? And how much is it going to cost the NHS? Thus, combining the needs of those across the whole health care ecosystem rather than those of only one stakeholder.

While the clinicians present at the roundtables spoke positively of their experiences with regulatory bodies, commending them for their openness, transparency and flexibility; the same sentiment was not shared with the same levels of enthusiasm amongst the patient and advocate group. To bridge the gap between them consideration should be awarded to creating a patient liaison or officer role within regulatory bodies, who serves as the vehicle through which communications and information are fed between the regulator and the patient groups.

Building upon these shared positive experiences, many reflected upon the lessons extrapolated form the Covid-19 pandemic. Many of these could bring substantial benefit if applied in the rare diseases space. For example, researchers and clinicians mobilised on a great scale and at pace. Consequently, trials were turned around very quickly, and many of the 'barriers' to adoption were removed.[42] This should embolden policy and decision makers to ensure such learning is not lost. It will therefore be essential for regulatory bodies and the NHS to reflect upon the lessons learned from the Covid-19 pandemic to work with industry, patient organisations and other stakeholders to minimise the time between medicines and drugs being discovered and reaching the patient.

ROCKING THE BOAT: THE IMPACT OF COVID-19

The Covid-19 pandemic, while unprecedented, served to shine a light upon the levels of inequality within the health care service; when resource had to be pulled en-masse from specialist areas, to resource the NHS' and nation's response. Rare disease clinicians, nurses, specialists etc. were re-deployed from their departments to support the 'front-line'. While indisputably necessary, the domino effect suffered by patients and those living with rare diseases and conditions will be felt for some time to come.

> *"As you can see with the vaccine programme that we have all had the benefits of in relation to Covid, that a huge part of that was the government being willing to invest in some innovative technologies. It is really just the same issue you have got with the rare disease community, so the community bring information together and being willing to support trials, and also being prepared to wait your turn as well is really important."*
> **Margarita Sweeney-Baird BEM, Founder and Chair, Inclusive Skating; [Former] Trustee, Bardet Biedl Syndrome UK**

Travel restrictions, shielding and isolation for the Clinically Extremely Vulnerable (CEV) RD patients, safety considerations, trial design, and the repurposing of rare disease trial-sites, amongst other changes, significantly increased the number of challenges posed when living with a rare disease or condition. The disruption caused by the Covid-19 pandemic created a knock-on effect which not only delayed the majority of the delivery of care, the conduct of trials, and the potential development of therapeutics and drugs, despite willingness, on behalf of patients and clinicians to not lose momentum, it also impacted on the number of people diagnosed.[43] Much of the post-Covid debate at present focuses upon the cancer backlog, while this is of crucial importance, this must not be allowed to eclipse the rare disease backlog.

CASE STUDY 3 - QUEEN'S UNIVERSITY BELFAST: IMPACCT, COCOON, SHIELDING, AND CHARITY STUDIES

Our research demonstrated that access to information and support for individuals living and working with rare diseases across the UK and Ireland is inadequate. More than 110,000 people across Northern Ireland are affected by a rare disease; the average time to receive an accurate rare disease diagnosis is five years, with half of patients receiving at least one misdiagnosis. Many rare diseases are severely life limiting and/or often associated with complex care needs. Many families live with more than one rare disease and/or have multiple family members affected by the same rare disease. More than one-third of rare disease patients also provide care for other people they live with, providing additional challenges for clinically vulnerable individuals.

The Covid-19 pandemic was declared on 12th March 2020 as an unprecedented global public health emergency. We conducted research over the past two years, including our IMPaCCT, COCOON, Shielding, and Charity studies, with input from >3,000 individuals, to provide robust evidence describing the disruptive impact of the Covid-19 pandemic for diagnosing, treating, and communicating with patients diagnosed with a rare disease and their caregivers. "My whole world has been completely changed" [P23].

There is a significant and sustained lack of support for caregivers of a person with a rare disease and often very complex care needs. Rare disease patients and their caregivers reported high levels of stress or anxiety (72 per cent), physical exhaustion (54 per cent), and increased social isolation (94 per cent), which was dramatically exacerbated by the Covid-19 pandemic. Quality of life questionnaires confirmed rare disease patients and their caregivers experienced more negative impacts compared to population norms. Sixty-six percent described a negative impact of the Covid-19 pandemic on their health; 84 per cent on mental health. "It's worsened my health physically and mentally. Struggling to deal and cope with everything. It's hard to manage when you lose all you are dependent on" [P57]

A major negative impact across the UK, Ireland and Canada was significant restrictions on domiciliary care and specialist support provided in schools with reported 50 per cent reduction in physical or occupational therapy services, >60 per cent reduction in nursing care, and 25 per cent reduction in respiratory therapy services. Many schools were closed with respite services unavailable. The burden on family carers has been unparalleled; many parents became responsible for their child's care 24 hours a day, seven days a week without their usual support structures. "I love my child, but there is no break – 24/7 with schools and respite facilities closed" [P1,856]. Half of participants did not have access to infection control advice or relevant health and safely protocols to help manage their disease; more than half of patients refused much needed homecare support due to concerns about inappropriate personal protective equipment or unsafe practices from care providers. "I was terrified" [P4]; "We cancelled Trust supplied carers as they were not washing hands, pulling gloves from a full pocket, said they were reusing masks in multiple homes, shops etc" [P18]. Many parents were concerned about who cared for their vulnerable child with complex needs if they caught Covid-19.

Shielding guidelines were introduced for many people living with a rare disease, but >70 per cent of participants found these confusing. The rapid changes in advice during the pandemic have been particularly challenging for rare disease communities. “I just continued what I was doing but it became more stressful with no breaks or relief… It has been exhausting” [P2107]; “Don’t leave house now, see no one, no work, no contact with anyone except a disabled son who is unable to communicate in any way. Feel very lonely” [P981]. Eighty percent believe personalised, specialist and hospital-based information focused on each patient’s current risk of contracting Covid-19, the effect on their rare disease, and availability of relevant therapies for more vulnerable individuals would reduce stress and anxiety.

While advances in digital healthcare such as telemedicine and videoconferencing, with patients often submitting readings from medical devices at home, were significantly enabled during the pandemic, the majority of families (84 per cent) described major negative impacts from cancelled appointments, delayed tests and treatment, and lack of face-to-face evaluation with general practitioners or specialists. Participants described managing their own condition without professional support and not having access to some medications. “We depend on regular medication reviews that are not happening. Specialist drugs were impossible to get” [P9]. Patients expressed concern over longer-term impacts of the Covid-19 pandemic on the health service and were also worried about the deterioration of their health due to reduced medical care. Rare disease clinical trials were cancelled, with patients reporting concerns that their inability to participate in the trial may have more impact on their quality and duration of life than being diagnosed with Covid-19.

Charities supporting people with a rare disease were also impacted by the pandemic, which necessitated changes to their operations and service provision. Many charities experienced more than doubling of calls for support; recurrent concerns included shielding advice and help with reduced access to medical care. Several groups experienced significant financial challenges with reduced fundraising and limited or no government support meaning many activities such as critical support for members and provision of research funding was stopped.

Restrictions associated with the Covid-19 pandemic have exacerbated long-established challenges faced by the rare disease community and created new issues that will have long-lasting effects. Emerging opportunities for better access to specialist services, more convenient/virtual access to clinical research, improved digital health strategies alongside new information and communication tools could make major differences to the lives of people living with rare disease(s). There is an urgent need to codevelop and implement innovative strategies to support rare disease communities during the pandemic and for long-term future practice.

If it can be done for cancer, do it for rare disease

The held discussions explored lessons and learning derived from the Action for Rare Disease Empowerment (ARDEnt) 2021 report, ‘Making the Unseen Seen: Rare disease and the lessons learned from the COVID-19 pandemic’.[44] This reflected upon the impact suffered by patients and individuals

living with rare diseases and conditions and in some cases, found the only UK based trial for their condition be indefinitely paused or shut-down.

It must be ensured that the lost momentum in rare disease clinical research as a result of the Covid-19 pandemic is minimised as much as possible, it is essential that the Government's and NHS's addressing of the Covid-19 backlog, does not continue to disproportionately impact the rare disease and conditions community. While the Government, DHSC and the Secretary of State for Health and Social Care the Rt Hon Sajid Javid MP,[45] have launched the 10-year 'national war on cancer' through the 10-year cancer plan,[46] the same attention should be awarded more publicly to the rare disease patient communities.

The silver lining

Despite its role in increasing the difficulties faced by those living with rare diseases and conditions, the Covid-19 pandemic has forced some changes in approach which hold the potential to greatly benefit the rare disease community in the future.

The pandemic saw an unprecedented uptake of remote patient monitoring. This not only served to protect the patient and their family during the peak of the pandemic, but it also served to address many of the aspects of rare disease and condition care and management which had, until then, been accepted as part of the process. Travelling to appointments, for instance, used to be routine for many of the patients and advocates participating in the discussions. While face to face consultations will remain essential for many aspects of the management of rare conditions, the pandemic introduced virtual alternatives, including patient-clinician consultations via video link, telemonitoring, test procedures performed by home visit nurses and an uptake in wearable devices, into the mix.[47]

While the Covid-19 pandemic will not be remembered as a period of positive impact upon the health and social care service, it forced the breaking and reshaping of the mould to better adapt to the circumstances beyond previously accepted protocols. As services continue to emerge from the depths of the pandemic and begin to readjust, it will be essential that they do not return to old models of working. Rather, they should continue to operate with similar levels of flexibility as those experienced during the Covid-19 pandemic to ensure distance from a specialist centre, for example, is not an inhibitor to the delivery of care to a patient or individual living with a rare disease or condition. It is positive that this is articulated under Action 10 of England's Rare Disease Action Plan.

> *"Following the discussion around the Covid-19 pandemic there are clearly some lessons to be learned about what we could do in the future based upon our experience of having run trials on scale. One of the key points that was made was around accessibility. We can and should maintain this as a priority."*
> **Dr Shehla Mohammed, Consultant and Paediatric Clinical Geneticist, Guy's and St Thomas' NHS Foundation Trust; Project Co-Chair**

THE NEED FOR GREATER DATA COLLECTION

More data is now being collected about our health than ever before. Health data is being used for research aids in the deepening of understanding diseases and conditions, their causes and symptoms, the number of people affected, and the manner in which they are impacted.[48] This data can ultimately play a role in improving diagnosis, developing better care, treatments and therapeutics, and improve our understanding of new or ultra-rare conditions. Data therefore is essential in helping to drive innovation for rare diseases and conditions.

Collecting data on rare diseases and conditions however is not without its challenges. Patients 'bouncing' around the health service, fragmented systems, and the diagnostic odyssey, all act as barriers in rendering the collection of rare disease data more challenging. This is made harder because of the number of conditions presently identified, and the small patient communities for many of these.

> *"You need to understand what your population is so if you have not registered and recorded it, where do you start?"*
> **Tony Thornburn OBE, Chair, Behçet's UK**

Patient registries

Throughout our discussions, the idea of patient registries was met with mixed responses by both by the patient and advocate group and the stakeholder and expert panel. While some felt they were essential if we are to gain a deeper understanding of population size for rare diseases and conditions, who should hold responsibility for the ownership and regular updating of registries was a matter for debate.

The existing examples of the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) and RedCap (virtual Clinical Registries) registries were both positively received. However, questions were raised regarding the resource available and time commitments required to keep them updated to a level that benefits both the patient community and is of most use to clinicians and specialists. In the instance of patient charities and organisations, the potential burden of extra cost associated to registries, which may be unfeasible, must be considered.

It would add great pressure on many patient and condition support groups if the onus were to be placed on them, especially considering the substantial differences in organisation size and funding potentially available to support such efforts. Therefore, while patient registries could play a crucial role in providing greater contextual information on patient and condition communities, establishing who will support their operation and how this would effectively feed information into a UK wide registry needs to be addressed if this is to happen.

A fragmented system

The case for greater data collection on rare diseases and conditions is not a new one. Efforts have been made across the UK to improve this; however, the system remains highly fragmented.

In England, NCARDRS supports clinicians and patients in the collection of data. Northern Ireland by comparison, in their Rare Disease Action Plan, have committed to establishing "a steering group to

develop a rare disease registry",[49] one which will engage with equivalent UK registries. Equivalents have also been set-up, or are in process of being established, in Wales and Scotland.[50]

The increase in collected data as a result of the Newborn Screening Programme in England, for example, could play a central role in deepening understanding of rare diseases and conditions. While this is being rolled out across the devolved administrations, to begin fixing the fragmented system, establishing a UK wide rare disease and condition federated dataset must thus be a commitment and aim shared by the UK National Screening Committee (UK NSC), four nations and UK Government.

> *"I think we need to look at how we can put resource into things like NCARDRS in England and the comparable registers in the other parts of the UK to make sure that they are properly able to gather proper relevant data about clusters of rare diseases and also, because we are talking about very rare conditions, how we can make sure that that data is systematically collected internationally across national boundaries if we are ever going to get the critical mass that we need to enable a proper clinical development programme."*
> **Alastair Kent OBE, Independent Patient Advocate; Project Co-Chair**

THE END GOAL: A MORE EQUITABLE SYSTEM

The ultimate goal this report seeks to explore, is how do we work towards building a more equitable system across the UK. We should consider where clinical trials for rare diseases and conditions could and should sit in the future. As the Newborn Screening Programme in England, for example, holds the potential to relinquish some of the pressure on the need of a clinician led diagnosis, effective use of the additional resource must therefore be considered. We explored whether trials that do not sit within a defined medical specialty, such as immunology for instance, could sit under clinical genetics.

As diagnosis may become more automated, through the introduction of novel methodologies such as artificial intelligence and expansion of the newborn screening programme, this may provide the opportunity for rare diseases specialties to begin to grow and be enhanced. Building upon this, owing the extremely low numbers of cases for certain conditions, developing Rare Disease Collaborative Networks to focus on them,[51] drawing together expertise across the UK would pool resources to better support patients and families, as well as share learning, stimulate research and develop good practice, and, in so doing help to break down barriers between what are often seen as highly siloed services.

The shift towards virtual consultations and monitoring, as a result of the Covid-19 pandemic, enables issues regarding patient access and geographical locations to also be addressed. Ensuring this is maintained following the pandemic will further enable the provision of access for patients to expert clinicians, and vice-versa. Reducing such geographical barriers would also serve to reduce the impact on the patient and their family of travelling to attend face to face clinic appointments. However, it should not be assumed that virtual appointments can replace face to face consultations completely, that all patients will be able to benefit from these equally, or that some will prefer face to face meetings even if the virtual opportunity is offered.

Virtual consultations, while a useful alternative that has been successful adopted into hybrid models of monitoring in many services, should not become the default model owing to inherent sensitivities such as those surrounding patient confidentiality, and the discussion of personal and sensitive issues.

It must be recognised that in the shift to a more digitally enabled and supported health service, there are many individuals that are either digitally excluded or illiterate. Presently, according to research conducted by the Good Things Foundation, 10 million people in the UK lack the very basic foundation skills needed for our digital world.[52] Acknowledging that digital inequalities will negatively impact some patients with rare diseases and condition's ability to access or fully participate in their care, will be essential.

In a health care system underpinned by the principle of equity all rare disease patients and their families should expect to receive services and support that reflects current understanding and best practice. A relatively small number of these are the subject of active research and clinical development programmes. The opportunity these create to change the course of the disease and the potential improvement that this brings to patients and their families has been widely welcomed. However, it remains the case that there is widespread unmet need and that the vast majority of rare diseases have not yet benefitted from targeted research. Recent advances offer hope, but a sustained investment will be necessary for the benefits of innovation to reach the majority of rare disease patients and families.

Clinical research and developments for rare diseases and conditions will not solely benefit those living with such rare diseases and conditions. While it is essential to provide those living with rare diseases and conditions with effective drugs and treatments, rare disease research has the potential to positively impact other areas of health research.[53] Thus, expanding their impact beyond those in immediate need.

Lastly, as discussed in this Chapter, while the Covid-19 pandemic generated an unprecedented call-to-arms to address the sudden extreme pressures felt by the health service, the cracks in the system were present long before that. This is not a new problem. The will and ability to implement long-lasting change exists. The Government and NHS need to embed such change into the delivery of care for patients and those living with rare diseases or conditions.

Recommendations

Recommendation 5: To level up the delivery of care, building upon the lessons learned from the Covid-19 pandemic and the commitment to develop a toolkit for virtual consultations, a hybrid approach to clinical assessments must be adopted. This should form a core part of the patient's care plan which enables, where suitable, all patients and NHS trust with the flexibility to build care and monitoring plans which make use of both in-person and virtual consultations.

Recommendation 6: The increase in collected data as a result of the Newborn Screening Programme in England, could play a central role in deepening understanding of rare diseases. Building a federated dataset, available across the UK, which accounts for and records those identified by WGS would begin to build the foundations on a UK rare disease patient registry. While it may not initially account for existing patients, it would serve to deepen understanding and build a platform into which they may later wish to submit their data.

Chapter Three

ENGAGEMENT, EDUCATION AND AWARENESS

With over 7,000 known rare diseases and conditions, raising the levels of awareness amongst healthcare professionals has become a shared priority. This is essential to the improvement of the delivery of accurate and timely diagnoses, the development and delivery of treatment and medical plans, as well as long-term care planning. Increasing levels of awareness and education will ultimately serve to make often invisible conditions more recognised, benefiting the patient community as a whole.

Parents and patient advocates spoke of negative experiences with healthcare professionals, owing to their limited awareness of rare diseases and conditions. This lack of awareness was also unfortunately experienced more widely in interactions with society - a theme frequently raised by the patient and advocate group. This critique was reflected in the sharing of unsatisfactory experiences with healthcare professionals, both as the patient or individual presenting with symptoms or managing their condition and the parent or carer advocating for the patient.

The Government's "vision" is for healthcare professionals to have "an increased awareness of rare diseases and use of genomic testing" to address the shortcomings described by those with lived experience.[54] However, whilst a focus on the lack of awareness amongst professionals within the medical ecosystem is important, it is also essential to consider how increasing the levels of awareness and engagement amongst wider society would have a knock-on positive impact.

This apparent failure in the system is not attributable to one party, institution or profession, but rather a failing of the rare disease and condition community by the healthcare system as a whole. It should not be expected that the patient, family, carer or even patient group of charity should be responsible for filling any knowledge gaps experienced by professionals.

Increasing levels of engagement, education and awareness of rare diseases plays a central role in building a more equitable system of health and care delivery for patients and those living with rare diseases and conditions. Presently, those immediately impacted by the disease or condition often feel isolated and insufficiently supported. Healthcare professionals may feel overwhelmed by symptoms and features presented by patients to them if they do not point to a diagnosis of a common condition with which they are familiar. Finding a balance between the two is essential.

With over 7,000 identified rare conditions, a number which is ever-growing, it cannot be expected that every health professional be able to name and diagnose every rare disease and condition. It is therefore vital that future education and engagement plans establish what information is the right information to ensure that rare disease patients and families are able to receive an accurate diagnosis and access to expert care and information promptly. This is important for both the patient, or individual living with the rare disease or condition, but also the healthcare professionals in their ability to "provide a good standard of practice and care."[55]

> *"Medical professionals are beginning to understand "the frequency of how often they see rare disease patients in practice. They are just not realising that they are seeing a rare disease patient in the moment, either because it is not labelled as such, or they are not familiar with that disease."*
> **Dr Jo Balfour, Managing Director, Cambridge Rare Disease Network**

PATIENT GROUPS AND ORGANISATIONS: DRIVING THE AGENDA FORWARDS

During the roundtable sessions, patients and patient advocates discussed their wide range of personal and professional experiences regarding levels of engagement, education and awareness. These reflected the unpredictability of experiencing either positive or negative encounters with healthcare professionals based largely on the extent to which they were familiar with the condition.

Patients with rare diseases and conditions, their families and carers described the support they received upon receiving a diagnosis, reflecting the important role patient groups and organisations play. However, with stories of symptoms being overlooked and dismissed, often resulting in patients waiting many years for a diagnosis, it is apparent that more needs to be done if patients and families are to receive timely support.

It is acknowledged that healthcare professionals cannot be expected to be expert in every rare disease. However, knowledge opens doors. It is essential that we find ways in which effective knowledge sharing can be facilitated. Not only for healthcare professionals but also for the patient or individual living with a rare disease or condition, and their family, parents, and carers if we are to improve services.

CURRENT LEVELS OF AWARENESS AMONGST HEALTHCARE PROFESSIONALS

The heterogeneous nature of rare diseases and conditions, limited system support, and patchy levels of expertise all play a role in making the identification of any given rare disease difficult for healthcare professionals, especially as present levels of awareness outside specialist services are frequently low. There is a lack of data on the attitudes and extent of awareness amongst healthcare professionals, resulting in a patchy picture of who knows what with regards to rare diseases and conditions.

Rare diseases are not seen as a core element of the curriculum in many medical schools around the UK. Organisations such as Medics4RareDisease (M4RD) are seeking to address this through programmes

such as Rare Diseases 101. However, a four-nation wide approach, supported by the Government and University Schools of Medicine must be adopted if doctors and other healthcare professionals are to be enabled to effectively support those with rare diseases they will meet in the course of their work.

Pre-registration, Universities and Students

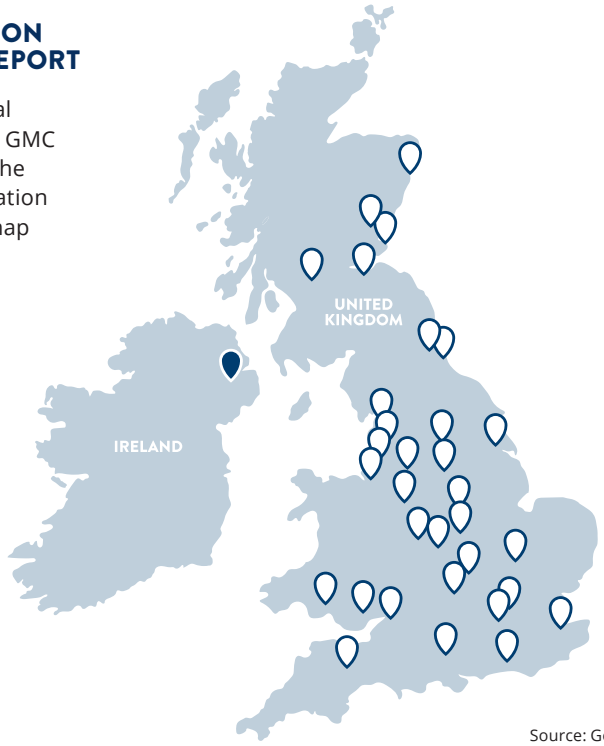
It cannot be expected that universities should try to make their students aware of all rare diseases. Medicine training courses, are already extremely demanding for students, given the content packed into every module and year. Nevertheless, it should not remain the case that universities are free to choose whether or not to address rare diseases as an element of initial medical education.

The General Medical Council (GMC) receives annual reports from institutions with medical schools in which the standard of teaching is reported on. As of April 2022, not every available report was for the previous year, making the collection of data limited. This serves to strongly depict that there is no systematic form of data collection regarding the contents of university medical courses.

As depicted in the following map, of the 42 universities for which medical school reports were available, only one mentioned the inclusion of rare diseases in the curriculum: Queen's University Belfast (QUB). This does not mean that the other 41 omit rare diseases and conditions from teaching entirely, for example, Cardiff University was praised for their rare disease centric module, and many universities cover certain rare conditions within their specialities. Nonetheless, it does not depict an education system which adequately recognises the value of and need for including rare disease teaching.

UNIVERSITIES WHICH MENTION RARE DISEASE IN ANNUAL REPORT

UK medical schools submit a Medical School Annual Return (MSAR) to the GMC each year. This report summarises the key themes arising from the information provided by medical schools. This map displays which universities list rare diseases as a priority.



Source: General Medical Council

CASE STUDY 4 -
QUEEN'S UNIVERSITY BELFAST: OVER A DECADE OF RARE DISEASE TEACHING

The past decade has seen tremendous advances in laboratory and computational analyses to improve the diagnosis and treatment of rare diseases. Developing novel strategies to raise awareness of rare diseases across a range of disciplines and professions, including improving education and training for rare diseases is critical.

Initially rare diseases were introduced to first year undergraduate medical students as a stand-alone lecture (2006), transitioning in 2013 to multiple sessions where undergraduate medical students would speak directly with patients and their families living with rare diseases in both a traditional lecture setting (~250 students) and more conversational tutorial-based sessions (~20 students) across years one, two and five; these are often highlighted by students as the best thing about their module. In 2021 rare disease teaching was enhanced through the use of individual case-based learning where medical students follow a patient with a rare disease through pregnancy, diagnosis, and treatment. For the past five years our final year medical students attend a session in their 'Preparation for Practice' training, reminding them of key rare disease facts, discussing expert patients/caregivers, and providing critically important signposting to useful resources.

Biomedical scientists will be providing rare disease diagnostics/therapeutics in the future. Rare disease teaching was explicitly introduced to our biomedical science students in 2018 as a dedicated lecture, including patient speakers, to help provide context and engage the students. This has resulted in our being overwhelmed with students seeking research placement opportunities for rare diseases.

Dedicated rare disease teaching is now embedded in undergraduate medical, biomedical and nursing curricula at Queen's University Belfast, additionally providing focused postgraduate and professional training with continuing professional development accreditation. Rare diseases have a significant impact on many other disciplines such as dentistry, education, psychology, and social work; we are keen to introduce rare disease teaching to other Faculties across QUB. Work has been ongoing in the last two years to provide harmonised rare disease teaching between QUB, Ulster University (where rare disease sessions have now been integrated to personalised medicine and nursing modules), and with several Universities in the Republic of Ireland. All dedicated rare disease teaching delivered at QUB from 2018 has been codeveloped with patients, their caregivers and multiple charities who support them. This includes QUB working closely with the Northern Ireland Rare Disease Partnership who are an overarching charity supporting rare disease in NI.

Local charities are supported by facilitating accreditation of relevant events and hosting disease-specific education and training courses. Professional support includes developing quick reference guides, such as our rare disease toolkit for GPs, and delivering training hosted by Royal Colleges in NI.

STEM events are regularly hosted to help raise awareness of rare diseases and stimulate interest in a future career helping the rare disease community. In 2021 we launched an All-Ireland

Students for Rare Disease Network, with quarterly rare disease discovery research meetings (public and professional components) and bi-monthly All Ireland webinars.

Our NI rare disease plan 2022 explicitly states an action to, "Establish a rare diseases education and training steering group" reporting to the Department of Health.

Clear consideration must therefore be given into how rare disease and condition teaching is appropriately embedded into the curriculum, across the four nations. Whether that be as an additional qualification students can earn, as a core module, or a lecture series delivered by a mix of patients, parents, clinicians, etc.

Northern Ireland, in their Action Plan, have committed to introducing a "dedicated education co-ordinator to take the education and training work forwards" and address many of the shortcomings explored in this Chapter. Such commitment must be a priority across the other nations of the UK.[56]

Northern Ireland's Action Plan commits to building "on existing RD awareness sessions and deliver 12 sessions per year in partnership with relevant bodies",[57] England's Action Plan commits to review the current landscape and collate the findings "into a report which will include recommendations to address identified gaps for consideration by curriculum developers."[58] In addition, Wales' has articulated its commitment to "incorporate rare diseases module in the undergraduate curriculum for medical students."[59] It will be interesting to monitor how this is rolled-out and implemented within the 2022-2026 window of time.

Building upon learnings derived from the Covid-19 pandemic, virtual lectures could be the part of the solution to such knowledge and teaching gaps. With limited cost and wide-spread levels of accessibility, a series of virtual mandatory lectures should be introduced while each of the UK's four nations establish how best to include rare diseases and conditions in the curriculum. While not a long-term solution, this would, in the interim, ensure students become familiarised with rare diseases and conditions.

> *"Good Medical Practice dictates that if you are outside of your knowledge or skillset, then you ask for help. Doctors might not know that in rare disease that the most appropriate help might not be someone in their hospital or even someone in their region. It might even be a patient group who can signpost or support them and their patient. I think that is the key part about why we need fundamental rare disease education."*
> **Dr Lucy McKay, CEO, M4RD**

Post-registration healthcare professionals

Available data is patchy, but from that which is available, the levels of engagement and awareness amongst post-registration healthcare professionals is frequently low. With the more widespread introduction and adoption of genomic technologies, for example, it must be recognised that unless the need for continuing professional development is addressed it will be increasingly challenging for healthcare professionals to keep up to date.

Recent polling data of GPs, share at a webinar hosted by the Royal College of General Practitioners (RCGP) in collaboration with Alexion, Dr Lucy McKay, Dr Will Evans, and Karen Harrison (Alex TLC Trust), indicates that upon being asked to define a rare disease, only 22 per cent of those surveyed could define a rare disease as one affecting fewer than one in 2000 people. The majority assumed it being either one in 20,000 or even one in 2 million.

Additionally, the question 'how many people in the UK do you think are living with a rare disease?' was met with equally patchy responses as only 30 per cent of participants correctly estimated 3.5 million people. Thus, underestimating prevalence and overestimating rarity of the disease or condition is common.

Research examining 'how genomic information is accessed in clinical practice' by GPs, highlighted that even five years after the 100,000 Genomes Project was launched and following the launch of the genomics education programme, 41 per cent of those surveyed had never heard of the programme and 91 per cent of those surveyed relied on search engines such as Google to search symptoms and conditions.[60] Only four per cent had accessed a rare disease specific resource. This highlights the need to do more if awareness of the needs of rare disease patients and families is to be improved.

Given existing low levels of awareness of rare diseases, we face a stiff challenge to change this among non-specialist clinicians and other healthcare professionals. Owing to the demands on the NHS, time for training and professional development is limited and any measures must be appropriately targeted and seen to be relevant if they are to be effective and more easily accessible.

> *"Respect your colleagues, respect patients, respect patient advocates who are experts in their own body and conditions, respect parents who know their children better than anybody else can. My mother was called a neurotic mother, when it took them how many months to diagnose me as a baby, so I think there needs to be changes like those, that is what I would do."*
> **Roanna Maharaj, Patient and Advocate, United Kingdom Thalassaemia Society Trustee**

Efforts have been made to address this issue. The RCGP for instance, has introduced a virtual course 'Rare diseases in primary care: assessment and management'.[61] Nonetheless, this does not always adopt a patient-centric approach, and instead focuses on the assessed need and not the expressed need.

Low levels of awareness must be addressed if rare disease patients and families are to be able to expect better services and support from the NHS. Awareness of rare diseases should be a continuous process, starting with initial education and training courses and continuing throughout a healthcare professionals practice. Timely, relevant and accessible continuous professional development opportunities should be provided to ensure professionals are able to keep their practice up to date in the care they provide for their rare disease patients and families. Reports and cases, such as those referenced in the Sickle Cell Society and All-Party Parliamentary Group for Sickle Cell and Thalassaemia 'No One's Listening',[62] highlight the true impact and suffering felt if levels of awareness are not raised.

To address this, funding and resource must be allocated to develop a central hub through which reliable information can be easily accessed by healthcare professionals. As it is subsequently explored, resources such as GEL's Language Guide and GeNotes,[63] amongst others, are excellent, but they must be accessible through a centralised portal. This would reduce the time and effort exercised by healthcare professionals to conduct the needed independent research.

CASE STUDY 5 - MEDICS4RAREDISEASES: DRIVING ATTITUDE CHANGE TOWARDS RARE DISEASES AMONGST MEDICAL STUDENTS AND DOCTORS IN TRAINING

M4RD exists to provide education and practical tools targeted at medical professionals, enabling them to reduce the diagnostic odyssey and improve the patient experience. M4RD understands it would be practically impossible for doctors to know about every single one of the 7000+ rare diseases. M4RD aims to give medical students and doctors-in-training the tools they need to appreciate that rare diseases are collectively common and recognise the exceptional challenges faced by patients with rare diseases.

M4RD's online training course, Rare Disease 101, is a flexible, eight lesson online module hosted on its M4RD: Learn platform. It is a crash course, covering the basics of rare disease education, as well as practical tips and useful tools that many doctors will not have heard of. It is designed to be used as an introduction to this area of medicine and signposts to readily available resources such as the Genomics Education Programme and FindZebra. With four doctors in the team, the charity understands where the gaps in medical curriculums lie but also how busy working NHS doctors are. M4RD worked closely with clinicians, educators and most importantly, those with lived experience to create an easily accessible, flexible and pragmatic course. M4RD is committed to keeping up with the dynamic landscape of rare diseases, to keep its educational tools up-to-date and relevant. Since the launch of Rare Disease 101 a mini-module has been launched on Clinical Trials and Early Access Programmes. A deep-dive module on mental health in rare disease is also in authoring stages with the help of Rareminds. M4RD: Learn is just part of M4RD's work to raise awareness and educate on the subject of rare conditions. Some of its other activities include:

Unusual Suspects: Rare disease in everyday medicine

Annual symposium for healthcare professionals at all levels, trainees and students to learn more about the importance of understanding the relevance of rare disease in clinical medicine, with a large focus on the expressed needs of those with rare conditions. This meeting has been held in association with The Medical Genetics Section of The Royal Society of Medicine since 2014.

The Student Voice Prize

An international essay competition for medical and natural science students, in collaboration with charity Beacon (formerly Findacure). The winning essay is published in the Orphanet Journal of rare Diseases annually on Rare Disease Day.

M4RD Ambassadors Programme

There are two types of Ambassadors: Clinical and Patient. Clinical Ambassadors help inform the projects, identify teaching opportunities, spread the word about events and opportunities for medics. Patient Ambassadors are really important for making sure that the patient voice is heard through M4RD's work.

The Rare Disease Podcast 4 Medics

Weekly interviews with people from across the rare disease and medical world, looking at different experiences and perspectives while providing pragmatic tips and advice for healthcare professionals.

UK Rare dIsease Student Evaluation (RISE) study

A project to collect essential data on the current understanding of and learning needs of medical students in the rare disease field.

Need for and Availability of Resources

Access to educational materials is essential. However, these must be regularly updated by experts who are given time and resources to undertake this task to ensure they reflect current best practice in a rapidly changing world.

Patient and advocacy groups often working in collaboration with expert clinicians and others provide validated and contemporaneous information and resources for professionals, patients and families. However, this is often a Sisyphean task as patient and advocacy groups cannot often boast of the resources required to sustain this long-term as the level of benefit from patient groups to the NHS in resources and services is not matched by the financial support. Funding and support must be allocated to rendering this a more sustainable process. Focus on funding, while essential, should not lie disproportionately on testing and diagnosis. An example of personal insight and expertise collaborating with professional knowledge is reflected in GEL's 'Language and Terminology Guide' published in May 2022.

CASE STUDY 6 - GENOMICS ENGLAND'S LANGUAGE AND TERMINOLOGY GUIDE

The Participant Panel comprises people who are participating in the 100,000 Genomes Project and their carers. The Panel's primary remit is to oversee what GEL and its partners in academia and industry do with our whole genome sequences and associated health data, and to help keep research participants' interests at the heart of the organisation. This includes providing direct advice to GEL about the various participant communities' priorities and values.

The Participant Panel prepared a Language and Terminology Guide for researchers in genomics and launched it at Genomics England's Research Summit on 4th May 2022.

It came about because we feel that it's important for the people using our data, and making such rapid progress in this field, to remember that there is a person behind every data point. These participants may be very interested in the outcome but may also sometimes feel uncomfortable about some of the language that scientists and/or clinicians use to describe that progress or the people who are personally affected by it.

The Panel held a workshop in early 2022 where we discussed helpful and unhelpful language and terminology, based on our own experiences as people living with rare health conditions, disabilities and/or cancer. The Panel Chair then distilled these ideas into a short Guide which was shared with the Panel members and Genomics England's Head of Engagement, Vivienne Parry, for revision and further refinement. The finished text was sent to Genomics England for typesetting and publication: genuine co-production!

The guide begins by setting out a series of principles for talking about genomics research and explains some of the motivations behind people's willingness to participate. It continues with some handy reference tables recommending terminology to use when talking about disability, cancer and genomics research, and concludes with a short section specific to the Participant Panel and the 100,000 Genomes Project.

We hope that it will be of interest and value to anyone in the genomics field, and beyond, if they have ever wondered what their patients or research participants are thinking.

The guide has been very well received to date. It has been shared widely amongst clinical and research colleagues across the UK and on social media. We hope this will raise awareness and improve the delivery of genomics services in the UK and beyond, by bringing participant and patient voices into clinics and laboratories across the genomics ecosystem. We also anticipate that this will continue to bring benefits to patients, research participants and their families in the longer term, by helping professionals to bridge the gap between their technical clinical language and their patients' lived experience.

GeNotes, genomics notes for clinicians, are an educational resource currently in development for healthcare professionals which focus on two tiers. One focuses upon the point of care, and the other on providing up-to-date and relevant resources. They are emerging as an increasingly valuable resource for the genetics community. However, not all rare diseases and conditions are genetic, and a parallel initiative is needed to address the needs of those affected by non-genetic rare diseases if they are not to be left behind.

It is positive and timely that England's Action Plan is committed to developing and rendering accessible such resources, which should thus be driven, managed and overseen by bodies such as Health Education England (HEE). To ensure relevance and utility it will be essential for the patient and family voice to be included alongside that of other experts. and for these resources to include the needs of those with both genetic and non-genetic rare diseases.

CASE STUDY 7 – COGNITANT

Cognitant supports the improvement and development of rare diseases education and awareness. Cognitant's mission is to empower people with clear, reliable health information for a world where everyone understands their health and treatment. By doing this, Cognitant helps patients ➤

and their carers to manage their own health and reduce the sense of feeling overwhelmed, unsupported and isolated, which is so often the case in particular for rare diseases.

Cognitant's focus is therefore to make health information that is accessible, easy to understand, memorable and impactful so that people of all ages and abilities are able to fully understand and make informed decisions about their health, and treatment.

Research around a rare disease is an example of an area where education of patients and their families who may participate is critical. Participants must be empowered with information about what is involved throughout and how the research may benefit them or their community. The PRONTO case study is an example of this.

The background:

The PROspective Neurological Disease TrajectOry study (or PRONTO) is a natural history study that will follow children who have, or are at risk of developing, GM1 and GM2 gangliosidoses, a class of rare inherited disorders that include fatal childhood disease, Tay-Sachs.

The study, run by Azafaros, will follow 60 to 200 patients in Brazil, Germany, and Spain for five years, in collaboration with Acción y Cura para Tay-Sachs (ACTAYS), Cure & Action for Tay-Sachs Foundation (CATS) and the National Tay-Sachs and Allied Diseases Association.

It will follow children at risk of infantile Tay-Sachs disease, a fatal neurological disorder caused by the toxic build-up of GM2 ganglioside in neurons in the brain and spinal cord. Usually detected at three to six months of age, children with infantile Tay-Sachs rarely live beyond early childhood.

The challenge:

Recruiting participants to take part in natural history studies can be challenging, which is particularly true in the rare disease community where there are often lower sample sizes to recruit from. Motivation to participate in observational studies is often further reduced by the lack of effective information materials shared with patients and their families about the implications of participation.

Azafaros engaged with Cognitant to overcome the challenges of recruiting children with this rare neuro disease for their study.

The solution:

Azafaros with Cognitant created a campaign to explain to the caregivers of children with a rare neuro disease the different elements involved when participating in a natural history study. Through the utilisation of a co-creation process, ensuring a user-centred design, the group developed a patient-led digital education resource about the upcoming PRONTO study.
The resource includes unique videos that detail what a natural history study is, the benefits of participation to GM1 and GM2 patient communities, and what participation will entail – including information about the study assessments.

As the brain processes visual information 60,000 times faster than text, presenting information in video format promotes accessibility.

By hosting this content on a digital hub, clinicians and researchers will be able to send curated content directly to participants and caregivers, meaning that the videos can be viewed, and shared, away from the clinic and in their own time.

Cognitant's approach:

Cognitant brought together key stakeholders, including KOLs, clinicians, patients and caregivers from Europe and the US, and advocacy groups (the Cure & Action for Tay-Sachs (CATS Foundation), Accion y cura para tay-sachs (ACTAYS) and the National Tay-sachs and Alied Diseases Association (NTSAD). The group were included in a series of virtual co-creation workshops to design an educational video series.

Cognitant facilitated stakeholders to discuss the unmet needs and what the curriculum should cover, and prepared concepts for discussion, such as animation styles & colour schemes. Each group was given time to discuss their opinions about the pros and cons of the different approaches. Through productive discussion, an educational curriculum and the materials required for maximised impact were agreed upon.

Measuring the impact

The PRONTO resource has been designed to educate and empower individuals and their families, and reduce attrition throughout the course of the research. The impact of this digital intervention will be assessed through patient feedback and engagement metrics collected through Cognitant's Healthinote platform.

BEYOND HEALTH CARE: ENGAGING WIDER SOCIETY AND POLICYMAKERS

The role of the patient and support groups and organisations cannot be underestimated or overlooked. There are over 200 charities which support patients, children, families, carers, and individuals affected by rare diseases and conditions in the UK. Much of the work in building and developing awareness and engagement for rare diseases and conditions stems from these patient support groups. They build the platforms from which the patient voice is heard. However, they cannot address the awareness and engagement gaps on their own. Other bodies such as HEE and the medical royal colleges should partner with rare disease support groups to ensure that needs are recognised and met in a timely manner.

During the roundtables, comparison was drawn between the experiences of those in cancer and rare disease communities. More people are affected by rare diseases than have cancer yet awareness of cancer is immeasurably greater. "If it can be done for cancer, it can be done for rare diseases" was a view expressed by those participating. Examining the high levels of public awareness and engagement with cancer, the disparity in exposure between the two was all too apparent.

With more than 200 types of cancer,[64] it is not possible to assume all policymakers, practitioners, or the wider public know or can identify each one. However, the levels or awareness when compared to rare diseases and conditions are polar opposites. Government sponsored campaigns, charity events, and national media campaigns all play a key role in building levels of awareness and engagement. Rare diseases and conditions cannot compete with this at present. Ideally rare diseases should be promoted in the same manner, and with the same levels of support, across all sectors, as cancer.

With the announcement of the Government's '10-Year Cancer Plan',[65] it is evident that political and Ministerial will is essential. The creation of the role of Parliamentary Under Secretary of State for Vaccines and Public Health to address the roll-out and building of public trust in the midst of the Covid-19 pandemic,[66] showcases what can be achieved when such support is harnessed.

The Northern Ireland Action Plan explored "the potential for a Rare Disease Champion role",[67] and in the USA, there is the Office for Rare Diseases.[68] It is positive to note the monitoring of the value of the Clinical Lead and Clinical Champion for rare disease, aimed at raising the profile of rare diseases in Wales, as another example.[69] If the UK as a whole is to deliver world-leading care for those living with rare diseases and conditions it must do more. This does not underestimate the value of groups such as the All-Party Parliamentary Group (APPG) on Rare, Genetic and Undiagnosed conditions.

Nonetheless, to appropriately address the issues, priority must be given, emulating the models adopted in the US and proposed in Northern Ireland, which is exclusively responsible for Rare Diseases and Conditions within the heart of Government to drive forward the agenda and deliver the commitments made in the UK Rare Disease Framework, the Action Plans, and future commitments.

Recommendations

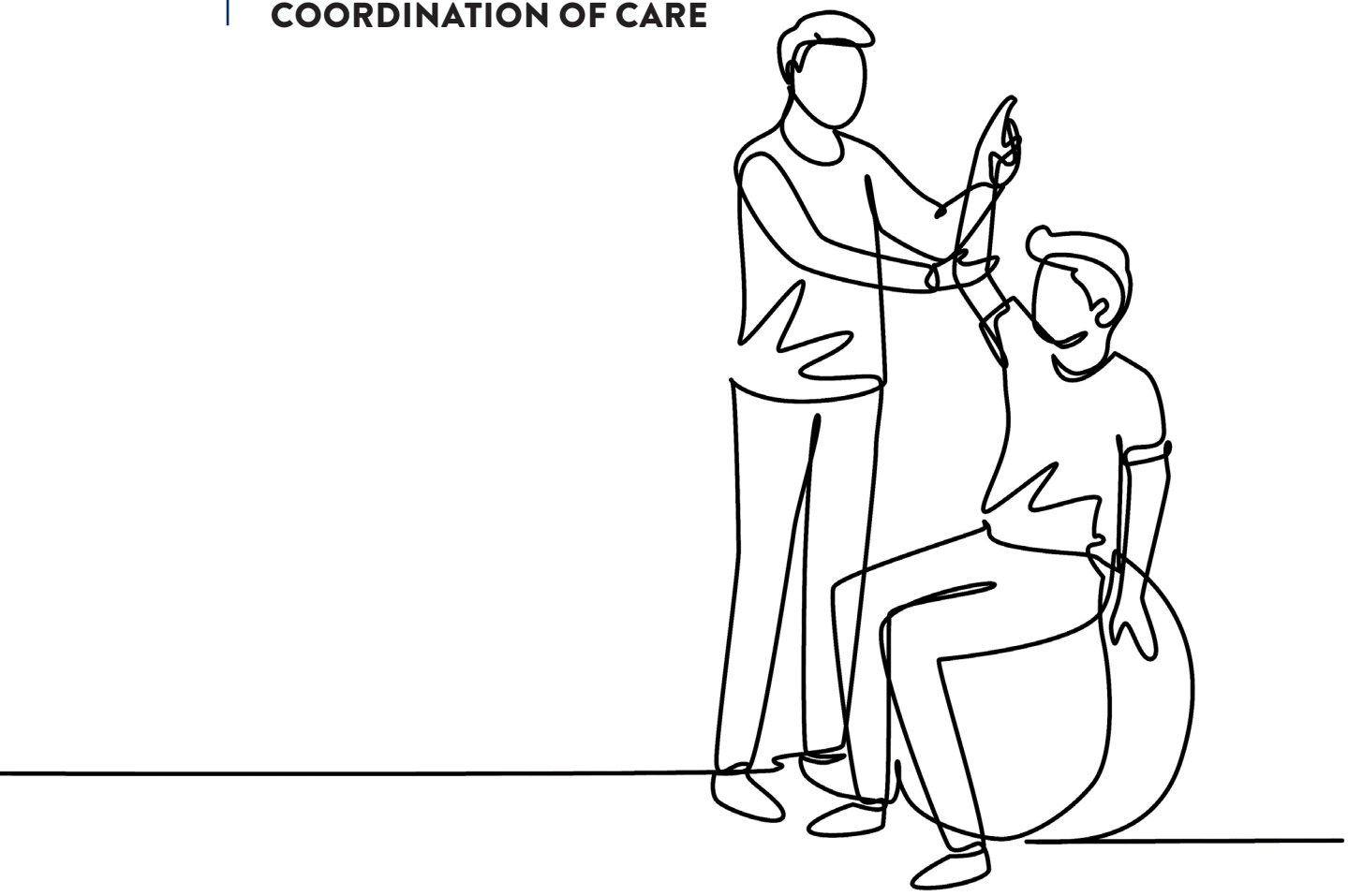
Recommendation 8: Rare Disease Multidisciplinary Teams should be established, beyond the remit of Rare Disease Collaborative Networks, to promote the raising of education levels and awareness amongst current healthcare professionals. The need for an effective education and awareness programme for members of clinical teams involved in the care of rare disease and condition patients is evident. Cross-pollination of expertise is at the core of furthering professional education.

Recommendation 9: To harness widespread engagement and raise awareness of rare diseases beyond the healthcare ecosystem, the conversation must be rephrased. A collaborative and cross-sectoral recasting of public perception and understanding through the lens of 'population health impact and intervention', should work towards harnessing an understanding of the health impacts of rare diseases beyond those directly affected.

Recommendation 10: Universities, Royal Colleges, Health Education England, and other professional bodies and academic institutions should promote the upskilling and further education of their students and healthcare professionals. It is also essential that these be completed by key decision-makers within the health service, for example those allocating resource for commissioning services, to ensure impact is felt across the health ecosystem. These may be delivered through virtual and in-person workshops.

Chapter Four

COORDINATION OF CARE



The management of long-term care for many of those living with rare diseases and conditions, whether diagnosed or not, can prove incredibly challenging. The complexity of the condition can result in the involvement of multiple specialists and healthcare professionals, requiring the individual, and their family or carer, to attend multiple appointments and visits. Sometimes covering a large geographical area. This can pose a great challenge to the patient, and those supporting and caring for them.

Coordination of care is pivotal to a good quality of life, both for families and for those affected by rare conditions, whether children or adult. Appealing for this coordination can put a huge strain on parents and carers and often leads to pressures which can have an adverse impact on the mental health of those who should be receiving support but instead find themselves in a more combative relationship with the health service.

As has been explored throughout this report, scientific and medical discovery and development are escalating the rate of progress in enabling better identification and management of certain rare diseases and conditions. Advancements are being introduced more rapidly. Genomics and genomic screening, for instance, is enabling faster diagnoses; resulting in an estimated 3,000 plus more babies and children being diagnosed every year.[70] The system therefore must be ready for the expected influx of patients.

Owing to the additional requirements beyond the core hospital and specialist appointments, which could be time off work or school for instance, opportunities to improve the delivery and coordination of care must be harnessed. Wherever existing cases and examples of best practice exist, the system must allow for those approaches and systems, to be passed on as learnings and thus replicated.

Lastly, with more patients in the system, and patients living for longer, transition from childhood to adult care brings with it impending anxieties and exposes potential dislocations with the alignment of the system. Coordination of care is core to ensuring the delivery and management of care is effective and not burdensome.

> *"We can find excellence in places, but it is turning that into some consistent practice."*
> **Kye Gbangbola, [Former] Chair, Sickle Cell Society**

UNDERSTANDING WHAT IS MEANT BY 'COORDINATION OF CARE'

While the UK is able to boast of world-leading rare disease experts, the health service is currently fractured in its coordination and delivery of primary, secondary and tertiary care for those patients. This points back to the issues raised in Chapter One regarding patients and their families feeling as though they are being made to 'bounce' around the system in search of a diagnosis. It was acknowledged through the held discussions however, that such feelings of being a nomad through the system, continue long after diagnosis. For some, this sentiment never leaves.

Even though highly specialised services exist for some conditions, the lack of a basic care pathway from the outset, to act as a roadmap, is the cause of much concern and frustration. This results in many parents, carers, and patients, feeling as though the coordination of their care falls entirely upon them.

Untangling the system arises further challenges, as presently, the health service fails to agree upon a shared definition for 'coordination of care'. While examples of best practice exist, such as specialist rare disease nurses, for example, for the coordination of care to be truly beneficial to all patients and individuals living with a rare disease or condition, access to such assets cannot be summarised as another 'postcode lottery'.

> *"It is vital that when something works somewhere (abroad or in other areas of the country) there is a mechanism for it to be taken up and translated into services across the country."*
> **Dr Sarah Wynn, CEO, Unique - Understanding Rare Chromosome and Gene Disorders**

The CONCORD study (see below Case Study),[71] looking at how care services for those with rare diseases are coordinated in the UK, and how people affected by rare diseases and health care professionals who treat rare diseases would like them to be coordinated, is seeking to untangle this problem. It is a collaboration between patients and carers affected by rare conditions, health care professionals with expertise in rare conditions, and health services researchers. The recommendations made by the CONCORD study should be used as the framework through which care coordination pathways are developed.

CASE STUDY 8 - COORDINATED CARE OF RARE DISEASES STUDY (CONCORD)

The Coordinated Care of Rare Diseases Study (CONCORD) was funded by the NIHR Health and Social Care Delivery Research Programme from 2018 to 2020. The CONCORD study used quantitative and qualitative research methods to find out whether and how care services for people with rare diseases are coordinated in the UK, and how patients and their families and healthcare professionals would like them to be coordinated.

The CONCORD study contributes to understanding of care coordination for rare conditions and consideration of how services could be coordinated in future. The CONCORD study contributes knowledge to the topic: 'Aiding the delivery of long-term care for patients, beyond clinical settings, and aiding the paediatric to adult transition'.[72]

A summary of key findings from CONCORD:

What does coordinated care mean for rare conditions?
The CONCORD study developed a definition of care coordination for rare conditions:
"Coordination of care involves working together across multiple components and processes of care to enable everyone involved in a patient's care (including a team of healthcare professionals, the patient and/or carer and their family) to avoid duplication and achieve shared outcomes, throughout a person's whole life, across all parts of the health and care system, including: care from different healthcare services [...] care from different healthcare settings [...], care across multiple conditions, or single conditions that affect multiple parts of the body [...], the movement from one service, or setting, to another. Coordination of care should be family-centred, holistic [...], evidence-based [...]"[73]

How are patients with rare diseases and their families impacted by the way care is coordinated?

This study found many reports of uncoordinated care which resulted in burden on patients and carers, including impact on their physical health, finances, and psychosocial wellbeing.[74]

Is care for people with rare diseases in the UK coordinated and, if so, how?

Findings from the study's UK wide survey of 1457 patients, parents/carers and healthcare professionals found that in the UK, care is not well-coordinated currently. Findings indicated that patients have limited access to care coordinators, specialist centres and care plans.
For example:

- 12 per cent of patients and 14 per cent of parents/carers reported having a formal care coordinator
- 32 per cent of patients, 33 per cent parents/carers reported attending a specialist centre
- 10 per cent of patients, 44 per cent of parents/carers reported having a care plan.

Very few patients and carers reported having access to a care coordinator AND a specialist centre AND a care plan (two per cent of patients and five per cent of parents/carers).[75]

What are the preferences of patients and families and healthcare professionals in relation to how care for rare diseases is coordinated?

Findings indicated that for all stakeholder groups (patients/parents and carers/healthcare professionals) it was important that the cost of attending appointments is low, electronic health records are accessible, care is led by an expert in the condition and supported by a care coordinator, and that there is a specialist centre and a documented emergency plan available.[76]

What are the different ways in which care for people with rare diseases might be coordinated?

The findings indicate that there are lots of different ways to coordinate care for people with rare conditions.[77] Care coordination involves coordinating the care itself but also the way teams are organised, where responsibilities lie, how appointments are scheduled, access to records and how stakeholders communicate with each other.

Different models of care coordination may be appropriate in different situations and that there are many factors influencing care coordination. A flow chart was developed that outlines how care could be coordinated in different situations within and beyond the clinical setting, and in paediatric to adult transition. In addition, 10 hypothetical 'models' of care coordination were generated that could be used to inform practice. These models of care coordination include transition elements.[78]

CASE STUDY 9 - XP SUPPORT GROUP

We support families in the UK with Xerocderma Pigmnetosum (XP), we give grants for UV protective equipment for homes, schools and workplaces. We provide accommodation and travel to the UK national XP clinic. We run an annual respite weekend for families with XP and put families in touch with each other to share their experiences.

Over the 24 years of our existence, we have worked hard with the medical profession to improve the lives of XP patients and their families. When we started it was common for children to die as a result of their skin cancers that they developed. We instigated the wearing of UV protective clothing to limit exposure to UV light and within a few years we were seeing less and less children with skin cancers. This was picked up by the doctors who were becoming more interested in our patients and in 2010, the National XP service was founded at St Thomas Hospital. Before that we had been holding specialist clinics in Brighton and the St John's Institute using a multi-disciplinary approach. Doctors gave their services and time unpaid.

Since the establishment of the service, we have been able to gather information about the different variants of XP, which helps with the prognosis. Some of our patients sunburn seriously where others do not. Doctors have now been able to identify the variants that burn and do not burn. Patients who burn are more likely to protect themselves than the ones who do not. Children with XPC variant do not burn and often diagnosis does not occur until the child has had an early skin cancer. Doctors also know which variants are likely to have neurological problems.

The clinic has held two very successful research projects. One looking at the psychological reasons why patients choose not to protect from UV even though they know it's harmful. This has led to individual interventions for patients to improve their photoprotection. This is particularly important for a condition that has no cure.

The second project is the development of a UV protective face mask which is currently ongoing.

Our Specialist XP Nurses attached to the clinic see patients in their homes, schools and workplaces and co-ordinate with all the interested bodies. They organise workshops for schools with XP patients and provide advice wherever it is needed. They manage a very successful transitional process, where patients begin transitioning from 16-21 years.

In 2018 the XP National Team was awarded the BMJ Dermatology Team of the year.

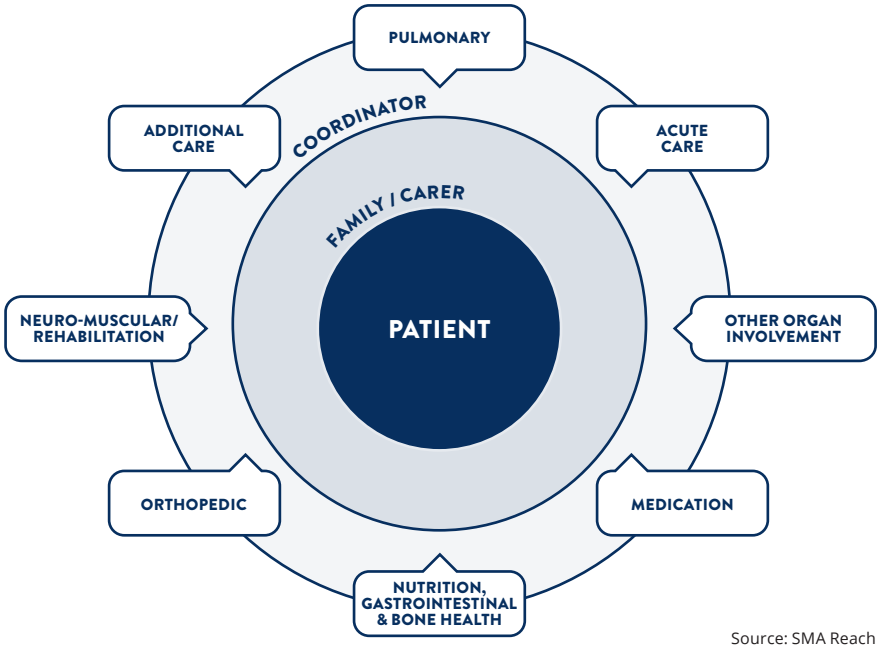
For many, support seemingly ends following the establishment and provision of a diagnosis. In some cases, patients, and their families, were left feeling as though the healthcare professional's job was complete because they had been 'solved'. However, the need to understand long-term care requirements is dependent upon up-to-date information and resources being provided, an experience not many participants spoke of.

As detailed in the England Rare Disease Action Plan, the Rare Disease Collaborative Networks (RDCNs), of which there 13 at the time of writing, are an example of the system working collaboratively to provide patients and their families with a central hub through which care is effectively managed and coordinated. In some instances, the Networks work across multiple hospitals in England, seeking to reduce issues regarding accessibility and lack of care coordination. To provide the highest standard of care they combine various approaches to care delivery, for instance, the use of both in-person and video consultations.

The need to see multiple specialists (see the below Figure for example), requires delicate coordination and time-management. Coordinating care can produce an intricate web which is difficult to navigate, placing significant additional burden upon the parents, carers and patients. While some rare conditions are able to benefit from dedicated nurse specialists, who can provide support with care coordination, such instances are too few and far between. It is not acceptable that patients, their families and carers should have to act as a care coordinator when using NHS services. Funding must therefore be allocated to enable the hospitals to create a 'rare disease care coordinator' role, through whom the coordination of the patient's care is centrally managed, and through which information and resources are funnelled.

"They have got developmental conditions that mean they often have multiple healthcare professionals involved and they are never seen together, they are often seen at different hospitals. Quite a lot of our parents talk about it being a part-time or even a full-time job just coordinating their child's care and it is quite patchy."
Dr Sarah Wynn, CEO, Unique - Understanding Rare Chromosome and Gene Disorders

COORDINATION OF CARE FOR SMA PATIENTS



Source: SMA Reach

WIDER SYSTEM COORDINATION

As has been repeatedly expressed throughout this report, owing to the breadth of information circumnavigating the 7,000 plus rare diseases and conditions, it is unrealistic to expect all healthcare professionals to be knowledgeable about all rare diseases and conditions. The same approach must therefore be adopted when approaching the coordination of a patient's care. Building upon some of the themes explored in Chapter Three, it is essential that healthcare professionals be able to readily access information and resources, in order to provide the highest standard of care to their patients.

> *"I think for all of this coordination there needs to be a level of information, there needs to be clear, helpful information which can be disseminated readily to patients and clinicians for each rare disease."*
> **Dr Anjana Kulkarni, Clinical Geneticist, Guy's and St Thomas' NHS Foundation Trust**

Ensuring information is readily available is crucial to providing a more coordinated care plan to patients and individuals living with rare diseases and conditions. The sharing of patient records, data and information across the health service will play a core role in providing the highest standard of care possible. In order to appropriately plan for the future care of the individual, it is essential to know their care history, and it cannot fall solely on the patient, parent or carer to fill that void.

While still in their infancy as the new and localised service delivery model, Integrated Care services (ICSs) should play a central role in the coordination of care of patients living with rare diseases and conditions going forwards.[79] The ICS networks will provide the chance to generate greater alignment between the "design, development and provision of services – including specialised services",[80] to better support patient care.

While not explored in intricate detail in the hosted discussions, the call for the development of patient passports was positively met by all in attendance. The Wales Rare Diseases Action Plan makes Wales the first of the home nations to commit to the development of a passport by establishing an easily used "app" to enable a "patient passport" for rare disease patients".[81] A similar approach has already been developed on an individual organisation basis by The Ehlers Danlos Society, the 'EDS wallet card',[82] which provides an easily accessible card print-out providing key information on the condition to help the patient if required. Generating a summarised point of reference for patients holds great potential and it will be of great interest to monitor the impact this has in Wales, and broader implementation across the other nations would be greatly welcomed.

UNDERSTANDING THE COST OF CARE

Understanding the complexities which accompany rare diseases and conditions poses a challenge in and of itself. The impact of care stretches beyond the realms of the health service and seeps into the work, school, social and home lives of those living with a rare disease or conditions, and those of their family or carers.

Parents and carers take time out of work, drop down to part time, or do not work, in order to best support the individual living with a rare disease or condition. In order to travel to, and attend appointments, in most instances, patients who are children must take time off school, and adults, off work. During the discussions, many spoke of caring for a child with a rare disease or condition as equivalent to a job itself, owing to the present feelings around the coordination of care.

Participants spoke of the cost of travel, time off school and work, modifications made to homes and impacts on siblings, among other aspects which often go unconsidered or are overlooked. The disruptive impact of poorly coordinated care must therefore be understood and appreciated beyond the realms of the health service.

Additionally, while outside of the remit of this paper, it must be understood that failures in care coordination negatively impact the NHS as well. Repeat appointments, additional hours of work undertaken by the healthcare professionals, among other features, will all add unnecessary cost onto the NHS. As such, developing sustainable care pathways for those living with rare diseases and conditions will serve to alleviate unnecessary financial and resource pressures upon the health service.
In developing more coordinated and established long-term care pathways for those living with rare diseases and conditions, impacts beyond health must be considered and accounted for, to ensure quality of life is impacted a little as possible.

PLANNING FOR LONG-TERM CARE

Navigating the health system as a patient or individual living with a rare disease or condition is not a one-off or series of individual instances, it is a journey that follows them, and their family or carer, through their life. There are key milestones, such as transitioning from paediatric to adult care, or even into palliative care, for which sustainable and easily navigable pathways must be developed.

Presently, examples of best practice do exist across the UK. The issue, or dissonance, lies in the very fact that such models are not standardised. In the instance of transitioning from paediatric to adult care, in many cases the standard of care within the paediatric side of the health service is far more joined-up and well-established than that experienced in adult care.

Transitioning into adult care may see the expertise required further dispersed across a wider geographical area, covering multiple NHS trust and specialist centres. Managing what can often be an awkward and possibly uncomfortable transitioning between care models, is rendered more complicated by a lack of long-term care plans or care pathways.

While it was acknowledged that for certain conditions such pathways and models do not exists as patients are now living longer, requiring care never needed previously, this provides the chance to bring together specialists, GPs, and other relevant healthcare professionals to begin scoping and building what the care pathways may look like. Providing both physical and psychosocial support, as outlined by the below All Wales Adult Cystic Fibrosis Centre Case Study and their Action Plan commitment to "establish Rare Diseases as a "Community of Practice" and develop example/exemplar clinical pathways for rare disease conditions, including MDT involvement."[83]

> *"I just feel that any coordinated approach needs to have the medical prescription and the psychosocial prescription hand-in-hand for it to be successful for the patient with the lived experience and their support system"*
> **Dr Sondra Butterworth, Community Psychologist; Founder, RareQol**

Enabled by virtual platforms, healthcare professionals should meet, supported by the 'care coordinator' if adopted, to map the patient's long-term care plan to ensure it is coordinated in a manner that not only benefits their health but also has as minimal an impact as possible on their social and familial lives.

CASE STUDY 10 - ALL WALES ADULT CYSTIC FIBROSIS CENTRE: PROVIDING HOLISTIC CARE FOR ADULTS LIVING WITH CYSTIC FIBROSIS

People living with CF (pwcf) have complex healthcare needs and are not allowed to mix with one another. They have been classed as vulnerable throughout COVID-19 and hence have felt extremely isolated.

Working alongside pwcf we have designed and implemented a virtual health hub, allowing virtual clinics but also virtual support groups (allowing pwcf to mix safely which was not possible previously), Q+A sessions from the team (to provide information and answer questions live) and group exercise sessions which have helped to motivate pwcf to remain active and exercise as part of a group from their individual homes.

We have incorporated team challenges online such as the Tour de France challenge, 12 days of Christmas and daily marathon challenge where pwcf and staff work together to reach exercise goals as our patients were keen to have shared goal setting to maintain their health targets e.g. staff and pwcf totalling their daily cycle distance against the Tour de France peloton. We have developed home monitoring as part of a funded trial to give pwcf reassurance regarding their lung function, weight, activity levels and oxygen that they can be safely cared for from their own home and have 100pwcf on the trial- helping to avoid admission and reduce unneeded clinic attendance. We have run patient leadership courses and have changed the way we run multidisciplinary meetings to enable pwcf to ask three questions that matter to them.

We have built upon the biobank for pwcf to expedite translational research and working with Microsoft and our pwcf to enable automated texts to inform pwcf when their samples donated to the biobank are used as pwcf wanted to feel part of research and research outcomes. We are working with pwcf to design and pilot decision making tools around starting a family now that many more pwcf are staying well due to a novel drug therapy (kaftrio) which has also been able to be rolled out during the pandemic by the MDT.

MENTAL HEALTH

Navigating the health service with a rare disease or condition, whether diagnosed or not, can, and has, place severe mental strain upon patients and individuals. In struggling to understand what their condition is and how it impacts them, some have described trying to live like a fully 'well person', despite not entirely knowing what one is. As detailed by the Northern Ireland Rare Disease Action Plan, it is essential that the system is developed to "ensure the mental health needs of the rare diseases population are included across all appropriate Northern Ireland government strategies and programmes."[84]

Feelings of battling to have their experiences listened to, symptoms dismissed as just anxiety, parents' concerns dismissed as overbearing, are a few of the experiences spoken of which have since weighed heavily on the minds of patients, parents and carers alike. While the effort and time of multiple experts may be going into preserving and caring for the physical health of the patient, their mental health cannot be overlooked in the process.

> *"Good care coordination from my point of view is integral to the support of mental health of our patient community"*
> **Kym Winter, CEO, Founder and Clinical Director, Rareminds**

To begin addressing the intersect between the psychological-physical-social impacts caused by a condition, Birmingham Women's and Children's hospital established specialist rare disease nurse roles.[85] Their role is to coordinate and enhance the care for patients within the trust, of which a core aspect is providing information and emotional support. This model can be compared to that of the MacMillan Nurse Specialists, further reinforcing the previously stated notion that 'if you can do it for cancer, do it for rare disease'.[86]

While mental health was not directly addressed by an Action in England's Rare Disease Action Plan, it did address the crucial support awarded by the Government more broadly in "investing an additional £2.3 billion per year by 2023 to 2024 to expand and transform mental health services."[87] This in an incredibly positive step in the right direction however, as the Mental Health Act is set to be reformed during the 2022/2023 sitting of Parliament, it will be essential that parliamentarians and Ministers recognise the need for suitable mental health support for those living with rare diseases and conditions.

Good mental health, and mental health support, is integral to looking after patients with rare and complex diseases and conditions. Not just supporting mental health provision at that time for patients

in clinic or being seen by a clinician, but also ensuring that it is a continuum throughout their care for their condition. This is pivotal to patient care. Mental health services currently face many challenges in terms of resources and funding. Therefore, funding should be allocated so that clinical psychologists can provide some useful support as well as guidance, and perhaps ongoing support, not just for patients, but for parents and siblings who are inevitably affected by individuals with long-term conditions.

CASE STUDY 11 - RAREMINDS CIC

Rareminds is a non-profit organisation founded in 2020. Recognising the need for specialist, accessible counselling and psychotherapy services for individuals and family members impacted by rare, genetic and undiagnosed conditions, they work primarily in partnership with patient advocacy organisations providing online individual/couples counselling, group programmes and workshops.

They established the first Counselling for Rare Diseases CPD training for qualified mental healthcare professionals, which is currently seeking external validation. The team currently has trained 8 psychotherapists in their approach, who are now working with 8 patient organisations covering a wide range of rare conditions. The team includes a liaison psychiatrist, and a mindfulness practitioner specialising in pain, anxiety and fatigue.

The founding therapists have been working with rare diseases since 2013 and have established an integrative online model incorporating aspects of a relational psychodynamic approach, CBT, ACT and Mindfulness. They are currently working with Medics4RareDiseases on a module for Mental Health and Rare Disease.

They also provide supervision and consultancy to healthcare professionals and patient advocacy group leaders including their innovative Building Rare Resilience 12-week programme for patient leaders in partnership with Genetic Alliance UK. Their aim is for specialist rare disease mental healthcare support to be embedded, and accessible, at the point of need across all stages of the rare disease journey.

Recommendations

Recommendation 11: The key findings and recommendations from the CoOrdiNated Care of Rare Diseases (CONCORD) study should be viewed as a foundation upon which the basis for the planning and delivery of coordinated care is established.

Recommendation 12: To deliver the maximum possible health gain to the patient and utilise resources to the highest level of efficiency possible, an interdisciplinary and holistic health economic evaluation must be undertaken of current services and resource allocation. To truly analyse the economic impact upon the patient, their family and carers, the health service, as well as the societal cost of lost opportunity and productivity, enabling evidence-based decision-making on the use of financial resources.

Recommendation 13: Living with a rare disease places substantial strain on mental health. In anticipation of the reforming of the Mental Health Act, a focus on effectively integrating mental health services and support into rare disease services is essential. Not only for the individual living with the rare disease or condition, but for their family and carers as well.

Additional Evidence

CASE STUDIES

CASE STUDY 12 - NCBRS WORLDWIDE FOUNDATION: UK BASED BUT SUPPORTS INDIVIDUALS DIAGNOSED WITH NCBRS AND THEIR FAMILIES ON AN INTERNATIONAL LEVEL

Since becoming the only global registered charity/organisation representing Nicolaides-Baraitser Syndrome in June of 2020, we have made tremendous strides in our efforts to support our global community. We have created a private safe space where over 220 families, wherever they are located, can share their worries and/or joys with each other and get lived experience advice from other parents.

We have declared October 9th each year as "Global NCBRS Awareness Day", to further spread awareness of this rare condition amongst the general public, medical professionals, researchers and more.

The Foundation has partnered with many rare disease organisations across the globe since we formed, to raise awareness and support for people living with NCBRS. This includes the Facematch project in Australia, where they aim to help people with a possible genetic condition find a diagnosis by matching their facial features with people who already have a diagnosis using facial recognition technology. We are encouraging all our families to join this project.

We have created our global patient registry in partnership with the Coordination of Rare Diseases at Sanford, so we can start to gather our disease-specific data ready to facilitate future research studies into NCBRS.

We are partnered with Healthinote part of Cognitant, which enables doctors, nurses, and pharmacists to prescribe our trusted information to their patients. Integrated with eConsult's patient messaging tool, Healthinote can be accessed by over 3,000 GP practices, to serve over 29 million patients in the UK.

One of our main focuses going forward is to increase research into the condition, as still very little is known about NCBRS. This is why we have formed our patient registry to kickstart the data for this research to happen.

CASE STUDY 13 - ATAXIA: IMPROVING ACCESS TO SPECIALIST SERVICE FOR PATIENTS LIVING WITH RARE DISEASES

The ataxias are a group of rare progressive neurological conditions, with complex needs involving multi-disciplinary care. In collaboration with the patient support group Ataxia UK, two Specialist Ataxia Centres have been established in the UK in response to patients' needs (integrated within the NHS in London and Sheffield).

A fundamental part of the London Ataxia Centre are the Ataxia UK representatives, who are volunteers with expertise in living with ataxia and provide emotional support and advice to the

patients after they have seen clinicians. Another role of the volunteers is to collect feedback from the patients that is shared with the Ataxia Centre team. The comments and suggestions made are used to modify the service to respond to patients' needs.

In recent surveys (Ataxia UK source), patients have shared their challenges in accessing the Specialist Ataxia Centres in the UK. Barriers identified are: the time to travel, the costs including transport and potential need for accommodation, and because of the journey itself, the fatigue experienced by people living with ataxia. As a result, patients sometimes stop going to such centres for the management of their ataxia. During the early stages of the Covid19 pandemic the London Ataxia Centre responded by swiftly moving all ataxia clinic appointments to phone clinics with the Head of the London Ataxia Centre Prof Paola Giunti and the Ataxia Nurse Suzanne Booth. A new survey was devised to collect feedback from service users of the phone clinic to help monitor and improve the service. It was encouraging that the average rating of the experience of the service was 80 per cent. The most common advantage of attending a telephone clinic (selected by 84 per cent of respondents) was the lack of travel and waiting time.

40 per cent of respondents said that they would have preferred a video consultation to a phone clinic, and indeed video consultations were subsequently established, and were well received by patients.

Such implementation of telemedicine can help to address the difficulty in accessing the Specialist Ataxia Centres and make the expertise in treatment and care available to patients remotely in their own setting. We have been able in this way to care for these rare diseases that are usually long- term.

Here is some feedback from survey participants on the telephone appointment they had:

'I didn't know what to expect as I had never had a telephone consultation before. I was totally impressed with the efficiency and professionalism of this consultation.'

'By adding a video element to highlight places on my body which are cramping or hurting.'

'It is difficult for some patients to understand and to be understood so perhaps a Zoom or Skype consultation would be preferable where the patient can be seen and can see the healthcare professionals.'

After this feedback the service moved to the use of video platforms like Attend Anywhere or Zoom.

Ataxia UK accredited Specialist Ataxia Centres are centres of excellence, where people with ataxia receive the best possible quality of care and a co-ordinated service combining diagnosis, treatment, support and research. They have been set up in direct response to needs identified by people affected by ataxia in partnership with clinicians with expertise in the condition. To achieve accreditation, centres have to comply with criteria devised following consultation with patients with ataxia and clinicians with an expertise in ataxia, to provide "excellence of care for the diagnosis and management of the ataxias, and access to a wide range of integrated services, as well as links to research programmes".

The Ataxia Centre at the NHNN London was established in 2005, and is a robust model of translational clinical service. This has been accredited as the first centre of clinical excellence in the UK by Ataxia UK. On this model, three other centres have been established in the UK.

CASE STUDY 14 - INCLUSIVE SKATING: A WORLD-RECOGNISED CHARITY THAT PROVIDES EVENTS, ACTIVITIES, EDUCATIONAL RESOURCES, TRAINING & CHAMPIONSHIPS FOR SKATERS WITH ADDITIONAL NEEDS.

Inclusive Skating is an organisation that is striving to make skating accessible. We have devised a scoring system that allows disadvantaged skaters to compete alongside able-bodied competitors and their peers with a wide range of additional needs. Participants with rare diseases often have complex needs and there's few with the exact same needs. Disability sport usually excludes many with rare diseases for these reasons. There are not enough of them to form a class suitable for Paralympic participation. If they are in a class that includes one aspect of their condition, their complex additional needs make them uncompetitive.

The innovative classification system used by Inclusive Skating converts all the additional needs to a percentage that is simply added to the skating score and all additional needs are recognised and compensated for. This creates a level playing field that makes participation fair and inclusive. The skaters are grouped into their functional development and progress seamlessly through sympathetically structured activities that commence with a development badge program and moves into a competitive development and championship structure.

As a result, our events and activities include a wide range of skaters, many with complex and rare conditions. Everyone gets the opportunity to progress and lots of medals are awarded. Torvill and Dean recently presented the medals at our Virtual World Inclusive Skating Championships where nearly 100 skaters from four continents participated in more than 300 events.

Inclusive Skating also regularly hosts the Inclusive Skating for Genes Championships. Inclusive skating created this event with the purpose of increasing awareness specifically of those with rare and genetic diseases. This event is extremely popular and all the participants enjoy engaging with others who have similar experiences of the diagnostic journey and the difficulties that having a rare disease presents. The event has contributed to increasing the profile of those with many genetic diseases. The Inclusive Skating for Genes event also featured on television during the launch of 100,000 Genome project.

My own daughter has benefited hugely from the Inclusive Skating system. When she first started skating competitively at the age of 9 her impairment was considered minimal and she had 5 per cent added to her skating score. As the years progressed her sight deteriorated and she is now registered partially sighted. Eventually at the age of 12 Juliana was diagnosed with Bardet Biedl Syndrome and she now has 52 per cent added to her skating score as the full extent of her additional needs are better understood and recognised. This is an example of how the system allows for progressive conditions.

Similarly, juvenile conditions that improve are also catered for. When the child needs the additional help, the skater is included and supported. As the condition improves and they return to full health the percentage can reduce and the child has a better chance of becoming a healthier adult, as having been able to participate in sport during their formative years.

The need to increase awareness of rare and genetic diseases is clear and we have shared many of our stories. BBC Three did a feature on Juliana which went viral on social media and was watched by millions. Juliana has also spoken at the Bardet Biedl Syndrome UK conference about her perspective on rare disease and we seek to increase the profile of BBS and rare disease generally.

CASE STUDY 15 - ADA HEALTH: AI AND RARE DISEASES

Ada is a global health company founded by doctors, scientists and industry pioneers to create new possibilities for personal health and transform knowledge into better outcomes. Its core system connects medical knowledge with intelligent technology to help people actively manage their health and medical organisations to deliver effective care, and the company works with leading health providers, organisations and governments to carry out this vision. The Ada platform has 12 million users worldwide and has completed 26 million assessments since its global launch in 2016.

The challenge

There are 300 million people living with rare diseases worldwide, 30 million of whom live in Europe. Unfortunately, for these individuals, gaining a diagnosis can be incredibly difficult. The average time to diagnosis for a rare disease is more than five years, and the average patient will attend at least five appointments in that time. This puts undue strain and cost on the individual and health services around the world.

The burden of rare diseases

Undiagnosed rare diseases are a huge burden, both on patients and health systems alike. Without access to the right treatments, a patient's quality of life can be severely and negatively impacted. The uncertainty caused by not knowing what is wrong can also lead to psychological, physiological, and financial challenges as the affected individual seeks to understand their disease and has to pay for care while doing so. In some cases, the financial burden can also fall on the caregivers who may be forced to leave their employment to focus on the provision of care full time. Patients may even be subjected to incorrect treatments and unnecessary operations in an attempt to address symptoms without addressing the true underlying cause, putting the patient at further risk.

The cost of rare diseases to healthcare systems is also huge. A study undertaken in 2021 found that "paediatric and adult discharges with rare diseases show substantially higher health-care utilisation compared to discharges with common condition diagnoses, accounting for nearly half of the US national bill."

How Ada is addressing the problem

Ada is an AI-based symptom assessment tool built by doctors, clinicians, and technology experts to help people better understand their symptoms and navigate healthcare systems appropriately. Ada's medical knowledge base covers all common diseases and hundreds of rare diseases. With over 12 million users worldwide, and 26 million completed assessments, Ada reaches a significant segment of the global population enabling it to achieve positive impact at scale.

Ada can help its users understand and identify rare disease symptoms by suggesting potential causes following a brief interview via chatbot, which works in much the same way as a conversation with a doctor would. Ada, however, is able to overcome human limitations when providing its suggestions, such as the ability to rapidly draw on its vast medical knowledge base while avoiding availability heuristics, enabling faster detection of potential rare diseases. Ada's suggestions then empower users to better navigate healthcare systems, helping them communicate their issues to caregivers more effectively and seek out the right specialists to expedite diagnosis and treatment. A retrospective study aimed at evaluating the potential of Ada's accuracy in recognising rare inflammatory systemic diseases found that 89.2 per cent of Ada's top suggestions matched the patient's confirmed diagnosis, and that 33.3 per cent of participants could have received the correct rare disease diagnosis in their first documented clinical visit, had they used the Ada app.

Ada is able to support its users in this way because it has, from the beginning, demonstrated a strong commitment to the inclusion of rare diseases in its medical knowledge base. It can be difficult for both physicians and AI systems to recognise rare diseases due to the often-unspecific symptoms, and the necessity to diagnose them by differentiation. By focusing on these issues from the outset, Ada has been able to gather significant data such that it already covers hundreds of rare diseases. To ensure continual improvements to this data bank, Ada also works closely with life science partners and independent experts from the healthcare community to build more rare diseases into its medical knowledge base. Most recently, Ada has been working with leading physicians and scientists to model Familial Mediterranean Fever (FMF) and lysosomal storage diseases such as Gaucher, Fabry and Pompe.

Ultimately, Ada believes that raising awareness is key to combatting rare diseases. Using its social media channels, Ada undertakes regular activities to inform its thousands of followers worldwide of the symptoms, risks, and potential treatment options for rare diseases. In collaboration with its life science partners, Ada also undertakes joint awareness initiatives leveraging its advanced AI capabilities and its partner's reach to help people find out more about rare diseases and ultimately shorten the time to diagnosis for as many patients as possible. Ada was recently integrated into Novartis's awareness website for FMF, enabling people who may be living with the disease to find out more about their symptoms.

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