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Publication of the Rare Disease Framework Action Plan for England

In January 2021, the UK government published the UK Rare Diseases Framework as a successor to the UK Strategy for Rare Diseases. The framework, which cuts across all four UK nations (England, Scotland, Wales and Northern Ireland), sets out the intention to improve the lives of the 3.5 million people in the UK living with rare diseases.

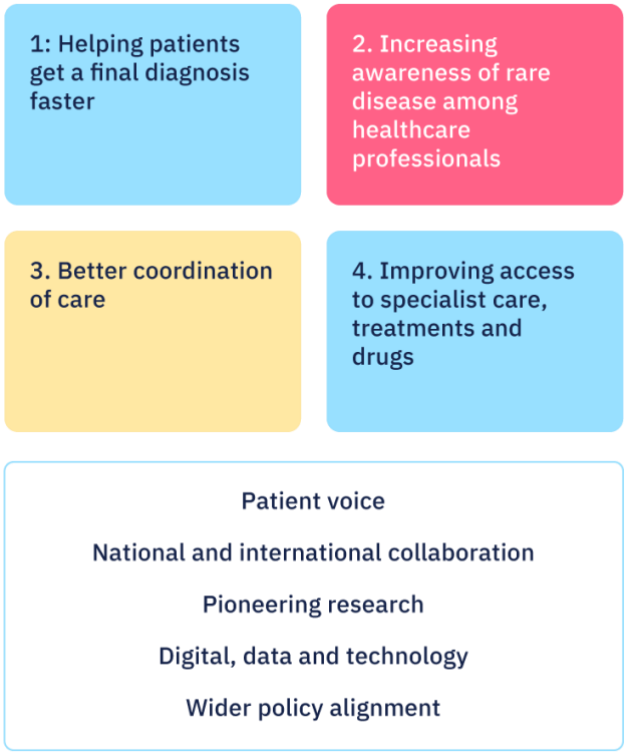
Rare diseases impact 1 in 17 of us, but disproportionately impact children to the extent that 75% of affected individuals are children. They can be both life limiting and life threatening and only a few have effective therapeutic interventions. Tragically 30% of children with rare diseases die before their 5th birthday.

Whilst collectively common, each condition is rare and people with rare diseases and their families often require complex care, with many experiencing a long and protracted journey to diagnosis. This can profoundly impact individuals and families, not just in regard to their medical care but also social care provision, education, mental health and financial stability.

80% of rare diseases are thought to have an underlying genetic aetiology and so improvements in knowledge of genomics and technology to help understand genomic data in the context of patient data is expected to play a central role in the delivery of some of the key priority areas. It is this that is the focus of this commentary. However, it is important to highlight that not all rare diseases are genetic, and the aim of the framework is to deliver equity of care to all patients irrespective of underlying causality.

Rare Disease Framework Priorities

Developed with patients, their families, and other key stakeholders the framework identified four key priority areas and five underpinning themes essential to support its delivery.



Whilst the framework sets out a high-level vision for each priority area and forms the strategic direction for rare disease provision in the across the UK for the next 5 years, it is the responsibility of each of the four nations to develop and deliver their own plans to meet the commitments laid out.

To ensure close collaboration and shared best practice across the four nations of the UK, all plans have been developed under the governance of the UK Rare Diseases Framework Board and in consultation with a wide range of stakeholders. These include delivery partners, such as the NHS in each nation, the Medicines and Healthcare products regulatory agency (MHRA), the National Institute for Health and Care Excellence (NICE), NHS Digital and the Medical Research Council etc, as well as rare disease clinicians and most importantly representation from rare disease patients and their families to ensure that the patient voice has been central to the process.

Today England has published the first of the Rare Diseases Action Plans to coincide with Rare Disease Day, with plans expected from Scotland, Wales, and Northern Ireland later this year. It contains a total of 14 actions under each of the four priority areas identified in the UK Rare Diseases Framework and describes expected outcomes and accountabilities. Funding for all actions has been committed, including support for Genomic England's "Generation Genome" initiative

This commentary aims to set the scene and describe the 14 main action points. The underpinning themes highlighted as being needed to drive delivery will be the topic of other articles by Congenica.

Priority 1: helping patients get a final diagnosis faster

Patients and families with rare disease often experience a protracted route to diagnosis, the so-called diagnostic odyssey. Mapping and understanding this journey from first referral to diagnosis (or no diagnosis) may be different for each patient and is arguably critical to ensuring this (and the other priorities) are achieved.

If you are interested in the typical stages involved in the diagnosis of rare disease, take a look at Congenica's 'Opening the Black Box' series, which though a series of short films documents the journey from first appointment to diagnosis for George and his family.

Genomics is expected to play a central role in meeting the ambitions of Priority 1 and significant progress has already been made in helping patients get a final diagnosis faster in England in the last few years. Initiatives include the establishment of the Genomic Laboratory Hubs (GLHs), the Genomics Medicine Service (GMS), and the new Genomic Medicine Service Alliances (GMSA). Hundreds of thousands of genomic tests have already been carried out, many for rare diseases, and clinical grade whole genome sequencing (clinical GS) provision has begun.

Evidence supporting the use of genomics in helping address priority 1 has been published recently in two articles in Nature (1) and the New England Journal of Medicine (2) where it has been demonstrated that not only can clinical GS shorten the journey to diagnosis but for some patients and their families it has improved patient outcomes by informing tailored therapeutics, enabling early intervention and entry onto clinical trials.

Given the disproportionate impact on children it is no surprise that timely diagnosis early in life, especially for patients being treated in acute clinical settings such as neonatal/paediatric intensive care units and prenatal clinics, has been shown to significantly improve outcomes for patients (3). To address this the NHS Genomic Laboratory Hubs (GLHs) in England have established a network to provide rapid genomic analysis to ensure that individuals in these settings get rapid access to genomic testing.

Congenica has contributed with authors on both ground-breaking articles (1, 2). We are also the exclusive genomic data analysis and clinical decision support partner to the GMS, and many of the GLHs in both a routine and acute setting.

Another opportunity to provide timely diagnosis and improved outcomes is via newborn screening programmes (NBS) where actionable disorders are screened for soon after birth and before symptoms of the condition appear. Unfortunately, the conditions which are screened for in NBS programmes differ significantly across the world and even within individual countries resulting in potential health inequality. Furthermore, NBS testing strategies and methods take many forms and currently genomic analysis is not the primary test for many conditions.

Genomic technology has the potential to improve NBS by allowing the analysis of rare conditions which are not amenable to testing via other methods. In addition, genomic tests can more easily provide analysis of multiple conditions simultaneously. Consequently, the addition of genomic analysis, including genome sequencing, to increase the range of actionable conditions which can be tested for at birth has been the subject of a national dialogue in England to explore public views.

England's Rare Diseases Action plan for priority 1 includes five actions point

1) Improving how decisions are made on newborn screening for rare diseases forms the first action point of England's Rare Diseases Action Plan. A new and improved UK National Screening Committee (UK NSC) with new terms of reference will be established and a UK NSC Bloodspot Task Group will be established to evaluate accuracy and approaches for use in NBS. In addition, a formal comparison with EURODIS will be undertaken to facilitate an understanding of how UK screening compares.

2) Whole genome sequencing to screen for genetic conditions in healthy newborns. Funding has been identified to support Genomic's England's "Generation Genome" initiative to undertake an ethically approved pilot study of up to 100,000 newborns using genome sequencing to detect rare diseases. The pilot will develop a framework to identify up to 200 genes for inclusion and will include investigation of how the programme could be rolled out in the NHS; from diagnosis, through genetic counselling and care and patient experience.

3) Defining testing strategies provided in the NHS is the responsibility of the National Genomic Test Directory and the third action point related is to further develop this resource to help improve diagnostic yield.

The 100,000 Genomes Project provided a diagnosis for around 25% of participants. Many patients already had standard of care investigations and genetic testing prior to entry for a wide range of disorders and clinical presentations. This leaves up to a potential 75% of

individuals without a molecularly confirmed diagnosis. Improving the ability to provide diagnoses is a key theme for the remaining actions/commitments highlighted for delivery of Propriety 1.

4) A commitment to maximise the utility of the information (genomic and otherwise) held within the Genomics England infrastructure by further developing the clinical-research interface to support collaborative work between clinicians and researchers on consented deidentified patient data. This will allow them to work more closely together to provide a diagnosis for more rare disease patients, solve complex cases, make new discoveries, and ultimately increase our understanding of how genetic factors contribute to rare disorders.

5) This important action point recognises that not all patients will receive a genetic diagnosis, either because their disorder is not genetic in origin or because we do not currently have the knowledge to recognise the underlying genomic cause. For these undiagnosed patients and families, it is essential that they receive the support they require and that those looking after them are equipped to recognise and manage their condition. Whilst still in the design phase it appears that these pilots, which will be selected by summer, may take a similar approach to that seen used by the US Undiagnosed Diseases Network (4), and an example provided in the document includes a multidisciplinary "holistic one-stop paediatric clinic" which will include healthcare professional with specific expertise in the management of syndromes without a name (SWAN)

Priority 2: increasing awareness of rare diseases among healthcare professionals

There are over 7000 rare diseases, and all, by definition, are rare, so raising awareness across the healthcare profession is a priority not only to improve the speed and accuracy of diagnosis but also to ensure appropriate management across the health service, including during episodes of medical emergency.

As it is not possible to provide in-depth training in all rare diseases, this priority aims to raise general awareness of rare diseases and point healthcare workers to specific training, access to resources, signposting to care pathways and support and raise their awareness of potential specialist treatments.

6) Commits to complete the development of an innovative educational resource called GeNotes. GeNotes aims "to help healthcare professionals make the right genomics decisions at each stage of a clinical pathway by providing concise 'just-in-time' clinical information to support patient management" and point clinicians to extended learning resources/opportunities. GeNotes which is currently in the beta phase of development

7) This action point describes the work required and commitment to provide a formal report and recommended guidance on how to include rare diseases in UK health professional education and training frameworks; from undergraduate training all the way through to continuing professional development. This work will be led by Health Education England and will include engagement with a variety of stakeholders including rare disease individuals and their families, charities, professional organisations, and curriculum developers.

8) A commitment has been made to extend the remit of the highly successful Genomics Education Programme, which is available to NHS staff, to include non-genetic rare diseases.

9) This action point outlines how epidemiological evidence from large population datasets collected by the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) will be leveraged to increase understanding of rare diseases. To reflect this initiative NCARDRS has target of publication of at least six papers describing "novel findings or methods relevant to rare disease" by the end of 2022 to ensure dissemination of findings across the community.

Priority 3: better coordination of care

Many rare disease patients do not have a dedicated service within the NHS, and even where they do, the diversity of the signs and symptoms of their conditions often necessitates multiple appointments with multiple specialties at different hospitals and services. Often patients and families are left to coordinate appointments and services themselves, significantly increasing the burden of care. An additional challenge may also be faced when transitioning from paediatric to adult services.

The CONCORD (CoOrdinated Care Of Rare Diseases) study was initiated in 2017 to improve our understanding of care coordination for rare disease individuals and examine how it might be focussed around the needs and preferences of individuals and their families. Whilst not a discrete action point, England's action plan commits to considering CONCORDs findings to determine how they can be progressed to provide the evidence needed to operationalise improvements in coordination of care for rare disease patients.

10) Action point 10 describes how the use of technology and digital tools will be used in the context of rare disease. Adoption of technology and digital tools has been accelerated by necessity during the COVID-19 pandemic which resulted in a shift from face-to-face appointments to virtual consultations. These approaches have the potential to improve care coordination and reduce the burden on patient and families by removing the necessity to travel, at least some of the time. This action point commits to developing a toolkit for

virtual consultations for rare diseases. The toolkit will be published in spring of 2022 and it is expected that knowledge will be shared with other work ongoing in the NHS on Integrated Care Systems.

Whilst not specifically called out as an action point, the England Action plan also highlights the impact of mental health and wellbeing in rare diseases and the requirement for coordination within health and social care.

Priority 4: improving access to specialist care, treatments and drugs

The NHS GMS infrastructure and service specification has been established in part to ensure that rare disease patients and their families have access to specialist genomics services and care delivered as locally as possible. This is managed through a national network of the seven NHS GLHs and clinical services and the Clinical Genomics Service Specification which "covers the provision of a National Clinical Genomics Service in England, including diagnosis, lifelong management, risk assessment and treatment, of "patients and their families who have, or are at risk of, rare genetic diseases". It is hoped that by embedding genomics into mainstream clinical care will improve accurate diagnosis which can in turn lead to the development of and access to precision medicines.

Currently precision medicine is a reality for a minority of rare disease individuals with only around 5% of rare diseases thought to have a tailored treatment. It is also notable some rare diseases have multiple treatments being developed, whereas others have none. However, for those rare diseases that have access to these therapies the impact can be transformational and lifesaving.

Development of treatments and therapies for rare diseases is challenging as the small numbers of patients affected by a single condition usually means that the usual clinical trials process may not be possible. In addition, consideration of rare diseases clinical trial design and data by health assessment and regulatory bodies is more complex.

Whilst organisations/initiatives already exist in the UK to facilitate early access to novel and high-cost treatments, such as the Innovative Medicines Fund, the Early Access to Medicines Scheme, the Innovative Licencing and Access Pathway, MHRA Innovation Office, the Medicines Repurposing Programme etc., understanding the complex research, organisational and regulatory landscape has been identified as a significant obstacle to improving access to specialist treatments and drugs. The following three action points outlined in the plan are intended to address this:

11) A commitment to supporting rapid access to drugs for rare disease patients by proactively horizon scanning for new therapies, identifying challenges at an early stage, and providing clarity by mapping the schemes outlined to promote understanding of the evaluation pathway.

12) The development of a strategic direction for gene therapies and other advanced therapy medicinal products. This strategy document will be produced by summer 2022 and will set out the commissioning position of NHSE/I.

13) A commitment to ensure that NICE "continues to support the rapid adoption of effective new treatments for NHS patients with rare diseases".

14) Finally, to ensure that the strategies and actions described are effective, the NHS will monitor both overall use by rare disease patients and map across the country to determine equity of access.

Conclusion

The publication of Rare Disease Framework Implementation Plan for England is an important and exciting document which commits to improving the care of rare disease patients and their families in England and the rest of the UK. Congenica is excited and privileged to play a part in supporting colleagues in the NHS and other delivery partners in achievement of its aims.

Quote from Alistair Kent, Chair of Congenica's Patient Advocacy and Engagement Board

"I am delighted to see the publication of the Rare Disease Framework Implementation Plan for England. The provides a range of tangible commitments that will move us towards achieving the goals laid out in the Rare Disease Framework, and improving the services and support for patients and families with rare diseases. There is much to do to bring this about, and the plan will be reviewed annually. This will ensure that progress can be monitored and new targets set that will incorporate new opportunities and reflect advances in our understanding of how best to respond to the needs of the 1 in 17 who are affected by rare diseases."

References

1. Smedley, D., Smith, K.R., Martin, A et al. The 100,000 Genomes Project Pilot Investigators. Impact of the 100,000 Genomes Pilot on Rare Disease Diagnosis in Health Care – Preliminary Report. *N Engl J Med* 2021;385:1868-80

2. Turro, E., Astle, W.J., Megy, K. et al. Whole-genome sequencing of patients with rare diseases in a national health system. *Nature* 583, 96–102 (2020).

3. Dimmock D, Caylor S, Waldman B et al. Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. *Am J Hum Genet*. 2021 Jul 1;108(7):1231-1238.

4. The Undiagnosed Disease Network (UDN). https://undiagnosed.hms.harvard.edu/