Rare diseases deserve equity in the Irish healthcare system

Once you start counting a specific rare disease, you realise it is not that rare at all, writes

Prof Sally Ann Lynch

THE DEFINITION OF a rare disease is that is affects five in every 10,000 people (~1 in 2,000). However, as there are many thousand rare diseases collectively, when counted together, they are common. Rare diseases are often chronic complex disorders affecting all parts of the body. Approximately 75% are genetic in origin, hence my interest.

Accurate estimates of any epidemiological indicators of rare diseases in the Republic of Ireland are impeded by a number of factors, including inadequate coding, lack of unique identifier and disjointed datasets. The resulting health information gaps contribute to an inability to appropriate resource allocation, re-enforcing the myth that rare diseases are uncommon and compounding health neglect for rare disease patients.

A recent study by Children's Health Ireland, Temple Street and the National Rare Disease Office at Mater Misericordiae University Hospital, followed children born in Ireland in the year 2000 through childhood and counted the number who had developed a rare disease throughout the childhood years.[1] This noted that 2,283/54,789 live-births were diagnosed with a rare disease (4.2%) by 17 years of age, with 11.8% (270/2,283) having died during this period. As 75% of rare diseases present in childhood, this means that 6% or so of our population suffer from a rare disease throughout their life. Notably, 2,013 of the 2,283 rare disease patients identified in this study were alive at the age of 18. We estimated that a significant proportion of these 2,013 people have chronic conditions that required transition to adult care, that is if adult services exist. Rare disease patients used 51.9% of paediatric bed days over the 18 years, and 59.9% of teenage bed days, despite representing only 4.2% of the complete paediatric cohort.

This work took enormous effort, using multiple data systems across two hospital sites and the general registration office, with no interconnectivity between any database. We also had to manually curate each possible rare disease case. The lack of interconnected IT systems, unique patient identifier and poor coding precludes live capture of data which is needed as trends in incidence are not being captured. New treatments mean some rare diseases will be more prevalent as survival improves and, conversely, new antenatal screening options are likely to be reducing the incidence of other rare disorders – without live capture, how can you even begin to plan services?

The significance of these disorders in terms of trauma to families and workload on hospitals was borne out by a previous study of ours, focusing on paediatric rare disease mortality using data extracted from the National Paediatric Mortality Register (years 2006-2016). We noted that 2,368/4,044 paediatric deaths (58.6%) had an underlying rare disease.[2] Rare disease patients occupied 87% of bed days used by children < 15 years who died during hospitalisation from January 2015 to December 2016.

Impact of research

Last December, I was awarded the Health Research Charities Ireland (HRCI) inaugural impact award, which was a huge honour. This made me reflect (and cause a minor panic) on what impact my research really has had. My research (funded by the Health Research Board (HRB)/HRCI award scheme), had utilised newly developed next generation sequencing approaches to try to reach diagnoses in children, adults and in the antenatal setting, where previous testing had been negative.

We followed up with various grants from the HRB, Children's Health Foundation and UCD, and started to develop short educational animated videos on genetic topics, which have proven very successful (viewed > 1.75 million times) and are used by the educational European Society of Human Genetics website **EuroGEMS.org**, and also by Unique, the rare chromosomal support group.[3,4]

Of course, good research is not down to just one person, I had the benefit of a brilliant postdoc researcher, Dr Jillian Casey, who analysed the DNA variants and suggested diagnoses, which I reviewed. We also collaborated for the second two years of our four-year funding with Dr Ellen Crushell, consultant paediatrician in the National Metabolic Unit in CHI, Temple Street, to help secure diagnoses for patients there. We worked on many genetic conditions occurring in families from the Irish Traveller population.

Given that Irish Travellers have among the worst health statistics in the European Union, by identifying some of the genes found in this population we have improved care by facilitating earlier diagnoses. This work resulted in a publication cataloguing all the known inherited conditions found in the Traveller population, which is utilised routinely by UK laboratories.[5] In some small way, I believe we have improved care for this population.

Our next aim is to consider developing a pilot study (with Dr Ellen Crushell and Pavee Point) to introduce antenatal testing for galactosemia for Traveller woman which would give them the option of breastfeeding immediately after birth. Currently, they have to wait for the first

three days after birth for a negative galactosemia test result to come through before being allowed to breastfeed. This needs to change.

The reality is there are a lot of people (one in 17 or ~300,000) in Ireland living with a rare disease. Many families require support from multiple governmental agencies (the HSE, Department of Education, Department of Social Protection) to live as healthily as possible, to minimise in-patient bed days, to be included in our educational system, to be supported into the workforce and to be allowed to be active members of society.

Patient advocacy groups and those of us working in the field do our best to champion the needs to improve the care and facilitate access to new therapies. The Cystic Fibrosis Ireland performed a study showing that it was financially cost-effective for the State to pay for expensive new CF drugs as any cost was offset against in-patient bed costs and would allow patients to continue their education and enter the workforce.[6]

Genetic testing

My current funded research, through the Adelaide Health Foundation, is looking at genetic counselling services in Ireland. One aspect of this is looking at risks in the genetic testing process from first meeting with a patient through to interpreting genetic test reports back to the patient or family. We want to learn what controls we could put in place to make this safer. All of us want to avoid the diagnostic odyssey rare-disease families go through waiting for a diagnosis, but it is critical that support is available to help specialists interpret complex genetic test reports. We have recruited four international groups in Romania (Craoiva), Northern Ireland, Oxford and Finland (Oulu) to collaborate and repeat our study. We are interested to compare where risks are occurring in each country and learn from others what controls work best to optimise safety in genetic testing.

The EU directive in the field of rare disease, which the Department of Health endorsed, pledges to improve access to services to speed up diagnostic testing and to facilitate clinical trials.

The recent launch of European Reference Networks (ERN)[7] covers all specialties involved in rare diseases and aims to foster collaboration across the EU. Firstly, this will allow patients with rare diseases to be counted through ERN specific databases/registries. Being able to identify patients with specific rare disorders is key to understanding more about each specific disorder – it allows clinical guidelines to be developed, research facilitated and clinical trials to be considered. Once you start counting a specific rare disease, you often realise it is not that rare at all, especially when you include all 440 million citizens of the European Union.

Next generation sequencing

Currently, the introduction of next generation sequencing technology allows diagnoses to be made where previous testing could not. Very often the diagnosis reveals a DNA variant in a gene one has never heard of, particularly in the field of intellectual disability, which is highly heterogeneous genetically (> 2,000 genes). Intellectual disability is the paradigm for rare disorders. It is relatively common but individual causes of intellectual disability are very rare. According to the 2016 national census, 66,611 people – representing 1.4% of the population – have an intellectual disability. This was 8,902 higher than in 2011, representing a 15.4% increase (**www.cso.ie**). In practice, intellectual disability diagnoses mean that, while the diagnosis is often a relief for families, it does mean they are now in a lonely world where they are the only family (or one of very few) in Ireland living with this rare disorder. Often times there is no patient friendly leaflet on the disorder (we search **www.orpha.net** and **www.rarechromo.org** to find leaflets for families). The world of social media has allowed families to connect across borders and find their tribe.

Each ERN has a European patient advocacy group, known as ePAGs. Patient advocates are funded to attend ERN meetings to ensure their presence is centre stage within each ERN. The ERNs are multidisciplinary aiming to cover all aspects of clinical and social care. One of the goals of ERNs is to ensure each patient has access to services throughout life. Transition is a key factor in this. The disease specific guidelines, all written with ePAG member involvement, aim to address this.

Nobody wishes a rare disease on themselves or their family. They just want to be counted, to be supported and to observe equity in healthcare.

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