The importance of rare diseases: from the gene to society

John A Dodge,[1] Tamara Chigladze,[2] Jean Donadieu,[3] Zachi Grossman,[4] Feliciano Ramos,[5] Angelo Serlicorni,[6] Liesbeth Siderius,[7] Constantinos J Stefanidis,[8] Velibor Tasic,[9] Arunas Valiulis,[10] Jola Wierzba[11]

What exactly do we mean by a rare disease (RD), and why are they important for paediatricians? The definition used for public health purposes in Europe is that an RD is one which affects fewer than one citizen in 2000; in the USA it is fewer than one in 1250.[1] There are estimated to be between 6000 and 8000 known RDs in the world, many of which are predominantly paediatric disorders. About 75% of the diseases meeting the criteria for RD affect children, and about 30% of all patients with RDs die before their fifth birthday.[2] Approximately 80% of RDs have a defined genetic basis.[2] The true incidence and prevalence of individual RDs are often unclear. When the condition is fatal in childhood or early adult life, the prevalence in the population (table 1) will be well below the birth incidence, and will not reflect the gene frequency. Thus, to take the familiar example of cystic fibrosis, the birth incidence in the UK is about one in 2500 live births, but the population prevalence is given as about one in 8000.

[1]Department of Child Health, University of Wales Swansea, Swansea, UK
[2]Foundation for Genetics and Rare Diseases, Tblisi, Georgia
[3]Service d'Hémato Oncologie Pédiatrique, Hôpital Trousseau, Paris, France
[4]Department of Pediatrics, Maccabi Health Services, Tel Aviv, Israel
[5]Pediatrician and Clinical Geneticist, Hospital Clinico Universitario "Lozano Blesa", Zaragoza, Spain
[6]Genetica Clinica Pediatrica, Università Milano Bicocca, Milan, Italy
[7]Youth Healthcare, Meppel, The Netherlands
[8]Department of Paediatric Nephrology, P&A Kyriakou Children's Hospital, Athens, Greece
[9]Department of Paediatric Nephrology, University Children's Hospital, Skopje, Macedonia
[10]Department of Paediatrics, Vilnius University Faculty of Medicine, Vilnius, Lithuania
[11]Department of Paediatrics, Gdansk Medical University, Gdansk, Poland

Correspondence to Professor John Dodge, Department of Child Health, University of Wales Swansea, Singleton Hospital, Swansea SA2 8QA, UK; j.a.dodge@btinternet.com

Although individually rare, the cumulative burden of RDs is significant. RDs may affect as many as 30 million Europeans, with at least 3 million in the UK and 4 million in Germany, and this statistic has not been lost on the European Union (EU). A Committee of experts on rare diseases (EUCERD) was set up in November 2009 to assist and advise the European Commission, including, inter alia, drawing up guidelines and recommendations for implementing EU policies relating to RDs. This followed the EU council communication of 9 June 2009 calling on member states to institute national plans for RDs before the end of 2013, and this policy was adopted by the EU Council of Health Ministers. In his final annual report for 2009, published in March 2010, the UK's Chief Medical Officer, Liam Donaldson, pointed to the lack of awareness and effective services for RDs in the UK. He highlighted the fact that affected children are dying needlessly, after living for years with undiagnosed or misdiagnosed conditions, and called for urgent measures to improve understanding and, crucially, for more funding for services for more than 6000 RDs.[3]

RDs are important to paediatricians for many reasons, including the following:

- Because cumulatively the RDs affect many children. In addition, there is a huge impact on their families, and many parents of children with RDs have no choice but to become full-time carers, with consequent economic and psychological effects on all family members.
- Because whether or not they have been accurately diagnosed, patients with RDs often have more than one clinical problem. With multisystem disorders, it is usually the responsibility of the paediatrician to act as the overall case manager.
- Because today's RDs can become tomorrow's major public health problems. For example, the conditions originally known as Caffey's disease and Kempe syndrome in the 1950s, and thought then to be uncommon, are now recognised as features of the far-too-common child abuse.
- Because by refining our diagnostic precision we can find means of cure or control of different conditions which were formerly lumped together, a process which has been made easier, if sometimes revealing unexpected complexity, by the advent of DNA diagnosis. For example, cystic fibrosis, an RD, now has a defined genetic cause, a much more variable clinical picture than we formerly recognised, and its mutant gene can account for distinct entities such as male infertility, and alcohol-induced pancreatitis with few or no other clinical features, but these would probably still be unknown consequences if the RD of cystic fibrosis had not been the subject of intensive research. Shwachman-Diamond syndrome, an entirely different condition, was discovered by investigating a patient attending a cystic fibrosis clinic who had unusual clinical features. By exploring its genetic and molecular background we are gaining

Table 1 Some examples of estimated European population prevalence given on the Orphanet website (http://www.orpha.net)[5]

	Per 100 000
Acrocephalosyndactyly	4.6
ADA deficiency	0.22
Ataxia-telangiectasia	1.0
Cockayne syndrome	200 total cases
Cystic fibrosis	12*
Cystinosis	0.5
Ectodermal dysplasia	<100 published cases
Fanconi anaemia	1.0
Menkes syndrome	0.7
Progeria (birth incidence)	0.25
Refsum syndrome	0.1
Rett syndrome	4.5
Shwachman-Diamond syndrome	1.0†
Zellweger syndrome	1.1

*This masks a wide range between for example, Finland where it is very low, and Ireland where it is significantly higher than the European average.
†This is almost certainly too high. There are about 200 known cases in Europe, which represents <10% of the estimate.
ADA, adenosine deaminase.

Table 2 Proposal accepted by the European Academy of Paediatrics 2010

European paediatricians, working together, will:
Provide sufficient services for expert diagnosis or confirmation of diagnosis
Ensure appropriate capacity and equal access to follow-up and management of children with rare diseases
Produce and adhere to good practice guidelines and implement outcome measures and quality control
Use and demonstrate a multidisciplinary approach in management of patients and families
Document and maintain a high level of expertise through publications, grants or honorary positions, teaching and training activities
Make a strong contribution to international research and support international trials of treatment of rare diseases
Provide epidemiological surveillance, such as by registries, preferably at a European level
Communicate with health authorities and policy makers in order to improve the finances for healthcare of children with rare diseases
Support, communicate with and advise patient rare disease networks and organisations
Collaborate with initiatives of the European Commission Rare Disease task force in developing national plans for integrated services and support for patients and families affected by rare diseases.

important insights into mechanisms which lead to the much commoner leukaemias.

- Because patients with an RD shed light on human biology. For example, the (very) RD of progeria can tell us much about the ageing process which affects us all. Far from seeing such investigations as intrusive, families anxious that their child's RD should be understood, and if possible cured or controlled, are usually only too eager to collaborate with medical scientists, whose ultimate motivation is to help them.
- Because separating out rare conditions may be lifesaving, such as by finding the child with long Q-T syndrome who has been referred for investigation of deafness. Identifying the child with Laurence–Moon–Biedl–Bardet syndrome, or Prader–Willi syndrome, in the burgeoning population of obese children, is not mere paediatric stamp-collecting; it is good doctoring.
- Because teaching our trainees to take a careful history, including a full family and genetic history, and to examine and investigate the patient thoroughly, is fundamental to training progammes. They must be taught to enquire 'why' when the history or findings differ from their expectations.
- Because population migration is now such an important feature of our changing world that conditions formerly thought of as rare, or only affecting unfamiliar ethnic groups, are now appearing in our clinics.

RDs do not recognise geographical boundaries, and for families with very rare conditions seeking expert advice, it may only be found outside their own locality, region, province, state, or even their own country. It should not be difficult for the clinician faced with a patient or family with a RD to find out where the requisite experience, expertise, advice and ongoing research can be found, and to refer the patient accordingly. More than 4600 web-based resources for more than 1500 RDs were listed by the organisation Orphanet in 2008.[4] With so many websites, the quality of information is bound to be variable, which underscores the need for a source of international information about where reliable and authoritative advice can be obtained. The often tiny charities which represent families with specific RDs should be able to count on the institutional support of national paediatric organisations, as well as clear directions towards the expertise they seek. For some of the well-known RDs, such as cystic fibrosis, diagnostic, clinical, research and support networks already exist at national and international levels and no new initiatives are needed; but families affected by other, less publicised RDs must know that they are not alone, and that their plight has been recognised by paediatricians as well as by the politicians.

A response to the EU challenge has been given by the European Academy of Paediatrics – UEMS Section of Paediatrics, which adopted a proposal for a policy on RDs in April 2010. This stated that, working together, 'we will ensure the provision of sufficient services for expert diagnosis or confirmation of diagnosis'. A key provision will be the provision of epidemiological surveillance of RDs, ideally using European registries where possible. They also resolved to work with patient support groups and RD networks**.** The full proposals are given as table 2.

The Working Group set up by the EAP will be coordinated by Dr Liesbeth Siderius, Meppel, the Netherlands, e.siderius@kpnplanet.nl who will be pleased to reply to enquiries and expressions of interest. It welcomes input from individual clinical and molecular geneticists, parents, patients, social workers, specialist nurses, research scientists, as well as clinicians of all descriptions including paediatric and adult primary, secondary and tertiary care physicians, and also single disease charities and national and European umbrella organisations such as Genetic Alliance UK and the European Organisation for Rare Diseases (EURORDIS). An inaugural meeting of the Working Group will be held at the Spring meeting of EAP in Vilnius in May 2011, which is open to all with an interest in this important health problem.

Competing interests JAD is a Trustee of Genetic Alliance UK and chairman of the Medical Advisory Board of Shwachman-Diamond Support UK.

Provenance and peer review Not commissioned; internally peer reviewed.

Accepted 1 July 2010
Published Online First 12 August 2010

Arch Dis Child 2011;**96**:791–792.
doi:10.1136/adc.2010.193664

REFERENCES

1. **Schieppati A,** Henter JI, Daina E, *et al.* Why rare diseases are an important medical and social issue. *Lancet* 2008;**371**:2039–41.
2. European Organisation for Rare Diseases (EURORDIS). What is a rare disease? http://www.eurordis.org (accessed 9 June 2010).
3. **Donaldson L.** On the State of the Public Health. Annual Report of the Chief Medical Officer 2009. London, HMSO 2010.
4. **Aymé S,** Kole A, Groft S. Empowerment of patients: lessons from the rare diseases community. *Lancet* 2008;**371**:2048–51.
5. Prevalence of Rare Diseases: Bibliography Data. Orphanet Report Series. Rare Diseases Collection November 2009. http://www.orpha.net (accessed 9 June 2010).